



# TandemHeart for Right Ventricular Failure

## Outreach for Clinical Guidance on Improving LVAD Outcomes

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### EXECUTIVE SUMMARY

Implantation of a left ventricular assist device (LVAD) may create or exacerbate right ventricular dysfunction, leading to suboptimal patient outcomes. Current treatment ranges from escalating medical therapy to temporary or long-term mechanical support for the right ventricle (RV). Increasing utilization of durable LVADs for the treatment of end-stage heart failure, either as a bridge-to-transplant (BTT) or destination therapy (DT), has created a need for new and improved RV support therapies. We hypothesize that the use of the TandemHeart system for percutaneous right ventricular support in conjunction with a durable LVAD will reduce the incidence of RV failure and improve patient outcomes.

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### RIGHT VENTRICULAR FAILURE | A GROWING PROBLEM

Dysfunction or failure of the right ventricle may originate from several underlying causes including acute myocardial infarction (AMI), pulmonary embolism (PE), acute respiratory distress syndrome (ARDS) and congenital heart disease, among others. However, RV failure secondary to LVAD deployment has become the most rapidly increasing pathophysiology.

Mechanical support and concomitant decompression of the left ventricle (LV) often results in a shift of the ventricular septum, effectively dilating the RV and reducing mechanical efficiency. Recent reports of patients treated with modern, continuous flow LVADs describe clinically significant RV dysfunction or outright failure in 8-40% of patients.<sup>1,2,3</sup> A review of 484 patients enrolled in the HeartMate II LVAD BTT clinical trial indicated that RV failure occurred in 20% of subjects.<sup>4</sup> As the utilization of durable LVAD therapy becomes more prevalent, a rise in the incidence of RV failure is widely expected.

The consequences of RV failure are serious for LVAD patients. Studies have shown that RV failure significantly

increases LVAD peri-operative mortality and that there is a trend toward reduced survival to cardiac transplantation.<sup>2,5</sup> Patients experiencing RV failure after LVAD implantation suffer with limited LVAD filling, diminished flow, reduced end organ perfusion and venous stasis. Resulting venous congestion in the hepatic system contributes to nutritional and coagulation abnormalities which in turn impact clinical outcomes.<sup>6</sup> Failure of the RV after LVAD insertion has also been associated with early mortality, more bleeding, longer hospitalization and higher rates of renal insufficiency and reoperation.<sup>2</sup>

Current therapy for RV dysfunction associated with LVAD implantation includes medical therapy with some combination of inotropes, nitrates, diuresis and inhaled nitric oxide in an attempt to maximize cardiac index and minimize right-sided filling pressures. However, even with optimal medical therapy, up to 40% of patients progress from RV dysfunction to outright RV failure. Despite the evidence that RV failure contributes to poor outcomes, there have been no controlled trials of RV mechanical support in this patient population.

Persistent ineffectiveness of the current standard of care for RV failure significantly limits the utilization of LVAD therapy. Transplant-eligible patients who progress to RV failure, either before or after LVAD placement, are typically considered for bi-ventricular durable mechanical support.<sup>7</sup> However, RV dysfunction has dire consequences for patients who are not eligible for transplant. With no approved bi-ventricular option for destination therapy patients, right heart dysfunction often eliminates an LVAD as a treatment option.

To address these issues, current clinical practice focuses on improving pre-operative hemodynamics using a variety of alternative treatment strategies. These include escalation of inotropes and diuretics, intra-aortic balloon counterpulsation (IABC), renal optimization with diuresis or renal replacement therapy, pre-operative coagulopathy correction, and pre-operative reversal of pulmonary vascular hypertension with oral nitrates or sildenafil.<sup>3</sup> The limited success of these

alternatives has prompted at least one group to speculate that perhaps only biventricular mechanical support is sufficient to augment the RV enough to allow for recovery.<sup>6</sup>

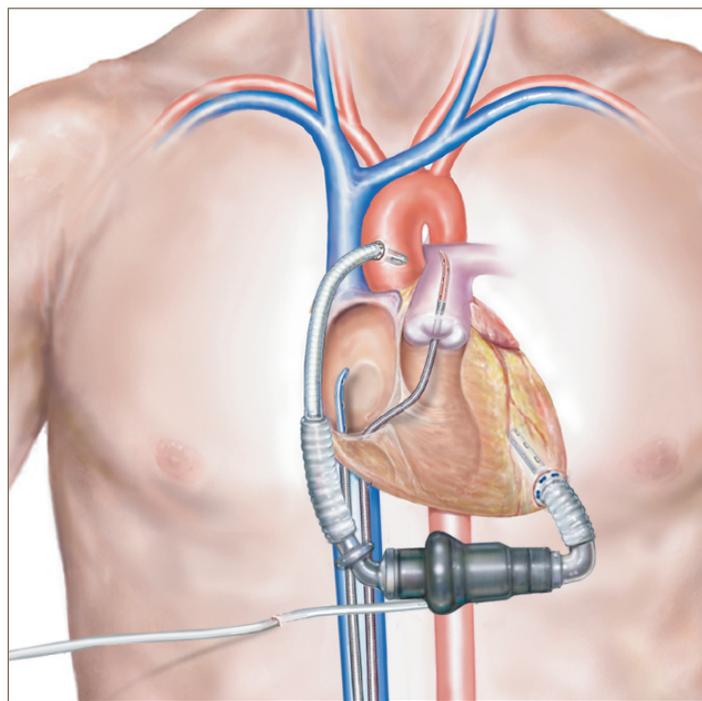
Recent studies have suggested that the early use of RV mechanical support can offer a substantial benefit to both short-term RV recovery and long-term patient outcomes. A review of planned versus delayed (up to 48 hours) BiVAD placement in BTT candidates found that timely restoration of cardiac output with planned BiVAD, rather than delayed insertion once RV failure is recognized, improved Kaplan-Meier 1-year survival from 25% to 48%.<sup>8</sup> Another group noted that the RV can recover with temporary support and that pre-operative mechanical support was not associated with increased risk of RV failure post-LVAD.<sup>2</sup> Despite this evidence, the lack of a proven, safe and effective mechanical support device for the RV has severely limited this treatment approach.

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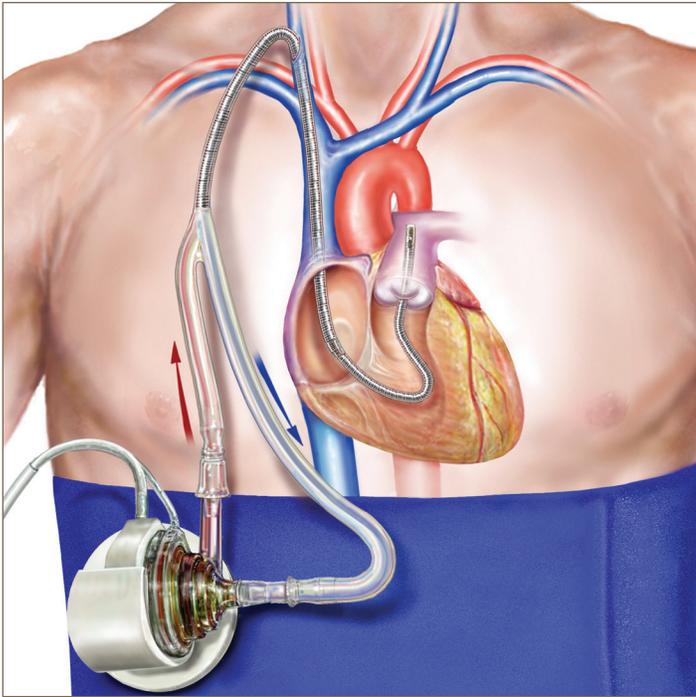
## PERCUTANEOUS MECHANICAL SUPPORT OF THE RIGHT VENTRICLE

The TandemHeart system has been used to provide temporary circulatory support in more than 3,500 patients, with more than 550 cases of right heart support. When deployed for percutaneous RV mechanical support, the most common configuration includes two femoral venous access sites. The first is used to draw blood from the right atrium into the TandemHeart pump using a 62cm cannula, while the second is used to return blood from the pump to the pulmonary artery via a 72cm cannula. This configuration bypasses the RV percutaneously, and has been used in conjunction with LVAD support, including the HeartMate II (Figure 1).

In 2013, a retrospective report on TandemHeart RV support was published including 46 patients across 8 hospitals. All cases were associated with improved RV hemodynamics and total cardiac output. Overall mortality across a wide range of diagnoses was 57%, but the lowest mortality in any subgroup was observed in patients who were supported for RV failure after LVAD insertion, with 20% mortality.<sup>9</sup>



**Figure 1.** Percutaneous right heart support via TandemHeart (dual access via femoral veins) with HeartMate II LVAD.



**Figure 2.** Percutaneous right heart support via TandemHeart with dual lumen cannula (single access via internal jugular).

Although there has been frequent use of the TandemHeart system for RV support, dual groin access is not ideally suited to the needs of ambulatory LVAD patients. As a result, CardiacAssist has developed a dual lumen cannula for RV support through a single access site in the neck, with commercial release expected in early 2014 (Figure 2). Blood is still withdrawn from the right atrium and returned to the pulmonary artery, but the entire extracorporeal circuit may be located above the patient's abdomen, away from the groin.

A rapidly deployed, cost-effective, percutaneous device such as the TandemHeart has the potential to avoid the additional comorbidities and expense of a surgically-implanted RV support device, due to its minimally invasive approach that can be explanted without returning to the operating room. This approach promises to unlock new treatment options for LVAD patients. For these reasons, CardiacAssist completed FDA pre-submission documentation for a right ventricular support trial in July 2013.

## TRIAL CONSIDERATIONS | TANDEMHEART FOR RIGHT VENTRICULAR FAILURE

CardiacAssist is considering several trial strategies in an attempt to accurately represent clinical practice while producing the best opportunity for meaningful improvement in patient outcomes. Several factors contribute to trial design including patient population, timing of RV support, inclusion criteria and clinical endpoints.

Currently, our preferred approach is a single arm trial of 100 patients from all groups (BTT, BTC and DT) with an INTERMACS registry control group. Clinical endpoints should include the rate of post-LVAD RV failure, survival to transplant or 90 days (whichever occurs first) and re-hospitalization rates. Four primary factors have informed this strategy: (1) the population of LVAD recipients is small (less than 2,000 per year) but fully represented within the INTERMACS registry; (2) INTERMACS data is unambiguous regarding right heart dysfunction and can provide appropriate

control data; (3) randomization would extend the trial timeline, increasing the risk of confounding results due to changes in treatment patterns over time; and (4) the number of patients required to demonstrate non-inferiority in a randomized trial would be prohibitively high.

If successful, this trial would support an FDA pre-market approval (PMA) submission for the TandemHeart system to provide right ventricular support for up to 5 days in patients with moderate RV dysfunction who are at risk of developing RV failure within 90 days of initial LVAD implantation.

CardiacAssist is currently soliciting clinical input from the physician community into trial design possibilities. To act as a clinical advisor or a participating hospital center for this trial, please contact us at [cardiacassist.com/contact](http://cardiacassist.com/contact).

## REFERENCES

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- <sup>5</sup> Boumwol J, et al. Right heart failure and “failure to thrive” after left ventricular assist device: Clinical predictors and outcomes. *J Heart Lung Transplant.* 2011;30: 888-95.
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- <sup>8</sup> Fitzpatrick J, et al. Early planned institution of biventricular mechanical circulatory support results in improved outcomes compared with delayed conversion of left ventricular assist device to a biventricular assist device. *J Thorac Cardiovasc Surgery.* 2009;137:971-977.
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This document is intended to provide information related to a proposed FDA clinical trial of the TandemHeart system. CardiacAssist makes no claims regarding the safety or effectiveness of the TandemHeart system when used for unapproved indications.

The TandemHeart system is intended for extracorporeal circulatory support using an extracorporeal bypass circuit. Intended duration of use is for periods appropriate to cardiopulmonary bypass, up to six hours. It is also intended to be used as an extracorporeal circulatory support system (for periods up to six hours) for procedures not requiring complete cardiopulmonary bypass (e.g., valvuloplasty, mitral valve reoperation, surgery of the vena cava and/or aorta, liver transplant, etc).