Partial Mechanical Long-Term Support with the CircuLite® Synergy® Pump as Bridge-to-Transplant in Congestive Heart Failure

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Key words
- assist device
- partial support
- new technologies
- end-stage heart failure
- heart transplantation

Abstract

Background: Full mechanical support with a left ventricular assist device (LVAD) is often limited to very sick patients, as the only survival option. This European multicenter study analyzes the effect of partial mechanical support as bridge-to-transplant in a less sick heart failure patient group.

Methods: The CircuLite® Synergy® device is implanted via a small right-sided thoracotomy with an inflow cannula in the left atrium and an outflow graft connected to the right subclavian artery without the use of extracorporeal circulation. The pump itself sits in a "pacemaker" pocket subcutaneously in the right clavicular groove. It is able to pump up to 3.0 l/min and partially unload the left ventricle.

Results: The device was implanted in 25 patients on the cardiac transplant waiting list (20 males), aged 55.5 ± 9.6 yrs with an ejection fraction of 21.6 ± 6.0%, a mean arterial pressure of 73.5 ± 8.5 mmHg, a pulmonary capillary wedge pressure of 27.2 ± 7.8 mmHg and cardiac index of 1.9 ± 0.4 l/min/m^2. Duration of support ranged from 6 to 238 days. Right heart catheterization showed significant hemodynamic improvement in the short- and intermediate-term after implantation with increases in arterial pressure from 72.6 ± 11.0 to 79.4 ± 8.6 mmHg ($p = 0.04$) and in cardiac index from 2.0 ± 0.4 to 2.7 ± 0.6 l/min/m^2 ($p = 0.003$) with a reduction in pulmonary capillary wedge pressure from 28.5 ± 6.0 to 19.7 ± 6.9 mmHg ($p = 0.012$).

Conclusions: The CircuLite Synergy device is a partial support pump, which is easy to implant and which provides hemodynamic benefits in bridging heart failure patients to cardiac transplant.

Introduction

The growing incidence of end-stage heart failure has resulted in an increased demand for donor organs for transplantation. However, data from the European Transplant Organization (Eurotransplant International, Leiden, The Netherlands) show an increasing shortage of organ donors [1]. As a result, it is mainly the critically ill patients with a "high-urgency" status who have a chance to receive a heart transplant [2]. Overall, waiting times for cardiac transplant exceed 2 to 3 years for patients with the blood groups A or 0. Because of the severity of their underlying disease [3–5], mortality among patients on the cardiac transplant waiting list is around 30%, which is the highest for solid organ transplant candidates [1]. If a patient is decompensating on the transplant waiting list and is not accorded high-urgency status, or if the rate of decompensation is rapid, the only option is implantation of a mechanical assist device [6]. However, this patient population is critically ill and candidate selection is of the utmost importance for a successful outcome [7–9].

We recently showed, through computer simulation, the potential beneficial effects of partial mechanical support in a slightly less sick heart failure population [10]. In particular, we proposed that implantation of a smaller device with less invasive surgical techniques could be a tool to reduce mortality and recurrent decompensations while on the waiting list. After large-scale animal experiments, the first implant of the Synergy CircuLite® partial support pump was performed in March 2007 in Leuven, Belgium [11]. The present publication summarizes the current status of the European multicenter CircuLite® Synergy® partial support study.

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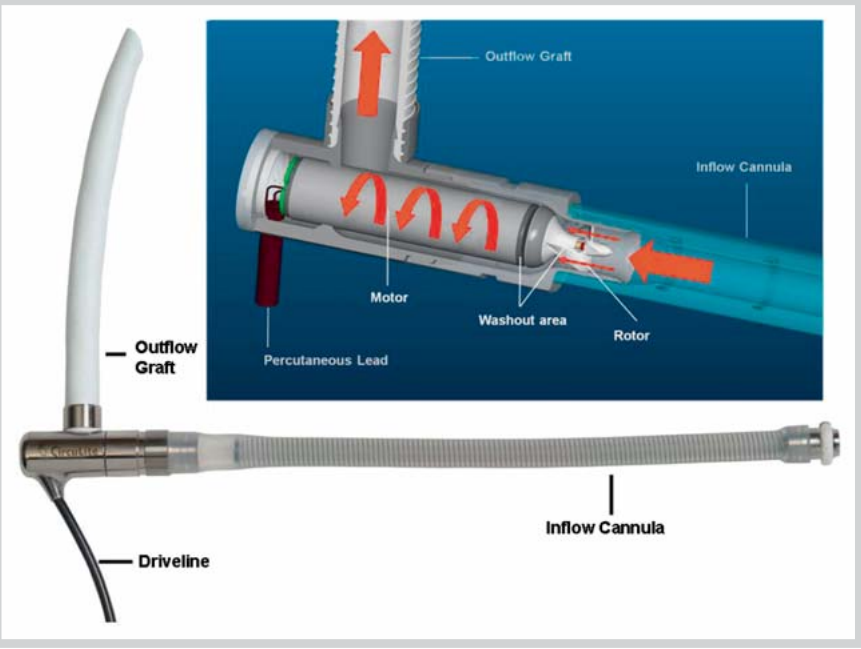

Fig. 1 The CircuLite device with inflow and outflow graft and a cross-section of the micro-pump (see text for details).

Patients and Methods

The CircuLite Synergy partial support trial is a European multicenter study performed in the Departments of Cardiac Surgery at the University of Leuven, Belgium; the University of Hannover, Germany; the University of Muenster, Germany; the University of Cologne, Germany; and the University of Freiburg, Germany. These centers were chosen because of their overall experience with mechanical support and heart transplantation.

Patients were included in this study according to the following criteria: age between 18 and 70 years; on the cardiac transplant waiting list with a predicted waiting time > 6 months; in New York Heart Association Class (NYHA) III B or IV A despite appropriate treatment with diuretics, angiotensin converting enzyme inhibitor or angiotensin receptor blockade and β-blocker as tolerated; ambulatory; not inotropic dependent and with limitations in the activities of daily living. The latter was ascertained using the University of Minnesota Living with Heart Failure and by the SF-36 Health Survey Questionnaires. Exclusion criteria included acute decompensated heart failure, acute post-cardiotomy heart failure, existing thrombus in the left atrium, mechanical mitral or aortic valve, significant aortic regurgitation, severe depressed renal function (creatinine > 2.5 mg/dl or BUN > 80 mg/dl), elevated liver enzymes ≥ 2 times the upper limit of normal, and contraindications to anticoagulation.

A preoperative heart failure assessment including application of a questionnaire, blood chemistry evaluation, right heart catheterization, transthoracic echocardiography and spiroergometry were performed in each potential study patient. These data were presented to an independent clinical review committee (CRC) composed of two heart failure surgeons and one heart failure cardiologist. The purpose of the CRC was to ensure that the baseline data were complete, that the patient was not "too sick" to potentially derive a clinical benefit from ~ 3.0 l/min and that there were no unforeseen contraindications to implantation.

Statistics

Descriptive statistics are used to summarize the data, with results expressed as means with standard deviations, unless otherwise noted. Comparison of data between time points was made with paired *t*-tests. SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis.

This study was conducted in accordance with the Declaration of Helsinki and approval was given by the local institutional human research and ethics committee.

The CircuLite Synergy pump

The pump combines axial, centrifugal and orthogonal flow paths with a single-stage impeller that is powered by an integrated brushless micro-electric motor (**Fig. 1**). The pump is the size of an AA battery with an outer body diameter of 14 mm and a length of 49 mm. It weights 25 g. The pump design features a unique magnetically stabilized, hydrodynamically levitated rotor design. The design allows the motor to be sealed thus eliminating blood contact in the motor. The pump also features a self-washing flow path intended to reduce the risk of thrombus formation in or around the rotor. The rotor spins with 20 000 to 28 000 rpm and, depending on the afterload, is able to pump up to 3 liters of blood per minute. The inflow cannula is made of silicon reinforced with nitinol with a length of 20.5 cm and an inner diameter of 6 mm. It has a Dacron cuff on the tip made of titanium. The inflow cannula is easily connected to the pump during surgery. The outflow graft is a 1 mm thick polytetrafluoroethylene (PTFE) prosthesis with an inner diameter of 8 mm and a length of 15 cm. It has a fixed connection to the pump and can be sized according to the desired length. The drive line has a length of 100 cm with a diameter of 3.2 mm. At 32 cm there is a 16 cm Dacron reinforcement at the exit site in the right abdominal area to limit drive line infections. The drive line connects the pump to a rechargeable dual battery pack system and controller. The power system weighs approximately 1.5 kg and the dual battery pack will power the system for approximately 16 to 18 hours. The control-

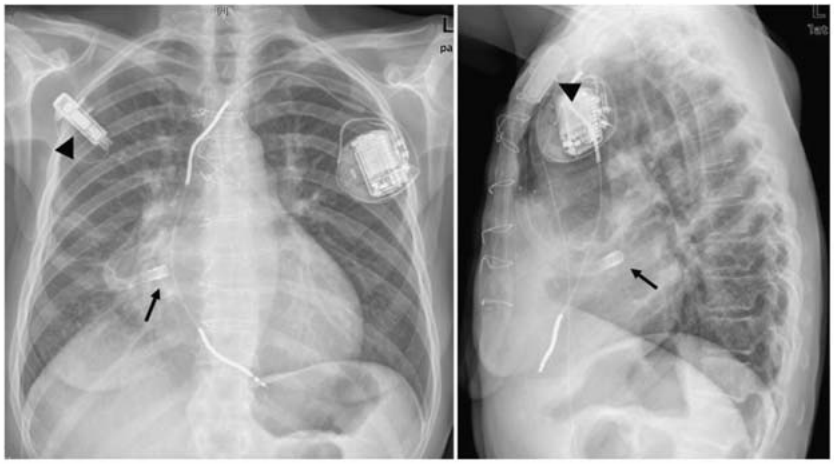

Fig. 2 Female patient with ischemic cardiomyopathy and previous coronary artery bypass grafting with the implanted CircuLite Synergy device (arrowhead) and the inflow cannula in the left atrium (arrow). The outflow graft is not made of radiopaque material.

ler provides the patient with information on the battery status and alerts the patient to any change that needs attention.

Surgical procedure

Surgical procedures were performed at the University Hospitals in Leuven, Belgium (n = 13); Hannover, Germany (n = 6); Muenster, Germany (n = 4); Cologne, Germany (n = 1) and Freiburg, Germany (n = 1). After induction of anesthesia with standard, nonselective tracheal intubation or with a selective Robertshaw tube, cannulation of the left radial artery with a central venous line and Swan-Ganz implantation were performed. The patient is placed in a supine position with a pillow under the right side of the chest. After a 4-cm subclavicular incision the right subclavian artery is isolated. If the subclavian artery has a normal diameter without any signs of calcifications, a subcutaneous pocket is formed anterior to the right pectoralis muscle similar to a pacemaker pocket. Thereafter, a 10-cm anterolateral thoracotomy in the 4th right intercostal space is performed. The pericardium is opened with respect to the phrenic nerve and after full heparinization two 4–0 polypropylene (Prolene, Johnson & Johnson Medical GmbH, Norderstedt, Germany) purse-string sutures are placed in the left atrium between the insertions of the right upper and lower pulmonary veins. After insertion of a guidewire and confirmation of the position in the left atrium with transesophageal echocardiography, the nitinol-reinforced silicon inflow cannula is inserted on a trocar over the guidewire using the Seldinger technique and secured with the two purse-string sutures. The proximal end of the inflow cannula is tunnelled through the 2nd intercostal space to exit the thorax in the area of the subcutaneous pocket. The CircuLite pump is then tested and the PTFE outflow graft is sized to the right length and anastomosed to the subclavian artery. The driveline of the pump is then tunnelled to exit the body over the right upper quadrant of the abdomen. The pump is deaired retrograde via the subclavian artery and the inflow cannula is connected to the pump. Thereafter the pump is turned on and the speed is increased slowly from 20 000 to around 26 000 rpm while cardiac output, pulmonary artery pressure and arterial pressure are measured continuously. The final speed is generally set at the level at which no further increase in cardiac output and no further decrease in pulmonary artery wedge pressure is observed. After implanting a chest tube, the wound is closed in layers. **Fig. 2** shows an X-ray of a patient with an implanted CircuLite device.

After surgery, patients are taken to the intensive care unit and generally extubated within the next 4 hours. Normally the patient is kept in the intensive care unit until the Swan-Ganz catheter is removed 2 days after the procedure according to the study protocol. Thereafter the patient is brought to the regular medical ward, ambulated and physical therapy is initiated.

Surgical procedures generally took 90 to 120 min. A previous cardiac operation is not a contraindication for performing this procedure. The median duration of intensive care unit stay was 4 days. After appropriate training of patients and family members on how to change batteries and how to deal with potential controller alarms, patients are discharged home. Hospital stays lasted a median of 17 days.

Patients were anticoagulated with aspirin (100 mg/day) and warfarin. The initial international normalized ratio (INR) target is 2.5 to 3.0.

Clinical Results

Patient characteristics

The basic patient characteristics of the first 25 patients recruited are summarized in **Table 1**. Mainly male patients with ischemic cardiomyopathy were recruited. 39.1% had prior cardiac operations with sternotomy (8 coronary artery bypass grafting (CABG), 1 CABG plus aortic valve replacement, 1 Dor procedure). Almost half of the patients were in permanent atrial fibrillation and more than two-thirds of the study group had an implantable cardioverter defibrillator. Medication use was appropriate for end-stage heart failure. Hemodynamic and echocardiographic baseline parameters confirmed an end-stage heart failure population with reasonably well preserved end-organ function (**Table 1**).

Acute and chronic effects for partial mechanical support

At 24 hours after surgery estimated pump flow was 2.97 ± 0.39 l/min with a range between 2.3 and 3.5 l/min. With this additional pump output, immediate hemodynamic improvements were noted in an increase of the total cardiac index (from 1.9 ± 0.4 to 3.5 ± 1.1 l/min/m², $p < 0.001$), and a decrease of pulmonary systolic pressure (from 55 ± 15 to 48 ± 15 mmHg, $p = 0.035$) and pulmonary diastolic pressure (from 26 ± 9 to 19 ± 7 mmHg, $p < 0.001$) at 24 hours postoperatively. At an average follow-up of 10 ± 5.4

Table 1 Patient demographics and baseline functional data (n = 25).

Age (years)	55.0 ± 9.6
BMI (kg/m²)	25.8 ± 3.5
Male gender	20 (80%)
ICM	20 (80%)
Prior sternotomy	10 (40%)
Atrial fibrillation	12 (48%)
ICD	17 (68%)
Peak VO_2max (ml/kg/min)	9.7 ± 2.4
Medication	
▸ diuretics	25 (100%)
▸ β-blocker	19 (76%)
▸ ACE Inhibitor	17 (68%)
▸ ARB	5 (20%)
▸ aldactone	18 (72%)
▸ aspirin	11 (44%)
▸ warfarin	4 (16%)
▸ statin	12 (48%)
▸ inotropes	2 (8%)
Hemodynamics	
▸ MAP (mmHg)	73.5 ± 8.5
▸ CVP (mmHg)	13.1 ± 4.6
▸ PAPm (mmHg)	37.2 ± 9.4
▸ PCWP (mmHg)	27.2 ± 7.8
▸ CO (l/min)	3.8 ± 0.8
▸ CI (l/min/m²)	1.9 ± 0.4
Echocardiography	
▸ EF (%)	21.6 ± 6.0
▸ LVEDD (cm)	6.9 ± 0.8
▸ MR (grade)	1.6 ± 0.7
Laboratory values	
▸ NT-proBNP (pg/ml)	6452 ± 5470
▸ creatinine (mg/dl)	1.4 ± 0.5
▸ total bilirubin (mg/dl)	0.9 ± 0.6
▸ AST (U/l)	29 ± 13
▸ ALT (U/l)	38 ± 23

BMI, body mass index; ICM, ischemic cardiomyopathy; ICD, implantable cardioverter defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MAP, mean arterial pressure; CVP, central venous pressure; PAPm, mean pulmonal arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; MR, mitral regurgitation; BNP, brain natriuretic peptide; AST, aspartate aminotransferase; ALT, alanine aminotransferase

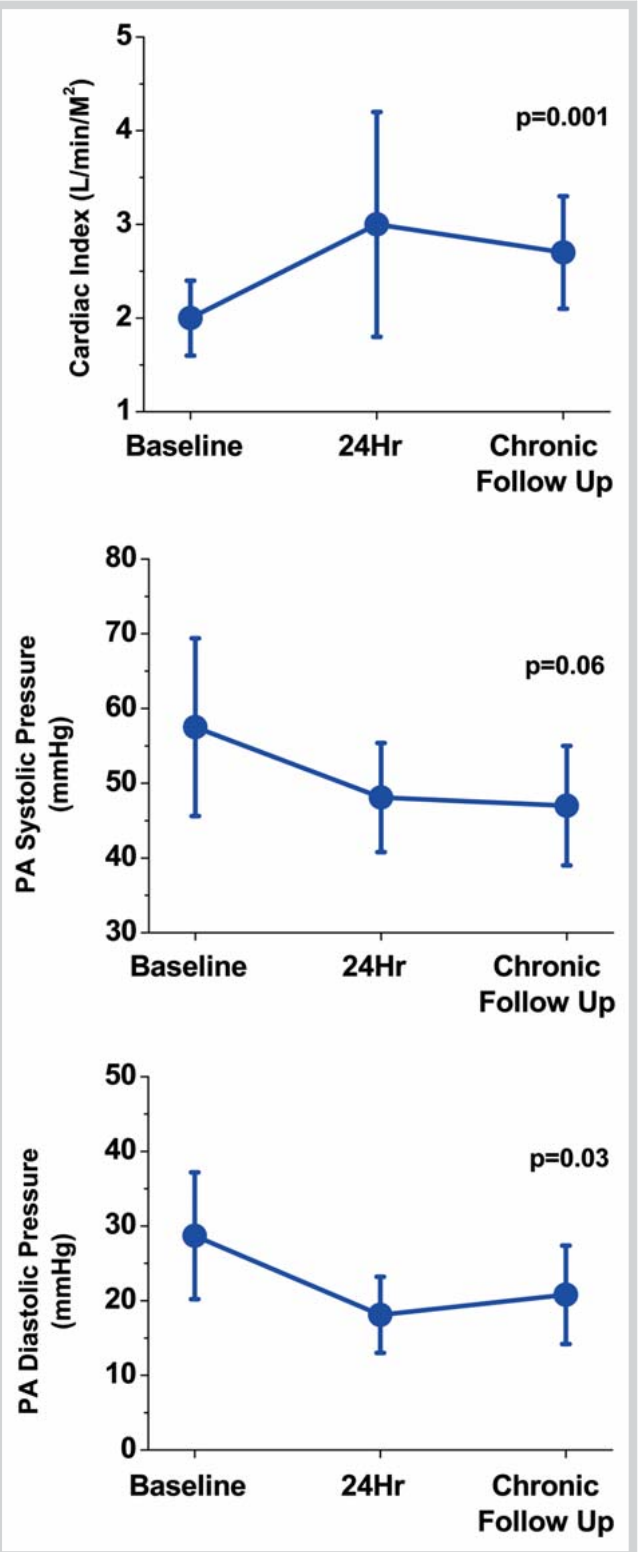

Fig. 3 A significant increase in cardiac index and decrease in pulmonary capillary wedge pressure after 24 hours of support with the CircuLite device, both of which were maintained in the long-term follow-up after an average of 10 weeks.

weeks, data available from 10 patients showed sustained improvements in all of these parameters (**Fig. 3**).

At one month of partial support (for patients for whom data were available) NT-proBNP was significantly reduced from a baseline value of 6452 ± 5470 to 3209 ± 2379 pg/nl ($p = 0.05$, n = 10). In addition, exercise testing showed a significant increase in the 6-minute walk test (227 ± 154 vs. 475 ± 96 m, $p = 0.012$, n = 6) and an increase in VO_2max (9.3 ± 2.1 vs. 11.5 ± 4.0 ml/kg/min, $p = 0.075$, n = 8). Renal function measured by creatinine was maintained and even trended towards improvement (1.4 ± 0.5 vs. 1.1 ± 0.4 mg/l, $p = 0.07$, n = 14).

Outcomes

The total experience includes 6.7 patient-years of support. Of the 25 patients, 10 patients (40%) were successfully bridged to transplantation after an average support duration of 89 ± 64 days (median 93 days, range 27–213 days). Currently 8 patients are ongoing with an average support duration of 127 ± 76 days (range 17–238 days). Devices were explanted from four patients (one on POD 7 for HIT who was transitioned to a biventricular VAD, one after 189 days due to liver failure who was transitioned to a full support VAD, one after 122 days of support for fatigue, and

one following a stroke on POD 16). Three patients died on support (one due to sepsis on POD 70 following the 1-month protocol-specified right heart catheterization, one due to stroke during a procedure to exchange a clotted pump in a patient who was noncompliant with the anticoagulation medication on POD 167 and one due to sepsis secondary to an undiagnosed renal abscess on POD 6).

Adverse events

In 7 of the first 10 patients the CircuLite device had to be exchanged due to pump thrombosis with pump stoppage. The pump thrombosis occurred after an average support duration of 42 ± 20 days. The exchange procedure is relatively simple and can be performed with just an incision at the subclavicular pump pocket. The inflow cannula is deconnected from the device. The PTFE outflow graft is then clamped and cut. After flushing both grafts and ensuring that both are free of thrombotic material, the new pump is placed in the old subcutaneous pocket and reconnected with the inflow graft. The new PTFE outflow graft is anastomized with a 5–0 or 4–0 prolene running suture to the old outflow graft as a graft-to-graft anastomosis. The device exchange procedure lasts approximately 45 minutes. The thrombotic material usually sits in the impeller area in front of the motor housing. Due to the small space for the blood stream between motor housing and device housing it is unlikely that thrombus material can leave the pump. As noted above, of the 8 patients with device thrombosis, one had a stroke. However, this particular patient consciously stopped his anticoagulation medication and came to the hospital one week after device thrombosis. Due to pump thromboses in the initial phase the design of the rotor was changed with a larger wash-out channel. Eighteen of these new pumps have been implanted and, in these patients, thrombus caused pump stoppage in 4 patients: 1 in a patient with HIT, 2 in patients in whom chest CT showed the inflow cannula to be in a suboptimal position (**Fig. 4A** and **B**), and one in a patient after 227 days of support. In addition, two patients had to be brought back to the OR for replacement of the system when it was discovered that the tip of the inflow cannula was not inside the left atrium and there was no flow through the system (**Fig. 4C**).

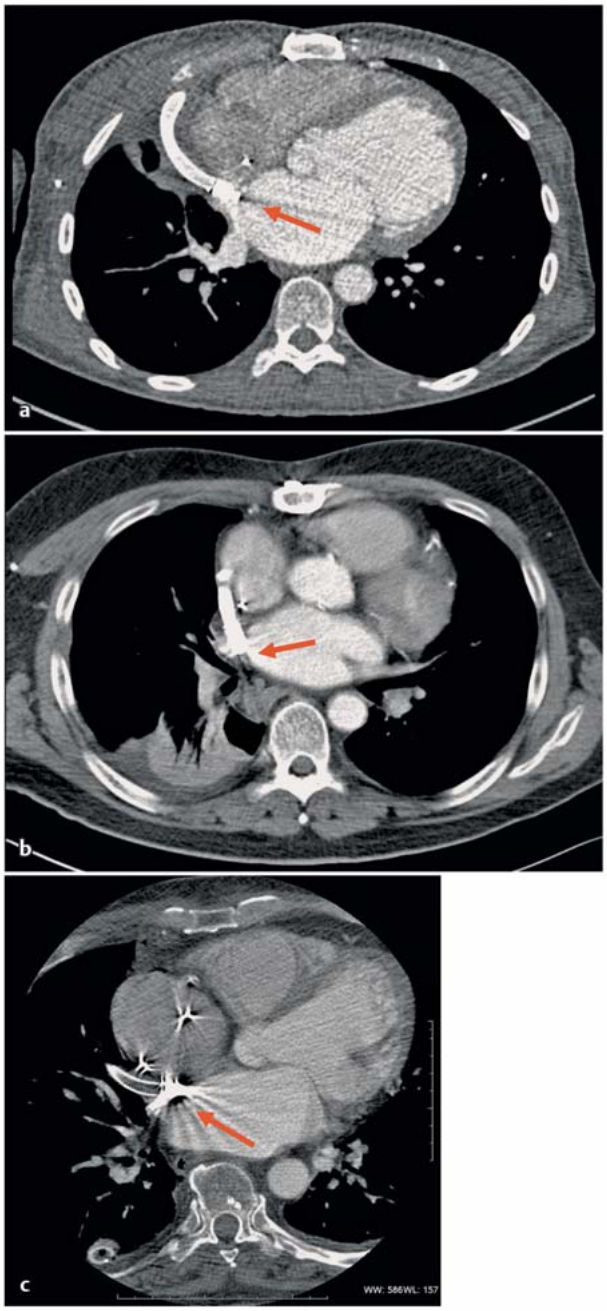

Fig. 4a to **c** Chest CT of a patient in whom the inflow cannula tip is positioned appropriately so that there is unobstructed flow from the atrium (**a**). Chest CT of a patient in whom the inflow cannula was inserted such that the tip was pointing to the wall of the pulmonary vein, impeding inflow (**b**). Chest CT of a patient in whom the inflow cannula was outside the left atrium so there was no flow going through the device (**c**). Arrows point towards the tip of the inflow cannula.

Discussion

With increasing waiting times for cardiac transplantation and changes in the allocation process of the European Transplant Organization (Eurotransplant International Foundation, Leiden, The Netherlands), heart transplants will only be available to the sickest patients [12]. At least in Germany, only patients who are inotrope dependent or have complications during mechanical assist device support have a chance to get a heart within a relatively short time [2,6]. Accordingly, the time frame to bridge patients with optimized medical therapy, including resynchronization therapy, to heart transplantation is relatively long.

Partial mechanical support could be a useful tool in this setting. With a relatively short operation not requiring a heart-lung machine and without a sternotomy, implantation of such a device is an attractive option. Nearly half of the patients had had prior cardiac operations and implantation of the CircuLite device in this patient group was not problematic. Heart failure patients who are ambulatory, but with low activities of daily living and waiting times of more than a year, could profit most from such a strategy. In addition, because implantation of the CircuLite© device involves a right-sided thoracotomy, no adhesions develop to complicate the sternotomy needed for cardiac transplantation.

The present European multicenter study is still ongoing. Nevertheless, we showed that partial mechanical support with the CircuLite Synergy device is a feasible option for this patient group. With a hospital stay of less than 3 weeks we could significantly improve hemodynamics and exercise tolerance. Even in patients

with previous cardiac operations, implantation of the device and inflow cannula was generally uncomplicated. Nevertheless, as a greater number of surgeons gain experience in a greater number of patients with different body sizes and shapes, significant variability in system implant anatomy (e.g., location of pump, course of inflow and outflow cannulae) has been noted. It is clear that in several cases, "inappropriate" positioning of either the inflow or outflow cannula has led to adverse outcomes and a poor pump performance. However, it is only after these prior experiences that we can appreciate the sensitivity of the system's performance to implant anatomy which may help us define "appropriate" and "inappropriate" anatomy.

With the new pump design with its enlarged wash-out channel the initial issues with pump thrombosis have been significantly improved. Future device improvements are planned to incorporate rapid connect/disconnect mechanisms between the pump and the outflow graft and between the pump and the drive line, similar to the already existing easily removable connection between the pump and the inflow graft. With these features a potential pump exchange could conceivably be performed under local anesthetic similar to a pacemaker exchange. Another future application is an even less invasive implantation of this device with a percutaneous inflow graft inserted via the subclavian vein and advanced through the interatrial septum into the left atrium, which would obviate the need for a thoracotomy. In this case only a small subclavian incision would be necessary to implant the whole device system.

Conclusion

▼

Partial mechanical support with the CircuLite Synergy device is a feasible option for heart failure patients on the cardiac transplant waiting list. It appears that less sick patients in NYHA stage III B/IV A with anticipated long waiting times could profit most. With a fast and less invasive operative procedure partial support of up to 3 l/min shows beneficial effects on end-organ function and exercise capacity. After completion of the European multicenter study and obtaining the CE mark, additional indications (e.g., destination therapy) could be considered.

Conflict of interest

Dr. Meyns is consultant to CircuLite Inc., Dr. Burkhoff is an employee of CircuLite Inc.

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