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Clinical Investigation

Improvement in Biventricular Cardiac Function After Ambulatory Counterpulsation

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ABSTRACT

Background: The NupulseCV intravascular ventricular assist system (iVAS), which consists of a durable pump placed through the subclavian artery, provides extended-duration ambulatory counterpulsation. This study investigated the effect of iVAS on biventricular cardiac function.

Methods and Results: We reviewed all heart failure patients who received iVAS implantation as a bridge to transplantation or a bridge to candidacy since April 2016 as part of the iVAS first-in-humans and subsequent feasibility study. We compared data of transthoracic echocardiography performed just before implantation (without iVAS support) and again at 30 days or just before explantation (on iVAS support). Eighteen patients (58.8 ± 7.4 years old and 15 male) received iVAS support for 53 ± 43 days. Fourteen patients were bridged to cardiac replacement therapy after 35 ± 19 days and the remaining 4 patients had been supported for 118 ± 41 days. There were no deaths during iVAS support. At 30 days, there was a significant improvement in left ventricular ejection fraction (16.5% ± 11.9% vs 24.4% ± 12.8%; $P = .007$) and marked reduction in left atrial size (62.7 ± 35.7 mL/m^2 vs 33.8 ± 17.2 mL/m^2; $P < .001$). Right ventricular fractional area change improved dramatically (25.4% ± 12.9% vs 42.1% ± 12.4%; $P < .001$). All other right ventricular and right atrial parameters improved significantly as well (size, tricuspid annular plane systolic excursion, and velocity of tricuspid annular systolic motion).

Conclusions: Improvement in biventricular cardiac function was observed after 30 days of iVAS support. Further studies should examine the use of this technology as a bridge to recovery. (*J Cardiac Fail 2018;00:1−7*)

Key Words: Heart failure, unloading, inotropes, echocardiography.

Survival rates in patients with advanced heart failure (HF) have improved since the development of heart transplantation (HT) and left ventricular assist devices (LVADs).[1,2] However, these treatment modalities are associated with complications that may adversely affect quality of life. Ideally, strategies that encourage recovery of native myocardial function would provide the best long-term solution to chronic HF.

Recently, clinical use of the intra-aortic balloon pump (IABP) has increased in patients with advanced HF, mainly as a bridge to cardiac replacement therapy.[3−6] Theoretically, IABP may be an optimal tool to promote reverse remodeling,[7] owing to its ability to augment left ventricular (LV) unloading without increasing myocardial work.[8−11] Furthermore, IABP has the advantages of a simple implantation and explantation procedure, straightforward management, low cost, and advantageous safety profile.[12] Nevertheless, conventional IABP support requires the patient to stay in the intensive care unit, limits mobility, and is typically short term in nature, making it difficult to determine if it can promote improvement in cardiac function.[13,14]

We recently reported our first-in-human experience with the NupulseCV intravascular ventricular assist system (iVAS),[15] which consists of a durable counterpulsation pump placed through the subclavian artery (Fig. 1). It provides an extended duration of ambulatory counterpulsation outside of the

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intensive care unit or, in select cases, outside of the hospital. The iVAS overcomes the limited support duration of the IABP and may serve as a promising device to improve cardiac function. In the present study, we investigated the improvement in biventricular cardiac function during 30-day iVAS support in patients with advanced HF.

Methods

Patient Selection

In this prospective first-in-humans and subsequent feasibility study, clinical data were collected from patients who received iVAS implantation as a bridge to transplantation or bridge to candidacy. Patients without paired echocardiographic assessments before and during iVAS implantation were excluded. All patients were either listed for cardiac transplantation at United Network for Organ Sharing status 1A, 1B, or potentially transplantable before iVAS implantation.

An aortic diameter >20.0 mm and a subclavian artery diameter >7.0 mm were required to qualify for iVAS implantation. Exclusion criteria included aortic dissection, significant aortic valve regurgitation, uncontrollable arrhythmias, acute coronary syndrome, aortic abnormalities including aneurysm or severe calcification, and active bloodstream infections. Informed consents were obtained from all patients, and the study was approved by the Food and Drug Administration and the local Institutional Review Board.

Devices

The iVAS is an external heart assist device consisting of several components (Fig. 1), as previously described.[15] The intravascular element is a 50-cm^3 displacement pump located in the descending aorta. The skin interface device is an electromechanical and pneumatic conduit with a chimney that allows for shuttling of air between the pump and external driver and for communicating of the captured electrocardiographic signals that are transmitted to the driver from 3 subcutaneous electrodes. An external and wearable drive unit provides compressed ambient air to inflate and deflate the pump.

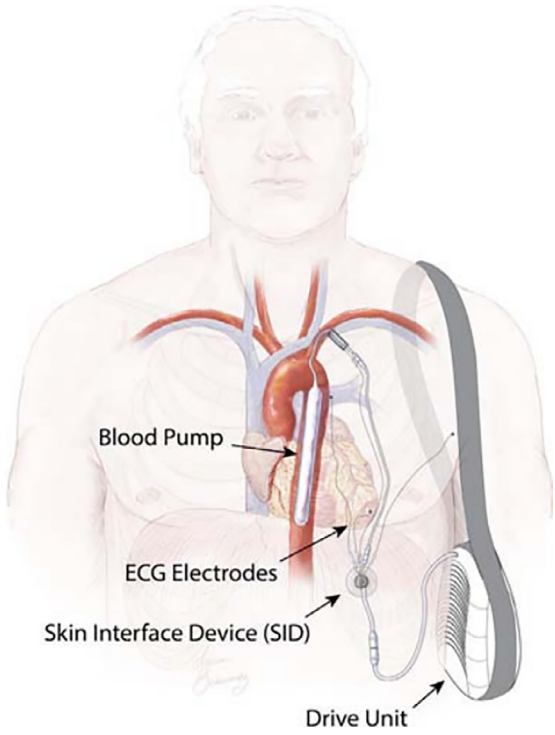

Fig. 1. Scheme of intravascular ventricular assist system.

Variables Evaluated

Baseline characteristics, including invasive hemodynamic, demographic, and laboratory data just before iVAS implantation, were collected. Transthoracic echocardiography was performed within 1 week before iVAS implantation (without iVAS support) following current American Society of Echocardiography guidelines.[16] Repeated echocardiographic studies were performed 30 days after iVAS implantation or just before the iVAS explantation if support was discontinued before 30 days. All echocardiographic data were reviewed by independent readers blinded to the results of this study. Patients without paired echocardiographic studies were excluded. Medication data from the same day as echocardiography were also collected.

Left Ventricular Assessment. Left ventricular ejection fraction (LVEF) was calculated with the use of the biplane modified Simpson methods from 4- and 2-chamber views. Left atrial (LA) volume index (LAVI) was measured by means of he biplane method of disks from the apical 4- and 2-chamber views at end-systolic phase, then corrected according to body surface area. LV end-diastolic septal and posterior wall thicknesses and internal dimensions were used to calculate LV mass with the use of the formula: $1.04 \times 0.8 \times (\text{LV wall thickness} + \text{LV internal dimension} - \text{LV internal dimension}) + 0.6$ g, and LV mass index was calculated according to body surface area.

Pulse-wave Doppler was used to record mitral inflow for 3−5 cardiac cycles at the mitral valve leaflet tips, and the mitral valve peak early diastolic velocity (E) was measured. Tissue Doppler was recorded to measure mitral annular early velocities (e′) at the septal and lateral annulus. E/e′ was calculated with the use of the average of the lateral e′ and septal e′. Valvular regurgitation was assessed with the use of color Doppler and categorized into 5 grades: none, 0; trace, 1; mild, 2; moderate, 3; and severe, 4.

Right Ventricular Assessment. The right heart was assessed according to the guidelines of the American Society of Echocardiography.[17] Right ventricular (RV) end-diastolic and end-systolic areas were traced from the apical 4-chamber RV-focused view including the RV apex, and RV fractional area change (RVFAC) was calculated. The right atrial (RA) area also was traced from the apical 4-chamber view at end-systolic phase.

An M-mode cursor was oriented at the junction of the tricuspid valve plane and the RV free wall to measure tricuspid annular plane systolic excursion (TAPSE). Lateral

tricuspid annular systolic motion velocity (TV S′) was measured with the use of tissue Doppler imaging.

Statistical Analyses

Data are expressed as mean ± SD or median (interquartile range [IQR]). Continuous echocardiographic variables before and after iVAS implantation were compared with the use of Wilcoxon signed-rank tests. General estimating equations with robust standard errors were used to investigate the impact of iVAS on cardiac function by adjusting inotrope use and the timing of echocardiography procedures. Medication data before and after iVAS implantation were compared with the use of McNemar tests. All statistical analyses were performed with the use of SPSS Statistics 22 (SPSS, Chicago, Illinois), and 2-tailed $P < .05$ was considered to be significant.

Results

Baseline Characteristics

Out of 21 patients that underwent iVAS implantation, 3 did not have a second echocardiographic assessment on iVAS support and were excluded (they received HT relatively soon after iVAS implantation [at days 4, 16, and 25] without repeated echocardiographic assessment). Eighteen patients who completed both pre-iVAS echocardiography and on-iVAS echocardiography were enrolled. Out of this cohort, 10 were also included in our previous paper.[15] The mean age was 55.4 ± 12.3 years, 14 were male (78%), and 9 had an ischemic etiology of HF (50%). Table 1 summarizes the baseline characteristics.

Medication

The administration rates of HF medications remained unchanged before and after iVAS implantation, except for intravenous inotropes (Table 2). Almost all patients (94%) received intravenous inotrope infusion before iVAS implantation, whereas only 33% were receiving inotropes at the time of echocardiography on iVAS support ($P < .001$).

Table 1. Baseline Characteristics (n = 18)

Age, y	59.0 ± 7.1
Sex male	14 (78%)
Ischemic etiology	9 (50%)
Body surface area, m^2	2.15 ± 0.25
Hypertension	8 (44%)
Diabetes mellitus	5 (28%)
History of ventricular tachyarrhythmias	8 (44%)
Atrial fibrillation	8 (44%)
History of stroke	0 (0%)
NYHA functional class IV	18 (100%)
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	66.9 ± 22.0
NT-pro BNP, pg/mL	3076.3 ± 2434.4
Central venous pressure, mm Hg	11.4 ± 4.7
Mean pulmonary arterial pressure, mm Hg	37.0 ± 11.3
Pulmonary capillary wedge pressure, mm Hg	24.2 ± 8.9
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	1.91 ± 0.44

Values are presented as mean ± SD or n (%). NYHA, New York Heart Association; eGFR, estimated glomerular filtration ratio; NT-proBNP, N-terminal pro−B-type natriuretic peptide.

Table 2. Changes in Medication

Medication	Before iVAS Support	On iVAS Support	*P* Value
Beta-blocker	9 (50%)	10 (56%)	1.0
ACE inhibitor or ARB	3 (17%)	3 (17%)	1.0
Aldosterone antagonist	4 (22%)	1 (6%)	.15
Diuretics	18 (100%)	13 (72%)	.063
Intravenous inotropes	17 (94%)	6 (33%)	<.001*

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.
*$P < .05$ (McNemar test).

Clinical Outcomes

Patients were supported with iVAS for a median of 28 days (IQR 25−51 days). Two patients were bridged to mechanical circulatory support at days 28 and 49. Twelve patients were bridged to HT after a median of 29 days (IQR 24−46 days). Four patients remained on iVAS support at the time of this report (range of support 80−176 days). No patients died during the observational period.

Echocardiographic Data

The results of echocardiography before and during iVAS support are summarized in Table 3. The size of the LV and as adjusted by body surface area tended to decrease, with a 7.4% decrease ($P = .059$ and $P = .055$; Supplemental Fig. 1A), and the size of the LA decreased significantly, with a 43.7% decrease ($P < .001$). Both systolic and diastolic LV function improved significantly ($P < .05$ for all). Notably, LVEF had an absolute increase of 7.9% ($P = .007$; Supplemental Fig. 1B). The grade of mitral valve regurgitation (MR) improved significantly ($P = .030$), whereas aortic valve regurgitation remained unchanged at a low level ($P = .10$).

Both the RV and RA were significantly reduced in size, with 9.0% and 21.1% decreases, respectively ($P = .039$ and $P = .014$). RV function, as assessed by RVFAC, TAPSE, and TV S′, improved considerably, with 161.6%, 29.1%, and 19.6% increases, respectively ($P < .001$, $P = .008$, and $P = .047$; changes in TAPSE are shown in Supplemental Fig. 1C). Tricuspid regurgitation (TR) was minimal before and during iVAS therapy. Fig. 2 shows echocardiographic results from a representative patient, who had marked reductions in the size of all 4 chambers and improvement in biventricular function.

Six patients remained dependent on inotropes during iVAS support, and 8 patients received echocardiography procedures before 30 days. iVAS implantation was significantly associated with improvements in LVEF (β-value 9.48, 95% confidence interval [CI] 0.09−18.9; $P = .048$), LVDd (β-value −0.42, 95% CI −0.76−-0.08; $P = .016$), and TAPSE (β-value 0.30, 95% CI 0.05−0.55; $P = .30$) after adjustment by inotrope use and the timing of the echocardiography procedure.

Table 3. Changes in Echocardiographic Parameters (n =18)

Parameter	Before iVAS Support	On iVAS Support	Change	*P* Value
Left ventricle				
LVEDD, cm	7.13 ± 1.27	6.45 ± 1.46	−7.4%	.059
LVEDDI, cm/m^2	3.31 ± 0.59	3.04 ± 0.67	−7.4%	.055
LVMI, g/m^2	120.03 ± 35.13	103.81 ± 32.19	−5.5%	.16
LAVI, mL/m^2	62.74 ± 35.72	33.77 ± 17.20	-43.7%	<.001*
LVEF, %	16.53 ± 11.91	24.43 ± 12.79	79.5%	.007*
E/e′ (n = 14)	20.97 ± 7.94	14.01 ± 5.53	-33.1%	.009*
AR, grade	0.5 ± 0.7	0.3 ± 0.5	–	.10
MR, grade	1.8 ± 1.4	1.2 ± 1.2	–	.030*
Right ventricle				
RVEDA, cm^2	23.31 ± 8.51	19.59 ± 5.61	−9.0%	.039*
RA area, cm^2	20.12 ± 5.71	14.83 ± 6.39	−21.1%	.014*
RVFAC, %	25.35 ± 12.91	42.05 ± 12.43	161.6%	<.001*
TAPSE, cm	1.48 ± 0.51	1.77 ± 0.52	29.1%	.008*
TV S′, cm/s	8.96 ± 2.62	10.39 ± 3.22	19.6%	.047*
TR, grade	0.8 ± 0.9	0.8 ± 0.7	–	.82

LVEDD, left ventricular end-diastolic diameter; LVEDDI, left ventricular end-diastolic diameter index; LVMI, left ventricular mass index; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; E/e′, ratio between early mitral inflow velocity and mitral annular early diastolic velocity; AR, atrial valve regurgitation; MR, mitral valve regurgitation; RVEDA, right ventricular end-diastolic area; RA area, right atrial area; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; TV S′, lateral tricuspid annular systolic motion velocity; TR, tricuspid valve regurgitation.

*$P < .05$ (Wilcoxon signed-rank test).

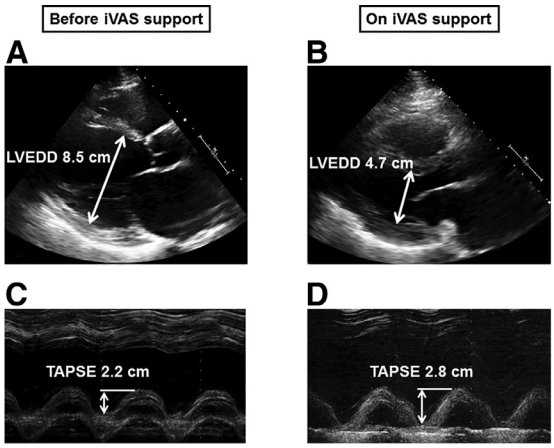

Fig. 2. A patient who received transthoracic echocardiography before (A, B) and on (C, D) intravascular ventricular assist system support. (A, C) Parasternal long-axis views, showing a decrease in left ventricular end-diastolic diameter from 8.5 cm to 4.7 cm. (B, D) M-mode views oriented at the junction of the tricuspid valve plane and the right ventricular free wall, showing an increase in tricuspid annular plane systolic excursion from 2.2 cm to 2.8 cm.

Discussion

We assessed the improvement in biventricular cardiac function 30 days after implantation of an ambulatory counterpulsation device with the use of transthoracic echocardiography performed just before iVAS implantation (without iVAS support) and 30 days after iVAS implantation (on iVAS support). Our main findings were as follows. (1) All patients survived on iVAS support and were either bridged to cardiac replacement therapy or remained on iVAS support during the observational period. (2) LV systolic and diastolic function improved along with a reduction in the MR grade. (3) There was a significant reduction of LA size along with a numeric reduction in LV size. And (4) RV and RA sizes decreased significantly, and RV function improved.

Differences Between Conventional IABP and iVAS

IABP has been used in advanced HF patients for almost 50 years. However, it is only recently that IABP has been inserted via the subclavian artery to provide a longer duration of support.[4,5,18,19] The newly developed iVAS offers the advantage of increased durability, allowing a longer support duration (months), as well as more efficient augmentation owing to an internal electrocardiographic tracing and enhanced patient mobility in the ambulatory setting.[15] The previous iVAS study reported increased cardiac index (38.8%) and decreased pulmonary capillary wedge pressure (−21.7%) with only 2 weeks of support.[15] These findings were better than what has been reported with conventional IABP.[20]

Structural and Functional Improvement of the LV During iVAS Support

Counterpulsation can produce immediate hemodynamic improvement,[15] but the effects of chronic counterpulsation on reverse remodeling and myocardial recovery remain uncertain.[14] Increased coronary flow due to continuous diastolic augmentation may improve LV contractility and facilitate active myocardial relaxation.[9] Furthermore, counterpulsation reduces LV afterload,[8] diminishes LV energy consumption, and improves mechanical performance. Consistently with these effects, we observed that both systolic and diastolic LV function improved significantly. Afterload reduction also increases forward flow and may reduce MR grade,[21] leading to volume unloading and decreases in the

size of the LV and LA. Earlier studies have shown the necessity of cardiac reserve to achieve maximal benefit from counterpulsation support, highlighting the importance of patient selection for iVAS therapy when used with the goal of recovery.[19] Whether the changes observed in this study represent a reversal of the underlying structural changes that accompany LV remodeling or are due solely to LV unloading can not be determined from these data, and will need to be investigated further in a study dedicated to use of the iVAS as a bridge to recovery (BTR).

Structural and Functional Improvement of the RV During iVAS Support

In the present study, RV function improved and the size of the right heart decreased during iVAS support. This is a critical advantage of iVAS therapy over LVAD therapy, as discussed subsequently. Ntalianis et al also demonstrated an improvement in RV function and decrease in RV size during prolonged IABP support.[22] In their study, patients remained bedbound with an IABP inserted via the femoral approach. Our results add to those findings by demonstrating the improvement in cardiac function that occurs with the use of ambulatory counterpulsation.

The precise mechanism in the improvement of RV function remains uncertain, but a decrease in pulmonary arterial pressure via LV unloading reduces RV afterload and, in combination with augmented diastolic blood flow, may enhance RV function.[9,23,25] Also, LV unloading may allow the interventricular septum to assume a more natural position and provide more contribution to RV contraction. Pressure unloading of the RV may reduce the degree of TR. In our cohort, there was no significant TR before iVAS in most patients, but TR did diminish in 2 patients (from mild to trace in one patient, and from moderate to mild in the other).

Clinical Implications of iVAS Therapy for Myocardial Recovery

Multiple studies have demonstrated the ability of LVADs to promote myocardial recovery during an intermediate term of support in a very restricted population. However, in the first 30 days of support, Drakos et al showed only a 3% increase in LVEF from 17% to 20%.[24] In the present study, LVEF increased by 7.9% during 30 days of iVAS support.

In contrast to iVAS, the effect of LVAD support on RV function remains controversial. Continuous LVAD support alters the shape of the RV through a shift in the interventricular septum and reduction of the myocardial torsion that is needed for RV function.[25] Elevated RV afterload as represented by the decoupling between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure,[26] increased afterload sensitivity,[27] the loss of pericardial integrity, and increased RV preload due to the enhanced cardiac output during LVAD support may all contribute to the worsening of RV function.[28] Considering the high frequency of early and late RV failure after implantation and its adverse clinical impact,[29] LVADs may not be the preferred type of device to improve RV function, in contrast to iVAS therapy.

There are other advantages of using iVAS compared with LVADs. The implantation is minimally invasive without need for sternotomy or thoracotomy. This eliminates any trauma to the heart during explantation. Recovery can be fully assessed before explantation. The frequency of support (1:1, 1:2, or 1:3), as well as the amount of augmentation can be adjusted. In addition, initial clinical experience has demonstrated that the pump can be turned off for extended periods of time.[15] A recovery protocol can be envisioned that sequentially decreases the intensity of support, then progresses to decreasing the time on support. Partial recovery may permit the use of iVAS as an on-demand type device. If full recovery is attained, the intravascular component can be removed, leaving a blank plug in the graft. This permits the lumen of the graft to be maintained as well as the skin interface device. This allows easy reimplantation of the pump if necessary. If recovery status is stable after extended periods of time, all the components can be removed through a simple operation involving only subcutaneous tissue.

Considering the improvement of biventricular cardiac function seen during 30 days of iVAS support, this device has the potential to promote myocardial recovery with longer duration of support. In this study, we observed a wide variety of responses to iVAS therapy. For example, 3 patients had a decrease in LVEDD of $\geq$1.0 cm and 3 patients had a decrease in LVEDD of $<$0.5 cm. As a next step, it is imperative to identify predictors of response to iVAS and to further delineate the group of patients that are most likely to benefit from iVAS therapy. The device is well suited for use in a less-sick HF population owing to its less invasive implantation and improved safety profile. In conjunction with guideline-directed HF therapy and aggressive cardiac rehabilitation, iVAS implantation with a BTR strategy may be particularly useful in patients with recent-onset cardiomyopathies.[14]

Chronic HF patients who are not candidates for advanced therapies but are inotrope dependent also may have better long-term outcomes with the use of iVAS support because of the benefits of improvement in cardiac function, even though complete recovery is unlikely to occur.[24] Many patients dependent on inotropes were able to discontinue inotropes after iVAS implantation in the present study (Table 2). Although there are many advantages to iVAS therapy, we should also pay attention to several potential adverse events. As reported in our previous paper,[15] many patients have transient shoulder and arm pain, which resolves within the first week. Some patients experienced a transient drop in hemoglobin and platelet count, which typically resolved without any blood product infusions. As with other mechanical circulatory support devices, trauma and superficial infection can occur around the driveline. Thrombotic events seem to be rare under the appropriate anticoagulation therapy.

Study Limitations

This was a prospective single-center study with a relatively small number of patients. Although we observed significant improvement in biventricular cardiac function during an intermediate duration of iVAS support, further investigation is required to establish the durability of these findings and demonstrate reverse remodeling by means of assessing molecular, cellular, and intestinal changes in the myocardium. Also, we did not perform an off-test of iVAS support, owing to the risk of hemodynamic deterioration, and did not have any data on cardiac recovery without iVAS support. Follow-up after iVAS explantation in patients with significant cardiac reverse remodeling would be necessary to determine the ability of iVAS therapy to promote myocardial recovery and the usefulness of the iVAS as a BTR therapy.

Our findings of improvement in biventricular cardiac function were based on 2-dimensional transthoracic echocardiography, but other methodologies, such as 3-dimensional echocardiography, could be used to more precisely define the mechanism of improvement in cardiac function during iVAS support.[30] We excluded the impact of several suspected confounders on the outcome, but other unknown confounders may exist. Because this is a first-in-humans study, we did not have a control group. Furthermore, BTR was not the objective of iVAS implantation in this cohort, and therefore medications were not necessarily optimized with this goal in mind.

We recognize that the discussion above regarding the potential for reverse remodeling and cardiac recovery with iVAS remains speculative. Nevertheless, we think that the improvement in biventricular cardiac function on iVAS support that we observed here is a promising finding and a necessary step in the investigation of iVAS as a BTR device.

Conclusion

Improvement in biventricular cardiac function was observed after 30 days of iVAS support. Further studies should examine the use of this technology as a BTR device.

Disclosures

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Supplementary Material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2018.11.001.

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