Clinical outcomes of sustained ventricular arrhythmias in recipients of Left Ventricular Assist Devices

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A. Purpose and Rationale

Heart failure afflicts one percent of the U.S. population. Although recent trials have demonstrated medical treatment can alter the course of heart failure, the current five year survival is still less than 50%. An estimated 60 thousand patients with end-stage heart failure could benefit from heart transplant each year. Despite efforts to increase popular awareness of the need for and import of organ donation, only 2500 hearts are donated annually, and an estimated 10% of those awaiting transplant die each year. Recently, mechanical left ventricular assist devices, which were previously used as only a bridge to transplant, have been shown to improve survival as a destination device. The REMATCH trial demonstrated that in those patients who were not candidates for heart transplant because of clinically irreversible end-organ damage, a left ventricular assist device (LVAD) doubled the one-year survival. Although still inferior to transplantation, the LVAD is a promising alternative therapy. The study used the Thorotec (brand name, Heartmate) device. In this device, blood is pumped by a rotary electric motor and is lined with a textured biological surface that has been demonstrated to reduce the risk of thrombus formation within the device. The Heartmate is implanted in the apex of the left ventricle and pumps blood from the left ventricle to the ascending aorta. The FDA has approved the use of the Heartmate as a destination device in end-stage heart failure who are not transplant candidates.

Still, we are only beginning to learn the about the clinical complications faced by these patients and the appropriate supportive treatments. The clinical ramifications of arrhythmias and therefore the necessary treatments have yet to be delineated. Sustained ventricular arrhythmias, in particular, have been met with some ambivalence. Based mostly on clinical experience, but as well on a small nine patient case series, otherwise hemodynamically unstable rhythms such as ventricular tachycardia and fibrillation have been considered relatively well tolerated in LVAD patients. While in any other population such rhythms would result in a spectrum of hemodynamic instability ranging from severe hypotension to frank cardiac arrest, the patient supported by an LVAD enjoys continued strake volume and relative stability. The LVAD functions independent of the native cardiac electrical activity. But these arrhythmias are not considered benign. Up to 40% result in clinically significant decreased blood flows through the LVAD. Furthermore, based on experience with patients without LVADs prolonged arrhythmias raise concern for thrombogenesis and tachycardia induced heart failure. In LVAD patients tachycardia induced failure would presumably result in right heart failure. Although with normal pulmonary physiology right heart dysfunction results in few symptoms with LVAD patients, it is postulated that LVAD patients with pulmonary hypertension would suffer markedly reduced flows. The poor passive blood movement across the pulmonary vasculature in such a case would result in decreased left sided filling pressure and therefore LVAD output. Despite the limited data available, clinical experience has led to providers to develop a common approach to sustained ventricular arrhythmias. First, anticoagulation is avoided. LVAD patients are prone to hemorrhaging, especially at the intra-abdominal pouch created where the motor sits. Second, the arrhythmias are cardioverted, though the time to cardioversion tends to vary with clinical appearance of the patient. Finally, the decision to use anti-arrhythmic agents has primarily involved the presence of significantly decreased LVAD flows. The frequency of arrhythmias has generally not been a factor.

The REMATCH trial describes a ventricular arrhythmia rate of 25% per patient year. The small case series describing specifically these arrhythmias in LVAD patients demonstrated a rate of 40% (9 out of 21 patients). The REMATCH trial also describes a 39% per patient year rate of neurological events, which include TIA and stroke. Two of the 41 deaths recorded during the 30-month follow up period were

caused by pulmonary embolism and four were caused by stroke. Although prolonged arrhythmia is considered a possible risk for thrombogenesis, no evidence has successfully linked or refuted a link between thromboembolic events and arrhythmias in LVAD patients. Furthermore, a possible relationship between arrhythmias and survival with LVAD has yet to be fully investigated.

Currently, 210 LVADs have been placed in all patients, both as a bridge to transplant and as destination treatment. An initial survey of these patients charts is underway. The survey focuses on both atrial and ventricular arrhythmias and correlations to outcomes and treatments. This survey, however, will be limited in its power to delineate these relationships for a number of reasons. The 210 LVAD implants over a ten year span include several different devices, some having with higher risk of thromboembolic events than others. Furthermore, through the ten year span the mechanism of dealing with arrhythmias has changed. Finally, the group includes both future transplant recipients and those who are not transplant candidates. The who are not candidates for transplant are generally a sicker group and have as a group had a higher incidence of thromboembolic events than those awaiting transplants. There are already 66 patients who have received LVADs as destination treatment. With the new FDA approval of LVAD as destination therapy, we propose a prospective observational study of sustained ventricular arrhythmias and their correlation with adverse outcomes in recipients of LVADs as destination treatment. As destination therapy with LVAD becomes more common, it behooves us to better understand the clinical significance of sustained ventricular arrhythmias.

B. Study Design and Statistical Analysis

This multi-center observational study will compare the presence of negative outcomes among those patients with LVAD as destination therapy with and without the existence of sustained ventricular arrhythmias. The study will combine retrospective data from the REMATCH trial and prospective data from patients at these same centers who will receive LVADs as destination therapy. The specific outcomes looked at will be death from all causes and thromboembolic events, including stroke, transient ischemic attack or pulmonary embolism. Subjects who receive an LVAD as a destination treatment will be asked to participate prior to implantation. They will be followed for the presence of sustained ventricular arrhythmias after their implantation. Ventricular tachycardia for greater than 30 seconds or ventricular fibrillation would be considered sustained arrhythmias. Patients will be placed in the arrhythmia group during the analysis if an arrhythmia is present at any time during their initial hospitalization. The median hospital time is expected to be two months. As with current accepted treatment, patients will not be anticoagulated during the arrhythmia. All patients are placed on aspirin 325 mg. The arrhythmia will be terminated by cardioversion. The time to cardioversion will be left up to the discretion of the clinician. In general, patients who have a decrease in their LVAD flows will be cardioverted earlier than those who are stable. Furthermore, those who show a decrease in LVAD flows of greater than 2 liters per minute will be started on amiodarone as secondary prevention of arrhythmias. From the REMATCH trial and unpublished data at CPMC, we expect that about half of patients will end up on anti-arrhythmic agents, primarily amiodarone. Patients placed on anti-arrhythmics will be placed in a separate group for analysis. From previous experience, patients on anti-arrhythmics before the LVAD is placed are taken off after surgery, since it is believed that the potential adverse effects are more likely than any benefit once the LVAD is in place. From our unpublished data and the REMATCH trial, we expect supraventricular tachycardias to be as common as 30-50% of the patient population. These tachycardias will be treated in a similar fashion, cardioverted without anticoagulation with the introduction of amiodarone only if LVAD flows drop. These arrhythmias will be recorded for later analysis, but we will not attempt to separate these patients from the ventricular tachycardias for analysis. We expect that the supraventricular arrhythmias will occur independently of the occurrence of ventricular tachycardias. Furthermore, they should distribute evenly among the patients with and without ventricular tachycardias. In the end, we will create four separate cohorts for analysis: Patients without ventricular arrhythmias off any antiarrhythmics, and those on antiarrthythmics for supraventricular tachycardias

because of drops in LVAD flows; patients with sustained ventricular arrhythmias, and those with the ventricular arrhythmias on anti-arrhyythmic agents because of reduction in LVAD flows.

The study will include patients recruited and followed by 20 separate medical centers with experienced LVAD programs. We will recruit 198 patients over 3 years, as estimated by the time course of the REMATCH trial. This group will include the 66 LVAD recipients from the REMATCH trial and 132 newly recruited patients. Although combining retrospective and prospective data may create a detection bias, this bias should be distributed equally among the groups. The use of retrospective data would shorten the length of the study by 1.5 years and would allow for the power to find a significant difference within 1.5 years. Analysis will be done when 66 new deaths occur. Based on our unpublished data, the REMATCH trial and the small arrhythmia case series, we expect a 25% per patient year occurrence of thromboembolic events and a 33% prevalence of ventricular arrhythmias in our group. Assuming about a 50% use of antiarrhythmics, as seen in the REMATCH trial, we would expect that of the total 198 patients, 87 will have ventricular tachycardias, and 44 without use of anti-arrhythmics. We will compare both all patients with and without arrhythmias, regardless of anti-arrhythmic use and the subgroups of patients with and without ventricular arrhythmias who did not receive anti-arrhythmics. The study will have 80% power to be able to demonstrate a 3 fold increase in thromboembolic events in patients with arrhythmias in the subgroup analysis of patients not receiving anti-arrhythmics (N1=33, N2=66, p1=.45, p2=.15). With a 50% death rate expected, the study will have 80% power to detect a 1.8 fold risk increase of all cause mortality in the arrhythmia group at the 1.5 year period (N1=44, N2=88, p1=.70, p2=.39).

Power analysis

time	total N	1	2	1	2	R el Risk
0	66					3
		2	4	54	15	.6
1.5 yrs	132					2
		4	8	50	23	.0
3.0 yrs (sub-group)	198/2 =99 no anti-arrhythmics					3
		3	6	45	15	.0

We will use a Kaplan-Meier Analysis for the primary outcome of death from any cause. Those who have their LVADs removed due to improved left ventricular function will be censored in the final analysis of death from all causes. Thromboembolic events will be analyzed by a Chi-Squared test. P values of 0.05 will be accepted as statistically significant. We will also conduct multiple variable analysis to adjust for differences in characteristics that may affect outcomes including: age, gender, ejection fraction, type of cardiomyopathy, supraventricular arrhythmias, time to cardioversion, sepsis, use of antibiotics, baseline pulmonary disease, hepatic failure, renal failure, use of anti-arrhythmics, and beta-blocker use.

C. Study Procedures

Patients will receive a Heartmate, Left Ventricular Assist Device, implanted by the surgical transplant team in the usual fashion. Patients will be followed on telemetry initially in the ICU, and once stable on the floor. The telemetry readings will be reviewed by two separate cardiologists each day at each participating center, who will both be blinded to any clinical events of the subjects. While the patients are followed in-house, when ventricular arrhythmias are noted, every effort will be made to capture the arrhythmia on a twelve-lead electrocardiogram. These 12-leads will be reviewed in a similar fashion by two separate cardiologist. A neurologist who is blinded to the presence of arrhythmias will follow the patients and interview and examine them daily while in-house. The neurologist will use a

standard questionnaire to screen for embolic neurological events. Pulmonary embolism will be recorded if clinically diagnosed. Once discharged from the hospital patients will be followed closely in clinic and will be seen monthly unless it is clinically warranted to see a physician earlier. At clinic visits patients will be interviewed using the same neurological questionnaire. A twelve-lead EKG will also be done. The questionnaire is the only part of the study that is not part of the usual clinical management of the patients. The REMATCH study required 3 years to recruit 130 patients (66 LVAD recipients). We expect 44 LVADs to be placed yearly at the 20 centers; about 2 LVADs per year per location. We expect the study to take 6 years for recruitment and follow-up. The mean follow-up time is expected to be 1 year, as per the 50% 1-year survival of patients in the REMATCH trial.

D. Study Subjects and Recruitment

Patients are eligible if they have end-stage congestive heart failure, an ejection fraction of 25% or less, NYHA class III or IV for 28 days or more with dependence on ionotropes, with 2 failed weaning attempts, or dependence on intra-aortic balloon pump. Patients were also eligible if they had an EF of 25% and requiring ionotropic support for continued pulmonary congestion, symptomatic hypotension, or decreasing renal function. All patients must be ineligible for heart transplantation. Reasons for this contraindication are usually either due to age greater than 65, diabetes with evidence of end-organ damage, or irreversible end-organ damage such as pulmonary dysfunction, chronic renal failure with a baseline creatinine of greater than 2.5 mg/dl or hepatic failure. Once patients are eligible for LVAD as destination therapy, they are asked whether they are interested in participating in the study. Patients' decisions do not affect their ability to receive an LVAD.

E. Confidentiality of the Study Data

Patients will be given a study ID number and all study data will be filed under this ID number. The patients ID will be accessible only to the clinicians in charge of the study at each center.

F. Potential Risks

Because the trial does not involve changing of clinical management, there will be no medical risk specific to the study for the patients. The risks of receiving an LVAD are infection, bleeding and operative complications.

G. Potential Benefits

The study may benefit patients with LVADs by clarifying the clinical significance of arrhythmias and may help delineate changes in future standard of care of arrhythmias in LVAD recipients.

H. Compensation

After the patients are discharged, they will be seen every month in clinic. The clinic visit will include a neurological questionnaire. Patients will receive 10 dollars for each questionnaire that they complete