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Ambulatory Extra-Aortic Counterpulsation in Patients With Moderate to Severe Chronic Heart Failure

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ABSTRACT

OBJECTIVES The study sought to assess feasibility, safety, and potential efficacy of a novel implantable extra-aortic counterpulsation system (C-Pulse) in functional class III and ambulatory functional class IV heart failure (HF) patients.

BACKGROUND 30% to 40% of HF patients suffer from poor functional status and quality of life (QoL) but are not in need of end-stage treatments. We undertook a multicenter single-arm study to assess the C-Pulse System in such patients.

METHODS New York Heart Association (NYHA) functional class III or ambulatory functional class IV HF patients were eligible. Safety was assessed continuously through 12 months. Efficacy measurements included changes from baseline to 6 and 12 months in NYHA functional class, Minnesota Living with Heart Failure (MLWHF) and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, 6-min walk distance (6MWD), and exercise peak oxygen consumption (pVO_2; 6 months only).

RESULTS Twelve men and 8 women (56.7 ± 7 years, 34 to 71 years of age) with ischemic (n = 7) or nonischemic (n = 13) cardiomyopathy were implanted. There was no 30-day mortality and no neurological events or myocardial infarctions through 12 months. At 6 months, there were 3 deaths (1 device-related). One-year survival was 85%. At 6 months, C-Pulse produced improvements in NYHA functional class (3.1 ± 0.3 to 1.9 ± 0.7, p = 0.0005), MLWHF (63.6 ± 19.9 to 40.2 ± 23.2, p = 0.0005), and KCCQ scores (43.6 ± 21.1 to 65.6 ± 21.5, p = 0.0002), but not 6MWD (275.5 ± 64.0 to 296.4 ± 104.9, p = NS) or pVO_2 (14.5 ± 3.6 to 13.1 ± 4.4, p = NS). Improvements continued at 12 months, with 6MWD change becoming statistically significant (336.5 ± 91.8, p = 0.0425).

CONCLUSIONS Use of C-Pulse in this population is feasible, appears safe, and improves functional status and QoL. A prospective, multicenter, randomized controlled trial is underway. (C-Pulse IDE Feasability Study-A Heart Assist System; NCT00815880) (J Am Coll Cardiol HF 2014;2:526–33) © 2014 by the American College of Cardiology Foundation. Open access under CC BY-NC-ND license.

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Functional status and quality of life (QoL) remain poor for at least 30% to 40% of chronic heart failure patients, who remain categorized in New York Heart Association (NYHA) functional class III or IV despite optimal evidence-based drug and electrophysiological device therapies (1). These patients with advanced heart failure are also at the greatest risk for heart failure-related hospitalization and mortality, with a 1-year mortality rate of at least 10% to 15% (2–4). While therapies such as cardiac transplantation or left ventricular assist devices (LVADs) may benefit the subset of this population with end-stage disease defined by the American College of Cardiology/American Heart Association as Stage D heart failure, these measures are generally not indicated for the vast majority of patients with Stage C heart failure (5). Moreover, the small number of available donor organs limits the application of cardiac transplantation, and LVADs are limited by the blood-contacting nature of their design and need for chronic anticoagulation, resulting in significant device-related adverse events of stroke, major bleeding, infection, and device failure (6). Thus, there is an unmet need for additional therapies for American College of Cardiology/American Heart Association Stage C and NYHA functional class III and ambulatory functional class IV heart failure patients.

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One emerging approach to these patients is through the use of chronic ambulatory aortic counterpulsation (7–9). Aortic counterpulsation is a well-established mode of circulatory support that works by reducing left ventricular after-load during systole and augmenting blood pressure and systemic and coronary perfusion during diastole (10–12). While the application of aortic counterpulsation in acutely ill patients involves the use of an intra-aortic system (the intra-aortic balloon pump), implantable intra- and extra-aortic counterpulsation systems have been developed for chronic ambulatory use (13–16). One such system, the C-Pulse System (Sunshine Heart, Inc., Eden Prairie, Minnesota), includes a novel implantable, nonobligatory, non-blood contacting counterpulsation heart assist pump developed for minimally invasive implantation without the need for cardiopulmonary bypass (15,16).

The C-Pulse System was designed to provide an effective low-risk and low-cost mechanical heart assist device for use in patients with chronic American College of Cardiology/American Heart Association Stage C and NYHA functional class III and ambulatory functional class IV heart failure. The device is designed to be turned off safely or weaned if there is sustained cardiac recovery and similarly, in failure modes, is considered to have a low risk of death or disability, other than the recurrence of heart failure symptoms. No anticoagulants are required, reducing the risk of bleeding complications, and the extravascular nature of the implant mitigates the risk of intravascular thrombus formation, thromboembolism, and blood-borne infection. Preliminary studies suggest that this method of counterpulsation is feasible and safe (15,16). The present study was designed to further assess the feasibility, safety, and potential efficacy of the C-Pulse System in the intended population.

ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CT = computed tomography

LVAD = left ventricular assist device

NYHA = New York Heart Association

pVO_2 = peak oxygen consumption

PIL = percutaneous interface lead

QoL = quality of life

METHODS

PATIENTS. Patients 18 to 75 years of age were eligible for this study if they had American College of Cardiology/American Heart Association Stage C heart failure with a left ventricular ejection fraction ≤35% and remained in NYHA functional class III or ambulatory functional class IV despite optimal medical therapy. Patients were required to have been receiving optimal drug treatment (e.g., angiotensin-converting enzyme inhibitors, beta-blockers) for at least 3 months and to have had a biventricular pacemaker for at least 3 months, if indicated. Patients were also required to have an implantable cardioverter-defibrillator, if indicated. Other major inclusion criteria included a 6-min walk distance (6MWD) between 100 to 350 m and exercise peak oxygen consumption (pVO_2) between 10 and 18 ml/kg/min for men and 9 and 16 ml/kg/min for women. Major exclusion criteria included severe renal failure (estimated glomerular filtration rate <40 ml/min/1.73 m^2), severe chronic respiratory disease (forced expiratory volume ≤0.9 l/min), severe right heart failure (central venous pressure ≥20 mm Hg, elevated liver function tests beyond 3 times the upper limit of normal, or the

Thoratec; and has served on the Data Safety and Monitoring Board for BioStable. Dr. Peters holds intellectual property, stock, or stock options in Sunshine Heart, Inc.; and has received consulting fees. Dr. Verta is an employee of Sunshine Heart, Inc. and holds stock options. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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presence of ascites), significant ascending aortic disease and/or calcification, moderate or severe aortic valve incompetence, previous aortic surgery, or the presence of aortocoronary artery grafts. Eligible patients underwent computed tomography (CT) scanning of the chest to ensure the ascending aorta was free of significant disease and/or calcification and within anatomic constraints. A complete list of inclusion and exclusion criteria may be found at www.clinicaltrials.gov (NCT00815880).

The study was conducted in accordance with Code of Federal Regulations Parts 11, 50, 54, 56, and 812, Declaration of Helsinki and International Conference for Harmonization Guidelines for Good Clinical Practices. The institutional review board of each participating center approved the study protocol, and all patients provided written informed consent. The study was performed under an Investigational Device Exemption from the U.S. Food and Drug Administration.

STUDY DESIGN. The C-Pulse study was a prospective, open-label, single-arm feasibility trial undertaken at 7 centers in North America (Online Appendix). Following baseline testing, eligible patients underwent implantation of the C-Pulse System (Figure 1). The C-Pulse System consists of a surgically implanted extra-aortic balloon cuff and epicardial electrocardiography sense lead; an exchangeable, wire-wound percutaneous interface lead (PIL); and an external battery-powered pneumatic driver (Figure 1A). Under general anesthesia, the cuff was wrapped around the ascending aorta and the bipolar epicardial lead was placed on the left ventricle. The surgery did not require use of cardiopulmonary bypass or systemic anticoagulation. The implantation was done through a standard median sternotomy incision or minimally invasively through either a limited right parasternal thoracotomy procedure or via a hemisternotomy approach. The gas-line and lead were connected to the "Y" connector of the PIL, which was tunneled under the rectus sheath to an exit site located on the abdomen. A driver was attached to the patient connector and a programmer was used to adjust cuff inflation volume and timing of inflation and deflation in relation to the cardiac cycle to optimize the counterpulsation effect (Figure 1B). Balloon inflation was timed via the programmer to begin right after the dicrotic notch, while deflation started during the pre-ejection phase and continued during the ejection phase of systole in such a way that 70 ± 10% of the balloon was deflated at the start of ejection. Patients were discharged from the hospital once heart failure medications were re-established and the patients were ambulatory and able to demonstrate the ability to care for the exit site and manage the driver.

Patients were scheduled to be seen by the heart failure clinician-investigator and study coordinator at 1, 3, 6, and 12 months post-implant. During the primary

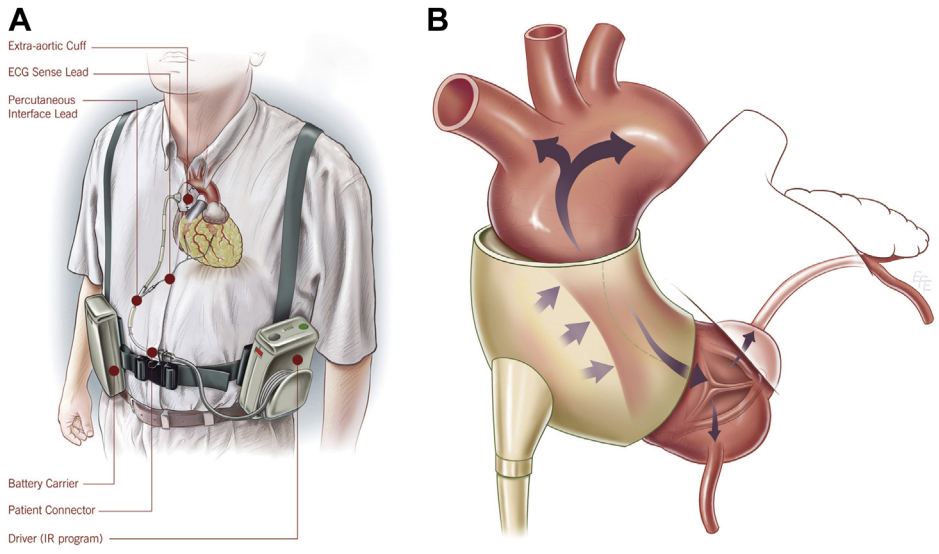

FIGURE 1 Overview of the C-Pulse System

(A) Components of the C-Pulse System (see text for details). **(B)** Cuff inflation causes a "thumbprint" deflection of the aortic wall, thus minimizing strain in the balloon and the aortic wall and maximizing volume displacement per beat (10 to 24 cc/beat).

period of follow-up (the first 6 months), the C-Pulse System was intended to be used at least 20 h per day. The non-blood contacting feature of the C-Pulse System allows the device to be intermittently turned off as tolerated. This enables the patient to be "untethered" from the device, allowing freedom for personal hygiene and convenience. Follow-up visits included a repeat of baseline tests: physical examination, medication summary, and assessment of NYHA functional class, QoL as measured by the Minnesota Living with Heart Failure questionnaire and the Kansas City Cardiomyopathy Questionnaire, 6MWD, and pVO_2 (repeated at 6 months only). Safety data, including adverse events, was collected continuously. The CT was repeated at 6 months only. Data were collected via electronic data capture screens referred to as e-case report forms and independently monitored. Core laboratories were used to provide data on CT scans (Cardiovascular Core Labs, Washington, DC), echocardiograms (Cardiovascular Core Labs, Washington, DC), and pVO_2 testing (Henry Ford Health System, Detroit, Michigan). Functional status assessments and QoL testing (NYHA functional classification and QoL scoring, respectively) were conducted using standardized and validated approaches and questionnaires (1,17). Adverse events were recorded by the clinical sites and adjudicated by an independent Clinical Events Committee (see the Online Appendix). Adverse event definitions were based on Version 2.2 adverse event definitions for the Intermacs registry (2,18).

STATISTICAL ANALYSIS. This feasibility study was designed to assess the safety and potential benefit of the C-Pulse System in patients with NYHA functional class III-ambulatory functional class IV heart failure. As with most Investigational Device Exemption feasibility studies, the primary focus of the U.S. Food and Drug Administration and device manufacturer is on device safety and whether its potential benefit justifies the risks of use. At this stage, endpoints and sample size are not statistically driven; however, study results may be useful in designing the pivotal study, in particular for endpoint selection and assumptions used in power calculation. A sample size of 20 implanted patients was considered clinically sufficient by the U.S. Food and Drug Administration to provide preliminary data on both safety and potential efficacy. Absolute changes in efficacy measures from baseline to follow-up were included in the statistical plan. An independent Data and Safety Monitoring Board (see the Online Appendix) monitored safety. SAS statistical software (release 9.3 TS1M3, SAS Institute, Cary, North Carolina) was used.

The safety of the C-Pulse System was evaluated by reviewing a composite of the device-related adverse events through 6 months, as adjudicated by the Clinical Events Committee. The composite device-related adverse event rate included death, major infection, aortic disruption, neurological dysfunction, myocardial infarction, or any other device-related adverse event. Safety was defined as the composite device-related adverse event rate and reported with its 95% 2-sided exact confidence interval. The composite device-related adverse event rate is assumed to follow the binomial distribution and defined as the percent of patients who experience at least 1 of the

TABLE 1 Characteristics of the Study Patients (N = 20)

Age (range), yrs	56.7 ± 9.1 (34.0-71.0)
Sex	
Female	40.0% (8/20)
Race	
Black/African American	15.0% (3/20)
Caucasian	80.0% (16/20)
Comorbidities	
Arrhythmia	55.6% (10/18)
Hyperlipidemia	65.0% (13/20)
Diabetes mellitus	25.0% (5/20)
Smoking history	75% (15/20)
Cardiomyopathy	100% (20/20)
Ischemic	35.0% (7/20)
Nonischemic	65.0% (13/20)
Blood chemistry	
Creatinine, mg/dl	1.3 ± 0.5 (20) [0.7, 2.4]
Bilirubin, mg/dl	1.0 ± 0.5 (20) [0.5, 2.1]
AST, U/l	22.9 ± 10.5 (20) [8.0, 52.0]
ALT, U/l	25.7 ± 19.0 (20) [2.4, 95.0]
Intermacs patient profile	
3: Stable but inotrope dependent	15.0% (3/20)
5: Exertion intolerant	40.0% (8/20)
6: Exertion limited	35.0% (7/20)
7: Advanced NYHA functional class III	10.0% (2/20)
NYHA functional class	
III	90.0% (18/20)
IV	10.0% (2/20)
Drugs	
Beta-blocker	100.0% (20/20)
Angiotensin-converting enzyme inhibitor	50.0% (10/20)
Angiotensin II receptor blocker	25.0% (5/20)
Aldosterone antagonist	55.0% (11/20)
Loop diuretic	85.0% (17/20)
Thiazide	20.0% (4/20)
Nitrate	20.0% (4/20)
Non-nitrate vasodilator	20.0% (4/20)
Inotrope	20.0% (4/20)
Digoxin	75.0% (15/20)
Cardiac resynchronization therapy	45.0% (9/20)
Implantable cardioverter-defibrillator therapy	100.0% (20/20)

Values are mean ± SD (range), % (n/N), or mean ± SD (n) (minimum, maximum).
ALT = aspartate aminotransferase; AST = alanine aminotransferase; NYHA = New York Heart Association.

TABLE 2 Characteristics of the Implant Procedure (N = 20)

Incision to dressing time, min	165.7 ± 42.4 (19) 156.0 [98.0, 247.0]
Anatomical approach	
Full sternotomy	70.0% (14/20)
Partial sternotomy	10.0% (2/20)
Right vertical parasternal	20.0% (4/20)
Time in ICU, days	2.2 ± 2.6 (19) 1.1 [0.6, 11.1]
Time in hospital, days	9.9 ± 4.2 (19) 8.0 [4.0, 19.0]

Values are mean ± SD (n), median (minimum, maximum) or % (n/N).
ICU = intensive care unit.

primary adverse events. All patients are included in reporting of safety.

Baseline and follow-up data were used to assess differences in NYHA functional class, QoL, and exercise variables before and after implant. The statistical analysis used data from paired samples. Only those patients providing paired assessments were included in the efficacy analyses. The mean point estimates and their respective standard deviations are presented for NYHA functional class, QoL scores, 6MWD, and pVO_2. Comparison of paired data was performed using mean difference, standard deviation, and Wilcoxon signed rank test p value for each variable. A nominal p value of <0.05 was considered statistically significant. No adjustment was made for multiple comparisons.

RESULTS

Between April 15, 2009 and June 20, 2011, 32 patients were screened for study inclusion; 20 were confirmed eligible and implanted and 12 were considered as screen failures. Reasons for exclusion included ascending aortic disease or nonconforming dimensions (n = 3), decreased functional capacity (6MWD and/or pVO_2 below criteria, n = 2), withdrawal of consent or were withdrawn by the investigator (n = 5), left ventricular ejection fraction >35% (n = 1), and recent stroke (n = 1). The characteristics of study participants are presented in Table 1. As required by protocol, all patients were on stable optimal medical therapy. All had an implantable cardioverter-defibrillator, and 45% had a combined biventricular pacer-implantable cardioverter-defibrillator. Characteristics of the implant procedures are detailed in Table 2.

TABLE 3 Device-Related Primary Safety Endpoints (6 and 12 Months) (N = 20)

Composite device-related AE	50.0% (10/20) [27.2–72.8]
Device-related death*	5.0% (1/20) [0.1–24.9]
Within 30 days	0.0% (0/20) [0.0–16.8]
30 days to 12 months	5.0% (1/20) [0.1–24.9]
Neurological events	0.0% (0/20) [0.0–16.8]
Aortic disruption*	5.0% (1/20) [0.1–24.9]
Myocardial infarction	0.0% (0/20) [0.0–16.8]
Major infection	
Localized non-device infection (peripherally inserted central catheter line)	5.0% (1/20) [0.1–24.9]
Exit site infection	40.0% (8/20) [19.1–63.9]
Internal percutaneous interface lead	5.0% (1/20) [0.1–24.9]
Sepsis	0.0% (0/20) [0.0–16.8]
Any other device-related AE Acute renal dysfunction†	5.0% (1/20) [0.1–24.9]

Values are % (n/N) [95% confidence interval]. All event types and relationship to device have been adjudicated by the Clinical Events Committee. *Device-related adverse event of aortic disruption at time of re-do surgery for mediastinitis with an outcome of death. †Computed tomography with contrast for the assessment of possible device infection resulted in acute renal dysfunction.
AE = adverse event.

SAFETY. In general, the implant procedure was safe. There were no operative deaths (i.e., there was no mortality within 30 days of the implant procedure). Three deaths occurred between 31 days and 6 months follow-up, including 1 adjudicated as device-related. This last patient developed a procedure-related sternal wound infection post-operatively with presence of Methicillin resistant Staphyllococcus aureus (MRSA) in cultures. The infection remained unresolved over several months despite repeated antibiotic treatments and debridement. After a CT identified a fistula track from the sternum to the device, the patient was taken to the operating room for sternectomy and pectoral flap reconstruction. During resternotomy, atrial and aortic tears occurred, and the patient died intra-operatively. One patient died 60 days after implant and another at 61 days after implant; both deaths were adjudicated as non-device related by the independent Clinical Events Committee. One patient underwent LVAD implant, another underwent heart transplant. One patient had the PIL and cuff removed at the 6-month visit because of a disrupted internal gas-line following a fall that damaged the line. Between 6 and 12 months, 1 patient had a heart transplant, 1 received an LVAD, 1 was weaned from therapy at 11 months for left ventricular recovery, and 1 discontinued therapy voluntarily and had the PIL explanted following the 6 months post-implant follow-up visit.

Some patients included in the study were in late-stage heart failure disease. While it was our intent to treat patients who were not candidates for LVAD or transplant, some of these patients were evaluated for transplant at baseline. Two patients continued having supraventricular arrhythmia despite cardioversion and/or ablation and went to transplant. One patient had opted out of LVAD, but repeat arrhythmias led to a LVAD implant. One patient was scheduled to have a PIL replacement when the surgeon made the decision to implant a LVAD instead.

One-year survival was 85%. Table 3 presents the primary safety endpoint analysis at 6 and 12 months. The composite device-related adverse event rate through 6 months, as classified by the Clinical Events Committee, was 50%. This result was influenced by the exit site infection rate of 40%. Between 6 months and 12 months, there were no additional patients with device-related serious adverse events.

EFFICACY. Table 4 presents the efficacy analysis at 6 and 12 months. Significant improvements were noted in NYHA functional class at both 6 and 12 months. Four (20%) and 3 (15%) patients were asymptomatic at 6 and 12 months, respectively, improving from NYHA functional class IV or III to functional class I (Figure 2). The Minnesota Living with Heart Failure QoL score significantly improved at 6 and 12 months. The Kansas City Cardiomyopathy Questionnaire score also significantly improved at 6 and 12 months. The 6MWD showed a trend toward improvement at 6 months and significantly improved at 12 months. There was no improvement in pVO_2 at 6 months.

There was a low rate of heart failure hospitalization in these patients. Over 12 months, 3 of the 20 implanted patients (15%) had 5 Clinical Events Committee-adjudicated heart failure hospitalizations. Few of these occurred during active therapy, and C-Pulse System nonadherence appeared to be related to most of these heart failure hospitalizations; specifically, 2 of these 3 patients were nonadherent (utilizing the system <30% of the time) in the weeks before their heart failure hospitalizations. Over 12 months, there were 40 non-heart failure related hospitalizations in 19 patients. Of these, 10 were related to PIL issues in 9 patients (45%), 11 to exit site infections in 8 patients (40%), 7 to other infections (urinary tract infection, sternal wound, pneumomediastinum, peripherally inserted central catheter) in 4 patients (20%), and 12 to other conditions (e.g., atrial fibrillation, respiratory failure, disseminated intravascular coagulation) in 9 patients.

DISCUSSION

The results of this feasibility study suggest that the C-Pulse System may be safe and effective in patients with moderate to severe heart failure. A majority of patients showed improvements in NYHA functional class and QoL scores, and statistically significant improvements in mean change from baseline to 6 and/or 12 months were demonstrated for NYHA functional class, QoL scores, and the 6MWD. Considering that this feasibility study was neither designed nor powered to demonstrate statistically significant improvements in any of the efficacy measurements, these findings should merely be considered as preliminary indicators of the potential efficacy of the C-Pulse System. However, in this context, the magnitude of these improvements is clinically meaningful when compared to prior drug and device trials in heart failure (3,4), and occurred on top of ongoing treatment with optimal heart failure drug and electrophysiological device therapies. Further support for these preliminary efficacy signals includes the successful weaning of inotropes in all patients receiving inotropes at baseline and the reduction in diuretic requirements in 6 patients (30%), implying improved cardiac output and peripheral perfusion. There was no increase in diuretics for any of the patients in the study. These findings require confirmation in an adequately powered randomized controlled trial.

From the safety standpoint, the composite adverse event assessment was dominated by the incidence of

TABLE 4 Efficacy Analyses at 6 and 12 Months

	NYHA	MLWHF	6MWD	KCCQ-Overall	KCCQ-Clinical	pVO_2
Baseline (n = 20)	3.1 ± 0.3	64.4 ± 17.6	275.5 ± 64.0	41.0 ± 18.7	47.9 ± 21.3	14.3 ± 3.4
Baseline (n = 15*)	3.1 ± 0.3	63.6 ± 19.9	272.3 ± 63.4	43.6 ± 21.1	51.3 ± 23.6	14.5 ± 3.6
6 months (n = 15*)	1.9 ± 0.7	40.2 ± 23.2	296.4 ± 104.9	65.6 ± 19.0	69.0 ± 21.5	13.1 ± 4.4
Mean change	-1.1 ± 0.7 (<0.0005)	-23.4 ± 19.0 (0.0005)	24.1 ± 62.6 (0.2239)	22.0 ± 15.6 (0.0002)	17.7 ± 12.7 (<0.0001)	-1.4 ± 3.7 (0.2612)
Baseline (n = 12)	3.1 ± 0.3	61.0 ± 19.2	289.7 ± 48.9	47.7 ± 21.0	56.3 ± 23.2	NA
12 months (n = 12)	1.9 ± 0.7	36.4 ± 21.7	336.5 ± 91.8	67.4 ± 21.1	73.6 ± 20.7	NA
Mean change	-1.2 ± 0.8 (0.0002)	-24.6 ± 16.5 (0.0005)	46.8 ± 64.9 (0.0425)	19.7 ± 17.3 (0.0024)	17.3 ± 16.2 (0.0093)	NA

Values are mean ± SD for baseline, 6-month, and 12-month numbers. Mean change are mean difference of the differences between the matched pairs ± SD (Wilcoxon signed rank test p value). *N = 14 for peak oxygen consumption (pVO_2). For Minnesota Living with Heart Failure (MLWHF), lower score indicates improvement; for Kansas City Cardiomyopathy Questionnaire (KCCQ), higher scores indicate improvement.

6MWD = 6-min walk distance; NA = not applicable; NYHA = New York Heart Association.

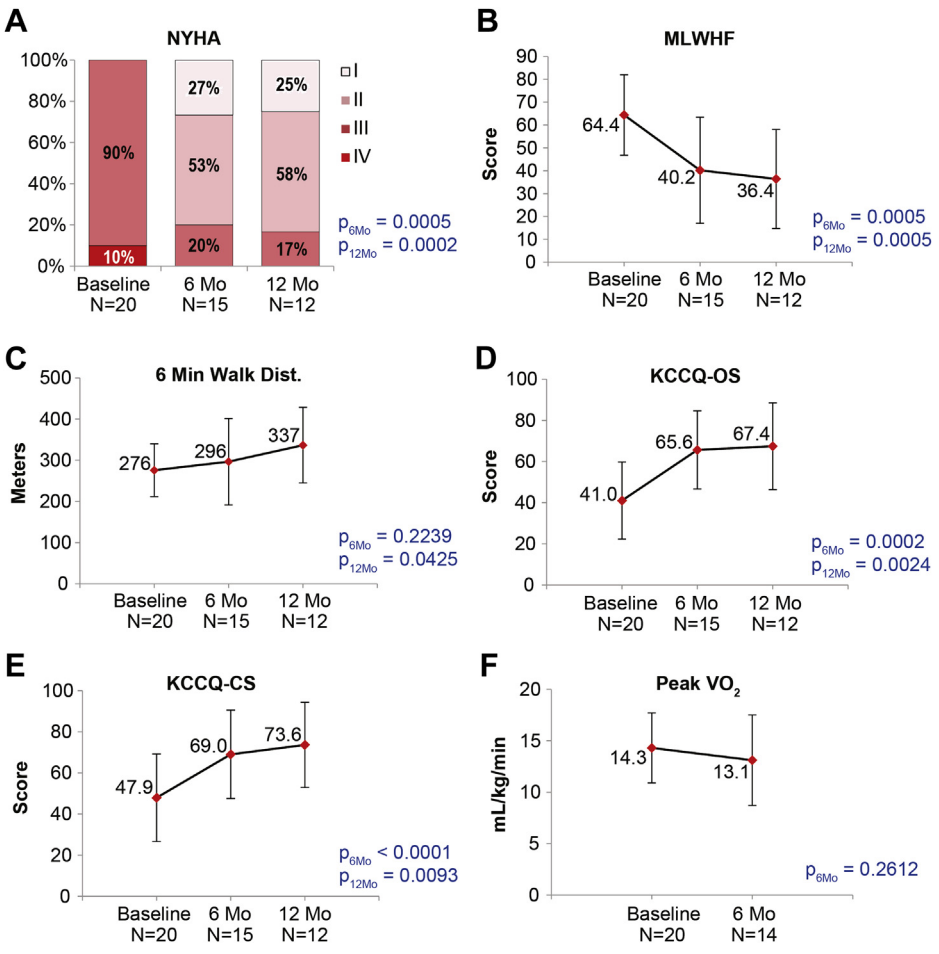

FIGURE 2 Efficacy Outcomes From Baseline to 6 and 12 Months

(A) Change in New York Heart Association (NYHA) functional class from baseline to 6 and 12 months. **(B)** Change in Minnesota Living with Heart Failure (MLWHF) score from baseline to 6 and 12 months (score decrease indicates improvement). **(C)** 6-min walk distance from baseline to 6 and 12 months. **(D)** Change in Kansas City Cardiomyopathy Questionnaire Overall score (KCCQ-OS) from baseline to 6 and 12 months (score increase represents improvement). **(E)** Change in Kansas City Cardiomyopathy Questionnaire Clinical score (KCCQ-CS) from baseline to 6 and 12 months (score increase represents improvement). **(F)** Change in peak oxygen consumption (peak VO_2) from baseline to 6 months (no cardiopulmonary exercise [CPX] test performed at 12 months, per protocol). All p values were computed using Wilcoxon signed rank test; p_{6Mo} for paired data comparison between baseline and 6 months, p_{12Mo} for paired data comparison between baseline and 12 months. All p values were calculated for educational purposes. No adjustments were made for multiple comparisons.

manageable exit site infections, which might be mitigated in the future by recently developed strategies for better drive line fixation and management. There were no neurological events, myocardial infarctions or periprocedural mortality. For the 12-month period, there was 1 device-related death reported, attributed to complications arising from a sternal wound infection in a patient who underwent repeated sternotomies and attempted sternectomy. With stricter guidelines for exit site management, including wound care, improved PIL fixation, regimented antibiotic therapy, as well as a less invasive (i.e., mini-thoracotomy vs. full sternotomy) approach to C-Pulse System implantation, the exit site infection risk may be reduced in future studies.

C-Pulse patients did not experience rehospitalizations for stroke, thrombosis, sepsis, and bleeding as is often observed with LVADs. This observation is consistent with the non-blood contacting design of C-Pulse as compared with LVADs. Another important difference between C-Pulse and LVADs is the non-obligatory nature of the system. The non-blood contacting nature of the C-Pulse System allows the device to be intermittently turned off as tolerated

for patient convenience. While this may improve patient acceptance of the system, it does create the possibility of poor patient adherence to the therapy. As observed in the present study, nonadherence to therapy might diminish the potential benefits of the system; future studies of this device must take this into account. Strategies to assure high levels of patient adherence to the therapy have been developed.

STUDY LIMITATIONS. This study is limited by its small size and the absence of a parallel control group. However, it was intended only to provide further proof-of-concept and enough preliminary data to support the design and conduct of a more definitive randomized controlled trial of the C-Pulse System. While measures of functional status and QoL were improved, pVO_2 was not. This may indicate that the effect of C-Pulse therapy is primarily on improving submaximal exercise, or this finding may simply represent the inherent limitations of metabolic exercise testing (19). The improvement in 6MWD supports a potential improvement in submaximal exercise capacity with C-Pulse.

The present feasibility study suggests that the C-Pulse System may be safe in patients with moderate to severe heart failure. It also offers preliminary insight into the potential effectiveness of the therapy in these patients. On the basis of review of the feasibility study data, a prospective, randomized, controlled trial designed to demonstrate and extend these observations was approved by the U.S. Food and Drug Administration in November 2012 and is currently underway.

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APPENDIX For a list of the committees, investigators, coordinators, and study centers participated in the C-Pulse Feasibility Study, please see the online version of this article.