TRIS
TRIAL

TandemHeart to **R**educe **I**nfarct **S**ize Trial

Percutaneous Left Ventricular Bypass for Infarct Reduction in STEMI

EXECUTIVE SUMMARY

Rapid and efficacious primary PCI has been correlated with improved outcomes in STEMI patients, but reperfusion injury limits the degree of myocardial salvage that may be attained. Most STEMI patients now survive the initial acute ischemic event but are later impacted by reduced myocardial function and eventual heart failure. Thus, the current practice of medicine has addressed acute survival of STEMI but shifted the final patient outcome into the future.

Studies have shown that unloading the left ventricle prior to reperfusion results in a significant improvement in myocardial salvage. However, the positive effects of ventricular unloading have yet to be realized in STEMI, due to the emphasis on speed to reperfusion and door-to-balloon time as the standard of care. With ventricular unloading historically delivered through surgical cardiopulmonary bypass, this therapy was not compatible with the emergent need for reperfusion in STEMI patients. Recent advancements in the capability to provide ventricular support with a percutaneous device have for the first time enabled the potential application of unloading as a therapy for STEMI patients.

The TandemHeart to Reduce Infarct Size (TRIS) Trial aims to combine the beneficial effects of rapid reperfusion with the benefits of myocardial unloading to minimize infarct size after STEMI and to improve long-term clinical outcomes. The TandemHeart approach to ventricular unloading has been shown to offer a level of unloading that is unique among the available percutaneous support platforms.

ACUTE MYOCARDIAL INFARCTION (AMI) THERAPY & OUTCOMES

Myocardial infarction (MI) or acute myocardial infarction (AMI), commonly known as a heart attack, results from the interruption of blood supply to a part of the heart, causing heart cells to die. This is most commonly due to occlusion of a coronary artery following the rupture of a vulnerable atherosclerotic plaque. The resulting ischemia (restriction in blood supply) and the ensuing oxygen shortage, if left untreated for a sufficient period of time, can cause damage or death (infarction) of heart muscle tissue (myocardium).[1]

An MI requires immediate medical attention. Treatment attempts to salvage as much myocardium as possible and to prevent further complications. Most cases of myocardial infarction with ST elevation on ECG (STEMI) are due to complete occlusion of the coronary artery and are treated with reperfusion therapy, such as percutaneous coronary intervention (PCI).[2] When performed rapidly by an experienced team, primary PCI restores flow in the culprit artery in more than 95% of patients.[3] Multiple clinical studies have shown that shorter "door-to-balloon" intervals correlate to improved myocardial salvage and better long-term clinical outcomes.[4,5] As a result, ACC/AHA guidelines recommend a "door-to-balloon" interval of no more than 90 minutes.[6]

Reperfusion has been shown to have beneficial effects on STEMI patients with regard to final myocardial infarct size, but significant myocardial damage remains. A recent randomized, controlled clinical trial of 337 STEMI patients undergoing PCI reported final infarct size of 40–50% of total left ventricular mass.[7] Although acute STEMI mortality rates have decreased significantly over the last 20 years, door-to-balloon improvements in recent years have failed to yield a significant improvement in 1-year mortality, which is estimated to be between 6% and 15%.[8] Even when PCI is performed within suggested guidelines, large infarct size is associated with adverse remodeling and decreased left ventricular (LV) function, leading to heart failure and long-term morbidity following STEMI (Figure 1).[9,10,11]

Based on these trends, it is clear that the next phase of evolution for STEMI therapy must look beyond reperfusion and door-to-balloon time to overcome stagnant outcomes. One area of improvement that has recently been targeted is the concept of reperfusion injury.

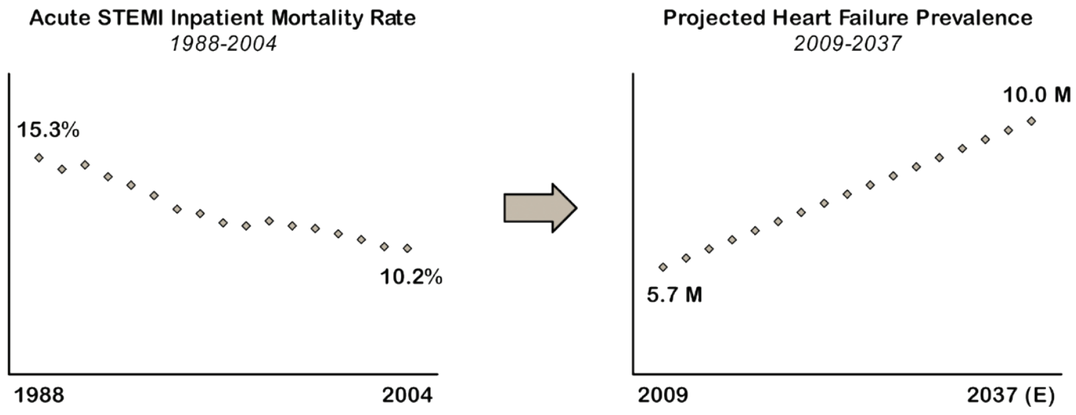

Figure 1 *Improved STEMI survival projected to increase future prevalence of heart failure.*

CLINICAL IMPACT OF REPERFUSION INJURY

Reperfusion injury is the tissue damage that is caused when blood supply returns to the tissue after a period of ischemia or a lack of oxygen. The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative cell damage. This phenomenon was first observed in 1960, when Jennings et al. found loss of cell architecture and death of myocytes during reperfusion after acute injury.[12] Today, it is believed that this form of myocardial injury may account for 30–50% of the final infarct size after STEMI (Figure 2).[13] This may in part explain why, despite optimal myocardial reperfusion, the rate of death after AMI approaches 10%, and the incidence of heart failure is almost 25%.

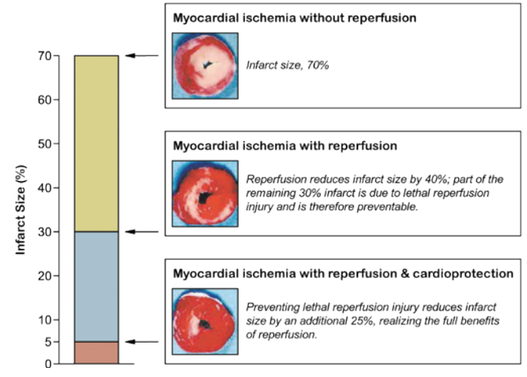

Figure 2 *Significant impact of reperfusion injury on final infarct size (reproduced from Yellon et al.)*

While great strides have been made in systematically providing rapid reperfusion therapy to STEMI patients, mitigating reperfusion injury has proven to be an elusive goal. However, the underlying principles have been studied for more than 30 years, and new technologies may unlock these clinical benefits for the first time in the near future.

MYOCARDIAL UNLOADING TO REDUCE REPERFUSION INJURY

The concept of myocardial unloading has been explored as a mechanism to reduce reperfusion injury in several previous studies and continues to be a strategy garnering great interest among the medical community today. Unloading is defined as a reduction of pressure and volume inside the left ventricle, resulting in workload reduction that leads to reduced myocardial oxygen consumption. The presumed effect of unloading during myocardial infarction is two-fold. First, reduced myocardial workload results in a reduction in anaerobic activity during myocardial muscle contraction, reducing total myocardial oxygen demand. Second, unloading may provide cellular protection during reperfusion.

The degree of ventricular unloading may be directly quantified by placing conductance catheters in the left ventricle. Measurements from these catheters reveal the pressure to volume relationship in the ventricle in real time under a variety of conditions over many cardiac cycles. These measurements may be plotted against one another—with pressure and volume on opposing axes—to form a pressure-volume (PV) loop (Figure 3). Each phase of the cardiac cycle correlates to one part of the PV loop: left ventricular filling (bottom) precedes isovolumetric contraction (right side), followed by LV ejection (top) and isovolumetric relaxation (left side). Likewise, each corner of the PV loop corresponds to the opening or closing of either the aortic

or mitral valve. The area inside the PV loop is equivalent to myocardial stroke work, and a smaller area inside the loop indicates less work being done by the left ventricle, with a corollary decrease in myocardial oxygen demand.

In STEMI patients, lethal reperfusion injury is theorized to result in additional cell death when blood flow is restored, which results in larger infarct size and impaired ventricular function. However, if myocardial oxygen demand is reduced below the level of supply, muscle contraction can occur aerobically. Reperfusion therapies, such as primary PCI, may be implemented more safely, without the dynamic stress of multiple myocardial cells demanding and sharing a limited supply of oxygen. Based on these foundational principles, multiple studies have evaluated the effectiveness of unloading on myocardial salvage.

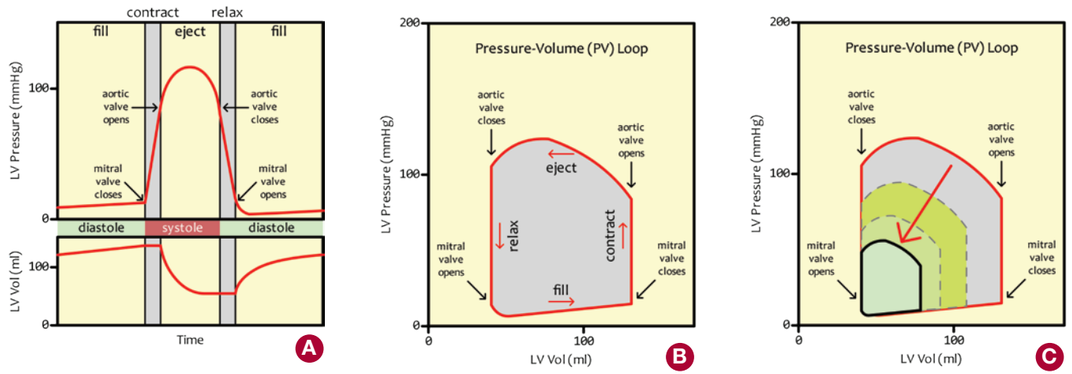

Figure 3 *(A) Left ventricular pressure and volume over a single cardiac cycle. (B) Left ventricular pressure-volume (PV) loop with one revolution corresponding to one cardiac cycle. (C) Smaller PV loop indicates ventricular workload reduction.*

INITIAL INVESTIGATIONS OF UNLOADING IN STEMI

From 1979 to 1994, multiple animal studies investigated the potential benefits of unloading the left ventricle on infarct size after AMI.[14,15,16,17,18,19] These studies generally involved the creation of an artificial AMI followed by unloading of the ventricle and vessel reperfusion. Histochemical analyses post-necropsy were then performed to determine infarct size. While these studies demonstrated the effectiveness of LV unloading on the reduction of infarct size, the protocols and surgical techniques used would not be applicable to the STEMI population commonly treated with percutaneous therapy alone.

From 2005 to 2008, three separate animal studies demonstrated that unloading of the left ventricle with Intra-Aortic Balloon Counterpulsation (IABC) prior to reperfusion reduces infarct size and improves myocardial salvage.[20,21,22] Based on the results of these pre-clinical animal studies, a multicenter randomized controlled trial was commenced in 2009: **C**ounterpulsation to **R**educe **I**nfarct **S**ize **P**re-PCI **A**cute **M**yocardial **I**nfarction (CRISP AMI).

The purpose of the CRISP AMI trial was to test the hypothesis that left ventricular unloading via IABC delivered prior to PCI would reduce myocardial infarct size in patients with large anterior STEMI, compared to treatment with PCI alone. The study enrolled 337 patients across 30 hospital sites in 9 countries between June 2009 and February 2011, with 176 patients randomized to the PCI-only control group and 161 patients randomized to the IABC+PCI treatment group. Unfortunately, the strategy of routine IABC use prior to PCI in STEMI did not result in a statistically significant reduction in myocardial infarct size, which was the study's primary endpoint. Additionally, none of the secondary endpoints—microvascular obstruction, LV ejection fraction, myocardial salvage index—indicated significant benefit in the treatment group.[23]

Multiple explanations for the failure of CRISP AMI were hypothesized. One explanation was that the beneficial effects of unloading with IABC were offset by the additional time required to insert the intra-aortic balloon. However, the overall ischemic time from reported symptom onset to first device was approximately 3 hours for all patients with only a 10-minute difference between the two groups. Another explanation offered that the potential protective effect of LV unloading occurred too late in the course of the MI to salvage significant myocardium. Several previous studies found that only a small degree of myocardial salvage occurs with ischemic times beyond 2 hours.[24,25]

One additional explanation for the failure of CRISP AMI is that IABC may not have provided enough left ventricular unloading to produce a treatment effect. In 2003, an animal study was conducted to test whether the degree and timing of unloading would impact myocardial salvage.[26] Twenty-six sheep were divided into four groups: (1) reperfusion with no unloading (control group), (2) partial unloading initiated after reperfusion, (3) full unloading initiated after reperfusion, and (4) full unloading initiated before reperfusion.

The results showed significant infarct reduction in all treatment groups, compared to the control, but each treatment group showed more infarct reduction than the previous one. Thus, the degree of unloading has a highly linear correlation with myocardial salvage, and the maximum benefit is only realized when a high degree of unloading is delivered prior to reperfusion (Figure 4).

Based on these findings, the degree of unloading offered by IABC is unlikely to produce the incremental clinical benefits that have been noted in smaller animal studies. In fact, further review of the original animal studies attempting therapeutic unloading in AMI indicates that significant myocardial salvage is achieved only when the LV is unloaded by at least 70%, with no significant benefit when LV unloading is less than 50%.[15,16,17,18,19,20] Thus, in order to extend the benefit of unloading to a human STEMI population, a circulatory device must approach full cardiac support levels.

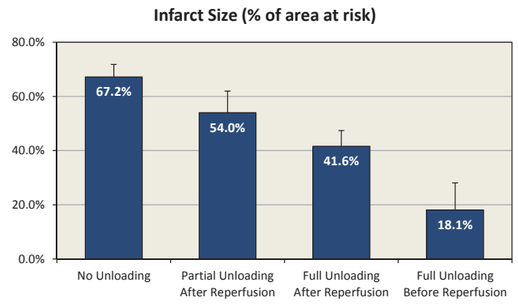

Figure 4. Infarct size sequentially reduced with higher degrees of unloading (reproduced from Meyns et al.).

TANDEMHEART UNLOADING CAPABILITY

The TandemHeart system is a unique circulatory support platform that enables a high degree of ventricular unloading. The system comprises three parts: (1) the TandemHeart Transseptal and Arterial Cannulae, (2) the TandemHeart Centrifugal Pump, and (3) the Escort Controller (Figure 5).

Figure 5 *Components of the TandemHeart Circulatory Support System: Cannulae, Pump, and Controller.*

The TandemHeart system is designed to access the left atrium of the heart via a transseptal puncture, so that oxygenated blood may be withdrawn from this chamber and returned to the femoral artery. This creates an extracorporeal blood circuit that bypasses the left ventricle, with the TandemHeart pump operating in parallel to the native heart (Figure 6).

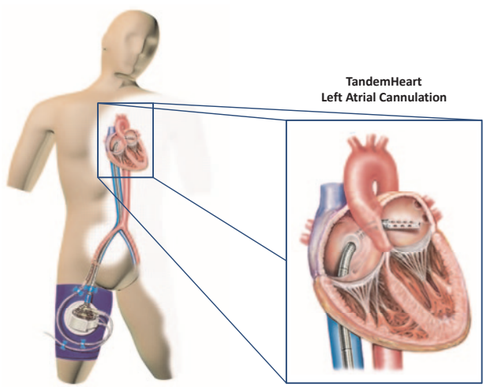

Figure 6 *The TandemHeart system utilizes transseptal access of the left atrium to enable percutaneous LV bypass.*

During TandemHeart support, the PV loop shifts to the left and down, indicating that the TandemHeart is reducing both volume and pressure in the ventricle, resulting in reduced myocardial stroke work. Overall, the TandemHeart system combines a strong centrifugal pump and left atrial cannulation to enable up to 90% reduction of left ventricular stroke work and myocardial oxygen demand (Figure 7).[27]

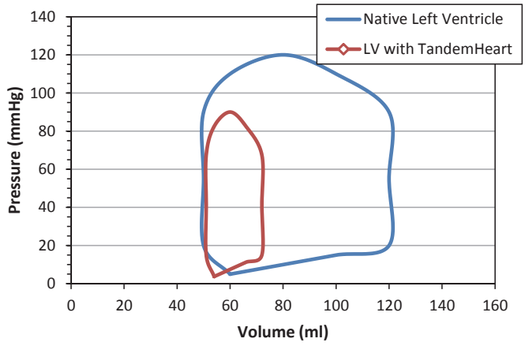

Figure 7 *TandemHeart support level measured via PV loop analysis in a large animal model.*

Several alternative percutaneous circulatory support platforms are commercially available. One platform utilizes a small intraluminal axial pump placed across the aortic valve directly into the left ventricle. This creates an intracorporeal circuit that operates *in series* with the native left ventricle, in contrast to the TandemHeart parallel circuit. As a result, while this platform may be delivered via a single arterial access point and does not require a transseptal puncture, the largest diameter version (21Fr) only offers a maximum 45% ventricular unloading, half the capability of TandemHeart.

Another alternative support platform withdraws deoxygenated blood from the venous circulation through the femoral vein to an extracorporeal pump, which then pushes the blood through an oxygenator before returning to the femoral artery. Unfortunately, this form of percutaneous cardiopulmonary bypass (pCPB), otherwise known as veno-arterial extracorporeal membrane oxygenation (VA ECMO), does not unload the left ventricle. In fact, the use of pCPB increases pressure and volume in the LV, which subsequently increases myocardial strain and oxygen demand.

Based on the aforementioned animal studies, these alternative platforms may not provide the necessary degree of unloading (>70%) to impact myocardial infarct size in a human STEMI patient population. Therefore, CardiacAssist commissioned pre-clinical animal studies with the TandemHeart platform to test whether its unique unloading capability would translate to a high degree of myocardial salvage, indicating the potential for positive long-term outcomes in a future human STEMI trial.

TANDEMHEART PRE-CLINICAL ANIMAL STUDIES

To consider the role of TandemHeart unloading in infarct reduction, we theorized that if the myocardium is reperfused while stroke work and myocardial oxygen consumption is low, then fewer myocytes would die and total myocardial infarct size would be reduced. Pre-clinical animal tests were performed with 50-kg pigs divided into two groups. In both groups, each animal's left anterior descending (LAD) artery —which supplies most of the blood flow to the left ventricle— was occluded using an angioplasty balloon for 120 minutes to simulate STEMI. After this point, the two groups received alternative treatments.

In the control group, the angioplasty balloon was deflated, removing the occlusion and allowing the myocardium to be reperfused. After an additional 120 minutes, each animal was sacrificed and its heart was harvested for analysis. In the TandemHeart group, instead of receiving reperfusion after 120 minutes of occlusion, TandemHeart support was initiated. This support was continued for 30 minutes while the occlusion remained, resulting in a total LAD occlusion time of 150 minutes, compared to 120 minutes in the control group. After 30 minutes of support, the balloon was deflated while circulatory support continued throughout the next 120 minutes, followed by sacrifice and harvesting for further analysis (Figure 8).

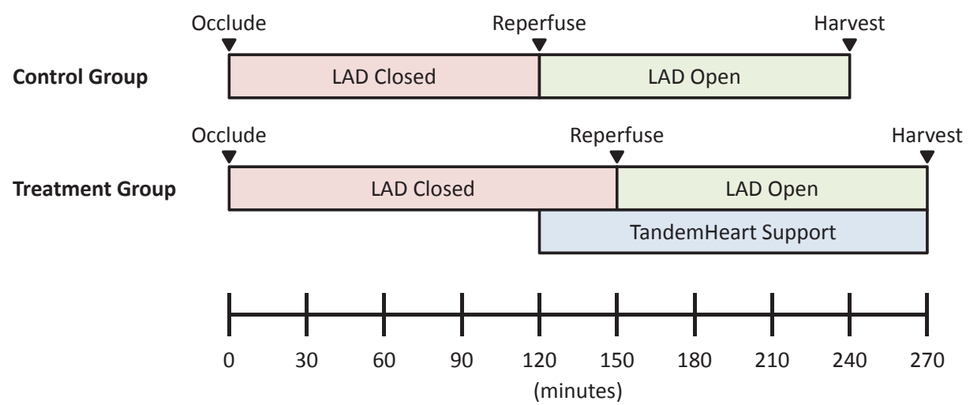

Figure 8 *Experimental design for TandemHeart in STEMI pre-clinical animal study.*

Pressure-volume loop data was obtained via conductance catheters during each of the significant experimental intervals across both groups. This data was used to calculate and compare left ventricular stroke work. As expected, animals in the TandemHeart group exhibited a high and statistically significant degree of left ventricular unloading (Figure 9).

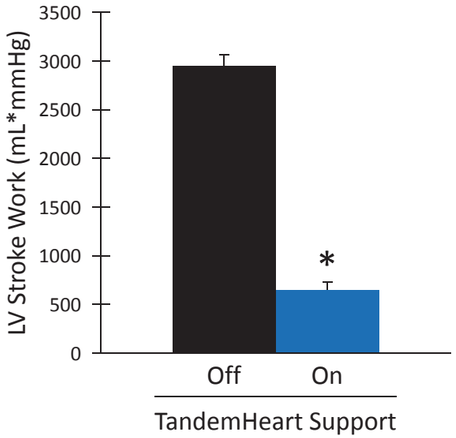

Figure 9 *TandemHeart support significantly reduces left ventricular stroke work.*

In both the control group and the TandemHeart group, baseline PV loops were similar in size and shape. Likewise, during LAD occlusion, each group's PV loop shifted rightward by a similar degree, indicating both diastolic and systolic volume increase in the left ventricle. However, after this point, the PV loops for each group exhibited marked differences.

Even after successful reperfusion, PV loops of animals in the control group shifted far to the right, indicating significant myocardial damage resulting in LV dilation and volume overload. This rightward PV loop shift also indicates decreased pumping capability of the heart and may eventually result in end organ hypoperfusion, which is a pattern commonly seen in heart failure patients with dilated cardiomyopathy (Figure 10).

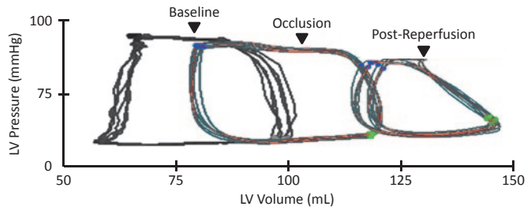

Figure 10 *Control group animals exhibited significant myocardial damage despite successful reperfusion.*

In contrast, TandemHeart-supported animals exhibited a PV loop shift downward and to the left while on support, indicating a high degree of pressure and volume reduction (unloading) with a corresponding reduction in myocardial oxygen demand. Additionally, after successful reperfusion, the treatment group's PV loops shifted back to their baseline position, indicating myocardial salvage and a return to normal pumping action for the LV (Figure 11).

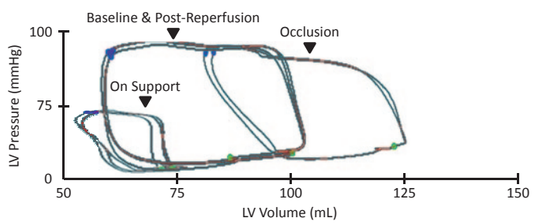

Figure 11 *TandemHeart group animals exhibited a return to normal left ventricular function after unloading & reperfusion.*

The positive functional results exhibited in PV loop analysis at different phases throughout the animal studies were later confirmed via histochemical staining of the harvested myocardial tissue, which was used to determine final infarct size.TandemHeart unloading prior to reperfusion enabled approximately a 50% decrease in myocardial infarct size compared to the control group (Control: 53% infarct; TandemHeart: 27% infarct), with a greater degree of myocardial salvage in each progressive section of the LV (Figure 12).

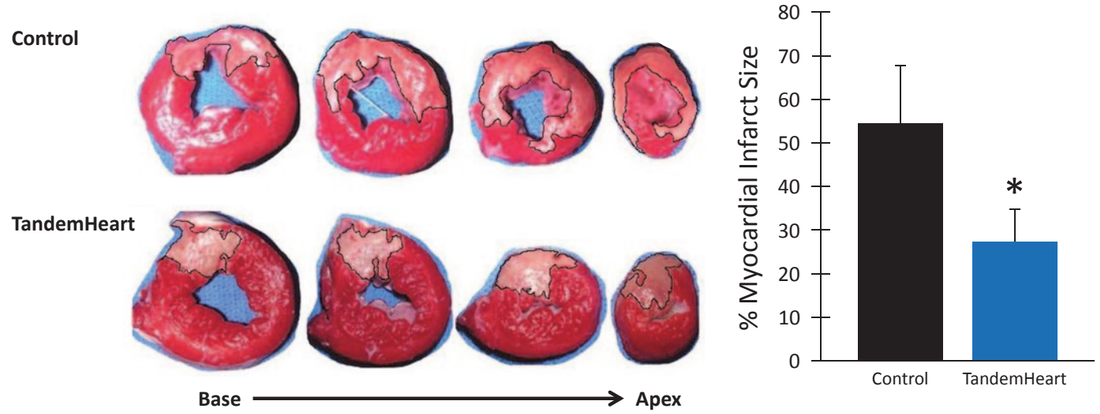

Figure 12 *TandemHeart group exhibited 50% reduction in myocardial infarct size versus control group.*

These results were confirmed to be statistically significant by repeating the protocol with multiple animals. Additionally, the degree of unloading as defined by LV stroke work was determined to be highly correlated to percent myocardial salvage (Figure 13).

Because reperfusion injury is now theorized to be attenuated by the activation of several cascades of pro-survival signaling pathways—specifically the reperfusion injury salvage kinase (RISK) pathway—this activity was also assessed. Two prominent measurable components of this molecular cardioprotection pathway are the AKT and ERK kinase cascades.[28] The pre-clinical animal study results showed evidence of these cell survival catalysts only in the TandemHeart group (Figure 14).

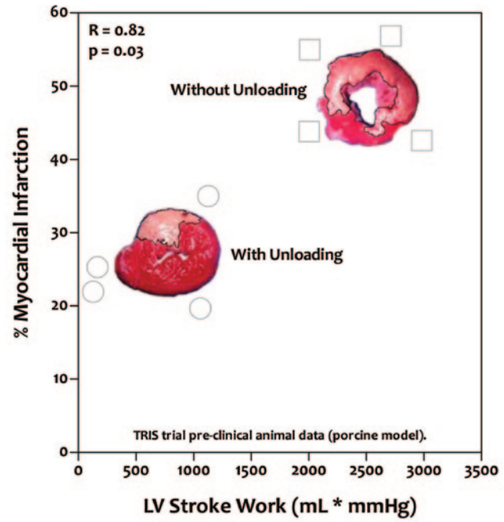

Figure 13 *Myocardial salvage was found to be closely correlated to the degree of unloading (R=0.82).*

Based on the uniformly positive results from these pre-clinical animal studies, CardiacAssist proposed a pivotal human clinical trial to the U.S. Food and Drug Administration (FDA) to investigate the use of TandemHeart to reduce infarct size in STEMI. Investigational Device Exemption (IDE) approval was received in December 2012, with hospital site recruitment and patient enrollment set to begin in 2013.

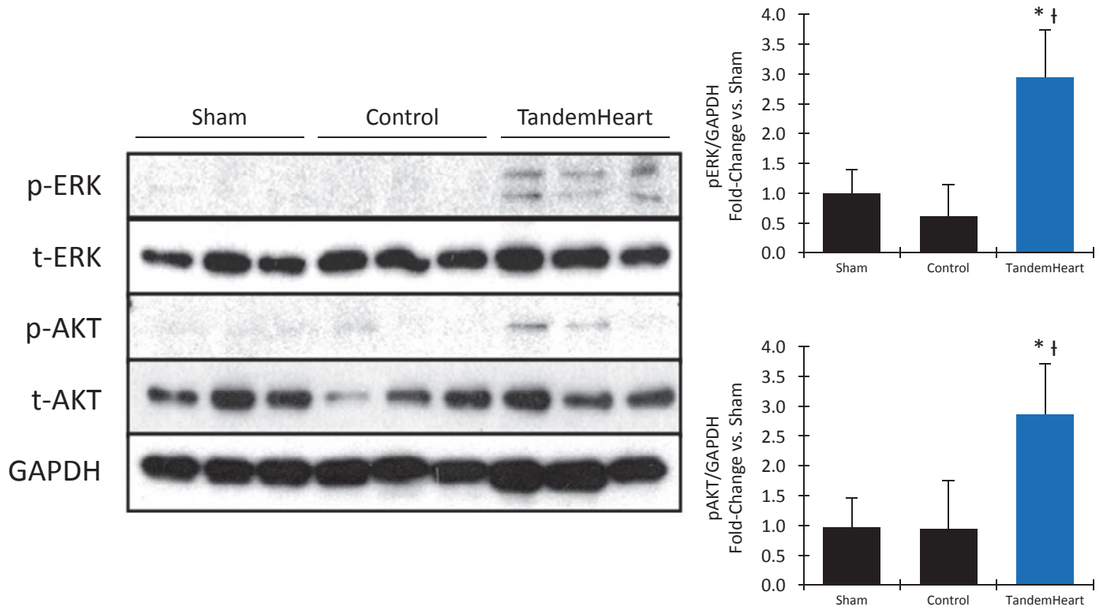

Figure 14 *Biochemical markers for cellular protection and survival were exhibited only in the TandemHeart group.*

TANDEMHEART TO REDUCE INFARCT SIZE (TRIS) TRIAL

The TandemHeart to Reduce Infarct Size (TRIS) Trial is a prospective, randomized, controlled trial to demonstrate superiority of PCI incorporating the TandemHeart system versus standard PCI treatment with respect to both safety and effectiveness. Subjects will be randomly assigned in a 1:1 ratio to treatment with TandemHeart support with PCI or to PCI treatment alone. This study is designed to evaluate the use of the TandemHeart system prior to revascularization (as compared to standard PCI therapy) to limit infarct size in subjects with an acute anterior AMI with an ST elevation of > 2mm in two or more contiguous anterior leads.

The TandemHeart system will be used for 12 hours and then weaned from use within the subsequent 12 hours (for a total of up to 24 hours of use). This system offers a unique solution for these subjects, as it is designed for percutaneous access to provide rapid ventricular unloading and increased systemic support. Specifically, the objective of this study is to demonstrate the ability of the TandemHeart system to limit myocardial reperfusion injury and infarct size in a human STEMI patient population.

The primary endpoint for the TRIS Trial is reduction in myocardial salvage index (MSI), which measures the effectiveness of interventions that aim to reduce final infarct size. MSI has previously been determined to be a valid and reliable surrogate for mortality in clinical trials testing the efficacy of reperfusion therapies in AMI. Secondary endpoints include 1-year mortality and the rates of cardiac re-hospitalization and implantable cardioverter defibrillator (ICD) placement within the first 365 days after treatment.[30]

For this study, a combined method of angiographic assessment and cardiovascular magnetic resonance (CMR) imaging performed 3–5 days after the infarct (reviewed by a core lab) will be used to determine the MSI. The literature and available data suggest an 11-point improvement in MSI corresponds to a 5% absolute reduction in infarct size. We can approximate that the 5 percentage point reduction in infarct size (used to guide prior AMI studies), corresponding to a 3.1% increase in EF, would be associated with an approximate 10% decrease in one-year mortality.[31,32] As a result, the TRIS Trial has the potential to show real clinical value and create a paradigm shift in STEMI care in the current era.

For more information regarding the TRIS Trial, or to be considered as a participating hospital site, please contact CardiacAssist at cardiacassist.com/contact.

TRIS TRIAL

FOOTNOTES

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7100-0100 Rev 1 | 07.26.2013