C-Pulse® System
European Multicenter Study

CLINICAL PROTOCOL
(Clinical Investigation Plan)

Clinical Investigation Number: 2012-01

Protocol Change Status	
Protocol Revision #	**Effective Date**
PRO-04654 Revision C	13 Jan 2014

Sponsor
Sunshine Heart, Inc.
12988 Valley View Road
Eden Prairie, MN 55344
USA

STATEMENT OF COMPLIANCE

The C-Pulse® System Study will be conducted in accordance with the Declaration of Helsinki and EN ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good Clinical Practices.) and any additional provisions outlined in the Study Agreement. In addition, the Study will comply with any applicable European or regional regulations.

The clinical investigation shall not begin until the required approval/favorable opinion from the local Ethics Committee (EC) or regulatory authority has been obtained, as appropriate.

SIGNATURES

Site Principal Investigator

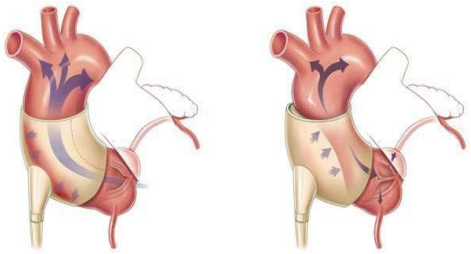
I have read and understand the contents of the C-Pulse® System European Multicenter Study protocol. I agree to conduct this study according to the requirements of the study protocol and in accordance with Good Clinical Practice and applicable regulations. I agree to supervise all Co-investigators at my site as well as the use of all devices and study materials at my institution and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study. I agree to hold all information related to the study in confidence and not to disclose it to any third parties for a period of five years from the date of this agreement, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose is entered into by the parties.

Name	Signature	Date
_____	_____	_____

STUDY SYNOPSIS

Title	C-Pulse® System European Multicenter Study
Study design	Multi-center, prospective, open label study.
Study objective	The study is designed to observe the clinical outcomes of heart failure patients treated with C-Pulse® System in the usual manner and according to the approved indications and contraindications.
Enrollment	Up to 50 patients with moderate to severe heart failure who receive the C-Pulse® System will be followed up for 5 years to collect performance and safety data.
Locations	A maximum of 15 European sites will participate. Study data from additional geographies may be included.
Estimated Time Course	First Patient In: May 2013 Last Patient In: Dec 2014 Last Patient Out: Dec 2019
Introduction	Pharmacological and device-based therapies for heart failure continue to be refined though still pose challenges. Now Sunshine Heart introduces the C-Pulse® System, designed to provide the well-known clinical benefits of counter-pulsation heart pumping support while allowing the patient to move and go back home, having a quite normal day-life style.
Technology	Sunshine Heart's C-Pulse® System is a new approach for patients with moderate to severe heart failure that can be used in combination with other heart failure therapies. The device is designed to assist the heart's function, not replace it and may be implanted using a minimally invasive approach. The C–Pulse® system is designed to provide an effective, low risk and low cost wearable mechanical heart assist device for use in patients in NYHA Class III–IV ambulatory. It is intended for use in hospital and at home.

Implantable C-Pulse Cuff.



External wearable components.

How does C-Pulse® System work?	The C-Pulse® implanted cuff is wrapped around the ascending aorta and is pneumatically driven, via a percutaneous line, by an external driver. Inflation and deflation are timed from the ECG, sensed via an epicardial lead that is connected to the percutaneous interface lead. The C-Pulse® System is simple to implant and accommodates aortic anatomic variability. C-Pulse® System allows patient mobility and can be turned off or used intermittently if recovery occurs or for day-life exigencies. In addition, the C-Pulse cuff sits outside the bloodstream, therefore eliminating the need for anti-clotting medications.
Regulatory status	CE marked
Study objective	Evaluation of the post-market clinical performance and safety of the C-Pulse® System for the treatment of Heart Failure in the population of patients who meet the approved clinical conditions provided in the indications and contraindications.
Patient population	A patient population of up to 50 patients with moderate to severe heart failure refractory to optimal medical therapy, who are implanted with the C-Pulse System as clinically appropriate, will be enrolled into the Study.
Inclusion Criteria	According to the CE mark authorization, patients with the following conditions can be included: • Patient is 18 years or older • Patients with moderate to severe ambulatory heart failure [American College of Cardiology/American Heart Association (ACC/AHA) Stage C; NYHA Class III/IV ambulatory], who are refractory to optimal medical therapy. • Patients who are non-responders to CRT pacemaker therapy • Patient has signed and dated the investigation informed consent form.
Exclusion Criteria	According to the CE mark authorization, patients with the following conditions (contraindications) have to be excluded: • Evidence of significant ascending aortic calcification on postero-anterior chest X-ray or CT scan • Moderate or severe atherosclerotic aortic disease • Ascending aorto-coronary artery bypass grafts • Any history of aortic dissection • Connective tissue disorder such as Marfans disease • Previous aortic root replacement • Aorta not conforming to specified dimensional constraints • Patient has severe mitral valve incompetence, grade 4+ • Patient has moderate to severe aortic valve incompetence, grade 2 - 4+ • Patient has systolic blood pressure less than 90 or greater than 140mmHg • Presence of active systemic infection • Presence of bleeding or coagulation disorder (relative)

Screening process

Patients diagnosed with moderate to severe heart failure and who are treated at the participating centers are eligible for screening evaluation. The investigator(s) will obtain informed consent for study participation from each patient prior to implementation of screening procedures.

Patients eligible for device implantation must meet all the inclusion and not meet the exclusion criteria (indications and contraindications based on device CE mark authorization and Instructions for Use). In addition, a screening process will be carried out with the objective of selecting ideal candidates for the C-Pulse System. Patients' suitability will be evaluated in agreement between the Investigator and Sponsor, based on the assessment of heart failure severity, concomitant cardiac disease, need for concomitant cardiac surgery, co-morbidity, life expectancy < 2 years, pregnancy and other conditions potentially interfering with the ability to manage the C-Pulse therapy.

As the C-pulse implantation procedure is clinically indicated patients may be enrolled prospectively with informed consent obtained prior to the procedure or retrospectively with informed consent for the collection of the patient's data obtained after the procedure as appropriate for an observational study.

Implantation procedure

The C-Pulse Cuff and the Sense Lead are implanted through a chest incision and without the use of cardiopulmonary bypass. Only a small pericardiotomy is required, limiting the potential for bleeding and for post-operative adhesions. The ascending aorta is isolated and its circumference measured. The circumferential length is noted on the pre-marked wrap. The Cuff is passed around the aorta such that the inflating aspect of the Cuff is positioned on the outside curvature. The Cuff is then checked to fit the aorta conformably and that the circumferential marks are appropriate prior to securing of the wrap with sutures. Pre-loaded interrupted 'mattress' sutures are placed through the tail of the Cuff at the appropriate circumferential marks with the Cuff 'open', and such that the inflation chamber of the Cuff is always visualized. The sutures are then tied down and the wrap checked to be conformal to the aorta. The excess wrap fabric is trimmed off. A bipolar ECG Sense Lead is placed on the heart, most preferably the left ventricular free wall. The gas line of the Cuff is trimmed to length and it and the ECG Sense Lead are attached to the intra-corporeal "Y- connector" end of the Percutaneous Lead. The Percutaneous Lead is then tunneled beneath the rectus sheath, the extra-corporeal end of the Lead having a Patient Connector permanently attached. Alternatively, the lines may be tunneled to an intermediary incision for connection, particularly if a less invasive surgical technique (sternal-sparing) is used. The Percutaneous Lead is designed to be exchanged or removed if required, the latter eliminating the exit site. If removal occurs, the Cuff and Sense Lead can remain within the thorax with the gas line of the Cuff and the connector of the Sense Lead capped off and accessible with minimal surgery in the subcutaneous tissue of the abdominal area. If the Cuff is infected, it should be removed.

Performance Endpoints	The following performance endpoints will be assessed during follow-up visits: • Improvement in INTERMACS™ and/or NYHA functional class • Freedom from worsening heart failure resulting in hospitalization, LVAD implantation, or death • Explant for recovery of ventricular function or cardiac transplantation Secondary endpoints assessed at 6 and 12 months post implant include: • Improvement in LVEF • Improvement in Quality of Life scores • Improvement in 6MWT
Safety Endpoints	The following primary safety endpoints will be assessed throughout each subject's participation in the investigation: • All cause and device-related mortality • Aortic disruption • Exit Site infection • Internal PIL/Cuff infection • Thromboembolism • Device malfunction • All protocol-defined adverse events
Data collection	The study will aim to collect patient data while supported with C-Pulse therapy (i.e. the subjects will be censored from analysis if the device is permanently "off" unless due to signs of recovery). Data will be captured at the following time points: Baseline, procedure, discharge assessment, clinical follow-up at 6 weeks, 6 months, 12 months, 18 months, 2 years and yearly thereafter. Data from any other additional time points may be collected and analyzed if available. Data from baseline and up to 5 years of follow-up will be captured in an electronic database. Hemodynamic performance and functional testing will be determined according to procedures based on standard center practices. Any protocol-defined adverse events, including adverse device effects and outcomes will be reported by the Investigator.
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ABBREVIATIONS

ACC	American College of Cardiology
AE	Adverse Event
AHA	American Heart Association
CABG	Coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CI	Cardiac Index
CIP	Clinical Investigation Plan
CO	Cardiac output
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CTS	Cardiothoracic Surgeon
DMC	Data Monitoring Committee
EAB	Extra Aortic Balloon
EC	Ethics Committee
EF	Ejection fraction
ECG	Electrocardiogram
HF	Heart Failure
HFC	Heart Failure Cardiologist
ICD	Implantable Cardiac Defibrillator
IFU	Instructions for Use
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
LVMI	Left Ventricular Mass Index
LVOT	Left Ventricular Outflow Tract
MDD	Medical Devices Directive 93/42/EEC
MRI	Magnetic Resonance Imaging
NLM	National Library of Medicine
Non-CNS	Non-Central Nervous System
PICC	Peripherally Inserted Central Catheter
PIL	Percutaneous Interface Lead

NCBI	National Center for Biotechnology
NIH	National Institute of Health
NYHA	New York Heart Association
RV	Right Ventricle
SAE	Serious Adverse Event
VAD	Ventricular Assist Device
6MHW or 6MWT	Six Minute Hall Walk or Six Minute Walk Test

Table of Contents

1. INTRODUCTION

1.1. . Study Sponsor

The Sponsor of this study is Sunshine Heart Inc.

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1.2. . Heart Failure Prevalence

There are over 1.4M people in the USA in Class III and IV heart failure. Biventricular pacemakers are indicated in patients with a wide QRS – approximately 30% of this population. Approximately 2200 heart transplants are done per year. A similar number might receive an LVAD as either a bridge to transplant or as destination therapy.

There remains a very large number of people that may benefit from an improvement in their clinical status from NYHA Class III/IV to Class I/II.

1.3. . Morbidity and Mortality

As the severity of heart failure disease increases, there is greater certainty regarding imminent death, and less certainty is required regarding the performance of a device and patient outcome after implantation. However, generally, increasing disease severity also increases the risk of adverse outcomes that are attributable more to the patient's co-morbidities than the device used. At lesser grades of disease severity, when death is not imminent, details regarding the expected function and quality of life with mechanical circulatory support become more critical.

Patient preference for quality of life versus survival shows remarkable variation at every level of disease severity. From a practical standpoint, apart from those with high predicted in–hospital mortality, many patients exhibit a dynamic state that fluctuates over months, with exacerbations related to dietary indiscretion, seasonal viral infections, and other exogenous factors. Ambulatory heart failure patients on oral therapy are generally not as sick, but experience discomfort during any physical activity and may have discomfort while at rest.

1.4. . Limitations of Existing Treatment

Chronic HF is conventionally treated with drugs. However there are many circumstances where drug therapy is insufficient or where the heart has become refractory to drug therapy. Cardiac Resynchronization Therapy (CRT) is suitable for approximately 30% of moderate HF (New York Heart Association - NYHA Class III) patients, and has been shown to provide significant clinical improvement. However, as many as 30% of patients who have CRT implants do not have a satisfactory response ("non–responders"). Further, many patients initially have a good response but then develop more advanced symptoms.

Heart transplantation is an effective therapy for end stage NYHA Class IV patients. However, the number of donor hearts falls short of meeting the needs of patients and many patients are excluded because of age (the upper limit for transplant being approximately 65 years)

Left Ventricular Assist Devices (LVADs) have been shown to offer the potential for the treatment of end stage NYHA Class IV HF patients. However, because of the blood–contacting nature, these devices have high associated risks such as bleeding, stroke, infection and device failure. Furthermore patients spend time in hospital due to these associated complications.

There is growing evidence that the unloading actions of LVADs can facilitate significant recovery and reverse remodeling of the heart. However, LVADs tend to be implanted late in the clinical course of heart failure, due to the risk profile versus the expected benefits.

Earlier implant may improve the chance of recovery of the heart. Therefore, there is a need for lower risk, lower cost devices that allow for long–term implant in less sick patients. Such a device could provide for partial unloading of the heart such that the patient can be weaned and for the device to not necessarily be removed.

1.5. . C-PULSE SYSTEM Innovation

Sunshine Heart's C-Pulse® System is a new approach for patients with moderate to severe heart failure that can be used in combination with other heart failure therapies. The device is designed to assist the heart's function, not replace it and may be implanted using a minimally invasive approach. The objective of the C–Pulse® system is to provide an effective, low risk and low cost mechanical heart assist device for use in patients in NYHA Class III–IV ambulatory.

2. IDENTIFICATION OF THE DEVICE

2.1. . C-Pulse System Description

The C-Pulse® System (C-Pulse or C-Pulse System) has been proposed as a non-blood contacting wearable heart assist device to perform long-term aortic counterpulsation in patients suffering moderate to severe heart failure. The device is designed:

- to be simple to implant,
- to accommodate aortic anatomic variability,
- to be safe for the aorta and have a high cycle-life,
- to provide measurable improvement in hemodynamic variables,
- to allow mobility,
- to be able to be turned off or used intermittently if left ventricular recovery occurs, and
- to be able to be disconnected.

Figure 1 below provides a graphic representation of the C-Pulse® System. The system provides cardiac assistance through an extra-aortic balloon Cuff and ECG sense lead connected by means of a Percutaneous Interface Lead (PIL) to an external pneumatic Driver. The PIL and external driveline are held securely externally with 2-3 simple adhesive clips for immobilization of the Driver lead and external part of the PIL at the exit site. The Driver is adjusted using a dedicated notebook computer (the Programmer) with specialized software. The Driver inflates and deflates the Cuff in counter-synchrony to the cardiac cycle. The C-Pulse® System has been designed to have simple, effective and safe implantable components (the Cuff and PIL) and an external wearable component (the Driver). The C-Pulse System sits outside the bloodstream, reducing the risk of stroke and blood clots and therefore eliminating the need for anti-clotting medications directly related to the C-Pulse System.

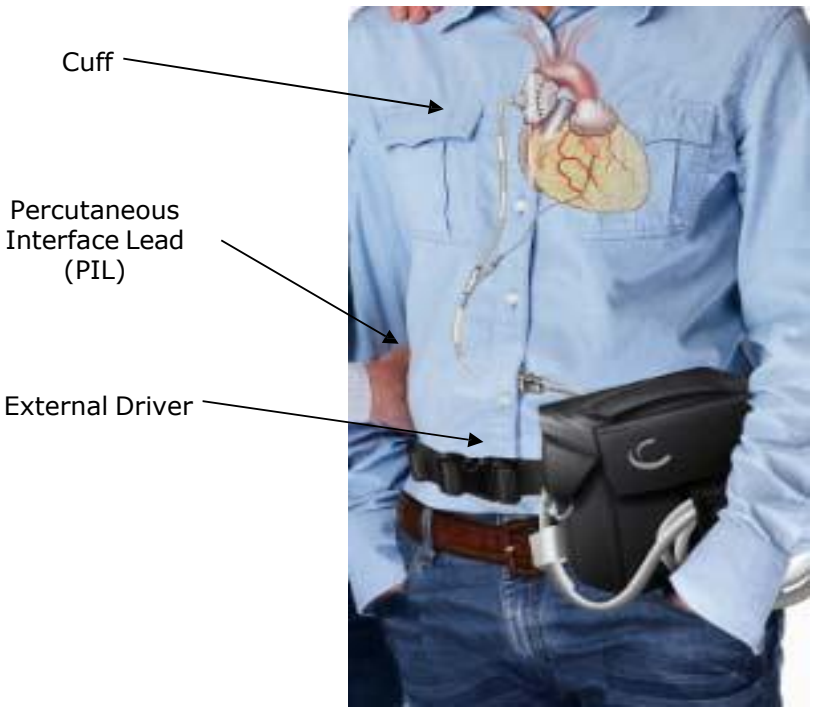


Figure 1. Sunshine Heart C-PULSE SYSTEM

2.2. . Intended Purpose and Indications

The C–Pulse® System is indicated for use in patients with moderate to severe heart failure [American College of Cardiology/American Heart Association (ACC/AHA) Stage C; NYHA Class III/IV ambulatory], who are refractory to optimal medical therapy. The C–Pulse® System is intended to relieve the symptoms of heart failure, improve quality of life and cardiac function.

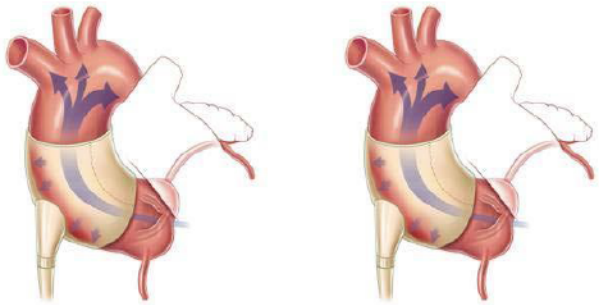
The C–Pulse® System is also indicated for use in patients who are non-responders to CRT pacemaker therapy. It is intended for use in hospital and at home. It is not intended as a replacement for heart function; it is not life sustaining or life–supporting therapy. It does not preclude the use of other heart failure therapies, such as valve surgery, heart transplantation or LVAD.

2.3. . Mechanism of Action

2.3.1. 1. C-Pulse Cuff Design and Operation

The C-Pulse® Cuff is designed to displace blood from the ascending aorta during diastole when inflated and to restore normal anatomic structure deflating before systole. The volume displacement of the extra-aortic cuff, by virtue of the short ascending aorta, is limited compared to the descending Intra-aortic Balloon (IAB) capacity, but the proximity of the C-Pulse to the aortic valve is expected to allow equivalent or better counterpulsation compared to methods of descending aortic counterpulsation.

The balloon is intended to inflate and deflate in a manner that causes the least possible strain to both the balloon material and to the aorta while maximizing blood volume displacement within the ascending aorta. The balloon is inflated to a volume typically 15-20% less than its



natural volume. Inflating the balloon further does not achieve significantly greater volume displacement but does lead to a higher intra-balloon pressure. Thus, the optimal balloon inflation point results in a small (approximately 5-10 mmHg) transmural pressure between the inflated cuff and the aorta whilst displacing close to optimal volume per beat.

The balloon is designed to not occlude the aorta when fully inflated. A dipping process is utilized to manufacture the balloon from DSM Biomedical's (DSM) proprietary BioSpan® segmented polyurethane (an FDA master file material). The balloon is manufactured in its inflated shape and is stored and supplied in this stress free state. This material exhibits high strength, flexibility, and fatigue resistance together with biological compatibility and biostability. Furthermore, the material has a long history of use in permanent cardiovascular implants.

The bushing provides a structural whilst flexible interface between the balloon and gas-line. It is shaped to correspond with the internal surface of the three sizes of balloon and the outer diameter of the gas-line. The three components are permanently bonded using a solution bonding process. The bonding solution is manufactured from urethanes and DMAC from a

registered manufacturer of biomaterials. The bushing is injection molded from DSM's Bionate® polycarbonate-urethane, also FDA master file material.

2.3.2. C-Pulse Cuff Gas-line

The cuff gas-line is connected to the Percutaneous Interface Lead (PIL) via a barbed fitting on the pneumatic arm of the PIL Y-junction. The Cuff is inflated using filtered air.

The gas-line is a flexible tube which provides the pneumatic interface between the balloon and PIL. It is extruded from Bionate material and formed into a 'Shepard's hook' shape adjacent to the bushing to promote routing through the thoracic cavity. The gas-line has a 4mm inner diameter and 6mm outer diameter and is provided with a length of velour fabric, known as 'flocking', bonded with master file silicone RTV adhesive, to promote anchoring of the gas-line by tissue in-growth and mitigate infection transmission. The flocking material is implant-grade loosely knitted polyester velour with complete biocompatibility testing and an established implant history. The placement of the flocking allows for trimming of the gas-line in the event of a PIL replacement.

2.3.3. C-Pulse Cuff Wrap Materials

The wrap is contoured and comes in three sizes to correspond to the outer surface of the balloon as well as conform to the typical range of aorta curvatures and diameters. It converts balloon inflation into aortic depression and blood flow. The wrap material is implant-grade woven polyester with complete biocompatibility testing and an established implant history. The wrap material is cut on the bias and the edges of the wrap have strain-relief design features. The wrap is bonded to the balloon with the same silicone RTV adhesive used to attach the flocking. The wrap is sutured to itself to secure the device around the ascending aorta using pre-loaded sutures and pre-printed alignment markings. The excess wrap is trimmed before completion of surgery.

2.3.4. C-Pulse Cuff Sizes and Volumes

The Cuff is pre-shaped to conform to the ascending aorta and comes in three sizes: small, medium and large. The external diameter of the ascending aorta (AA) determines the appropriate cuff size. Refer to **Table 1** below for cuff sizing specifications.

Table 1. Cuff Size and Aortic Dimension Relationship

Cat #	Cuff size	AA external diameter (mm)	AA circumference (mm)	Max Inflation Volume (Note 1) (cc)
93120	Small (S)	28—33	91—106	20
94120	Medium (M)	33—38	106—121	25
95120	Large (L)	37—42	118—133	26

Note 1: Maximum inflation volume when used with C-Pulse® Driver Cat# 97200.

The Cuff is packaged with a 60 cc syringe and an evacuation adapter consisting of a luer connector, a one-way valve and luer barb connector, which is used for manual deflation of the balloon prior to implantation to aid with correct placement of the Cuff on the aorta.

2.3.5. C-Pulse Cuff Safety Features

The balloon was designed to optimize volume displacement versus aortic and balloon wall strain. This was achieved by conducting finite element analyses on both deflection of the aortic wall, and on a proposed balloon mechanism of action. The inflation and deflation mechanism

employs a low strain rolling action to reduce or eliminate fatigue stresses resulting from long term use.

The Balloon is designed with a shape such that maximum inflation will not occlude the aorta and avoids aortic inner wall surface contact.

The Cuff is designed to be conformal to a defined range of aortic dimensions and to minimize pressure points during inflation, deflation, and non-operational states. This minimizes risk of cuff migration as well.

The Cuff is sutured in place using an "open" technique that allows the balloon to be clearly visualized throughout suture placement. This technique minimizes the risk of needle puncture of the balloon.

The wrap design allows some radial expansion of the aorta during systole; however containment of the balloon ensures the proper inward inflation profile for counter-pulsation displacement.

The Gas-line is designed for high flow rates, thus ensuring rapid balloon inflation and deflation (if the gas-line is disconnected from the driver or if driver power is lost). Natural blood pathways are maintained if balloon inflation is lost (e.g. due to hole in balloon).

The Gas-line is a small diameter and thick-walled to enhance kink resistance. The gas-line includes a velour polyester fabric portion (the flocking) to promote tissue in-growth.

The Implant procedure minimizes risk to the patient by avoiding the need for cardiopulmonary bypass.

2.3.6. Intended Duration of Use

The C-Pulse cuff and sense lead are implanted. The cuff has a minimum intended use period of 5 years. It is intended these are replaceable if there is a failure.

2.4. Components and Materials

The following components are available for the C-Pulse System:

Table 2. C-Pulse System Components and Accessories

Part/Cat Num.	Name	Description
93120 94120 95120	C-Pulse Cuff (Small, Medium, Large)	Implanted extra-aortic balloon Cuff. Available in 3 sizes. Provided sterile.
96500 96510	Percutaneous Interface Lead (PIL)	Percutaneous catheter that interfaces between the implanted Cuff and ECG sense lead and the Driver. Provided sterile.
96400	Test Lead	Used for intra-operative System testing. Bridges from the sterile field to the non-sterile Driver Lead. Provided sterile.
96340	Tunnelling Tool	Surgical tool used during implant of the PIL. Reusable, provided non-sterile. Must be cleaned and sterilized before use.
96330	Gas-Line Cap	Cap used for sealing the gas-line where the implanted components need to be partially explanted. Provided sterile.
97200	C-Pulse Driver	Control unit that pneumatically operates the Cuff. Communicates with the Programmer via an infrared link. It is intended to be operated in a Carry Bag.
97220	Driver Carry Bag	Carry Bag allows the user to carry the Driver and two spare battery packs.
97600	C-Pulse Programmer	Consists of a notebook computer together with software, communication module, and power pack. It is used to adjust Driver parameters and to obtain real-time and logged data.
02141	End Cap, PIL	Allows capping of PIL at Patient Connector for showering / bathing and whenever the Driver Lead is not connected.
02140	End Cap, Driver Lead	Allows capping of Driver Lead when the Driver is not in use.
91031	Battery Pack	A rechargeable Battery Pack for use with the Driver.
91021	Power Adapter, Driver	Power Pack with cable to plug directly into the Battery Carrier for running the Driver off mains power and slow charge the Battery Pack in the Battery Carrier. Includes power cord.
91011	Battery Charger	A fast charger for the spare Battery Packs. Includes power supply and power cord.

Various components are also available as spare and/or replacement parts. Contact Sunshine Heart for details.

3. PROCEDURES

3.1. . Pre-implant Considerations

In advance of surgery, have the patient carry the Driver to determine the most appropriate location of the percutaneous exit site. The goal is to minimize trauma to the exit site and to maximize patient comfort – pay particular attention to the costal margins, belt line, and impact of sitting and standing and lying on the exit site when wearing the Driver. The distance of the exit site from the costal margin should be considered in relation to the thickness of subcutaneous tissue, in order to prevent the PIL from rubbing against the costal margin. Also consider patients who inject insulin into the abdominal area.

After deciding on the exit site, plan the orientation of the PIL, and subsequently the path of the Cuff, Gas-line and ECG lead. The implanted PIL location should allow adequate access to the implanted end for future replacement if necessary.

Reference the System, Driver and Programmer IFUs for details on System start-up.

3.2. . Implant Procedure

The surgical procedure involves the implant of the C-Pulse Cuff, Epicardial ECG lead (IS-1 compatible, bipolar) and the C-Pulse PIL.

Note: The following is a summary of the recommended surgical procedure. The procedure may be modified subject to medical advice.

For more detail, consult the Instructions for Use provided with the Cuff, PIL, and Tunnelling Tool.

1. Prepare the patient for surgery. Establish physiological monitors, including invasive pressure monitoring.
2. Incise chest and implant Cuff as described in the Cuff IFU.
3. Implant the ECG sense lead as per the lead manufacturer's Instructions for Use and in conjunction with the Cuff IFU.
4. Implant the PIL as per the PIL and Tunnelling Tool IFUs.
5. Perform initial Driver adjustments and verify system function.
6. Inflate lungs fully to check PIL location and lay of Cuff gas line.
7. Check for hemostasis and irrigate with an antibiotic solution.
8. Insert mediastinal and any other drains as required, and close all wounds.
9. Apply occlusive surgical dressings to all wounds.
10. Immobilize the external portion of the PIL, removing the Test Lead if used.

3.3. Postoperative Patient Care

1. Educate patient and caregiver on how to operate the Driver, as per the Patient Manual.
2. Exit-site management by patient/care-giver demonstrated. Strict stabilization for the first 6 weeks to allow good ingrowth and anchoring of PIL.
3. Reconfirm Driver settings once patient is stable and re-established on oral heart failure medications. Ensure the backup Driver settings match the settings of the Driver in use.

4. C-PULSE SYSTEM STUDY RATIONALE

4.1 Study Classification

The Sunshine Heart's C-Pulse® System is CE marked under Active Implantable Medical Devices Directive 90/385/CEE.

Based on European legislation, this post-market Study is considered to be an observational study. The following rationale supports this consideration:

- This study is collecting the data of subjects treated with the study product - C-Pulse® System in the usual manner and in accordance with the CE mark authorization.

- The assignment of the patient to this study is not decided by this study plan but falls within the current practice, and the treatment decision is separated from the decision to include the patient in this study.

- As the C-Pulse implantation procedure is clinically indicated patients may be enrolled prospectively with informed consent obtained prior to the procedure or retrospectively with informed consent for the collection of the patient's data obtained after the procedure as appropriate for an observational study. Standard diagnostic or monitoring procedures are applied to the treated patients. Available data will be collected in a central database.

The purpose of this observational surveillance study is to monitor the safety and performance of the C-Pulse System in the intended use population and confirm the favorable results obtained in premarket clinical investigations, which are summarized below.

4.2 C-PULSE SYSTEM Benefits

The progressive design and mechanism of action incorporated into the C-Pulse® System has provided treated patients with opportunities that are different than most heart failure devices. The C-Pulse® System broadens the treatment options for heart failure patients by providing a therapy that improves quality of life for patients who have failed optimal medications and CRT therapy. Many patients have no other alternatives or do not want an LVAD or heart transplant. For these patients with no alternatives, progression of heart failure symptoms continues and they are frequently re-hospitalized for worsening heart failure.

The C-Pulse® is not intended to support patients in a manner similar to a VAD or transplant. The C-Pulse® is intended to allow patients' relief of symptoms of heart failure, improved quality of life, improved cardiac function and the opportunity to receive other therapies in the future. The clinical study results demonstrated that these intended outcomes were met. When faced with the option of a VAD or the C-Pulse® for treatment of heart failure, the risk profile is markedly reduced for the patients who received the C-Pulse® based on the fact the C-Pulse® is non-blood contacting and the patient has the ability to disconnect from the system.

The surgery to implant the device is relatively straightforward and with low risk. There is no need to place the patient on cardiopulmonary bypass during the procedure so the patient's heart remains continuously beating. No anticoagulation is required. The C-Pulse® may be implanted via a minimally invasive procedure, which can reduce procedural time, hospital stays, overall cost and patient risk as compared to a traditional sternotomy procedure. As such, C-Pulse® System is a leading innovation in the surgeon's portfolio for heart failure therapy.

In addition, the quality of life is markedly enhanced by being treated with a device like the C-Pulse® which is non-obligatory and non-life sustaining and allows safe disconnection as necessary for daily activities or any intervention (as the PIL substitution in case of exit site infection). The clinical study data at one year demonstrated continued improvement in quality of life, NYHA and 6MWT.

The C-Pulse provides the patient with a treatment option avoiding or delaying the need for VAD and/or transplant procedure. The average time on the C-Pulse® device for patients is 335 days (to date) and two patients were successfully weaned from C-Pulse® within one year. Therefore, treatment with the C-Pulse® may extend the time before a patient may require a VAD or transplant, if at all.

4.3 C-PULSE SYSTEM Risks

Implantation is an invasive procedure requiring a sternotomy or thoracotomy and the use of general anesthesia and mechanical respiratory support. The potential risks associated with the implant procedure also include those associated with any cardiothoracic surgery, including implantation of devices and include the following:

- Bleeding
- Infection
- Neurological Dysfunction
- Renal Dysfunction
- Cardiac Arrhythmias
- Pericardial Fluid Collection
- Aortic Disruption
- Device Malfunction

- Hemolysis
- Hepatic Dysfunction
- Hypertension
- Myocardial Infarction
- Psychiatric Episode
- Respiratory Failure
- Right Heart Failure
- Arterial Non–CNS Thromboembolism
- Wound Dehiscence
- Death

Potential Adverse Effects may include Damage to the C-Pulse Cuff on implantation or misplacement of the ECG lead – not able to sense 'R' wave appropriately. There have been no unanticipated adverse events during the premarket clinical study. Percutaneous Interface Lead (PIL) failures and infections were the two areas of risk identified by Risk Analysis and confirmed during the C-Pulse clinical study.

PIL Failures

The risk associated with the PIL failures are related to the PIL replacement procedure. The only risks would involve re-hospitalization and minor superficial surgery. There have been no observed complications with PIL removal and replacement during the C-Pulse® study. Therefore, based upon current clinical experience, the risk is low.

Sunshine Heart has addressed the cause of the device failures. The risk of PIL failure occurrence has been mitigated by design changes which address 1) the wire breakages related to cyclic fatigue, 2) kinking and 3) IS1 insertion. Implementation of these design changes will mitigate the risk of occurrence of the PIL failures to an acceptable low level. The changes will reduce the observed PIL failures to 5% (1/20).

The clinical benefit of the PIL and its design features, e.g. ease of accessibility, ability for the patient to temporarily disconnect, and modular design for ease of replacement outweigh the residual risk. The PIL is essential in order to reduce exit site infection clinical consequences.

Infections

The infections and associated risk levels observed during the clinical study may be subdivided into different levels based upon risk to the patient and clinical management:

1) Exit site related infection

Observed rate of exit site infections in the C-Pulse® clinical study was 40%. However the risks associated with this type of infection are low. Normally the resolution of this type of infection is managed through use of antibiotics, antiseptics, exit site management and PIL stabilization. Since C-Pulse® is not blood contacting, the risk of sequelae, particularly sepsis, is significantly less than observed with LVADs, thus exit site infections with the C-Pulse® device are not as high a risk as in LVADs. There remains a risk of ascending infection – exit-site pain, tenderness or swelling over the subcutaneous flocking, etc., should be investigated and treated aggressively. The PIL is specifically designed as a modular component of the C-Pulse® System, such that if an infection is chronic the PIL can be removed and the infection easily treated with antibiotics.

Adoption of the requirement for a stabilization device and new infection management techniques and protocol will require the sites to treat the C-Pulse® PIL as critically as the VAD drivelines to facilitate minimizing infection. The anticipated rate of residual risk in the post-market experience following implementation of the mitigations is expected to be no greater

than 30%. This rate is acceptable since it is consistent with what is currently being experienced with other devices having a drive-line exit site.

The clinical benefit of the PIL and its design features (e.g. ease of accessibility, ability for the patient to temporarily disconnect, removability) continue to support that the benefit outweighs the residual risk.

2) Sternal wound infection

During the C-Pulse® clinical study, one patient experienced a sternal wound infection resulting from the surgical procedure. The outcome of the management of the sternal wound after several attempts for debridement and a sternal flap was an aortic disruption. The rate of this incident is low, observed at 5% (1/20).

The risks associated with this type of infection are high if not properly managed. Resolution of this type of infection is normally managed through use of antibiotics and sternal wound debridement and drainage. If the sternal wound infection progresses to include the sternal bone the Cuff should be explanted to avoid infection of the Device.

3) Pneumo-mediastinum Infection

Another infection observed during the C-Pulse® clinical study was a pneumo-mediastinum infection that resulted from a breach in the PIL due to a patient fall. The rate of this incident is low, observed at 5%.

The risks associated with this type of infection are high if not properly managed. Resolution of this type of infection is normally managed through use of antibiotics and removal of the C-Pulse® System. Device related infections should be continuously monitored and treated accordingly to mitigate this risk (this statement is included in the C-Pulse System IFU). In addition, the revised exit site guidelines include lead stabilization techniques that will minimize trauma from falls or pulling on the exit site.

4.2. Clinical Risk/Benefit Assessment

The C-Pulse® uses proven balloon counter-pulsation technology to increase left ventricular coronary artery blood flow and cardiac output and to reduce the workload on the heart. The C-Pulse® System is an earlier intervention than other mechanical circulatory support therapies, such as LVADs, meeting a clinical need for relief of symptoms in heart failure patients that are refractory to optimal medical therapy and CRT therapy.

The C-Pulse® System is designed to treat clinical symptoms associated with Class III and ambulatory Class IV heart failure (INTERMACS™ category 4-7). These symptoms normally include shortness of breath, dizziness, low blood pressure and fluid retention. Patients associated with Class III and ambulatory Class IV heart failure are typically unable to engage in normal activities, compromising their quality of life.

C–Pulse® system has demonstrated patient benefits during the clinical studies to date which include the following:

- Reduction in NYHA classification by at least 1 class.
- Improvement in Quality of Life as demonstrated by MLWHF and KCCQ.
- Improvement in Ejection Fraction.
- Positive trend in 6 Minute Hall Walk capacity.
- Reductions of symptoms and the ability to be discharged and remain at home with their heart failure.

Other benefits characterize the device concept:

- C-Pulse® is designed to be implanted without the need for cardiopulmonary bypass or extensive dissection
- Device does not come in contact with blood, thus an anticoagulant therapy is not required.
- The C-Pulse® is not life-sustaining and can be disconnected as needed for personal hygiene.
- C-Pulse may be permanently stopped for patients who experience sustained left ventricular recovery.
- The device does not preclude future use of an LVAD or heart transplantation if required (bridge function).
- The C-Pulse® is provided with features that facilitate the management of adverse events.

C-Pulse® does not directly contact the patient's blood and it may be turned on or off at any time allowing the patient intervals of freedom to perform certain activities. Because the C-Pulse® remains outside the circulatory system, there is negligible risk of device-related bleeding, blood clots and stroke in comparison to other mechanical devices that reside or function in the bloodstream. The risk associated with device failure is also significantly less. C-Pulse® allows for weaning of the device if is there is sustained cardiac recovery. Heart function replacement therapies such as LVAD or heart transplantation remain therapeutic options if heart failure progresses.

5. STUDY DESIGN

5.1. Overview

The study is designed to observe the clinical outcomes of heart failure patients treated with the C-Pulse® System in the usual manner and according to the approved indications and contraindications.

A maximum of 15 European sites will participate. Study data from additional geographies may be included

The study will include a cohort of up to 50 patients with moderate to severe heart failure refractory to optimal medical therapy, who receive the C-Pulse® System at the study sites. Patients must have provided written consent that their data can be used in the study. The patients will be followed for up to 5 years to collect performance and safety data. All available follow-up data of patients treated with the study device at the participating sites will be recorded via electronic CRFs.

The study will have the following estimated time course:

First Patient In: May 2013

Last Patient In: Dec 2014

Last Patient Out: Dec 2019

5.2. Inclusion Criteria

The inclusion criteria are consistent with the indications section of the C-Pulse® System Instruction For Use (IFU). According to the CE mark authorization, patients with the following conditions can be included:

1. Patient is 18 years or older
2. Patients with moderate to severe heart failure [American College of Cardiology/American Heart Association (ACC/AHA) Stage C; NYHA Class III/IV ambulatory], who are refractory to optimal medical therapy.
3. Patients who are non-responders to CRT pacemaker therapy. When clinically indicated, CRT should be implanted ≥90 days prior to enrollment.

In addition:

4. Patient has signed and dated the investigation informed consent form.

As the C-pulse implantation procedure is clinically indicated patients may be enrolled prospectively with informed consent obtained prior to the procedure or retrospectively with informed consent for the collection of the patient's data obtained after the procedure as appropriate for an observational study.

5.3. Exclusion Criteria

Patients with the following conditions (contraindications in the IFU), as assessed within 90 days prior to enrollment, have to be excluded:

1. Evidence of significant ascending aortic calcification on postero-anterior chest X-ray or CT scan

2. Moderate or severe atherosclerotic aortic disease
3. Ascending aorto-coronary artery bypass grafts
4. Any history of aortic dissection
5. Connective tissue disorder such as Marfans disease
6. Previous aortic root replacement
7. Aorta not conforming to specified dimensional constraints
8. Patient has severe mitral valve incompetence, grade 4+
9. Patient has moderate to severe aortic valve incompetence, grade 2 - 4+
10. Patient has systolic blood pressure less than 90 or greater than 140mmHg
11. Presence of active systemic infection
12. Presence of bleeding or coagulation disorder (relative)

5.4. Patient Recruitment

Patient authorization and written informed consent must be obtained prior to the patient's enrollment into the study and in accordance with GCPs, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies.

The investigator(s) will verify each patient's inclusion/exclusion criteria before inclusion in the study. Selection criteria and completion of informed consent will be indicated on the Case Report Form.

All patients who sign a consent form will be assigned a study identification number. The identification number will be formatted using the abbreviation for the country, site identification number – sequential site recruited patient number (i.e. DE-005-004). Any patient meeting the study inclusion criteria, for whom this device is clinically indicated, can be recruited for the study after receiving and documenting informed consent.

5.5. Patient Screening and Suitability for C-Pulse Therapy

Patients diagnosed with moderate to severe heart failure and who are treated at the participating centers are eligible for screening evaluation.

Patients eligible for device implantation must meet all the inclusion and not meet the exclusion criteria (indications and contraindications based on device CE mark authorization and Instructions for Use). In addition, a screening process will be carried out for the objective of selecting ideal candidates for the C-Pulse System. Patient suitability will be evaluated in agreement between the Investigator and Sponsor.

Patients with one more of the following conditions may be considered unsuitable for implantation of the C-Pulse system.

With regards to the severity of heart failure, patients with the following conditions may be unsuitable for implantation:

1. Inotrope dependence – inability to wean from inotropic therapy
2. ACC/AHA Stage D heart failure or non-ambulatory NYHA Class IV subject
3. Need for biventricular support
4. Functional limitation due to heart failure as defined by a 6 Minute Walk test of ≤ 175 meters, measured within 30 days prior to implantation

5. Need for concomitant cardiac surgery

Patients with the following cardiac conditions may also be excluded based on clinical judgment:

1. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis, diastolic heart failure or technically challenging congenital heart disease
2. Reversible cause of heart failure that may be remedied by conventional surgery or other intervention
3. Cardiac surgery within 90 days prior to implantation
4. Prior cardiac transplantation, left ventricular reduction surgery, passive restraint device or surgically implanted left ventricular assist device

In addition, patients with severe co-morbidity may be excluded according to the judgment of the investigator. Condition of exclusion may include the following:

1. Body Mass Index (BMI) < 18 or > 45 kg/m^2
2. Serum creatinine ≥ 2.5mg/dL or any form of dialysis within 30 days prior to the planned implantation
3. Evidence of intrinsic hepatic disease as defined as biopsy proven liver cirrhosis; or liver enzyme values (AST, ALT or total bilirubin) that are > 3 times the upper limit of normal within 30 days prior to enrollment
4. Patient has severe intrinsic pulmonary disease in judgment of the investigator
5. Stroke or transient ischemic attack (TIA) within 30 days prior to the planned implantation; or > 80% carotid stenosis as determined by carotid Doppler ultrasound
6. ST elevation myocardial infarction (STEMI) within 30 days
7. Uncontrolled atrial fibrillation or other tachycardias
8. Patient has a condition, other than heart failure, which would limit survival to less than 2 years
9. Patient demonstrates compliance issues that in the opinion of the investigator could interfere with the ability to manage the therapy (i.e. uncontrolled diabetes, mental health issues, etc.)
10. Positive serum pregnancy test, for women of childbearing potential

5.6. Schedule of Assessments

The study will aim to collect patient data while supported with C-Pulse therapy (i.e. the subjects will be censored from analysis if the device is permanently "off"). Data will be captured at the following time points: Baseline, procedure, discharge assessment, clinical follow-up at 6 weeks, 6 months, 12 months, 18 months, 2 years and yearly thereafter. Data from any other additional time points may be collected and analyzed if available.

The treatment procedure will be performed according to the instructions outlined in the current approved IFU. The data will be recorded from baseline and during a 5 year follow-up period following the enrollment. Treatments will be performed according to standard hospital practices. The clinical assessments will be done as per routine practice at the participating institutions.

The clinical variables of interest are presented in **Table 8** below. Hemodynamic performance and functional testing will be determined according to procedures based on standard center practices. Any protocol-defined adverse events, including adverse device effects and outcomes will be reported by the Investigator. All available variables of interest, that will be collected by the investigators, will also be recorded in the Study electronic CRFs.

Table 3 .Data Collection Summary.

	Pre-Implant (Baseline)	Implant	Pre-Discharge[2]	6 week	6, 18 month	Annually[1] Yr 1-5
PATIENT ELIGIBILITY	X					
GENERAL						
Demographic Data	X					
Medical History	X					
General Physical Exam	X	X	X	X	X	X
Concurrent Cardiac Meds	X	X	X	X	X	X
Weight (Height at enrollment)	X		X	X	X	X
Pregnancy test (if applicable)	X					
VITAL PARAMETERS						
Heart rate/rhythm	X		X	X	X	X
Blood pressure	X		X	X	X	X
Respiration rate	X		X	X	X	X
CARDIOPULMONARY[3]						
ECHO	X				X	X
6MWT	X			X	X	X
QUALITY OF LIFE						
INTERMACS™/NYHA Classification	X			X	X	X
KCCQ	X				X	X
HEMATOLOGY						
Hemoglobin	X		X		X	X
Hematocrit	X		X		X	X
Platelet count	X		X		X	X
White cell count	X		X		X	X
C-reactive Protein	X		X		X	X
BIOCHEMISTRY						
Serum sodium	X		X		X	X
Serum potassium	X		X		X	X
Serum creatinine	X		X		X	X
BUN	X		X		X	X
NTProBNP or BNP[4]	X				X	X
Serum bilirubin	X		X		X	X
Serum ALT	X		X		X	X
Serum AST/GGT	X		X		X	X
IMPLANT DETAILS		X				
DEVICE LOG		X			X	X
DISCHARGE CHECKLIST			X			
ADVERSE EVENTS	X	X	X	X	X	X
DATA FROM THE FOLLOWING ITEMS WILL BE COLLECTED IF COMPLETED UPON PHYSICIAN REQUEST:						
MVO2	X					X
Right Heart Catheterization	X					X

[1] Annually post-implant for years 2-5
[2] At Discharge - within 36 hours prior and as close to discharge as possible
[3] Imaging within 90 days prior to implant may be included as Baseline data collection
[4] Complete NTProBNP or BNP consistently to the institution's standard practice (i.e. if BNP collected at baseline, continue BNP in scheduled follow-up)

6. STUDY DESIGN AND OBJECTIVES

6.1. Study Objective

This is a multi-center, prospective, open label observational study, designed to observe the clinical outcomes of heart failure patients treated with the C-Pulse® System in the usual manner and according to the approved indications and contraindications.

6.2. Enrollment

A patient population of up to 50 patients with moderate to severe heart failure refractory to optimal medical therapy, who are implanted with the C-Pulse System as clinically appropriate, will be enrolled into the Study. A maximum of 15 European centers will participate. Study data from additional geographies may be included.

Patients diagnosed with moderate to severe heart failure and who are treated at the participating centers are eligible for screening evaluation. The investigator(s) will obtain informed consent for study participation from each patient.

Patients eligible for the study must meet all the inclusion criteria and not meet the exclusion criteria (indications and contraindications based on device CE mark authorization and Instructions for Use). In addition, a screening process will be carried out the objective of selecting ideal candidates for the C-Pulse System (see Section 5.5). Patients suitability will be evaluated in agreement between the Investigator and Sponsor, based on the assessment of heart failure severity, concomitant cardiac disease, need for concomitant cardiac surgery, co-morbidity, life expectancy < 2 years, pregnancy and other conditions potentially interfering with the ability to manage the C-Pulse therapy.

After implantation of the C-Pulse System, patients will be followed up for 5 years to collect performance and safety data.

The estimated time course of the study is as follows:

First Patient In: May 2013

Last Patient In: Dec 2014

Last Patient Out: Dec 2019

6.3. Performance Endpoints

The following performance endpoints will be assessed during follow-up visits:

- Improvement in INTERMACS™ and/or NYHA functional class
- Freedom from worsening heart failure resulting in hospitalization, LVAD implantation, or death
- Explant for recovery of ventricular function or cardiac transplantation

Secondary endpoints assessed at 6 and 12 months post implant include:

- Improvement in LVEF
- Improvement in Quality of Life scores
- Improvement in 6MWT

6.4. Safety Endpoints

The following primary safety endpoints will be assessed throughout each subject's participation in the investigation:

- All cause and device-related mortality
- Aortic disruption
- Exit Site infection
- Internal PIL/Cuff infection
- Thromboembolism
- Device malfunction
- All protocol-defined adverse events

6.5. Statistical Methodology

The sample size for the European protocol (N= 50 patients) was calculated on the basis of preliminary discussions with the Scientific Advisors of Sunshine Heart, and predicted success and safety rates observed in the literature data. Consistent design, procedures and endpoints of this study, as compared with the US trial, may allow pooling of data and comparative analyses. Demographic and baseline data will be summarized using descriptive statistics, including %, mean, median, standard deviation, and 1st-3rd quartile, as appropriate. The performance and safety endpoints of the C-Pulse® System will be assessed by monitoring the patient clinical status, assessing the standard quality-of-life scores, and evaluating vital, cardiopulmonary, hematology, biochemistry and neurological parameters, cardiopulmonary test data during the visits within the follow-up period, as detailed in the Data Collection Summary shown in Table 8. Follow-up analysis will include both safety and performance analyses, at each of the defined intervals. Adverse event data will be summarized using descriptive statistics. These will include information concerning nature, severity and duration of all adverse events and their relationship to the different treatments. In addition, tables will be presented for the number of patients potentially available for follow-up and those actually followed. Reference rates for anticipated complications (adverse events), based on historical data on morbidity and mortality from previous device clinical experience, in similar populations and for analogous surgical procedures, are listed in the Literature Review. Overall mortality rate will be determined at the end of the study.

6.6. Sample Size Analysis

The sample size chosen in the post-market trial is 50 patients. The adequacy of this sample size was verified, see table below. The width of the confidence interval provide information about precision of the estimates about the unknown parameter. Confidence intervals are more informative than the simple results of hypothesis tests (namely, conclusion to "reject H0" or "don't reject H0") since they provide a range of plausible values for the unknown parameter.

Reference safety rates are based on published literature, and assume a 2-tailed alpha of 5% in order to build 95% confidence intervals for the outcome of interest. According to the computations, a sample size of 50 patients provides adequate precision for statistical inference concerning endpoints, even those with low incidence.

7. DATA COLLECTION AND MANAGEMENT

7.1. Data Management Activities

Data Management activities include, but are not limited to, collecting and tracking data and instituting quality control measures for data entry verification and trial compliance. The Sponsor and the Data Management Center will review significant new information, including adverse events and deviations from the clinical protocol, and ensure that such information is provided to relevant parties including Regulatory Authorities, Investigators, ECs as required by local and national regulations and this Clinical Investigational Plan.

Study data will be reviewed during regular Investigator meetings.

The Data Management Center for the study is:

Sunshine Heart Inc.
12988 Valley View Road
Eden Prairie, MN 55344
USA

7.2. Information Collected in the Electronic Case Report Forms (e-CRFs)

The study physician or his designee at each clinical site will perform primary data collection. Only the study physician or other pre-designated study personnel will be authorized to enter data (from source documents) via internet-based e-CRFs. Study personnel will each be assigned a unique user name and pass code to access the e-CRFs. Representatives, agents or consultants of the Data Management Center, the Sponsor or other designee will provide training, clinical monitoring, including review of e-CRFs with verification to the source documentation.

Study patients will be enrolled based on the current approved labeling (as outlined in the Instructions for Use). Eligibility for each patient enrolled will be based on the current CE mark labeling and will be documented appropriately in the medical records (source documents) and entered in the e-CRFs.

Only anonymous data will be collected after the patient has consented that personal data can be used. Patients treated with the study device are asked to consent in writing that their data can be entered into a central database.

7.3. Patients Lost to Follow-up

Patients that refuse to make their data available at a certain time point will be considered ”lost to follow-up”. The data that has been obtained from a patient that was subsequently lost to follow-up may still be used in any subsequent analysis.

7.4. Source Documents

The study physician or his designee at each clinical site will perform primary data collection. Only the study physician or other pre-designated study personnel will be authorized to enter data (from source documents) via internet-based e-CRFs. Study personnel will each be assigned a unique user name and pass code to access the e-CRFs. Representatives, agents or consultants of Data Management Center, the Sponsor or other designee will provide training, clinical monitoring, including review of e-CRFs with verification to the source documentation.

Source documentation may include any of the following:

1. Medical history/physical condition of the study subject before involvement in the study.

2. Dated and signed notes in the subject's medical record on the day of entry into the study that identify:
    a. the subject's date of entry into the study, the study Sponsor, the clinical site, the subject number
    b. A signed statement that informed consent was obtained.
    c. Dated and signed notes from each study subject visit with reference to the e-CRFs for further information, if appropriate (for specific results of procedures and exams).
    d. Description of device implantation procedure (material used, drugs administered during the procedure, date, time duration, echocardiographic and clinical findings, etc.).
3. Notations on abnormal lab results and their resolution.
4. Dated printouts or reports of special assessments, i.e., ECG reports.
5. Adverse event reporting and follow-up of the adverse events (event description, severity, onset date, duration, relation to study device, outcome and treatment for adverse event).
6. Notes regarding concomitant medications taken during the study (including start and stop dates).
7. Study subject's condition upon completion of or withdrawal from the study.

Periodic teleconference calls between Sponsor or CRO and each clinical site may be performed to resolve any issues concerning the e-CRF and data collection methods.

7.5. Site Documentation

Each clinical site will maintain a Regulatory Binder in which the following documents will be maintained:

1. Signed Investigator and Institutional Agreement
2. Signed Study Protocol and Amendments including:
    a. Device Instructions for Use
    b. Electronic Case Report Forms and completion guidelines
3. All Investigator and Co-Investigator CVs and Medical Licenses
4. If applicable for the participating site:
    a. EC documents, including member list and number
    b. EC approval letter and updates
5. Master copy of EC approved informed consent, advertising and recruitment materials
6. General Correspondence
7. Delegation of Responsibilities/Duties
8. Patient Enrollment Logs
9. Site Visit Log & Reports

10. Study communications including:

    a. Documentation of written and verbal communications with Sponsor

    b. Documentation of written and verbal communications with other Investigators

7.6. Quality Assurance and Access

The Sponsor or designee will create and maintain the database as per its internal procedures and policies and in accordance with applicable regulations on personal data protection. The Sponsor or designee will also be responsible for verification and validation of the database (including applicable security methods).

Data entered into the e-CRF database are the sole property of the Sponsor and the frequency for review and use of the data will be at its discretion. Only designated Sponsor personnel are authorized to access the database.

7.7. Monitoring Plan

The Sponsor or designee will perform site monitoring during the Clinical Trial to ensure compliance with the Clinical Investigation Plan and applicable regulations, that data is collected in a timely, accurate and complete manner and that the Investigator continues to have appropriate staff and facilities to conduct the Clinical Trial safely and effectively. Monitoring will performed in accordance with a pre-specified monitoring plan that is in compliance with applicable Standard Operating Procedures.

7.8. Data Retention

All study records and reports must remain on file for a minimum of ten (10) years after the completion or termination of the study. Study records are to be discarded only upon notification by the Sponsor.

The study physicians should contact the Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the Sponsor should be notified if the study physician plans to leave the institution.

7.9. Study Closeout

Upon completion of the study (when all subjects enrolled have been followed at 5 years and the e-CRFs and queries have been completed), a close-out visit will be performed. All unused study materials and equipment will be collected and returned to the Sponsor or designee. Items that will be reviewed at this visit include: discussing retention of study files, publication policy, and to ensure that the study physician will notify the local ethics committee and/or competent authority regarding study closure, if needed.

7.10. Final Report

The Sponsor will generate a final report at the close of the study. The final report will include a descriptive analysis of the clinical data for all study cohorts.

8. PROCEDURE FOR ADVERSE EVENT MANAGEMENT

8.1. Reporting Procedure

Adverse event information will be reported throughout the clinical investigation as they occur. Adverse events will be followed until they are adequately resolved or explained. *A list of potential AEs, which may result from the study procedure, is included as part of the IFU.*

The investigator(s) will report any serious adverse event to the Sponsor's Clinical Research department no later than three calendar days after the Investigator first learns of the event, followed by a written report within ten working days. This reporting will be done via data entry in the electronic CRF: the sponsor will receive an email alert for each serious adverse event that is entered.

In addition, investigational centers will report all serious adverse events to their local EC and National Competent Authority in accordance with the review committee's and national requirements.

The Sponsor or its designee will determine requirements of reporting adverse events according to its responsibilities for medical device vigilance.

8.2. Definitions

For purposes of this protocol adverse event definitions are taken from the guidance ISO document; please refer to EN ISO 14155:2011.

8.2.1. . Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

8.2.2. . Adverse Device Effect

An adverse device effect (ADE) is defined as any adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

8.2.3. . Serious Adverse Event

A serious adverse event (SAE) is defined an adverse event that:

a. led to death,

b. led to a serious deterioration in the health of the subject, that either resulted in:

1. a life threatening illness or injury, or

2. a permanent impairment of a body structure or a body function, or

3. in patient or prolonged hospitalization, or

4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to body structure or a body function,

c. led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a preexisting condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

The serious adverse events will be reported into the following categories:

8.2.4. . Adverse Event Definitions

Definitions are listed below for anticipated adverse events. The definitions are consistent with Version 2.2 adverse event definitions for the INTERMACS™ registry with the exception of Major Bleeding which does not have a minimum standard of transfusion. Aortic Disruption has been added in addition to the INTERMACS™ registry definitions as an additional screening for safety with respect to the C-Pulse unique application. Worsening Heart Failure has been added due to C-Pulse System not being a heart function replacement rather a heart assist device and based on the definition used by the CEC in the US Feasibility study.

Major Bleeding

An episode of suspected internal or external bleeding that results in one or more of the following:

1. death
2. re-operation
3. hospitalization
4. transfusion of red blood cells

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g. oliguria, pre-syncope or syncope) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types:

1) Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
2) Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical

signs of tamponade (e.g. increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

Aortic Disruption

Disruption to the intima of the ascending aorta. Disruption may be partial or complete (i.e. transmural), and the latter may result in contained or free rupture. Typically this would be documented initially by CT scan with or without contrast or by trans-esophageal echocardiography.

Device Malfunction

Device malfunction denotes a failure of one or more of the components of the MCSD system which either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. The manufacturer must confirm device failure. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure.
Device failure should be classified according to which components fails as follows:

1) **Pump** failure (implanted components of pump and any motor or other pump actuating mechanism that is housed with the implanted components). In the special situation of **pump thrombosis,** thrombus is documented to be present within the device or its conduits that result in or could potentially induce circulatory failure.
   Note: For C-Pulse system – this includes the Cuff and Gas line and/or ECG lead.
2) **Non-pump** failure (e.g., external pneumatic drive unit, electric power supply unit, batteries, controller, interconnect cable, compliance chamber).

   Note: For C-Pulse system – this includes the Percutaneous Interface Lead and the Driver.

Hemolysis

A plasma-free hemoglobin value that is greater than 40 mg/dl, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant. Hemolysis related to documented non-device-related causes (e.g. transfusion or drug) is excluded from this definition.

Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

Hypertension

New onset blood pressure elevation greater than or equal to 140 mm Hg systolic or 90mmHg diastolic (pulsatile pump) or 110mmHg mean pressure (rotary pump).

Major Infection

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the

need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection
Infection localized to any organ system or region without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pocket Infection (PIL Only)
A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage or leukocytosis.

Internal Pump Component, Inflow or Outflow Tract Infection (Cuff, ECG Lead and Gas line not including the PIL)
Infection of the implanted C-Pulse Cuff or surrounding tissue (e.g. aorta) documented by positive site culture.

Sepsis
Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Myocardial Infarction

Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction
The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following implant together with ECG findings consistent with acute myocardial infarction.

Non-Perioperative Myocardial Infarction
The presence at > 7 days post-implant of two of the following three criteria:

a) chest pain which is characteristic of myocardial ischemia,
b) ECG with a pattern or changes consistent with a myocardial infarction, and
c) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

Neurological Dysfunction

Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The NIH Stroke Scale (for patients > 5 years old) must be re-administered at 30 and 60 days following the event to document the presence and severity of neurological deficits. Each neurological event must be subcategorized as:

1) Transient Ischemic Attack (acute event that resolves completely within 24 hours with no evidence of infarction)

2) Ischemic or Hemorrhagic Cerebrovascular Accident/CVA (event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study.

Psychiatric Episode

Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress requiring intervention. Intervention is the addition of new psychiatric medication, hospitalization, or referral to a mental health professional for treatment. Suicide is included in this definition.

Renal Dysfunction

Two categories of renal dysfunction will be identified:

Acute Renal Dysfunction
Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL **(in children,** creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours.

Chronic Renal Dysfunction
An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy or (for patients older than age 5 years) the inability to discontinue ventilatory support within six days (144 hours) post-implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Right Heart Failure

Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.0 L/min/m2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD implantation; or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after implantation.

Worsening Heart Failure

A heart failure event requiring hospitalization including the following:

- Signs and symptoms of worsening heart failure; and
- Treatment with intravenous heart failure therapy (including but not limited to diuretic or inotropic therapy); and
- A minimum of one date change in the hospital or emergency room

Arterial Non–CNS Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) standard clinical and laboratory testing

2) operative findings

3) autopsy findings

This definition excludes neurological events.

Venous Thromboembolism Event

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Other

An event that causes clinically relevant changes in the patient's health (e.g. cancer).

8.2.5. . Serious Adverse Device Effect (SADE)

A serious adverse device effect (SADE) is defined as an adverse device effect that results in any of the consequences characteristics of a serious adverse event.

8.3. Deaths and Explants

8.3.1. . Subject Deaths

In the event of subject death, every effort should be made to obtain a copy of the autopsy report and/or death summary. Information on the cause of death and its relationship to the device used in this clinical investigation will be determined by the principal investigator. Copies of an autopsy report, if available, and/or a death summary are to be sent to the Investigation Sponsor.

If a device is explanted during autopsy, the device should be returned to the Investigation Sponsor for analysis. Return kits for devices will be provided upon request by the clinical monitor.

8.3.2. . Device Explants

In the event a device component is explanted in the intra-operative or early post-operative period (i.e., while the patient is hospitalized at the investigational center), a copy of the procedure report must be provided to the Investigation Sponsor. Information on the cause of explant and its relationship to the device component will be determined by the principal investigator. Explanted device components during this period must be returned to the Investigation Sponsor for analysis. Return kits for devices will be provided upon request by the clinical monitor.

In the event a device component is explanted in the late post-operative period, every effort should be made to obtain a copy of the explant procedure report, as applicable. Information on the cause of explant and its relationship to the device component will be

determined by the principal investigator. Copies of an explant report, if available, are to be sent to the Investigation Sponsor. Explanted device components during this period should be returned to the Investigation Sponsor for analysis. Return kits for devices will be provided upon request by the clinical monitor.

9. STUDY CONDUCT, RESPONSIBILITIES AND CONFIDENTIALITY

The study will be conducted in accordance with Good Clinical Practice (GCPs) and the Declaration of Helsinki and any additional provisions outlined in the Study Agreement.

The study physicians are responsible for obtaining the appropriate regulatory approvals (ethics committee and/or competent authority) prior to initiation of the study. The Investigator will provide current copies of the study protocol to all Co-Investigators or other staff responsible for study conduct.

9.1. Patient Authorization

Patient authorization and written informed consent must be obtained prior to the patient's enrollment into the study and in accordance with GCPs, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies.

9.2. Patient Confidentiality

Patient confidentiality must be maintained in accordance with GCPs, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies.

9.3. Physician Confidentiality

Study physicians will comply with the applicable provisions of the study agreement with regard to nondisclosure and confidentiality.

9.4. Device Accountability

The Investigator shall document in the surgery reports and e-CRFs the serial/lot number of all devices used during procedures.

9.5. Protocol Changes/Amendments

Protocol changes or amendments cannot be made by the study physician without prior written approval by the Sponsor and EC.

9.6. Patient Termination or Withdrawal

Once enrolled, patients may discontinue participation at any time by withdrawing informed consent or meeting the requirement for termination. Participation in the study is entirely voluntary.

10. PUBLICATION POLICY

All information related to the study device is considered confidential and remains the sole property of the Sponsor. This includes, but is not limited to the patent applications and the manufacturing process. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the Sponsor's written consent. The investigator understands that the information developed in the clinical study will be used by the Sponsor and may be disclosed as required to other investigators or competent authorities. To permit the information derived from the clinical studies to be used, the investigator is obliged to provide Sponsor (or designated representative) all data obtained in the study.

Sponsor and investigators are committed to the publication and widespread dissemination of the Study results. This study represents a joint effort between sponsor and investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

At various milestones in the C-Pulse System study, including the conclusion, it is intended that multicenter papers will be published, in peer reviewed scientific journals and scientific meetings. These publications/presentations will be coordinated by Sunshine Heart via the Investigator Meeting. Publication (abstracts and manuscripts) or presentation of the study results are subject to review by Sunshine Heart prior to submission or presentation. Sunshine Heart will review the manuscript within sixty (60) days after receipt with the purpose to ensure technical accuracy of the information presented. If any such proposed publication or presentation contains patentable subject matter which in Sponsor's sole discretion, warrants intellectual proprietary protection, the sponsor may delay any publication or presentation for up to 1 month after sponsor approval for the purpose of pursuing such protection.

Authors of publications will include the participating physicians who have enrolled significant numbers of patients. Final author lists will be based on direct involvement in hypothesis generation, data analysis, patient recruitment, and composition of abstracts and manuscripts. The final decision about author lists will be the prerogative of the sponsor and the participating Investigators in accordance with guidelines to authors for each journal.

If a multicenter publication is not issued after 1 year from the conclusion of the C-Pulse System Study (final database closure), single center results may be published with review by Sunshine Heart within 30 days of submission. Exceptions to this rule require prior approval from Sunshine Heart.

11. REFERENCES

1. Branch KR, Dembitsky WP, Peterson KL, Adamson R, Gordon JB, Smith SC Jaski BE. Physiology of the native heart and Thermo Cardiosystems left ventricular assist device complex at rest and during exercise: implications for clinical support. J Heart Lung Transplant 1994; 13: 641-50

2. Buchanan SA, Langenburg SE, Mauney MC, et al. Ambulatory intraaortic balloon counterpulsation. Ann Thorac Surg 58:1547-9; 1994.

3. Carpentier A, Chachques JC, Acar C et al. Dynamic cardiomyoplasty at seven years. J Thorac Cardiovasc Surg 106:42-54; 1993.

4. Davies A.N. et al., Extra-Ascending Aortic Versus Intra-Descending Aortic Balloon Counterpulsation—Effect on Coronary Artery Blood Flow, Heart Lung and Circulation 2005;14:178–186

5. Dipla K, Mattiello JA, Jeevanandam V, Houser SR, Marguiles KB. Myocyte recovery after mechanical circulatory support in humans with end-stage heart failure. Circulation 97:2316-2322; 1998.

6. Dreyfus GD, Dubroc D, Blasco, A, et al. Myocardial viability assessment in ischemic cardiomyopathy: benefits of revascularisation. Ann Thorac Surg 57:1502-8; 1994.

7. Farrar D. Ventricular interactions during mechanical circulatory support. Sem Thor Cardiovasc Surg 6:163-168; 1994.

8. Furman S, Attai L, Parker B. Cardiac support by periaortic diastolic augmentation. NY State J Med 70:64-69; 1970.

9. Gitter R, Cate C, Smart K, Jett GK. Influence of ascending versus descending balloon counterpulsation on bypass graft blood flow. Ann Thorac Surg 65:365-70; 1998.

10. Hayward C.S. et al., Chronic extra-aortic balloon counterpulsation: First-in-human pilot study in end-stage heart failure. Journal of Heart and Lung Transplantation, Vol 29, No 12, December 2010

11. Ho et al: The Epidemiology of Heart Failure: "The Framingham Heart Study" Journal of The American College of Cardiology, 1993, Volume 2(4) Supplement A: 6A-13A

12. Holman WL, Skinner JL, Waites KB, Benza RL, McGiffin DC, Kirklin JK. Infection during circulatory support with ventricular assist devices. Ann Thor Surg 68:711-6; 1999.

13. Igo SR, Hibbs CW, Trono R et al. Intra-aortic balloon pumping; theory and practice. Artif Organs 2:249-56; 1978.

14. Jeevanandam V, Jayakar D, Anderson AS, Martin S, Piccione W Jr, Heroux AL, Wynne J, Stephenson LW, Hsu J, Freed PS, Kantrowitz A. Circulatory assistance with a permanent implantable IABP: initial human experience. Circulation 2002 Sep 24; 106 (12 Suppl 1):I183-8

15. Kantrowitz A, Krakauer J, Rubenfire M, et al. Initial clinical experience with a new permanent mechanical auxiliary ventricle: the dynamic aortic patch. Trans Am Soc Artif Intern Organs 18:159-67; 1972.

16. Katz AM. Cardiomyopathy of overload: A major determinant of prognosis in congestive heart failure. N Engl J Med 322; 100-110; 1990.

17. Khan T, Levin HR, Oz MC, Katz SD. Delayed reversal of impaired metabolic vasodilation in patients with end-stage heart failure during long-term circulatory support with a left ventricular assist device. J Heart Lung Transplant 16:449-53; 1997.

18. Krum H. Sympathetic activation and the role of beta-blockers in chronic heart failure. Aust NZ J Med 29:418-27; 1999.

19. Lainscak M. Implementation of guidelines for management of heart failure in heart failure clinic: effects beyond pharmacological treatment. Int J Cardiol. 2004; 97:411-6.

20. Lazzara RR, Trumble DR, Magovern JA. Autogenous cardiac assist with chronic descending aortomyoplasty. Ann Thorac Surg 57:1550-4; 1994.

21. Lee SH, Doliba N, Osbakken M, Oz M, Mancini D. Improvement of myocardial mitochondrial function after hemodynamic support with left ventricular assist devices in patients with heart failure. J Thorac Cardiavasc Surg 116:344-9; 1998.

22. Legget M.E. et al, Extra-Aortic Balloon Counterpulsation - An Intraoperative Feasibility Study – Circulation, 2005, 112:1/26-1/31

23. Levin HR, Oz MC, Chen JM, Packer M, Rose EA, Burkoff D. Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. Circulation 91:2717-20; 1995.

24. Mancini DM, Beniaminovitz A, Levin H, et al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. Circulation 98:2383-2389; 1998.

25. Marelli D, Laks H, Amsel B et al. Temporary mechanical support with the BVS 5000 assist device during treatment of acute myocarditis. J Card Surg 12:55-59; 1997.

26. McCarthy PM, Nakatani S, Vargo R, et al. Structural and left ventricular histological changes after implantable LVAD insertion. Ann Thorac Surg 59:609-13; 1995.

27. Mehta SM, Aufiero TX, Pae WE, Miller CA, Pierce WS. Combined study for the clinical use of mechanical ventricular assist pumps and the total artificial heart in conjunction with heart transplantation: Sixth official report-1994. J Heart Lung Transplant 14; 585-93; 1995.

28. Noirhomme P, Jacquet L, Underwood M, El Khoury G, Goenen M, Dion R. The effect of chronic mechanical circulatory support on neuroendocrine activation in patients with end-stage heart failure. Eur J Cardiothorac Surg 16:63-7; 1999.

29. Pinkard J, Utley JR, Leyland SA, Morgan M, Johnson H. Relative risk of aortic and femoral insertion of intraaortic balloon pump after coronary artery bypass grafting. J Thorac Cardiovasc Surg 105:721-8; 1993.

30. Roell W, Goedje O, Vetter HO, Schmitz C, Dewald O, Reichart B. Improvement of heart-, lung-, and liver-performance during mechanical circulatory support by the Novacor-system. Eur J Cardiothorac Surg 11:1045-51; 1997.

31. Rose E A, et al. Long Term Use of a Left Ventricular Assist Device for End Stage Heart Failure. New England Journal of Medicine 2001 Volume 345:1435-1443

32. Salmons S. Permanent cardiac assistance from skeletal muscle: a prospect for the new millennium. Artif Organs 23:380-7; 1999.

33. The SOLVD Investigators. Effects of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. New Engl J Med 325:293-302; 1991.

34. Torre Amione G, Stetson SJ, Youker KA, et al. Decreased expression of tumour necrosis factor-alpha in failing myocardium after mechanical circulatory support: A potential mechanism for recovery. Circulation 100:1189-93; 1999.

35. .Trainini J, Cabrera Fischer EI, Barisani J, Christen AI, Mouras J, de Paz J, Elencwajg B, Chachques JC. Dynamic aortomyoplasty in treating end-stage heart failure. J Heart Lung Transplant 2002 Oct; 21(10):1068-73.