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Preliminary Results From the C-Pulse® OPTIONS HF European Multicenter Post-Market Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 Antonia Schulz
ABCDEF 2 Thomas Krabatsch
ABCDEF 3 Jan D. Schmitto
ABCDEF 1 Roland Hetzer
ABCDEF 4 Mirko Seidel
EF 5,6 Pascal M. Dohmen
ABCDEFG 1 Holger Hotz

1 Cardio Centrum Berlin, Academic Teaching Institution of Charité, Medical University Berlin, Berlin, Germany
2 Department of Cardiac Surgery, German Heart Center Berlin, Berlin, Germany
3 Department of Cardiac, Thoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany
4 Department of Cardiology, Unfallkrankenhaus Berlin, Academic Teaching Hospital of Charité, Medical University Berlin, Berlin, Germany
5 Department of Cardiovascular Surgery, Charité Hospital, Medical University Berlin, Berlin, Germany
6 Department of Cardiothoracic Surgery, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

Corresponding Author: Holger Hotz, e-mail address: holger.hotz@cardio-centrum.de
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Background: The C-Pulse® System is an extra-aortic balloon counterpulsation device. It is used to treat patients with heart failure disease in NYHA functional class III or ambulatory class IV.

Material/Methods: We present preliminary site-reported 6-month data from 3 centers in Germany as part of the prospective observational post-market OPTIONS HF study.

Results: Between May 2013 and March 2014, the C-Pulse System was implanted in 8 patients (7 male) with a mean age of 61.6±9.3 years. Four had ischemic and 4 had non-ischemic cardiomyopathy. No stroke, myocardial infarction, major bleeding, or major infection due to the device were reported. One patient developed non-device-related refractory tachycardia with worsening heart failure 12 h after surgery and underwent left ventricular assist device implantation. Within 6 months of observation, functional status improved from NYHA III to II in 5 patients, and 2 remained in NYHA III. Mean left ventricular ejection fraction increased from 24.3±7.9% to 44.5±4.5% ($p<0.0001$). Mean Kansas City Cardiomyopathy Questionnaire overall score improved from 28.6±19.1 to 59.1±22.5 ($p=0.0183$). Six-minute walk test was performed in 6 out of 7 patients at follow-up. The mean distance improved from 252.0±85.1 m to 279.2±87.5 m ($p>0.05$). One patient was weaned off the device after 6 months of support.

Conclusions: The C-Pulse System provides a therapeutic option for patients with moderate-to-severe heart failure and seems to improve quality of life and cardiac function over time.

MeSH Keywords: Counterpulsation • Heart Failure • Heart-Assist Devices

Full-text PDF: http://www.basic.medscimonit.com/abstract/index/idArt/896959

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Background

In high-income countries heart failure is the most common diagnosis of hospital admissions in patients aged 65 years and older and results in 1 million admissions every year in the United States, with similar numbers in Europe [1]. Despite major improvements in heart failure treatment, such as pharmacologic or cardiac resynchronization therapy, disease progresses in many patients, necessitating the use of advanced cardiac therapies such as mechanical circulatory support or heart transplantation [2–4].

The earliest form of mechanical circulatory support is counterpulsation therapy, which is most commonly used in the form of an intra-aortic balloon pump (IABP) [5]. Counterpulsation provides diastolic augmentation with increased coronary perfusion and pre-systolic unloading of the left ventricle in patients with heart failure. These proven benefits resulted in the development of a number of counterpulsation devices for various indications [5]. One less-invasive device for chronic ambulatory use in moderate-to-advanced heart failure patients is the C-Pulse System.

Material and Methods

C-Pulse System

The C-Pulse® System (Sunshine Heart, Inc., Eden Prairie MN, USA) is an extra-aortic balloon counterpulsation device placed around the ascending aorta for chronic ambulatory use in patients with moderate-to-severe heart failure according to American College of Cardiology/American Heart Association (ACC/AHA) stage C and New York Heart Association (NYHA) functional class III or ambulatory class IV. It is an investigational device in the United States and Canada. C-Pulse received CE mark in July 2012 and is currently being implanted in European centers participating in the OPTIONS HF trial.

The device consists of a pneumatically-driven balloon cuff that can be surgically placed around the ascending aorta using a minimally-invasive approach, a bi-polar epicardial sensing lead, and a percutaneous driveline connecting the system to an extracorporeal driver unit (Figure 1). Balloon inflation is ECG-triggered and programmed to start shortly after aortic valve closure, at the onset of diastole (Figure 2). Deflation starts before aortic valve opening and continues over the first period of systole. Inflation volume depends on the cuff size used, with approximately 20 to 30 ml of blood volume displaced per beat [3]. Based on the hemodynamics of counterpulsation therapy, the C-Pulse System reduces left ventricular afterload and increases diastolic coronary blood flow [6,7]. It has also been shown to reduce pulmonary artery pressure[3]. Most importantly,

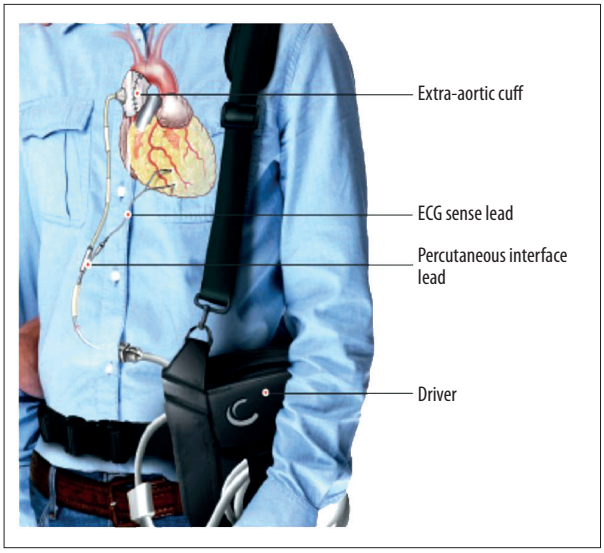

Figure 1. Components of the Sunshine Heart C-Pulse System (from Sunshine Heart Inc., with permission).

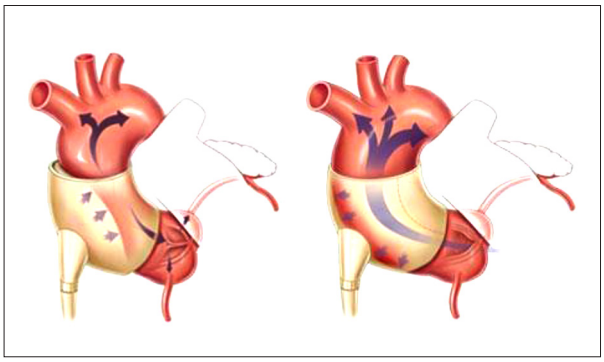

Figure 2. Inflating and deflating extra-aortic balloon cuff around the ascending aorta (from Sunshine Heart Inc., with permission).

the device is placed outside the bloodstream, eliminating the need for anticoagulation and avoiding complications like intravascular thrombus formation, thromboembolism, or hemorrhage, which are all associated with use of most mechanical circulatory support devices. It also enables the patient to temporarily disconnect from the system for personal convenience such as showering. The thumbprint shape of the balloon was designed to reduce stress on the arterial wall. Published reports of histopathologic evaluation of the ascending aorta tissue after C-Pulse explantation suggests that it does not significantly alter aortic wall structures [6,8,9].

The completed U.S. feasibility study with 20 patients at 7 centers in North America provided preliminary indications of safety and efficacy in patients with moderate-to-severe heart failure [7]. One-year survival was 85% and there was a 15% heart failure-related hospitalization rate after 12 months [10]. While not statistically powered to detect endpoint differences, the

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study showed significant improvements in NYHA functional class and quality of life score after 6 months and 6-minute walk distance after 12 months, but there was no change in pVO_2 at 6 months [10].

On the basis of these results, the C-Pulse System received the CE Mark and the European multicenter study OPTIONS HF was initiated to assess long-term outcomes.

Study design

The C-Pulse System European multicenter post-market study OPTIONS HF was designed to observe the clinical outcome of heart failure patients treated with the C-Pulse system according to the approved indications and contraindications. It is a prospective, observational, post-market trial of 50 patients to be followed for up to 5 years at up to 15 centers. Patient recruitment remains ongoing.

Performance endpoints include: improvement in INTERMACS™ and/or NYHA functional class; explantation for recovery of ventricular function or cardiac transplantation; and freedom from worsening heart failure resulting in hospitalization, left ventricular assist device (LVAD) implantation, or death after 12 months. Secondary endpoints are improvement in left ventricular ejection fraction (LVEF), quality of life and 6-minute walk distance (6MWD) after 6 and 12 months. Quality of life was assessed with the validated Kansas City Cardiomyopathy Questionnaire (KCCQ). In the KCCQ, the overall score scales from 0 (worst health status) to 100 (best health status) [11]. A mean difference over time of 5 points on the KCCQ overall summary scale reflects a clinically significant change in heart failure status. Continuously monitored safety endpoints are all-cause and device-related mortality, aortic disruption, exit site infection, internal lead or cuff infection, thromboembolism, device malfunction, and all protocol-defined adverse events. All safety endpoints are adjudicated by an independent Clinical Events Committee.

The study was conducted in accordance with the declaration of Helsinki and approved by local ethics committees. All enrolled patients gave written informed consent to participate in the study.

Inclusion criteria

Patients are eligible for the study if they are age 18 years or older and have moderate-to-severe heart failure (defined as ACC/AHA stage C; NYHA functional class III or ambulatory class IV) despite being on optimal medical therapy. Patients who are non-responders to cardiac resynchronization therapy (CRT) may be enrolled. When indicated, the CRT device should be implanted for at least 3 months prior to enrollment.

All patients must sign the investigation informed consent form before being enrolled in the study.

Exclusion criteria

Patients are excluded if they have evidence of significant ascending aortic calcification via X-ray or CT scan; moderate or severe atherosclerotic aortic disease; ascending aorto-coronary artery bypass grafts or any history of aortic dissection; connective tissue disorder such as Marfan disease; or previous aortic root replacement. Additional exclusions are: aorta diameter not conforming to available balloon cuff sizes; severe mitral valve incompetence (grade 4+); moderate-to-severe aortic valve incompetence (grade 2–4+); systolic blood pressure <90 mmHg or >140 mmHg; and active systemic infection or presence of a bleeding/coagulation disorder.

Depending on the severity of heart failure, patients with the following conditions may be unsuitable for implantation: inotrope dependence (inability to wean); ACC/AHA Stage D heart failure; need for biventricular support; functional limitation due to heart failure (defined as a 6-Minute Walk Test distance of ≤175 meters measured within 30 days prior to implantation); need for concomitant surgery; and cardiac conditions such hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, and diastolic heart failure (with preserved EF).

Due to the complexities of heart failure, severe co-morbidities or significant clinical events within 30 days of implantation should be considered for study exclusion: body mass index <18 or >45 kg/m^2; serum creatinine ≥2.5 mg/dL; intrinsic hepatic disease or liver enzyme values (AST, ALT or total bilirubin) that are >3 times the upper limit of normal; severe intrinsic pulmonary disease; stroke or transient ischemic attack; >80% carotid stenosis; ST elevation myocardial infarction; uncontrolled atrial fibrillation or other tachycardias; conditions other than heart failure that limit survival to less than 2 years; positive serum pregnancy test for females of childbearing potential; or history of compliance issues that interfere with the ability to manage the C-Pulse therapy.

Implantation procedure

Device implantation can be done via median or partial sternotomy or right parasternal thoracotomy. The ascending aorta is mobilized and, depending on the measured aortic circumference, 1 of currently 3 available balloon sizes is determined. The balloon cuff is then wrapped and sutured around the ascending aorta, and an epicardial lead is placed in an appropriate location on the heart to provide optimal R-wave detection. There is no need for cardiopulmonary bypass. The gas line from the balloon and the sensing lead are then connected via a Y-connector to the interface lead, which is tunneled

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percutaneously to the skin exit site and connected to an external wearable battery-powered driver. With an external programmer, balloon cuff inflation volume, inflation timing, and deflation timing can be individualized for each patient.

Follow-up visits

Regular follow-up visits are scheduled at 6 weeks, 6 months, 12 months, 18 months, 2 years, and then annually. At follow-up patients have a general physical exam, evaluation of current cardiac medications, echocardiography, 6-minute walk test, assessment of quality of life, blood tests, and device check according to standard of care guidelines. Safety endpoints are monitored continuously.

Statistical analysis

While the study is intended to provide long-term outcomes, the performance endpoints are not statistically powered. For purposes of this study, we provided paired comparison results for LVEF, 6MWD, and the KCCQ results at 6 months as compared to baseline, using the paired t-test.

Results

Between May 2013 and March 2014, the C-Pulse System was implanted in 8 patients. Baseline clinical characteristics are presented in Table 1. We are reporting preliminary 6-month data from 3 centers in Germany, where the first implants in Europe took place.

Surgical implantation was successful in all patients via full (n=7) or partial sternotomy (n=1). Cardiopulmonary bypass was used in 1 case for concomitant left internal mammary artery to left anterior descending artery bypass graft. No inotropic support or blood transfusions were needed. The median implantation time was 151 min, range 98–172 min.

In the follow-up period of 6 months, there were no reports of stroke, myocardial infarction, major bleeding, or major infection due to the device. One patient with a prior history of tachycardia developed non-device-related refractory tachycardia 12 h after surgery. The tachycardia prevented C-Pulse from supporting the heart properly and the patient underwent LVAD implantation 5 days after the index procedure. The patient improved rapidly without further complications. There were no changes of the aortic wall noticed during LVAD implantation.

The remaining 7 patients have reached their 6-month follow-up visit and were evaluable for analysis. Figure 3 provides an overview of the results. One patient was weaned off the device after 6 months of support due to cancer surgery and radiation therapy. He showed improvements in LVEF from 20% at baseline to 44% at 6-month follow-up. However, due to physical weakness because of his cancer treatment, he was not able to perform the 6-minute walk test and remained in NYHA class III after initial improvement. At 3-year follow-up the patient is stable at his level.

Table 1. Baseline clinical characteristics of 8 patients implanted with the C-Pulse System.

	Patients (n=8)	
Age (mean) ±SD [years]	61.6±9.3	
Sex		
Male	87.5%	(7/8)
Female	12.5%	(1/8)
Comorbidities		
Arrhythmia	50%	(4/8)
Diabetes mellitus	62.5%	(5/8)
Smoking history	87.5%	(7/8)
Cardiomyopathy	100%	(8/8)
– ischemic	50%	(4/8)
– non-ischemic	50%	(4/8)
INTERMACS profile		
4: resting symptoms	37.5%	(3/8)
5: exertion intolerant	37.5%	(3/8)
6: exertion limited	25%	(2/8)
NYHA class		
III	87.5%	(7/8)
IV (ambulatory)	12.5%	(1/8)
Cardiac resynchronization therapy	62.5%	(5/8)
Implantable cardioverter-defibrillator therapy	75.0%	(6/8)

Overall functional status at 6 months improved from NYHA class III to II in 5 patients and 2 patients remained in NYHA class III. Within 6 months of observation, mean LVEF significantly increased from 24.3±7.9% to 44.5±4.5% ($p<0.0001$). There was also an improvement in KCCQ overall score in all patients by an average of 30.5±22.2 (range 9.6–63.0) from 28.6±19.1 to 59.1±22.5 ($p=0.0183$). The 6-minute walk test was performed in 6 out of 7 patients at follow-up. The mean distance increased, albeit not significantly, from 252.0±85.1 m to 279.2±87.5 m ($p>0.05$).

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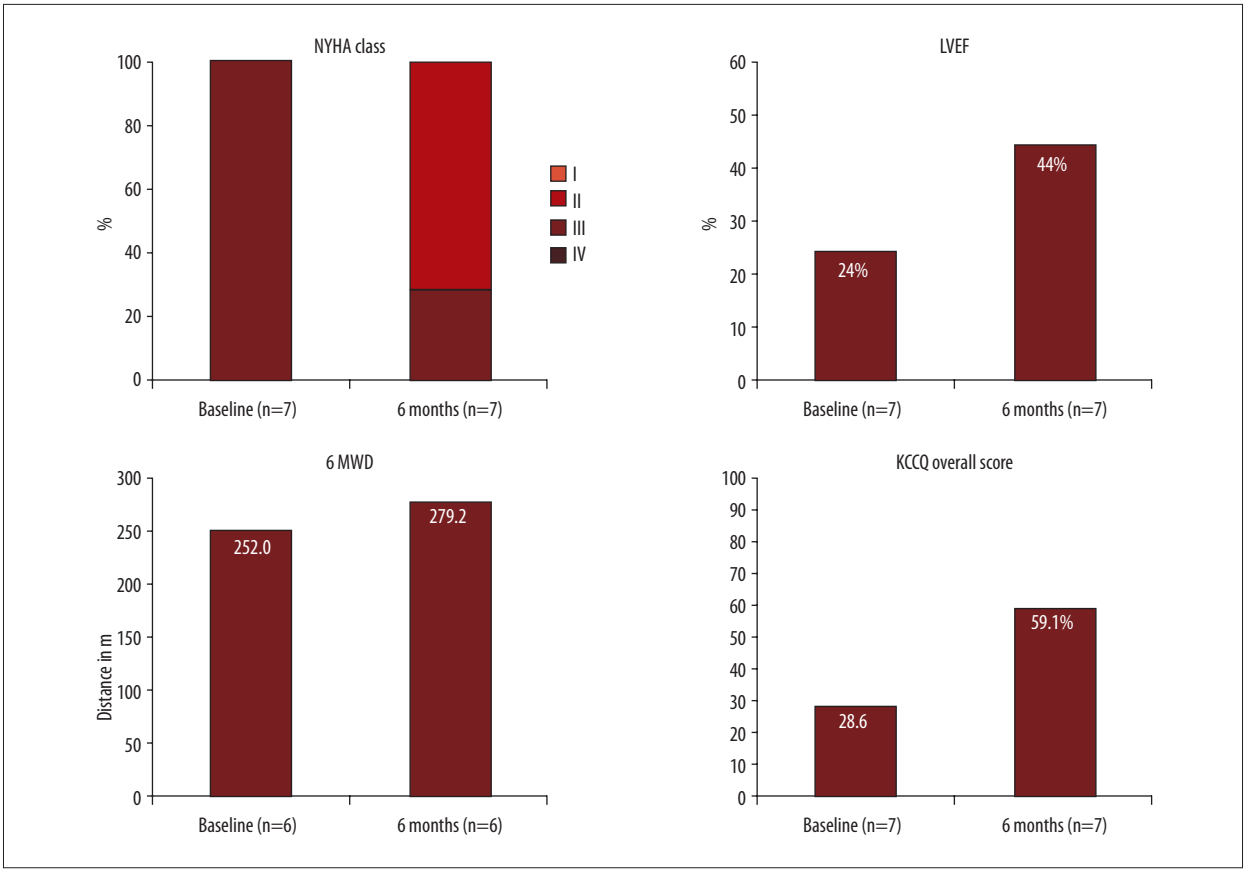

Figure 3. New York Heart Association (NYHA) class, mean left ventricular ejection fraction (LVEF), mean Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score, and mean 6-minute walk distance (6MWD) test at baseline and after 6 months.

Discussion

Many patients with moderate-to-advanced heart failure need further therapy despite optimal medical, and if applicable, cardiac resynchronization therapy. In contrast to left ventricular assist devices (LVAD), counterpulsation augments native heart function and might become a viable therapeutic option for class III and ambulatory class IV heart failure patients. While IABP is limited by its blood-contacting intra-aortic placement, restricted patient mobility and risk of limb ischemia, C-Pulse offers similar hemodynamic benefits while enabling patient mobility and long-term ambulatory use [5]. It also eliminates risks associated with device blood contact, mainly thrombus formation, thromboembolism, and bleeding. Although one might argue that the displaced volume is too little to achieve the same hemodynamic effects as an intra-aortic balloon pump, the proximity to the aortic valve allows equivalent or better counterpulsation. Several studies compared the effects of intra-descending and extra-ascending aortic counterpulsation in animal models and showed that pre-systolic unloading is comparable, while there is more efficient enhancement of diastolic coronary blood flow with the extra-ascending aortic balloon pump despite the difference in balloon volume [9,12]. Reasons for these hemodynamic effects could be better synchrony of the counterpulsation to cardiac cycle due to proximity to the aortic valve, minimization of pulse diffusion and thereby reduced counterpulsation efficiency loss, and unidirectional displacement of blood away from the ascending aorta, which results in a greater reduction in end-diastolic aortic pressure and arterial impedance [7,9,13].

The preliminary results from the OPTIONS HF trial show an improvement in NYHA functional class and quality of life score within 6 months of observation in the majority of patients. One patient had to undergo LVAD implantation. In addition, there seems to be an improvement in cardiac function in patients with ischemic and non-ischemic cardiomyopathy under C-Pulse treatment, resulting in an increased LVEF from 24.3±7.9% at baseline to 44.5±4.5% at follow-up, with 1 patient weaned off the system. While efficacy results were promising in the U.S. feasibility trial, infection remained a problem, with an exit site infection rate of 40% [10]. Subsequently, changes in drive line fixation at the skin exit site, improved patient education to continuously use therapy (minimize system disconnection and allow exit site to heal), and improved exit site cleaning/monitoring have been implemented. In our series there were

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no major infections due to the device within 6 months of observation. However, further results have to be awaited to confirm a reduction in infection rate.

While the number of patients is too small and the observational period too short to draw firm conclusions in the OPTIONS HF study, these results further support the outcomes of the U.S. feasibility trial of the C-Pulse System. One of the most important findings of both trials is the freedom from neurological complications (thus far), because the ischemic and hemorrhagic stroke rate for rotary flow LVADs is still approximately 10% per patient-year of support [14,15].

Conclusions

In conclusion, our preliminary experience indicates that the C-Pulse System is a safe extra-aortic counterpulsation device for long-term ambulatory use, which seems to improve cardiac function and may lead to relief of or recovery from chronic moderate-to-severe heart failure.

Disclosures

The authors declare no conflicts of interest.

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Clinical trial registration information: *www.clinicaltrials.gov*, Identifier: NCT01872949.

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