

Continuous internal counterpulsation as a bridge to recovery in acute and chronic heart failure

Christos D Kontogiannis, Konstantinos Malliaras, Chris J Kapelios, Jay W Mason, John N Nanas

Christos D Kontogiannis, Konstantinos Malliaras, Chris J Kapelios, John N Nanas, 3rd Department of Cardiology, University of Athens School of Medicine, 11527 Athens, Greece

Jay W Mason, Cardiology Division, University of Utah, Salt Lake City, UT 84132, United States

Author contributions: Kontogiannis CD, Malliaras K and Nanas JN wrote the manuscript; Kapelios CJ and Mason JW reviewed the manuscript and provided critical input; all authors approved the final draft.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: John N Nanas, MD, PhD, 3rd Department of Cardiology, University of Athens School of Medicine, 67 Mikras Asias Street, 11527 Athens, Greece. jnanas@ath.forthnet.gr
Telephone: +30-210-8236877
Fax: +30-210-7789901

Received: September 10, 2015
Peer-review started: September 10, 2015
First decision: October 16, 2015
Revised: December 27, 2015
Accepted: January 21, 2016
Article in press: January 22, 2016
Published online: March 24, 2016

Abstract

Cardiac recovery from cardiogenic shock (CS) and end-stage chronic heart failure (HF) remains an

often insurmountable therapeutic challenge. The counterpulsation technique exerts numerous beneficial effects on systemic hemodynamics and left ventricular mechanoenergetics, rendering it attractive for promoting myocardial recovery in both acute and chronic HF. Although a recent clinical trial has questioned the clinical effectiveness of short-term hemodynamic support with intra-aortic balloon pump (IABP, the main representative of the counterpulsation technique) in CS complicating myocardial infarction, the issue remains open to further investigation. Moreover, preliminary data suggest that long-term IABP support in patients with end-stage HF is safe and may mediate recovery of left- or/and right-sided cardiac function, facilitating long-term weaning from mechanical support or enabling the application of other permanent, life-saving solutions. The potential of long-term counterpulsation could possibly be enhanced by implementation of novel, fully implantable counterpulsation devices.

Key words: Counterpulsation; Recovery; Intra-aortic balloon pump; Heart failure; Cardiac remodeling; Reverse remodeling

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The counterpulsation technique induces beneficial effects on systemic hemodynamics and left ventricular mechanoenergetics. In this manner, it may facilitate myocardial recovery in acute and chronic heart failure (HF). The intra-aortic balloon pump (IABP) remains the main representative of the counterpulsation technique. Although recent data have questioned the effectiveness of short-term hemodynamic support with IABP in cardiogenic shock complicating myocardial infarction, the issue remains open to further investigation. Preliminary data suggest that long-term IABP support in patients with end-stage HF is safe and may mediate recovery of left- or/and right-sided cardiac function. Novel, fully implantable counterpulsation devices, which enable long-term counterpulsation, are described in this manuscript.

Kontogiannis CD, Malliaras K, Kapelios CJ, Mason JW, Nanas JN. Continuous internal counterpulsation as a bridge to recovery in acute and chronic heart failure. *World J Transplant* 2016; 6(1): 115-124 Available from: URL: <http://www.wjgnet.com/2220-3230/full/v6/i1/115.htm> DOI: <http://dx.doi.org/10.5500/wjt.v6.i1.115>

INTRODUCTION

Heart failure (HF) is a true pandemic, responsible for 5% of hospitalizations globally^[1]. HF, in its most severe forms, can manifest as two lethal clinical entities: (1) acute HF with cardiogenic shock (CS), with post-myocardial infarction (MI) CS mortality rates approaching 50%^[2]; and (2) end-stage chronic HF, with 1-year mortality of approximately 80% (worse than most types of cancer)^[3]. Despite significant advances in development of drug and device-based therapies, cardiac recovery from these two destructive forms of HF remains an often insurmountable therapeutic challenge. As we will see, the meaning of "recovery" and the remedial goal differ between acute and chronic HF.

RECOVERY IN ACUTE HF

Any cause of acute, severe left ventricular (LV) or right ventricular (RV) dysfunction may lead to CS. The most important cause of CS is severe LV dysfunction following a large acute MI^[4]. Despite the fact that the vast majority of these patients suffer from acute ST elevation MI, CS also occurs in approximately 2.5% of non-ST elevation MIs^[5]. Moreover, mechanical complications, such as ventricular septal rupture, acute severe mitral regurgitation and contained free wall rupture may lead to CS and must be suspected in patients with CS complicating non-anterior MI^[6]. Other less frequent causes include acute myopericarditis, isolated RV failure, Takotsubo cardiomyopathy, hypertrophic cardiomyopathy, acute valvular regurgitation (typically caused by endocarditis or chordal rupture), cardiac tamponade, excess beta or calcium channel blockade, dilated cardiomyopathy, peri-operative low output syndrome, and CS associated with cardiac catheterization complications^[7].

The meaning of "recovery" in the setting of acute HF and, thus, the treatment goal, is hemodynamic support during acute cardiac decompensation, including measures that allow the injured myocardium to recuperate and overcome the need for acute support^[8]. The therapeutic means to achieve this goal varies significantly depending on the cause of CS.

RECOVERY IN CHRONIC HF

Cardiac remodeling is a deleterious component of HF progression associated with poor prognosis^[9,10]. It

comprises molecular, cellular and interstitial changes, manifested clinically as changes in size, shape and function of the heart following cardiac overload or injury^[11]. Adverse changes at the organ level include alteration of LV geometry (less elliptical and more spherical LV shape)^[12,13], wall thinning^[14], LV dilatation (increase in LV end diastolic and end-systolic volumes) and decline in LV ejection fraction (EF)^[15]. Cellular and molecular changes include myocyte hypertrophy, loss of myocytes due to apoptosis^[16] or necrosis^[17], fibroblast proliferation^[18] and fibrosis^[19].

The therapeutic goal in chronic HF is to improve symptoms and life expectancy. That can be achieved by prevention of the adverse components of LV remodeling and reversal of already completed LV remodeling. Today we know that any level of reverse LV remodeling is associated with an analogous increase of survival in the patients suffering from HF^[20].

The term "bridge to transplantation" (BTT) for patients with chronic HF by use of mechanical assistance with an LVAD was introduced by the cardiac surgeons who were surprised to find a normal or almost normal recipient heart at the time of transplantation. Subsequently, "recovery" in chronic HF refers to sustained reversal of the aforementioned alterations, a process known as reverse remodeling with near normalization of LV function in patients on an LVAD as a BTT followed by a "safe" LVAD explantation. So, the definition of LV recovery presupposes that the patient can tolerate a large cardiac operation for LVAD explantation and remain clinically and hemodynamically stable thereafter.

This presupposition does not apply to patients assisted by a device easily explantable, like the percutaneous intra-aortic balloon pump (IABP). An example is one of our patient with chronic HF due to IDC complicated by CS requiring mechanical assistance by IABP. After 3 mo of continuous IABP support, he was successfully weaned from mechanical assistance and 5 years later he remains asymptomatic. He did not have to be subjected to a major cardiac surgical procedure to remove his bridging device, which may be the reason he did so well.

The patient mentioned above is now a 25-year-old man. He had had a history of progressively worsening HF when he presented at age 21 with CS, an LVEF of 17%, a BNP of 2800 pg/dL and a myocardial biopsy showed dilated cardiomyopathy. The patient was placed on intravenous infusion of inotropes and furosemide but further deteriorated. The patient was placed on IABP mechanical assistance and, although he was offered biventricular mechanical assistance (BiVAD), he preferred protracted IABP assistance. Initially he did not tolerate any anti-remodeling drug treatment. At the end of the 3 mo period on IABP his clinical and hemodynamic improvement permitted weaning from the IABP with a LVEF = 25% and a BNP = 207 pg/dL and 5 years later he remains asymptomatic with a LVEF = 30%, and VO_{2peak} =

Table 1 Criteria of sufficiency of recovery with easily-explantable counterpulsation devices and continuous flow left ventricular assist devices

Counterpulsation devices	
EF	↑ 5%
BNP	< 500 pg/mL
Continuous flow LVADs	
LVEDD	< 60 mm
LV end-systolic diameter	< 50 mm
EF	> 45%
LV end-diastolic pressure/PCWP	< 12 mmHg
Cardiac Index (resting)	> 2.8 L/min per square

EF: Ejection fraction; LV: Left ventricular; LVAD: Left ventricular assist device; PCWP: Pulmonary capillary wedge pressure; LVEDD: Left ventricular end-diastolic dimension.

29 mL/kg per minute. Thus, recovery no longer must presume a patient's ability to withstand an arduous LVAD explantation procedure.

In our experience, in patients who undergo mechanical assistance by a device that is easy and safe to explant (like the IABP), myocardial recovery can be considered adequate for termination of mechanical assistance when all of the following criteria are met (Table 1): (1) absolute increase in LVEF \geq 5% (measured by echo at the end of a 24-h reduced (1/4) pump function test) compared to baseline; and (2) BNP \leq 500 pg/mL (measured at the end of a 24-h reduced pump function test).

However, for the continuous flow LVADs which require a large and high risk operation for explantation, the recovery can only be considered adequate if the very demanding established criteria are met (Table 1): LVEDD < 60 mm, LV end-systolic diameter < 50 mm, and EF > 45%; LV end-diastolic pressure or PCWP < 12 mmHg, resting cardiac index > 2.8 L/min per square; and maximal oxygen consumption with exercise (mVO_2) > 16 mL/kg per square^[21].

COUNTERPULSATION

Counterpulsation was first conceived by Kantrowitz^[22] in the early 1950s, who managed to augment coronary blood flow by delaying arterial pulse in canine experimental models. In 1962, Mouloupoulos *et al.*^[23] developed the IABP, which was applied in human subjects 6 years later for the management of post-MI CS^[24]. Nowadays, IABP remains the single most widely-used short-term circulatory assist device in acute cardiac decompensation^[25]. However, the application of long-term IABP counterpulsation in the setting of chronic HF remains limited; the potential of long-term counterpulsation could possibly be enhanced by implementation of novel, fully implantable counterpulsation devices. These include the para-aortic counterpulsation device (PACD)^[26], representing the initial version of the pressure unloading LVAD (PULVAD) described below, the Kantrowitz CardioVAD (KCV)^[27], the

Table 2 Effects of counterpulsation on systemic hemodynamics and left ventricular mechanoenergetics

Decrease
Systolic aortic pressure
End-diastolic aortic pressure
LV systolic wall stress (afterload)
Myocardial oxygen/LV energy consumption
End-diastolic ventricular volume (preload)
Mean pulmonary capillary wedge pressure
Increase
Diastolic aortic pressure (augmentation)
LV mechanical performance (ejection fraction, stroke volume, cardiac output)
LV contractility and active relaxation (in the reperfused failing heart)
Coronary blood flow (post-ischemia, when coronary autoregulation is impaired and flow is pressure-dependent) ^[33]
Cerebral, renal, mesenteric and pulmonary blood flow
Mean arterial pressure (in patients with shock)

LV: Left ventricular.

Symphony counterpulsation device^[28,29] and C-pulse^[30].

How does counterpulsation promote recovery? Insights from experimental studies

Several experimental studies have demonstrated that counterpulsation exerts numerous beneficial effects on systemic hemodynamics and LV mechanoenergetics (Table 2), rendering it attractive for induction of recovery in both acute and chronic HF^[31-35]. In brief, counterpulsation unloads the LV (decreases LV afterload), decreases LV energy consumption and concurrently improves LV mechanical performance (EF, stroke volume, cardiac output). In addition, counterpulsation improves LV contractility and active relaxation of the reperfused failing heart, possibly through augmentation of coronary blood flow^[34]. However, it should be highlighted that the magnitude of the aforementioned beneficial effects varies widely, depending on several factors, such as the volume of counter-pulsated blood, the position of the device in the aorta, aortic compliance, heart rate/rhythm and systemic pressures and resistances^[36,37].

Counterpulsation in acute HF

IABP remains the most widely-used circulatory assist device in patients with CS complicating acute MI^[38]. Until 2012 IABP support was considered to be a class I treatment in the setting of post-MI CS^[39,40]. However, the clinical effectiveness of short-term IABP support in patients with CS post-MI has recently been called into question, mainly on the basis of the results of the IABP-SHOCK II trial, the largest randomized IABP trial to-date, which demonstrated no benefit of IABP support on either 30-d or 1-year all-cause mortality^[41,42]. Criticism of IABP SHOCK II study design and methodology have arisen^[43,44], mainly focusing on: (1) the late timing of IABP insertion (once revascularization had been completed), which could undermine the effectiveness of IABP support^[45];

and (2) the lower than expected mortality rate, which raises concerns about the severity of CS in the enrolled patient population. The interpretation of the trial's results is also complicated by methodological difficulties inherent to the design and execution of randomized trials in gravely ill patients with CS (*e.g.*, need for rescue LVAD implantation, need for rescue IABP insertion in patients randomized to the non-IABP group). Overall 17% of the patients randomized to conventional treatment received mechanical assistance by IABP or LVAD. Furthermore, in everyday clinical practice only 22% of patients with post-MI CS undergo IABP assistance^[46], most likely only those with the most severe CS. So, the strong message of that study is that not all patients with post-MI CS need mechanical assistance by the IABP. Nevertheless, the lack of hard evidence regarding clinical effectiveness of IABP support resulted in reconsideration of American and European guidelines, which have downgraded the routine use of IABP support in post-MI CS to class II a and III treatments, respectively^[47,48]. It should be noted, though, that the absence of evidence should not necessarily be interpreted as evidence of absence of clinical effectiveness; given that mortality in CS remains unacceptably high^[41,42], new, appropriately-powered and carefully-designed, clinical studies are needed to clarify the role of IABP support in promoting cardiac recovery in this setting.

Counterpulsation in chronic HF

Patients with advanced chronic HF face a grim prognosis, with 1-year mortality rates approaching 80%. These vulnerable patients have limited access to donor hearts for cardiac transplantation and chronic mechanical circulatory support is often used as a last resort. Intriguingly, clinical observation shows that chronic mechanical unloading can occasionally reverse the complex process of myocardial remodeling to the point that a subset of patients can be weaned from the device after restoration of basic cardiac function^[9]. Yet, myocardial recovery induced by conventional left ventricular assist devices (LVADs) is disappointingly rare^[49]. A prominent reason for the low rate of recovery is the physiologic mechanism through which conventional LVADs provide salutary hemodynamic effects. These LVADs bypass the LV and unload the failing LV independently of its systolic reserve. As a consequence, the LV is rendered ineffective to generate adequate pressure to surpass the mean arterial pressure generated by the LVAD itself. Thus, clinically available LVADs assist the LV at the cost of severely suppressing native LV function, rendering the LV incapable of sustaining its conditioning and therefore compromising recovery. In addition, pulsatility of flow seems to play an important role for cardiac reverse remodeling; recovery in patients with IDC may be as low as 3% for currently-used continuous flow LVADs, yet 25% with older-generation pulsatile alternatives^[50].

Chronic counterpulsation can overcome the aforementioned limitations of conventional LVADs and therefore appears attractive, at least from a theoretical standpoint, for promoting cardiac reverse remodeling and recovery, as it: (1) unloads the LV and decreases its energy consumption; (2) utilizes the LV systolic reserve; (3) enhances native LV functional performance (unlike clinically-used LVADs which suppress it); (4) retains pulsatility of flow and; and (5) preserves heart integrity.

The aforementioned reasons theoretically rationalize the expansion of the indications of counterpulsation implementation, beyond that of short-term hemodynamic stabilization. New potential indications could include use of long-term counterpulsation as a bridge to decision making (cardiac surgery, LV assist device implantation or transplantation), bridge to transplantation and bridge to myocardial recovery. However, long-term IABP support is not risk-free; major complications include acute limb ischemia, severe bleeding, embolic events, infection and sepsis^[51]. However, sheathless implantation technique in combination with thinner catheters application significantly minimized the rate of complications from 20.7% for 12 French catheters to 8.4% for 9.5 French catheters. Though more recent data are not available, it is reasonable to assume that the contemporary complication rate with the use of 6 and 7 French IABP catheters is significantly lower. In addition, several recent studies (described later in this review) have demonstrated that long-term IABP support appears to be associated with a favorable safety profile^[52-58]. The potential of long-term counterpulsation could possibly be enhanced by implementation of novel, fully implantable counterpulsation devices (described later) and mobilization of the patient.

IABP FOR CHRONIC LV HF

Converging data suggest safety and possibly efficacy of long-term circulatory support with IABP in patients with end-stage LV HF. In the study by Gjesdal *et al*^[52], 32 patients were successfully bridged to transplantation *via* IABP, after a mean IABP support of 21 d (range: 3-66 d), with few IABP-related complications. Importantly, mortality and hemodynamic indices at 1 year post-transplantation were similar in patients bridged to transplantation *via* IABP and in a control group, comprising 135 electively transplanted patients not needing circulatory support in the pre-transplant period. In the study by Cochran *et al*^[53], 4 patients with end-stage ischemic HF were successfully bridged to transplantation *via* IABP, after a mean duration of IABP support of 31 d (range: 12-70 d). Long-term IABP resulted in a 10 to 50-fold decrease in cost compared to the cost associated with the use of LV assist devices as a bridge to transplantation. In the study by Russo *et al*^[54], 14/17 patients with end-stage HF were successfully bridged

Table 3 Potential roles of long-term intra-aortic balloon pump support in chronic heart failure

Improves patients' clinical status and their hemodynamic indices, rendering them suitable candidates for heart transplantation (BTT)
Improves RV functionality and peripheral organ function, increasing the candidacy rates of patients who are ineligible for additional mechanical interventions (BTC)
Enhances native LV functional performance and unloads LV while maintaining its integrity, promoting reverse remodeling and cardiac recovery (BTR)

BTT: Bridge to transplantation; LV: Left ventricular; RV: Right ventricular.

to transplantation and 3/3 patients were successfully bridged to recovery *via* IABP after a mean support of 17 d (range: 3-48 d). In the study by Estep *et al*^[55], 50 patients received IABP support for a median of 18 d (range: 4-152 d) as a bridge to transplantation. Prolonged IABP support was associated with remarkable improvements in mean pulmonary artery pressure (MPAP) as well as in creatinine and total bilirubin concentrations. Forty-two patients (84%) were successfully bridged to transplantation and 38 of them (90%) were alive 90 d after transplantation. Additionally, in the study by Terrovitis *et al*^[56], 7 patients with end-stage HF (INTERMACS 2) due to idiopathic dilated cardiomyopathy underwent long-term circulatory support with IABP. One patient was successfully bridged to cardiac surgery, 4 patients were successfully bridged to assist device implantation, while the remaining 2 patients were successfully bridged to recovery and remained asymptomatic (NYHA class I) for at least 6 and 20 mo post-IABP removal^[56]. Finally, Tanaka *et al*^[57] investigated 88 patients with decompensated advanced HF who were implanted with IABP either as BTT and mechanical support ($n = 82$) or as bridge to recovery ($n = 6$). More than 90% of the patients succeeded the therapeutic goal with minimal rates of morbidity and mortality, while 3 out of 6 BTR patients experienced cardiac recovery.

IABP FOR CHRONIC RV HF

RV dysfunction is both a cause and an effect of HF progression, often leading to treatment dead-ends. On the one hand, patients with RV dysfunction are considered to be bad candidates for LVAD implantation^[59], as LVAD support aggravates pre-existing RV dysfunction through an increase in RV preload^[60]. On the other hand, the use of biventricular assist devices (often viewed as the only treatment option for these patients) is complicated and associated with poor long-term survival^[61]. We recently investigated the effects of long-term IABP support in a cohort of 15 patients suffering from biventricular end-stage HF (all classified as NYHA class IV, INTERMACS profiles 1 or 2), who were ineligible for any alternative LV interventional procedure^[58]. Long-term IABP support (median 72 d,

range: 13-115 d) resulted in substantial RV reverse remodeling, decreasing RV end-diastolic diameter and mean right atrial pressure. In addition, long-term IABP support increased cardiac index, increased RV stroke work index, and improved peripheral organ function. Clinical outcomes were encouraging, as 3 patients experienced complete clinical recovery and remained alive in NYHA class I at least 6 mo after IABP removal. Six patients exhibited partial clinical recovery, as long-term IABP support induced reversal of contraindications rendering them eligible for LVAD implantation. Four patients (all in INTERMACS profile 1) continued to deteriorate clinically and eventually died, while 1 patient died from septic shock on the 155th day of support and 1 from systemic inflammatory response syndrome on the 90th day. Putative mechanisms underlying the counterpulsation-induced recovery of RV function include an increase in RV myocardial blood flow and restoration of an optimal interventricular septal geometry, by relieving the septal shift induced by overload of the left ventricle. Regardless of the precise mechanism, these findings suggest that long-term counterpulsation may have a role in promoting recovery of the failing RV and could be used as a therapeutic strategy to increase the candidacy rates of patients who don't qualify for additional mechanical interventions.

The potential roles of long-term IABP support in chronic LV and RF HF are summarized in Table 3. Converging data suggest safety and efficacy of long-term IABP support as a bridge to transplantation or bridge to LVAD implantation. In addition, limited clinical data suggest that long-term IABP support may promote myocardial recovery. However, additional studies are warranted in order to clarify whether IABP-induced myocardial recovery can be consistently achieved or represents an anecdotal experience. The potential for myocardial recovery would undoubtedly be enhanced by prospective identification of patients who are more likely to undergo cardiac recovery^[62].

KCV FOR CHRONIC HF

KCV is a pneumatically-driven counterpulsation circulatory assist device, surgically implanted in the descending thoracic aorta by thoracotomy under cardiopulmonary bypass^[27]. The KCV system consists of a 60-cc pumping chamber (sutured to the descending aorta), a percutaneous access device (PAD, implanted in a subcutaneous pocket), and an external controller. With regard to clinical application, the device was implanted in 5 patients with end-stage HF refractory to pharmacological medical treatment, but responsive to IABP support. The first patient died intra-operatively due to technical complications, whereas the following 4 patients demonstrated improvements in cardiac index, pulmonary capillary wedge pressure,

right atrial pressure, and NYHA class.

C-PULSE FOR CHRONIC HF

C-Pulse is an implantable extra-aortic balloon (EAB) counterpulsation device, consisting of an inflatable cuff positioned around the ascending aorta^[63]. The polyurethane cuff is implanted through thoracotomy and is wrapped around the patient's ascending aorta without any contact with the aortic blood^[64]. The cuff is synchronized to inflate inwardly during the diastolic notch, producing a stroke volume between 20 and 30 mL, depending on the cuff size and the aortic diameter.

Hayward *et al*^[63] investigated the feasibility and safety of C-Pulse support in 5 patients with advanced HF (NYHA class III or IV). All patients improved by 1 NYHA class, however, infectious complications were observed in 3/5 patients (with 2 patients suffering mediastinal infection necessitating device explantation). Recently, Abraham *et al*^[64] performed a multicenter study to investigate the feasibility, safety and preliminary efficacy of C-Pulse support in 20 patients with advanced HF (NYHA class III or ambulatory class IV). No 30-d mortality was observed and no neurological events or myocardial infarctions were recorded during the 1 year of follow-up. However, one patient suffered a device-related death (due to mediastinal infection) and 40% of patients experienced drive line exit site infections. In terms of efficacy, C-Pulse support produced significant improvements in NYHA functional class, quality of life and 6-min walk distance. Currently, a prospective, multicenter, randomized trial investigating the safety and efficacy of C-Pulse support in moderate to severe HF is underway (NCT01740596); 388 patients will be randomized to undergo C-Pulse implantation of optimal medical treatment (1 year follow up)^[36]. The primary efficacy point of the trial is freedom from worsening HF resulting in hospitalization, LVAD implantation, cardiac transplantation or death during 1 year of follow-up.

THE SYMPHONY DEVICE FOR CHRONIC HF

The Symphony device (Symphony) is an implantable counterpulsation device designed to be implanted *via* a minimally-invasive superficial technique, without the need to open the thoracic cavity. Symphony comprises a valveless, single chamber 40-mL polyurethane-lined pumping sac, which is designed to fit in a pacemaker-like pocket on the right side of the thorax, in the subclavian fossa^[29]. The pumping sac is connected to the systemic circulation by a short vascular graft, which is anastomosed to the subclavian artery. The driveline is tunneled out through the skin and attached to the driving console.

An anatomical cadaver-fit study suggested that a 40-mL Symphony might not be suitable for a large

number of patients, including women and small-sized men and that a smaller-sized device (32 mL) should be examined^[29]. An experimental study in 8 calves with toxin-induced cardiomyopathy demonstrated that the 32 mL-Symphony device was superior to the 40 mL-IABP in decreasing LV myocardial oxygen consumption and increasing the ratio of diastolic coronary artery flow to left LV external work, and inferior to the IABP in decreasing aortic end-diastolic pressure. Giridharan *et al*^[65] compared the effects of Symphony and IABP on aortic, carotid and coronary flows in a bovine experimental model of monensin-induced heart dysfunction. Compared to IABP, Symphony eliminated retrograde systolic blood flow (observed during IABP support) and increased total blood flow (despite producing less diastolic flow augmentation compared to IABP).

The first clinical application of Symphony was performed in a 64-year-old man with ischemic HF (NYHA III b)^[66]. Within 72 h of implantation, Symphony support increased cardiac index, and decreased right atrial pressure, pulmonary capillary wedge pressure and serum creatinine. However, following the patient's ambulation and increased activity, low flow to the pump and loss of right radial pulse were observed with cephalad movement of the right arm. This was attributed to compression of the subclavian artery due to device movement and the Symphony was explanted on the 10th postoperative day.

PULVAD

The PACD^[67,68], consists of a round valveless pumping chamber driven by an IABP console. The PACD is implanted in the thoracic cavity and is connected to the ascending aorta *via* a Dacron vascular graft. The PACD is superior to IABP in unloading the failing heart and increasing cardiac output^[69]. The PACD was implanted in 3 patients suffering from CS refractory to conventional treatment, including IABP; one patient died 4 h after the device implantation due to anesthesia-induced peripheral vasoparalysis, while the other two died due to septic shock 8 and 54 d after implantation, respectively^[26].

The PULVAD is the improved version of the PACD (Figure 1). It is smaller than PACD and can be driven by any conventional IABP console. In pigs weighing 80-100 kg and calves weighing approximately 100 kg it proved to be 3 times more effective than an IABP in reducing the systolic and end diastolic aortic pressure^[70,71].

The PULVAD'S ease of implantation (not requiring extracorporeal circulation), low cost of manufacture, wide availability of driving consoles and the fact that it provides only pressure unloading of the LV (which should prevent myocyte atrophy^[72,73] and cardiac fibrosis^[74], and promote myocardial recovery) make the PULVAD an attractive long-term alternative to the more expensive and complex LV assist devices currently used

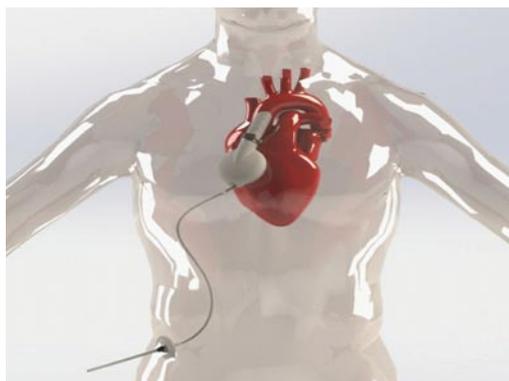


Figure 1 Pressure-unload left ventricle assist device.

in patients with end-stage decompensated HF.

DISCUSSION

Modern LVADs rely on continuous flow, and, while successful at prolonging life, LVAD-induced myocardial recovery is disappointingly rare. Clinically available LVADs bypass the LV and unload the failing LV independently of its systolic reserve. As a consequence, the dilated LV is rendered unable to generate at a basal pressure and LVEF is severely reduced because of the non-coupling of preload/afterload to LV systolic reserve. In other words, the continuous flow LVADs decrease LV preload but increase or maintain excessive afterload, driving LV function towards the bottom left of the Frank-Starling curve, reducing its functional performance. In general, we know that the lower the functional performance of the LV (*i.e.*, the lower the LVEF), the more vigorous is the process of adverse LV remodeling. In contrast to continuous flow LVADs the counterpulsation devices decrease LV afterload, thereby enhancing LV functional performance, and utilizing the LV systolic reserve to meet the peripheral metabolic demands. At the same time, the LV, based on the Frank-Starling curve, physiologically adjusts (decreases) its preload.

The IABP has been safely and effectively used for bridging chronic HF patients to transplantation^[52-56], to LVAD implantation and to recovery^[57,58]. Today, there are 4 counterpulsation devices (KardioVAD, C-Pulse, Symphony, and PULVAD) suitable for chronic mechanical assistance. These devices preserve heart integrity, unload the LV, decrease its energy consumption, enhance native LV functional performance and retain pulsatility of flow. In addition, the C-Pulse, Symphony and PULVAD counterpulsation devices do not require extracorporeal circulation for their implantation or explantation procedures. Knowing that recovery appears usually within the first 3-6 mo on mechanical assistance^[75], we propose that counterpulsation devices could be used temporarily (3-6 mo) as a bridge to recovery.

These devices appear suitable as a bridge to re-

covery not only for patients with acute HF but also for those with chronic HF, especially the ones with non-ischemic cardiomyopathy. We propose that when these patients become candidates for mechanical assistance the following practical rule can be followed: First assist them with IABP up to 2 wk and if the patients are hemodynamically stabilized (no need for IV inotropes/diuretics, no indication of peripheral organ malfunction, tolerance of HF medications, CVP \leq 10 mmHg, HR \leq 80 bpm, mean BP \geq 65 mmHg) then proceed to implantation of a counterpulsation device suitable for chronic mechanical assistance as a BTR. However, in the case of non-stabilization or further deterioration on IABP, proceed with implantation of a continuous flow LVAD or a BiVAD.

In conclusion, counterpulsation devices appear attractive for cardiac recovery not only for acute but also for chronic HF. Their simplicity of design and ease of implantation/explantation may allow much more widespread use compared to that of the currently-used continuous flow LVADs. To that end, further experimental and clinical studies are urgently needed to better define the role of counterpulsation devices in HF.

REFERENCES

- 1 **Butler J**, Fonarow GC, Gheorghiane M. Need for increased awareness and evidence-based therapies for patients hospitalized for heart failure. *JAMA* 2013; **310**: 2035-2036 [PMID: 24240925 DOI: 10.1001/jama.2013.282815]
- 2 **Ostenfeld S**, Lindholm MG, Kjaergaard J, Bro-Jeppesen J, Møller JE, Wanscher M, Hassager C. Prognostic implication of out-of-hospital cardiac arrest in patients with cardiogenic shock and acute myocardial infarction. *Resuscitation* 2015; **87**: 57-62 [PMID: 25475249 DOI: 10.1016/j.resuscitation.2014.11.010]
- 3 **Miller LW**, Guglin M, Rogers J. Cost of ventricular assist devices: can we afford the progress? *Circulation* 2013; **127**: 743-748 [PMID: 23401115 DOI: 10.1161/CIRCULATIONAHA.112.139824]
- 4 **Hollenberg SM**, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med* 1999; **131**: 47-59 [PMID: 10391815]
- 5 **Hasdai D**, Harrington RA, Hochman JS, Califf RM, Battler A, Box JW, Simoons ML, Deckers J, Topol EJ, Holmes DR. Platelet glycoprotein IIb/IIIa blockade and outcome of cardiogenic shock complicating acute coronary syndromes without persistent ST-segment elevation. *J Am Coll Cardiol* 2000; **36**: 685-692 [PMID: 10987585]
- 6 **Hochman JS**, Buller CE, Sleeper LA, Boland J, Dzavik V, Sanborn TA, Godfrey E, White HD, Lim J, LeJemtel T. Cardiogenic shock complicating acute myocardial infarction--etiologies, management and outcome: a report from the SHOCK Trial Registry. Should we emergently revascularize Occluded Coronaries for cardiogenic shock? *J Am Coll Cardiol* 2000; **36**: 1063-1070 [PMID: 10985706]
- 7 **Reynolds HR**, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation* 2008; **117**: 686-697 [PMID: 18250279 DOI: 10.1161/CIRCULATIONAHA.106.613596]
- 8 **McMurray JJ**, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure

- Association (HFA) of the ESC. *Eur Heart J* 2012; **33**: 1787-1847 [PMID: 22611136 DOI: 10.1093/eurheartj/ehs104]
- 9 **Malliaras KG**, Terrovitis JV, Drakos SG, Nanas JN. Reverse cardiac remodeling enabled by mechanical unloading of the left ventricle. *J Cardiovasc Transl Res* 2009; **2**: 114-125 [PMID: 20559975 DOI: 10.1007/s12265-008-9057-6]
 - 10 **White HD**, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987; **76**: 44-51 [PMID: 3594774]
 - 11 **Cohn JN**, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol* 2000; **35**: 569-582 [PMID: 10716457 DOI: 10.1016/S0735-1097(99)00630-0]
 - 12 **Cohen MV**, Yang XM, Neumann T, Heusch G, Downey JM. Favorable remodeling enhances recovery of regional myocardial function in the weeks after infarction in ischemically preconditioned hearts. *Circulation* 2000; **102**: 579-583 [PMID: 10920072]
 - 13 **Mitchell GF**, Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular remodeling in the year after first anterior myocardial infarction: a quantitative analysis of contractile segment lengths and ventricular shape. *J Am Coll Cardiol* 1992; **19**: 1136-1144 [PMID: 1532970]
 - 14 **Rumberger JA**, Behrenbeck T, Breen JR, Reed JE, Gersh BJ. Nonparallel changes in global left ventricular chamber volume and muscle mass during the first year after transmural myocardial infarction in humans. *J Am Coll Cardiol* 1993; **21**: 673-682 [PMID: 8436749]
 - 15 **Gaudron P**, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors. *Circulation* 1993; **87**: 755-763 [PMID: 8443896]
 - 16 **Olivetti G**, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, Quaini E, Di Loreto C, Beltrami CA, Krajewski S, Reed JC, Anversa P. Apoptosis in the failing human heart. *N Engl J Med* 1997; **336**: 1131-1141 [PMID: 9099657]
 - 17 **Tan LB**, Jalil JE, Pick R, Janicki JS, Weber KT. Cardiac myocyte necrosis induced by angiotensin II. *Circ Res* 1991; **69**: 1185-1195 [PMID: 1834362]
 - 18 **Villarreal FJ**, Kim NN, Ungab GD, Printz MP, Dillmann WH. Identification of functional angiotensin II receptors on rat cardiac fibroblasts. *Circulation* 1993; **88**: 2849-2861 [PMID: 8252698]
 - 19 **Weber KT**, Pick R, Silver MA, Moe GW, Janicki JS, Zucker IH, Armstrong PW. Fibrillar collagen and remodeling of dilated canine left ventricle. *Circulation* 1990; **82**: 1387-1401 [PMID: 2401072]
 - 20 **Kramer DG**, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol* 2010; **56**: 392-406 [PMID: 20650361]
 - 21 **Birks EJ**, Tansley PD, Hardy J, George RS, Bowles CT, Burke M, Banner NR, Khaghani A, Yacoub MH. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med* 2006; **355**: 1873-1884 [PMID: 17079761]
 - 22 **Kantrowitz A**. Experimental augmentation of coronary flow by retardation of the arterial pressure pulse. *Surgery* 1953; **34**: 678-687 [PMID: 13102153]
 - 23 **Moulopoulos SD**, Topaz S, Kolff WJ. Diastolic balloon pumping (with carbon dioxide) in the aorta--a mechanical assistance to the failing circulation. *Am Heart J* 1962; **63**: 669-675 [PMID: 14476645]
 - 24 **Kantrowitz A**, Tjonneland S, Freed PS, Phillips SJ, Butner AN, Sherman JL. Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *JAMA* 1968; **203**: 113-118 [PMID: 5694059]
 - 25 **Kapeliou CJ**, Terrovitis JV, Siskas P, Kontogiannis C, Repasos E, Nanas JN. Counterpulsation: a concept with a remarkable past, an established present and a challenging future. *Int J Cardiol* 2014; **172**: 318-325 [PMID: 24525157 DOI: 10.1016/j.ijcard.2014.01.098]
 - 26 **Nanas JN**, Lolas CT, Charitos CE, Nanas SN, Margari ZJ, Agapitos EV, Mouloupoulos SD. A valveless high stroke volume counterpulsation device restores hemodynamics in patients with congestive heart failure and intractable cardiogenic shock awaiting heart transplantation. *J Thorac Cardiovasc Surg* 1996; **111**: 55-61 [PMID: 8551789]
 - 27 **Jeevanandam V**, Jayakar D, Anderson AS, Martin S, Piccione W, Heroux AL, Wynne J, Stephenson LW, Hsu J, Freed PS, Kantrowitz A. Circulatory assistance with a permanent implantable IABP: initial human experience. *Circulation* 2002; **106**: 1183-1188 [PMID: 12354730]
 - 28 **Koenig SC**, Litwak KN, Giridharan GA, Pantalos GM, Dowling RD, Prabhu SD, Slaughter MS, Sobieski MA, Spence PA. Acute hemodynamic efficacy of a 32-ml subcutaneous counterpulsation device in a calf model of diminished cardiac function. *ASAIO J* 2008; **54**: 578-584 [PMID: 19033769 DOI: 10.1097/MAT.0b013e318186891f]
 - 29 **Koenig SC**, Spence PA, Pantalos GM, Dowling RD, Litwak KN. Development and early testing of a simple subcutaneous counterpulsation device. *ASAIO J* 2006; **52**: 362-367 [PMID: 16883113]
 - 30 **Mitnovetski S**, Almeida AA, Barr A, Peters WS, Milsom FP, Ho B, Smith JA. Extra-aortic implantable counterpulsation pump in chronic heart failure. *Ann Thorac Surg* 2008; **85**: 2122-2125 [PMID: 18498839 DOI: 10.1016/j.athoracsur.2007.12.049]
 - 31 **Scheidt S**, Wilner G, Mueller H, Summers D, Lesch M, Wolff G, Krakauer J, Rubenfire M, Fleming P, Noon G, Oldham N, Killip T, Kantrowitz A. Intra-aortic balloon counterpulsation in cardiogenic shock. Report of a co-operative clinical trial. *N Engl J Med* 1973; **288**: 979-984 [PMID: 4696253]
 - 32 **Urschel CW**, Eber L, Forrester J, Matloff J, Carpenter R, Sonnenblick E. Alteration of mechanical performance of the ventricle by intraaortic balloon counterpulsation. *Am J Cardiol* 1970; **25**: 546-551 [PMID: 5441342]
 - 33 **Kern MJ**, Aguirre FV, Tatineni S, Penick D, Serota H, Donohue T, Walter K. Enhanced coronary blood flow velocity during intraaortic balloon counterpulsation in critically ill patients. *J Am Coll Cardiol* 1993; **21**: 359-368 [PMID: 8425999]
 - 34 **Malliaras K**, Charitos E, Diakos N, Pozios I, Papalois A, Terrovitis J, Nanas J. Effects of intra-aortic balloon pump counterpulsation on left ventricular mechanoenergetics in a porcine model of acute ischemic heart failure. *J Cardiovasc Transl Res* 2014; **7**: 810-820 [PMID: 25376149 DOI: 10.1007/s12265-014-9600-6]
 - 35 **Bonios MJ**, Pierrakos CN, Argiriou M, Dalianis A, Terrovitis JV, Dolou P, Drakos SG, Koudoumas D, Charitos CE, Anastasiou-Nana MI. Increase in coronary blood flow by intra-aortic balloon counterpulsation in a porcine model of myocardial reperfusion. *Int J Cardiol* 2010; **138**: 253-260 [PMID: 18805599 DOI: 10.1016/j.ijcard.2008.08.015]
 - 36 **Solanki P**. Aortic counterpulsation: C-pulse and other devices for cardiac support. *J Cardiovasc Transl Res* 2014; **7**: 292-300 [PMID: 24554288 DOI: 10.1007/s12265-014-9548-6]
 - 37 **Weber KT**, Janicki JS. Intraaortic balloon counterpulsation. A review of physiological principles, clinical results, and device safety. *Ann Thorac Surg* 1974; **17**: 602-636 [PMID: 4601521]
 - 38 **Thiele H**, Allam B, Chatellier G, Schuler G, Lafont A. Shock in acute myocardial infarction: the Cape Horn for trials? *Eur Heart J* 2010; **31**: 1828-1835 [PMID: 20610640 DOI: 10.1093/eurheartj/ehq220]
 - 39 **Antman EM**, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004; **44**: 671-719 [PMID: 15358045]
 - 40 **Van de Werf F**, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A,

- Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; **29**: 2909-2945 [PMID: 19004841]
- 41 **Thiele H**, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebel H, Schneider S, Schuler G, Werdan K. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012; **367**: 1287-1296 [PMID: 22920912 DOI: 10.1056/NEJMoa1208410]
- 42 **Thiele H**, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Böhm M, Ebel H, Schneider S, Werdan K, Schuler G. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* 2013; **382**: 1638-1645 [PMID: 24011548 DOI: 10.1016/S0140-6736(13)61783-3]
- 43 **Perera D**, Lumley M, Pijls N, Patel MR. Intra-aortic balloon pump trials: questions, answers, and unresolved issues. *Circ Cardiovasc Interv* 2013; **6**: 317-321 [PMID: 23780295]
- 44 **Kapelijs CJ**, Terrovitis JV, Nanas JN. Current and future applications of the intra-aortic balloon pump. *Curr Opin Cardiol* 2014; **29**: 258-265 [PMID: 24686399]
- 45 **Abdel-Wahab M**, Saad M, Kynast J, Geist V, Sherif MA, Richardt G, Toelg R. Comparison of hospital mortality with intra-aortic balloon counterpulsation insertion before versus after primary percutaneous coronary intervention for cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol* 2010; **105**: 967-971 [PMID: 20346314 DOI: 10.1016/j.amjcard.2009.11.021]
- 46 **Anderson RD**, Ohman EM, Holmes DR, Col I, Stebbins AL, Bates ER, Stomel RJ, Granger CB, Topol EJ, Califf RM. Use of intraaortic balloon counterpulsation in patients presenting with cardiogenic shock: observations from the GUSTO-I Study. Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. *J Am Coll Cardiol* 1997; **30**: 708-715 [PMID: 9283530]
- 47 **O'Gara PT**, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **61**: e78-140 [PMID: 23256914]
- 48 **Kolh P**, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol Ç, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Sousa Uva M, Achenbach S, Pepper J, Anyanwu A, Badimon L, Bauersachs J, Baumbach A, Beygui F, Bonaros N, De Carlo M, Deaton C, Dobrev D, Dunning J, Eeckhout E, Gielen S, Hasdai D, Kirchhof P, Luckraz H, Mahrholdt H, Montalescot G, Paparella D, Rastan AJ, Sanmartin M, Sergeant P, Silber S, Tamargo J, ten Berg J, Thiele H, van Geuns RJ, Wagner HO, Wassmann S, Wendler O, Zamorano JL. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur J Cardiothorac Surg* 2014; **46**: 517-592 [PMID: 25173601]
- 49 **Lenneman AJ**, Birks EJ. Treatment strategies for myocardial recovery in heart failure. *Curr Treat Options Cardiovasc Med* 2014; **16**: 287 [PMID: 24492922]
- 50 **Krabatsch T**, Schweiger M, Dandel M, Stepanenko A, Drews T, Potapov E, Pasic M, Weng YG, Huebler M, Hetzer R. Is bridge to recovery more likely with pulsatile left ventricular assist devices than with nonpulsatile-flow systems? *Ann Thorac Surg* 2011; **91**: 1335-1340 [PMID: 21444064]
- 51 **Scholz KH**, Ragab S, von zur Mühlen F, Schröder T, Werner GS, Mindel L, Kreuzer H. Complications of intra-aortic balloon counterpulsation. The role of catheter size and duration of support in a multivariate analysis of risk. *Eur Heart J* 1998; **19**: 458-465 [PMID: 9568450]
- 52 **Gjesdal O**, Gude E, Arora S, Leivestad T, Andreassen AK, Gullestad L, Aaberge L, Brunvand H, Edvardsen T, Geiran OR, Simonsen S. Intra-aortic balloon counterpulsation as a bridge to heart transplantation does not impair long-term survival. *Eur J Heart Fail* 2009; **11**: 709-714 [PMID: 19515719]
- 53 **Cochran RP**, Starkey TD, Panos AL, Kunzelman KS. Ambulatory intraaortic balloon pump use as bridge to heart transplant. *Ann Thorac Surg* 2002; **74**: 746-751; discussion 751-752 [PMID: 12238834]
- 54 **Russo MJ**, Jeevanandam V, Stepney J, Merlo A, Johnson EM, Malyala R, Raman J. Intra-aortic balloon pump inserted through the subclavian artery: A minimally invasive approach to mechanical support in the ambulatory end-stage heart failure patient. *J Thorac Cardiovasc Surg* 2012; **144**: 951-955 [PMID: 22520721 DOI: 10.1016/j.jtcvs.2012.03.007]
- 55 **Estep JD**, Cordero-Reyes AM, Bhimaraj A, Trachtenberg B, Khalil N, Loebe M, Bruckner B, Orrego CM, Bismuth J, Kleiman NS, Torre-Amione G. Percutaneous placement of an intra-aortic balloon pump in the left axillary/subclavian position provides safe, ambulatory long-term support as bridge to heart transplantation. *JACC Heart Fail* 2013; **1**: 382-388 [PMID: 24621970 DOI: 10.1016/j.jchf.2013.06.002]
- 56 **Terrovitis J**, Ntalianis A, Kaldara E, Kanakakis J, Siskas P, Bonios M, Katsaros L, Vakrou S, Kontogiannis D, Nanas J. The role of prolonged mechanical support with counterpulsation in patients with idiopathic dilated cardiomyopathy and advanced stage heart failure. *Eur J Heart Fail Suppl* 2012; **11** (suppl 1): S87
- 57 **Tanaka A**, Tuladhar SM, Onsager D, Asfaw Z, Ota T, Juricek C, Lahart M, Lonchyna VA, Kim G, Fedson S, Sayer G, Uriel N, Jeevanandam V. The Subclavian Intraaortic Balloon Pump: A Compelling Bridge Device for Advanced Heart Failure. *Ann Thorac Surg* 2015; **100**: 2151-2158 [PMID: 26228596]
- 58 **Ntalianis A**, Kapelijs CJ, Kanakakis J, Repasos E, Pantsios C, Nana E, Kontogiannis C, Malliaras K, Tsamatsoulis M, Kaldara E, Charitos C, Nanas JN. Prolonged intra-aortic balloon pump support in biventricular heart failure induces right ventricular reverse remodeling. *Int J Cardiol* 2015; **192**: 3-8 [PMID: 25981570]
- 59 **Mathews JC**, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. *J Am Coll Cardiol* 2008; **51**: 2163-2172 [PMID: 18510965]
- 60 **Kavarana MN**, Pessin-Minsley MS, Urtecho J, Catanese KA, Flannery M, Oz MC, Naka Y. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. *Ann Thorac Surg* 2002; **73**: 745-750 [PMID: 11899176]
- 61 **Kirklin JK**, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Baldwin JT, Young JB. The Fourth INTERMACS Annual Report: 4,000 implants and counting. *J Heart Lung Transplant* 2012; **31**: 117-126 [PMID: 22305376 DOI: 10.1016/j.healun.2011.12.001]
- 62 **Wilcox JE**, Fonarow GC, Ardehali H, Bonow RO, Butler J, Sauer AJ, Epstein SE, Khan SS, Kim RJ, Sabbah HN, Diez J, Gheorghiadu M. "Targeting the Heart" in Heart Failure: Myocardial Recovery in Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail* 2015; **3**: 661-669 [PMID: 26362444]

- 63 **Hayward CS**, Peters WS, Merry AF, Ruygrok PN, Jansz P, O' Driscoll G, Larbalestier RI, Smith JA, Ho B, Legget ME, Milsom FP. Chronic extra-aortic balloon counterpulsation: first-in-human pilot study in end-stage heart failure. *J Heart Lung Transplant* 2010; **29**: 1427-1432 [PMID: 20817566 DOI: 10.1016/j.healun.2010.06.014]
- 64 **Abraham WT**, Aggarwal S, Prabhu SD, Cecere R, Pamboukian SV, Bank AJ, Sun B, Pae WE, Hayward CS, McCarthy PM, Peters WS, Verta P, Slaughter MS. Ambulatory extra-aortic counterpulsation in patients with moderate to severe chronic heart failure. *JACC Heart Fail* 2014; **2**: 526-533 [PMID: 25301151 DOI: 10.1016/j.jchf.2014.04.014]
- 65 **Giridharan GA**, Bartoli CR, Spence PA, Dowling RD, Koenig SC. Counterpulsation with symphony prevents retrograde carotid, aortic, and coronary flows observed with intra-aortic balloon pump support. *Artif Organs* 2012; **36**: 600-606 [PMID: 22591355]
- 66 **Cecere R**, Dowling RD, Giannetti N. Initial clinical experience with the Symphony heart assist system. *Ann Thorac Surg* 2015; **99**: 298-301 [PMID: 25555946 DOI: 10.1016/j.athoracsur.2014.07.094]
- 67 **Nanas JN**, Nanas SN, Charitos CE, Poyiadjis AD, Kontoyannis D, Melkaoui A, Kokolis G, Mouloupoulos SD. Effectiveness of a counterpulsation device implanted on the ascending aorta. *ASAIO Trans* 1987; **33**: 203-206 [PMID: 3675945]
- 68 **Nanas JN**, Nanas SN, Charitos CE, Kontoyannis D, Poyiadjis AD, Stamatopoulos G, Melkaoui A, Kokolis G, Mouloupoulos SD. Hemodynamic effects of a counterpulsation device implanted on the ascending aorta in severe cardiogenic shock. *ASAIO Trans* 1988; **34**: 229-234 [PMID: 3196512]
- 69 **Terrovitis JV**, Charitos CE, Tsolakis EJ, Dolou P, Pierrakos CN, Siafakas KX, Nanas JN. Superior performance of a paraaortic counterpulsation device compared to the intraaortic balloon pump. *World J Surg* 2003; **27**: 1311-1316 [PMID: 14586569]
- 70 **Marinakis S**, Nanas Y, Sarchosi S, Kontogiannis C, Kapelios C, Tachliabouris G, Charitos C, Nanas J, Malliaras K. A novel implantable counterpulsation assist device, the PULVAD, induced superior left ventricular pressure unloading compared to the intra-aortic balloon pump in a bovine model of acute heart failure. *Eur J Heart Fail* 2015; **17** (Suppl 1): 196
- 71 **Kapelios C**, Kontogiannis C, Nanas Y, Aravantinos D, Vlaras E, Tachliabouris I, Marinakis S, Charitos C, Nanas JN, Malliaras K. Profound pressure unloading induced by a novel implantable counterpulsation assist device in a porcine model of acute heart failure. *Eur J Heart Fail* 2015; **17** (Suppl 1): 120
- 72 **Kinoshita M**, Takano H, Takaichi S, Taenaka Y, Nakatani T. Influence of prolonged ventricular assistance on myocardial histopathology in intact heart. *Ann Thorac Surg* 1996; **61**: 640-645 [PMID: 8572780]
- 73 **Kinoshita M**, Takano H, Taenaka Y, Mori H, Takaichi S, Noda H, Tatsumi E, Yagura A, Sekii H, Akutsu T. Cardiac disuse atrophy during LVAD pumping. *ASAIO Trans* 1988; **34**: 208-212 [PMID: 3196510]
- 74 **Drakos SG**, Kfoury AG, Hammond EH, Reid BB, Revelo MP, Rasmusson BY, Whitehead KJ, Salama ME, Selzman CH, Stehlik J, Clayson SE, Bristow MR, Renlund DG, Li DY. Impact of mechanical unloading on microvasculature and associated central remodeling features of the failing human heart. *J Am Coll Cardiol* 2010; **56**: 382-391 [PMID: 20650360 DOI: 10.1016/j.jacc.2010.04.019]
- 75 **Birks EJ**, George RS, Hedger M, Bahrami T, Wilton P, Bowles CT, Webb C, Bougard R, Amrani M, Yacoub MH, Dreyfus G, Khaghani A. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. *Circulation* 2011; **123**: 381-390 [PMID: 21242487]

P- Reviewer: Grignola JC, Iacoviello M, Lazzeri C, Peteiro J

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wang CH





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

