

Treatment of Ventricular Arrhythmias in Patients Undergoing LVAD Therapy

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"When the heart is diseased, its work is imperfectly performed: the vessels proceeding from the heart become inactive, so that you cannot feel them ... if the heart trembles, has little power and sinks, the disease is advanced and death is near."
- Ebers Papyrus of Ancient Egypt: est. 1500 B.C

1. Introduction

Ventricular tachycardia (VT) and ventricular fibrillation (VF) are not uncommon in patients with end-stage heart failure. With the shortage of donor cardiac allografts, most potential heart transplant recipients are now being bridged with continuous-flow left ventricular assist devices (LVADs). In addition, with the recent FDA approval of the HeartMate® II LVAD (Thoratec Corp., Pleasanton, CA) as a destination therapy (DT) device, the potential pool of patients that may benefit from this therapy has expanded almost exponentially. While ventricular arrhythmias are common in patients with all types of cardiomyopathy and heart failure, the effect of LVAD therapy on the incidence of new, or the persistence of old ventricular arrhythmias is unknown. Recent evidence has suggested a possible increase in the rates of VT/VF in patients undergoing LVAD therapy with continuous flow devices as opposed to older pulsatile devices (Ziv et al, 2005);(Andersen et al., 2009). The potential utility of ventricular ablative procedures at the time of continuous flow LVAD placement is unclear. We have implanted 51 continuous flow LVADs over the past 21 months. Because the incidence of clinically significant post-operative VT/VF was initially higher than what he had experienced with earlier generation pulsatile LVADs, we have recently become aggressive at treating VT/VF at the time of LVAD placement. Any patient with a history of previous VT/VF has substrate localization performed via electrophysiologic (EP) mapping or systematic EKG analysis prior to LVAD placement. Intraoperatively, the endocardium is ablated through the LVAD ventriculotomy with cryoablation in addition to epicardial ablation also carried out with cryoablation. Since implementing this algorithm, the incidence of clinically significant post-operative VT/VF requiring additional catheter ablation has fallen to zero. We recommend aggressive localization and subsequent intra-operative ablation for all patients with a history of significant or worsening VT/VF prior to continuous flow LVAD placement to decrease the need for post-operative medical or catheter-based anti-arrhythmic therapy and to improve outcomes.

2. Background

2.1 Heart failure

Cardiovascular disease remains the leading cause of death in the United States and other industrialized nations (Kokolis, 2006). Heart failure represents the end stage of cardiovascular disease and continues to have a high prevalence in the U.S. despite advances in medical therapy. In developing countries, around 2% of adults suffer from heart failure, but in those over the age of 65, this increases to 6–10% (McMurray & Pfeffer 2005). Approximately 5 million Americans suffer from heart failure with over 550,000 new cases diagnosed each year (AHA, 2006). Community-based surveys show that 30–40% of patients die within a year of diagnosis and 60–70% die within 5 years, most from worsening heart failure or suddenly (probably because of a ventricular arrhythmia) (McMurray & Pfeffer, 2005). It is estimated that heart failure causes about 287, 0000 deaths in the US each year (AHA, 2006). In addition to the loss of life, heart failure poses a significant financial burden with estimated annual direct costs in the U.S. of \$35 billion dollars (AHA, 2006). Hospitalizations due to heart failure are increasing and this is expected to continue with the progressively aging population (Roger, 2004).

Despite the advances in the management of heart failure, there may be as many as 100,000 persons who have been treated with guidelines-based therapy but have remained relatively unresponsive in New York Heart Association (NYHA) Class IIIb or IV heart failure (O'Connell, 2009). Optimal therapy with angiotensin-converting enzymes inhibitors, angiotensin receptor blockers, beta blockers, aldosterone antagonists, nitric oxide enhancers, implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy have reduced hospitalizations and prolonged survival. However, the response is not uniform and at least a quarter of those who receive all therapies fail to respond (Hawkins, 2009). In these end-stage heart failure patients with recurrent hospitalizations, few options exist. Aggressive surgical approaches including cardiac restraint devices, mitral valve repair, and surgical ventricular reconstruction are under evaluation but have yet to demonstrate definitive benefit (Mann et al., 2007);(Jones et al. 2009). Only cardiac transplantation has been shown to definitively improve outcomes with median survival of 13 years, but this is restricted to a select relatively young population (Taylor et al., 2009). The number of heart transplants in the U.S. has remained stable at about 2,000 per year, only 2% to 4% of patients who need definitive therapy. With a growing population of end-stage heart failure patients and a static donor pool, it has become clear that heart transplantation will never meet the demands. Although there is great enthusiasm for innovative approaches, stem cell therapy is only entering preliminary clinical trials, gene therapy of calcium transport proteins is only completing the first step in the cascade of clinical trials, and xenografting research has been stalled (O'Connell 2009). To date, the most promising area of development has been mechanical circulatory support with LVADs, most recently with the Thoratec HeartMate II.

2.2 Left ventricular assist devices

Implantable left ventricular assist devices have become accepted as an important therapeutic modality for patients with end-stage heart failure. The most common uses for LVADs include bridge to heart transplantation (BTT) and long-term destination therapy (DT) for those patients not eligible for transplantation.

The development of ventricular assist devices began in earnest in 1964 with the National Institutes of Health establishment of the Artificial Heart Program, whose stated goal was

putting a man-made heart into a human being by the end of the decade (Sahuar 2004). Unlike the moon-landing, this lofty goal was not met. Nevertheless, progress proceeded slowly and clinical use of ventricular assist devices on a more routine basis began in the mid 1980s. Since then, the research and development of ventricular assist device technology, along with clinical progress, has accelerated. Several LVADs have now been designed and developed and are in various phases of clinical and preclinical evaluation. Currently, implantable LVADs can be classified into two main categories: volume-displacement (pulsatile) and continuous-flow (nonpulsatile) pumps. All LVADs are composed of an inflow cannula, the actual pump with its associated mechanical and electrical components, an outflow conduit, a percutaneous lead, and the external system components with varying degrees of portability. LVADs can also be grouped based on the engineering design of the pump with classification broadly as first-, second-, and third-generation devices (Nguyen & Thourani, 2010). First-generation devices are the pulsatile pumps. They include the HeartMate XVE and its predecessors including the HeartMate IP1000 and HeartMate VE (Thoratec Corp., Pleasanton, CA), the Thoratec PVAD and IVAD (Thoratec Corp.), and the Novacor LVAS (World Heart Corp., Oakland, CA). In contrast to the first-generation devices, both second- and third-generation LVADs are continuous flow, rotary pumps. Second-generation pumps, which include the HeartMate II (Thoratec Corp.), Jarvik 2000 FlowMaker (Jarvik Heart, Inc., New York, NY), and MicroMed-DeBakey (MicroMed Cardiovascular, Inc., Houston, TX), have an internal rotor within the blood flow path that is suspended by contact, blood-immersed bearings. Third-generation devices are similar, but lack contact bearings in an effort to prevent wear and prolong device life without failure. Third-generation devices are in varying stages of clinical development, but are not available for commercial use in the U.S.

First-generation LVADs came to clinical use in the mid 1980s and all of the first-generation devices listed above are approved for BTT. Despite this, only the HeartMate XVE is approved by the Food and Drug Administration for DT in the United States. As volume displacement pumps, first-generation LVADs have an internal reservoir chamber with inflow and outflow valves. The pumps function by cyclic filling and emptying of the reservoir chamber either by pneumatic or electrical drive systems. More than 5000 pulsatile HeartMate devices have been implanted worldwide and have been shown to provide excellent hemodynamic support (Frazier et al., 2001). In several studies, mechanical circulatory support with these devices is reported to bridge patients successfully to transplant with a perioperative mortality of 15% to 20% and an overall survival until transplantation of 60% to 70% (El-Banayosy et al., 2000). Unfortunately, first-generation devices have inherent limitations in their design, particularly when used for the purpose of prolonged support or DT. The pump size is quite large, thus requiring extensive surgical dissection with subsequent risk of hematoma formation and infection. The large size also limits implantation to patients with a large body habitus. In addition, a large-diameter percutaneous lead is needed for venting of air, which can lead to an increased risk of driveline infections. Finally, a critical drawback in first-generation devices is the high frequency of eventual device failure, requiring device exchange or causing possible death. In the landmark REMATCH trial, which was used as the basis for LVAD approval for DT, the failure rate of the HeartMate XVE after 2 years was 35%, with a mortality of more than 10% attributed directly to device failure (Rose et al., 2001).

The second-generation have now essentially replaced the first-generation devices for clinical use. The most extensive clinical experience is with the HeartMate II. Currently, this is the

only second-generation device approved for both BTT and DT in the United States (Miller et al., 2007); (Slaughter et al., 2009). These continuous flow, rotary pumps were introduced to overcome many of the shortcomings of the first-generation devices. They are simpler in design with only a single moving part: the internal rotor. Advantages over first-generation devices include smaller size requiring less extensive surgical dissection for implantation, the absence of valves that are a primary site of wear, higher efficiency with less energy requirement, and a smaller percutaneous lead (Nguyen & Thourani, 2010). With these improvements, the second-generation devices have shown to be much more reliable with device support of more than 6 years reported (Westaby et al., 2006). While the necessity for device replacement does still occur with the HeartMate II, the underlying causes have been related to thrombosis, infection, or damage to the percutaneous leads and not to mechanical failures of the pumping mechanism (Slaughter et al., 2009). In a recently-published randomized clinical trial for DT comparing the HeartMate II versus the first-generation HeartMate XVE, the HeartMate II was shown to be significantly better than the HeartMate XVE in achieving the primary end point of survival free from device failure or disabling stroke at 2 years (Slaughter et al., 2009). Moreover, patients with HeartMate II support also had significantly superior actuarial survival rates at 2 years (58% vs. 24%). In addition, device failure and other complications including infections were less frequent in patients supported with the HeartMate II.

3. Ventricular arrhythmias

Mortality in patients with heart failure is mostly due to progressive heart failure or sudden death related to ventricular tachyarrhythmias (VAs) (Jessup, 2003). The most important risk factor for VA is a reduced ejection fraction (EF) (Myerburg et al., 1997; Singh et al., 2002). Although medications such as beta-blockers, ACE inhibitors, and ARBs, and devices such as implantable cardiac defibrillators (ICDs) have been shown to decrease morbidity and mortality, the risk of sudden cardiac death (SCD) remains high. In fact, approximately 50% of patients with heart failure die from SCD (Guido et al., 1997).

While the precise mechanism of ventricular tachyarrhythmias is not entirely understood, VAs are generally thought to originate from cardiac scar tissue and from the border between normal myocardium and scar tissue. Ventricular scars are composed of variable regions of dense fibrosis that create conduction block and surviving myocyte bundles with interstitial fibrosis and diminished coupling, which produce the circuitous slow-conduction paths (Stevenson & Soejima, 2007). The effective refractory period in the action potential of this borderline ischemic, viable myocardium is altered and bears the risk of generating the re-entry circuits responsible for ventricular tachyarrhythmias (Doenst et al., 2007).

In all patients with heart failure, the elevation of plasma catecholamines that cause increases in sympathetic outflow along with decrease in parasympathetic activity correlate well with poor prognosis. Also significant in many patients are anatomic and mechanical factors such as wall stretch, abnormal wall motion, left ventricular stress, and increased myocardial length. These factors acting directly, or through alterations in hemodynamic factors, may lead to the genesis of cardiac arrhythmias in the setting of heart failure (Damiano et al., 1985). All of these causative arrhythmogenic factors merge in the dilated and failing ventricle, creating a perfect storm for arrhythmogenesis. The immediate trigger for the development of VT or VF in an individual patient with heart failure is often unclear but a composite of the major interacting factors will reveal those patients at highest risk for sudden death.

To properly understand ventricular tachyarrhythmias, it is necessary to distinguish monomorphic ventricular tachycardia (MMVT) on one hand, and polymorphic ventricular tachycardia (PMVT) and ventricular fibrillation (VF) on the other. Monomorphic VT is generally caused by fixed anatomic abnormalities such as scar from previous MI where border zone areas generate re-entrant circuits causing VT (Stevenson & Soejima, 2007). This ventricular scar can be caused by ischemia or other forms of injury including scar tissue resultant from LVAD cannula placement. In this case, 12-lead electrocardiogram and EP mapping can be used to localize specific areas of the ventricle where scar is present and re-entrant VT is initiated. On the other hand, PVT and VF are generally caused by a functionally deteriorating ventricle and result from repolarization abnormalities of the unhealthy myocardium (Aliot et al., 2009). Congestive heart failure caused by the failing ventricle creates ventricular dilation, increase wall tension, and with that, conditions ripe for subendocardial ischemia. These conditions alter the electric behaviour of the ventricle and can result in the disorganized contractions seen in PVT and VF. As a result of the often direct anatomic correlation between MMVT and myocardial scar, MMVT is usually more receptive to targeted ablation therapies (Aliot et al., 2009). Eliminating PMVT and VF is more difficult and often requires therapy guided toward functional improvement of the failing ventricle rather than ablation alone.

4. Arrhythmias in patients with VADs

4.1 Background

The prevalence of ventricular arrhythmias is highest in those patients with severe end-stage heart failure: the same cohort of patients who stand to benefit most from LVAD therapy. Therefore, it should come as no surprise that ventricular arrhythmias are relatively common in patients supported with LVADs. Despite this, the interaction between LVAD placement and ventricular arrhythmias is not well understood. On one hand, LVAD placement does ease the burden on a diseased left ventricle by decompressing the ventricle. This decompression in turn decreases the neurohormonal, hemodynamic, mechanical, and electrolyte abnormalities which predispose toward arrhythmia development; thereby reducing the frequency of post-op VTE, especially PMVT and VF. In contrast, LVAD placement does not treat areas of existing ventricular scar, and indeed the apical cannula placement necessarily requires creation of new myocardial scar tissue. This new scar tissue created by LVAD implantation places patients at risk for new monomorphic ventricular arrhythmias and does not impact existing MMVT resulting from other areas of scar. Indeed, many reports suggest a higher incidence of ventricular arrhythmias in patients after LVAD placement (Ziv et al., 2005);(Andersen et al., 2009). Postoperative ventricular tachyarrhythmia events (VTE) have been documented to occur in up to 35% of patients within 30 days of LVAD placement (Ziv et al., 2005);(Refaat et al., 2008).

The pathogenesis of increased arrhythmias post-LVAD is likely to be caused by direct mechanical irritation from the inflow cannula of the LVAD as well as scar tissue from the cannula placement. With the LVAD in place the ventricle is decompressed and the aortic root pressure improved, resulting in improved blood flow to scarred regions of the heart and actually allowing for the tissue to conduct and support VT. Post-VAD arrhythmias have also been attributed in the literature to a host of other mechanisms including acute left ventricular unloading with pulsatile VADs, altered ventricular repolarization (Grzywacz et al., 2006), mechano-electrical feedback from the VAD motor (Harding et al., 2001), and alterations in

calcium handling gene expression (Rodriguez-Way et al., 2005). In addition, continuous flow devices are theorized to predispose to arrhythmias by causing so-called "suction events" when the ventricle is completely decompressed and the endocardium is sucked against the inflow cannula (Vollkron et al., 2007). This suction phenomenon is thought to account for the apparent increased arrhythmia incidence with continuous flow LVADs as opposed to pulsatile LVADs. While all of these theories are interesting and may contribute to the existing understanding of the interaction between LVADs and ventricular arrhythmias, the reality is that the current paucity of published literature and surplus of theories reflect an inadequate understanding of the relationship. Most of the available data concerning arrhythmias in patients with LVADs constitute results from relatively small case series. In addition, most of these case series review data from patients with pulsatile LVADs, while newer continuous flow devices such as the HeartMate II now dominate the national clinical practice.

While the presence of an LVAD mitigates the profound hemodynamic collapse often seen in unsupported patients with VT or VF, studies have demonstrated a decrease in LVAD flow output with ventricular tachyarrhythmias (Bedi et al., 2007). Additionally, crude mortality as high as 52% has been reported for patients with VT/VF within 1 week postoperatively (Bedi et al., 2007). Ventricular tachyarrhythmias can reduce right ventricle output, thereby reducing left ventricular venous return. Therefore, even though the left ventricle is supported by the LVAD, the arrhythmia prevents adequate preload on left ventricle and can become hemodynamically unstable. Thus, elimination of ventricular tachyarrhythmias in LVAD patients is essential to maximizing outcomes.

4.2 Literature review

In order to begin understanding the relationship between ventricular arrhythmias and LVADs it is necessary to review of the existing literature. In 1991, the first known report of ventricular arrhythmias in patients with LVADs was published (Arai et al., 1991). In 1994, Oz et al. reported that ventricular arrhythmias are well tolerated in the immediate setting in patients LVAD support. Pulmonary perfusion was maintained even during rapid ventricular arrhythmias and cardiac arrest was well tolerated without syncope. Thus, delayed termination of ventricular fibrillation or flutter was reported to be safe and feasible in this setting (Oz et al., 1994). In 1997, the first case report documenting benefit from an implantable cardioverter-defibrillator (ICD) in a patient on LVAD support was published in a 51 year-old male who underwent LVAD implantation for refractory heart failure after having received an ICD five years earlier (Skinner et al., 1997).

Following these reports, it took until 2005 for a relatively large retrospective observational study to be performed (Ziv et al., 2005). This study remains of the best available, and reported a 32% incidence of VT/VF following pulsatile LVAD implantation for advanced heart failure, with particularly high rates during the early post-operative period (Ziv et al., 2005). Notable in this study was the comparison of pre-operative arrhythmias to post-operative arrhythmias. One hundred and eighteen episodes of documented sustained ventricular arrhythmia occurred in 30 (of 100) patients pre-operatively, one hundred and seventy nine episodes occurred in 32 patients post-operatively. Of those 9 patients with pre-operative MVT, 4 patients no longer had MVT and 5 continued to have MVT after LVAD. New-onset MVT was documented in 18 patients who had no pre-LVAD MVT, 12 of whom had no pre-LVAD arrhythmia of any type. With regards to PVT and VF, 23 patients had PVT/VF documented pre-operatively and 17 patients had PVT/VF post-operatively. PVT/VF was no longer observed in 16 patients who had this arrhythmia before LVAD

placement, whereas PVT/VF was a new finding in 10 patients who had not had this arrhythmia documented pre-operatively.

Summarizing these results, in 100 patients undergoing pulsatile LVAD implantation, there was a slight decrease in post-operative PVT/VF and a significant increase in post-operative MVT. This is exactly as one might expect given the LVADs role in decompression of the ventricle helping with PVT/VF, but creating a new site of scar and mechanical irritation in the ventricle and causing a new focus for MVT. In addition, the majority of the 32 patients who had post-LVAD ventricular arrhythmias had experienced the first episode by the end of the first postoperative week. Post-LVAD ventricular tachyarrhythmia was nearly incessant in 9 patients and highly frequent (>5 episodes/day) in 7 patients. Whereas the total number of patients with ventricular tachyarrhythmias of any kind before and after LVAD was similar, post-LVAD arrhythmias were more frequent and resistant to drug treatments. Trends were observed in all-cause mortality and stroke, but no statistically significant relationship between arrhythmia and these outcomes was demonstrated (Ziv et al., 2005).

The above retrospective review was followed by another retrospective review of 111 consecutive patients undergoing pulsatile LVAD placement for BTT between 1987 and 2001 (Bedi et al., 2007). In this study, clinically significant ventricular arrhythmias occurred in 24 patients (22%) during device support. 54% of these occurred during the first week post-implantation. The mortality was significantly higher ($p < 0.001$) during LVAD support in the group with ventricular arrhythmias (33%) vs. the group without ventricular arrhythmias (18%). In 2008 a smaller retrospective review of 42 patients (Refaat et al., 2008) documented post-operative ventricular arrhythmias in 15 patients (36%). Analysis of multiple pre- and post-operative factors revealed that non-usage of post-operative beta-blockade was strongly associated with arrhythmia development (odds ratio 7.04, $p = 0.001$). Unfortunately, this association has not been borne out in subsequent studies.

A 2009 retrospective review represents the first published description of ventricular arrhythmias in continuous flow LVADs. This study reviewed records of 23 consecutive HeartMate II recipients and documented a 52% incidence (12 of 23) of sustained VT or VF (Anderson et al. 2009). 75% of the patients experienced the arrhythmia within 4 weeks, and in all of these patients the arrhythmia predicted recurrent arrhythmic events. None of these patients died of the arrhythmia but most were symptomatic during the event. 32% of the patients required cardioversion or defibrillation. Based on the high incidence of post-operative arrhythmias, along with the fact that 3 patients experienced hemodynamic instability associated with the event, the authors recommended consideration for prophylactic ICD implantation for all patients expected to be supported by the LVAD for a longer period of time (Anderson et al 2009).

Other more recent reviews have concurred with Anderson et al.'s assertion that ICD implantation should be considered for primary prevention of VT/VF in all patients undergoing LVAD implantation. A Cleveland clinic review looked at all 478 patients undergoing VAD placement between 2001 and 2008; the majority (74%) of these being pulsatile LVADs, 8.2% continuous-flow, and 10.5% with extracorporeal systems (Cantillon et al, 2010). 90 of these patients (18%) had an ICD at the time of VAD implantation. Crude mortality was lower among patients with an ICD (24.4%) when compared to those without an ICD (36.9%; $P = 0.026$), Kaplan-Meier curve for survival shows divergence between patients with and without ICD beginning at 20 days and extending throughout the support period. 32% of the patients experienced a sustained ventricular tachyarrhythmia event in the post-operative period with the mean time to first event being 32.4 +/- 47.1 days. While

the retrospective nature and large cohort of patients with pulsatile LVADs limit the review, the survival difference in a large number of patients is intriguing.

The only prospective study looking at ventricular arrhythmias in LVAD patients is a recently published study from Hanover Germany. 61 consecutive patients underwent LVAD implantation between 2005 and 2008, 44 of these patients with the HeartMate II and 15 with the Heartware LVAD, a third-generation continuous-flow device (Oswald et al., 2010). After the acute perioperative period, all patients without a pre-existing ICD (40 patients) underwent ICD implantation (17 +/- 15 days after VAD placement). Ventricular arrhythmias leading to ICD interventions were frequent in the study population with 34% of patients receiving appropriate ICD interventions for ventricular arrhythmias during the study follow-up (median 12 months; range 13-1167 days). Even excluding the first 7 days when patients were most prone to arrhythmias, there was a still a 25% rate of appropriate ICD interventions. Observed arrhythmias were 52% monomorphic VT, 35% VF, and 13% polymorphic VT. Of the 21 patients with appropriate ICD interventions, there were a total of 144 episodes of spontaneous ventricular arrhythmias (average 6.8 per patient). Patients with no previous arrhythmia history had an estimated 1-year risk of 24% for appropriate ICD treatment, those with a secondary prevention indication had an even higher 1-year risk of 50%. In these secondary prevention patients, the calculated VTE rate per month was the same both before and after VAD placement. Interestingly, ventricular arrhythmia rate was higher in nonischemic heart failure (50%) than ischemic heart failure (22%) patients.

The observations from all of the above studies yield more questions than answers; however, several basic conclusions can be drawn from them. First, sustained ventricular arrhythmias are common in patients after LVAD implantation with a range of 22% to 52% of patients experiencing sustained VT/VF in the post-operative period. Second, most patients who experience post-operative VT/VF do so within the first few weeks after surgery. Third, patients who experience one episode of sustained VTE are more likely to experience future events. Fourth, while ventricular arrhythmias seem to be better tolerated in the LVAD population as compared to patients without assist devices, most ventricular arrhythmias do have associated symptoms, some cause hemodynamic instability, and all may impact long term survival and survival to transplantation. Fifth, prophylactic ICD placement may be indicated and a prospective randomized trial is needed to answer this question. Finally, as is always the case with any emerging medical technology, further prospective analysis is needed.

5. Arrhythmia treatment

5.1 Arrhythmia surgery

Cardiac surgery for arrhythmias was initiated in 1968 by Dr. Will Sealy with the first successful division of an accessory AV connection for the Wolff-Parkinson-White (WPW) syndrome. During the 1980s hundreds of cardiac surgeons learned the technique of open-chest surgical division of accessory AV pathways for the cure of WPW syndrome. However, as the 1980s ended, catheter-based radiofrequency ablation (RFA) emerged as a less invasive method of cure and Dr. Sealy's surgery was relegated to a historical footnote (Cox J, 2004). Subsequently, Cox and colleagues attained the first clinical cure of an AV nodal reentrant tachycardia in 1982 via a discrete cryosurgical procedure (Cox et al., 1987). Again, catheter-based RFA rapidly replaced the use of cryosurgery specifically for the treatment of AV nodal reentrant tachycardias. Nevertheless, this initially use of cryothermal energy in

cardiac surgery opened the door for other uses of cryosurgery throughout the 1980s and 1990s for treatment of other supraventricular tachyarrhythmias, atrial tachyarrhythmias via the Cox-Maze procedure, and ventricular arrhythmias via destruction of ectopic foci of excitation (Cox J, 2004).

Experiments in the 1960s had documented the heterogeneity of tissue injury in acute MI and the reentrant basis of ischemic ventricular arrhythmias was defined (Han et al., 1970);(Boineau & Cox, 1973). During the 1970s, it became apparent that simple revascularization with CABG failed to cure ischemic ventricular tachyarrhythmias and that revascularization alone had prohibitively high morbidity and mortality. In 1969, Kaiser and colleagues reported on intraoperative mapping in patients with heart disease to localize the area of ischemia injury (Kaiser et al., 1969). A decade later, Harken and associates described the endocardial resection procedure based on intraoperative mapping (Josephson et al., 1979). In the late 1980s, Dor and colleagues described the technique of both surgical resection and repair of LV aneurysms (Dor et al., 1989). Part of Dor's described procedure included cryoablation of the junction of scar and normal myocardium if spontaneous or inducible tachycardia was present preoperatively. When reporting on results of this procedure, the unexpected effect was that arrhythmias were essentially cured without need for intraoperative mapping (Dor et al., 1994). While ischemic VT remains the most common surgically treated ventricular arrhythmia to this day, these surgical procedures are only rarely performed primarily to treat arrhythmia. Most often, there is another primary indication, such as the improvement of left ventricular function (via the Dor procedure), the removal of apical thrombus, or the alleviation of heart failure symptoms (Doenst et al., 2007). Subsequent advances in the field of electrophysiology have replaced many open surgical techniques for the treatment of arrhythmias, however the use of open cryosurgery for treatment of ventricular arrhythmias in the Dor procedure, and for treatment of atrial fibrillation via the Cox-Maze procedure has persisted (Cox J, 2004).

5.2 Mechanism of cryoablation

Cryothermal energy is the preferred energy source for arrhythmia ablation in open cardiac surgery. Cryothermal energy destroys tissue through the formation of intracellular and extracellular ice crystals. These crystals disrupt the cell membrane and the cytoplasmic organelles. Following cryoablation, there is development of hemorrhage, edema, and inflammation over the first 48 hours. Healing is characterized by extensive fibrosis, which begins approximately 1 week after lesion formation. Cryoablation is the only available energy source that does not disrupt tissue collagen, thus preserving normal tissue architecture (Lall & Damiano, 2007). This makes it an excellent energy source for ablation close to valvular tissue or the fibrous skeleton of the heart. Histologically, cryoablation creates a dense homogenous scar which has been shown to have a low arrhythmogenic potential (Wetstein et al., 1985).

With conventional nitrous oxide cryoablation probes, 2 to 3 minute ablations have been shown to reliably create transmural atrial lesions and penetrate ventricular muscle to adequate depths for effective and reliable ablation. Nitrous oxide cryoablation has a history of extensive clinical use and an excellent safety profile. Thus the benefits of cryoablation include the ability to preserve tissue architecture and collagen structure, as well as a well-defined dose curve and safety profile. The potential disadvantage is the relatively long time necessary to create an ablation (2 to 3 minutes).

Two commercially available sources of cryothermal energy are available for use in cardiac surgery. The older, and more proven, technology utilizes nitrous oxide and is manufactured by Cooper Surgical, now recently purchased by AtriCure® (Cincinnati, OH). A variety of rigid and malleable probes are available for use. More recently, CryoCath Technologies (Montreal, Canada) developed a device using argon gas. This technology uses either a malleable probe or a two-in-one convertible device that incorporates a clamp and surgical probe. At one atmosphere of pressure, nitrous oxide is capable of cooling to -89.5°C , whereas argon has a minimum temperature of -185.7°C . Both types of probes consist of a hollow shaft, an electrode tip, and an integrated thermocouple for distal temperature recording. The liquid is pumped under high pressure to the electrode through an inner lumen. Once the fluid reaches the electrode, it converts to a gas phase, absorbing energy and resulting in rapid cooling of the tissue. The gas is then aspirated by vacuum through a separate return lumen to the console (Lall & Damiano, 2007). In our protocol, the AtriCure device was used with the malleable Cryo1™ probe. The probe is applied to the relevant areas selected for ablation and either a 2 or 2.5 minute cycle is used.

6. Our treatment protocol

6.1 The problem

Over the last 21 months, we have implanted 51 continuous flow HeartMate II LVADs at the University of Virginia. Following the first dozen HeartMate II implantations, we anecdotally noted that the rate of post-operative ventricular arrhythmias seemed higher than with the previously used HeartMate XVE, a pulsatile LVAD. Therefore, after the first 23 implantations of the HeartMate II, we analyzed our single-institution data and noted that the rate of post-operative VT and VF was higher in the HeartMate II population as compared to the 14 previously placed HeartMate XVE LVADs. 34.7% (n=8) of the HeartMate II patients had recurrent post-operative VT/VF, while 21.4% (n=3) of the HeartMate XVE patients had recurrent post-operative VT/VF. Importantly, pre-operative rates of VT/VF were the same in both groups (35%). While this difference did not demonstrate statistical significance, we decided that in conjunction with published data confirming a high rate of VT/VF in post-operative patients with continuous flow LVAD and the potential association of these events with poor outcomes, we needed to become more aggressive in treating for ventricular arrhythmias at the time of LVAD placement. Our group sought to devise with a method to reliably decrease, or completely prevent, the incidence of post-operative ventricular tachyarrhythmias. Through a combination of catheter-based EP approaches along with open surgical ablation techniques, we began instituting a protocol for open cryoablation of mapped arrhythmia loci at the time of LVAD implantation.

6.2 Catheter mapping and ablation

There are several methods for ablating a focus of ventricular tachycardia as mentioned previously. The most common method of ventricular arrhythmia treatment in all patients is via EP catheter-directed mapping and RFA of identified areas of endocardial border zone ischemic tissue (scar mapping) or RFA of other identified foci of arrhythmogenic substrate (activation mapping). While this represents the least invasive of potential methods for ablation of VT/VF, it suffers from several shortcomings, especially in the LVAD population.

First, with a continuous flow LVAD in place, such as the HeartMate II, the left ventricle is decompressed. In this decompressed left ventricle with the LVAD inflow cannula in the apex of the ventricle, there is very little room to maneuver the ablation catheter (see Figure 1), thus making the procedure exceedingly difficult despite the fact that reducing the LVAD flow can mitigate this issue. Second, traditional catheter-based RFA offers access only to endocardial sources of arrhythmogenic tissue. Evidence shows that up to 70% of patients with ventricular tachycardia have epicardial substrate as the source of their arrhythmia, especially those patients with non-ischemic cardiomyopathies (Sacher et al., 2009). While trans-cutaneous catheter-based epicardial ablation of ventricular tachycardia via a sub-xiphoid approach is becoming a more frequently used technique at our institution and others, it is associated with several complications including post-procedure atrial fibrillation and pericarditis, right ventricle puncture during access, and others (Aliot et al., 2009; Mahapatra et al., 2009). Third, it is difficult to reliably create transmural ventricular lesions using a catheter-based RFA approach. Therefore, post-operative catheter-based RFA for LVAD-associated ventricular arrhythmias suffers from too many shortcomings to be the primary method of ventricular tachyarrhythmia treatment in LVAD patients.

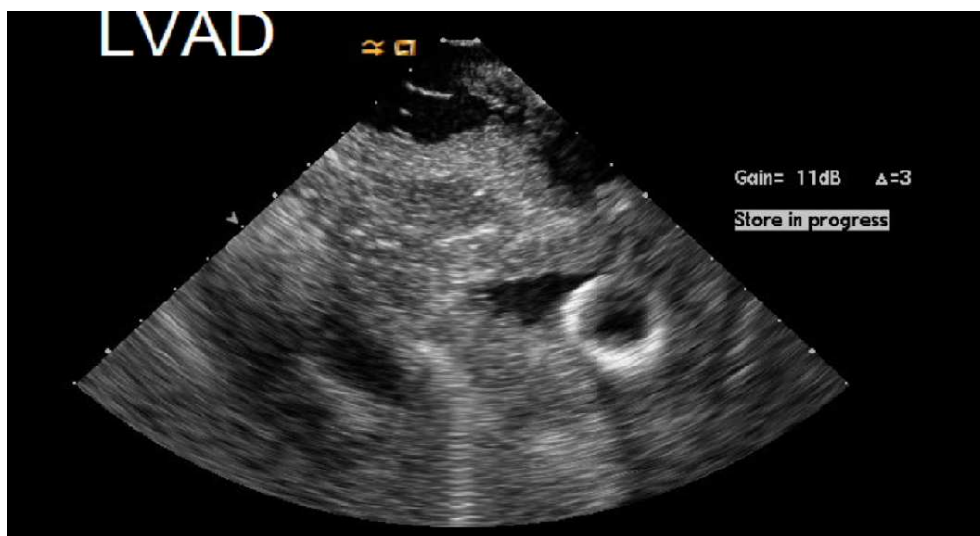


Fig. 1. Echocardiography demonstrating EP catheter in decompressed ventricle

6.3 Other options

Alternatively, given the difficulties and shortcomings associated with catheter-directed RFA, intra-operative ablation of arrhythmogenic substrate can be performed. Ideally this would be performed using simultaneous intra-operative EP scar mapping to identify areas of substrate to maximize the efficacy of cryoablation; however, this technique would require a hybrid EP suite and surgical operating room which is not available at our institution. A second option is mapping prior to planned LVAD implantation to define targeted areas for intra-operative cryoablation. Following localization of arrhythmogenic substrate via EP mapping or EKG analysis, patients can then undergo intra-operative cryoablation of the arrhythmia focus at the time of LVAD implantation.

As mentioned previously, arrhythmia surgery has in large part been replaced by catheter-directed EP therapies. However, in a case where another primary indication exists that requires sternotomy or thoracotomy with open access to the heart with or without cardiopulmonary bypass, arrhythmia surgery has remained as a mainstay of treatment. Examples of this include cryoablation at the time of surgical ventricular reconstruction, as seen in the Dor procedure, and the Cox-Maze procedure for atrial fibrillation performed in conjunction with mitral valve repair or replacement. We argue that LVAD implantation offers and equally opportune occasion for arrhythmia treatment via an open surgical approach.

6.4 Substrate mapping technique

Prior to any planned arrhythmia intervention, one must identify the target area for treatment. In our experience, this is done with either targeted EP mapping and/or systematic EKG interpretation. Using an established technique of electrophysiologic substrate mapping, a detailed schematic map of the heart is generated (Figures 3 and 4). This map is generated by measuring endocardial voltage potentials at a variety of locations. In the generated map, voltages greater than 1.5mV represent normal cardiac tissue and appear purple; voltages less than 0.5mV represent dead cardiac muscle and appear red; and voltages in between represent the borderline ischemic areas and are represented by a range of colors (Aliot et al., 2009). After substrate mapping is completed, the electrophysiologist and surgeon are able to carefully review the generated projection and can specifically target the border zone areas of potentially arrhythmogenic substrate for open intra-operative cryoablation at the time of LVAD placement. Note in figure 2 the visualized EP mapping catheter. In a hybrid EP suite/Operating room, the surgeon would be able to visualize and palpate the intra-cardiac catheter at the time of mapping in order to very specifically target the mapped arrhythmogenic substrate in real time.

Unfortunately, a hybrid suite is not available at this time and not all patients are stable enough to tolerate transport to, and mapping in, the EP suite. Given this logistic issue, we have devised a compromise technique for targeting the locus of arrhythmia-generating

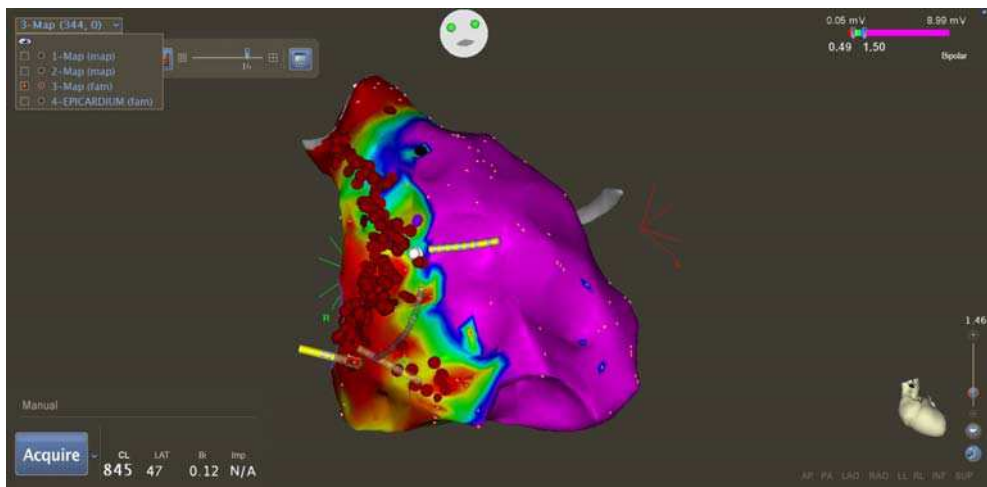


Fig. 2. Electrophysiologic Substrate Map

substrate. In patients with hemodynamic instability who would not tolerate substrate mapping in the EP suite, a systematic interpretation of 12-lead EKG results capturing episodes of ventricular arrhythmia is performed. Systematic EKG analysis of captured ventricular arrhythmia events is then used to localize the arrhythmia origin to an anatomic area of the heart (i.e. LV lateral wall).

Using Figure 3 as a guide, and Figure 4 as an example of sustained monomorphic VT, one first looks at lead V1. If a left bundle branch block (LBBB) is visible, the arrhythmia source comes from the RV or septum; if a right bundle branch block (RBBB) is visible, the arrhythmia is generated in the LV. One can then look at the direction of deflection of the QRS complex to more specifically localize the arrhythmia focus. First, looking at the inferior leads, II, III, and avF, a positive wave localizes the focus to the anterior aspect of the LV. Alternatively, a negative wave indicates posterior LV. Similarly, the precordial leads are analyzed and a positive deflection in avR and V4 indicates an apex source, a negative deflection points to the base of the ventricle. Finally, lead I and avL are analyzed, with a positive deflection indicating a septal source, a negative deflection pointing to a lateral wall source. In this manner, the focus of arrhythmogenic substrate can be localized to a specific area of the heart that allows the surgeon to target this area intra-operatively with cryoablation. For example, using Figure 4 below, the 12-lead EKG of captured ventricular tachycardia can be used to localize the arrhythmia source to the apical LV antero-lateral wall. RBBB points to the LV, then inferior leads point to the anterior surface, then precordial leads indicate an apical source, then I and avL point to the septum. Therefore, the LV antero-lateral wall close to the apex is the likely source.

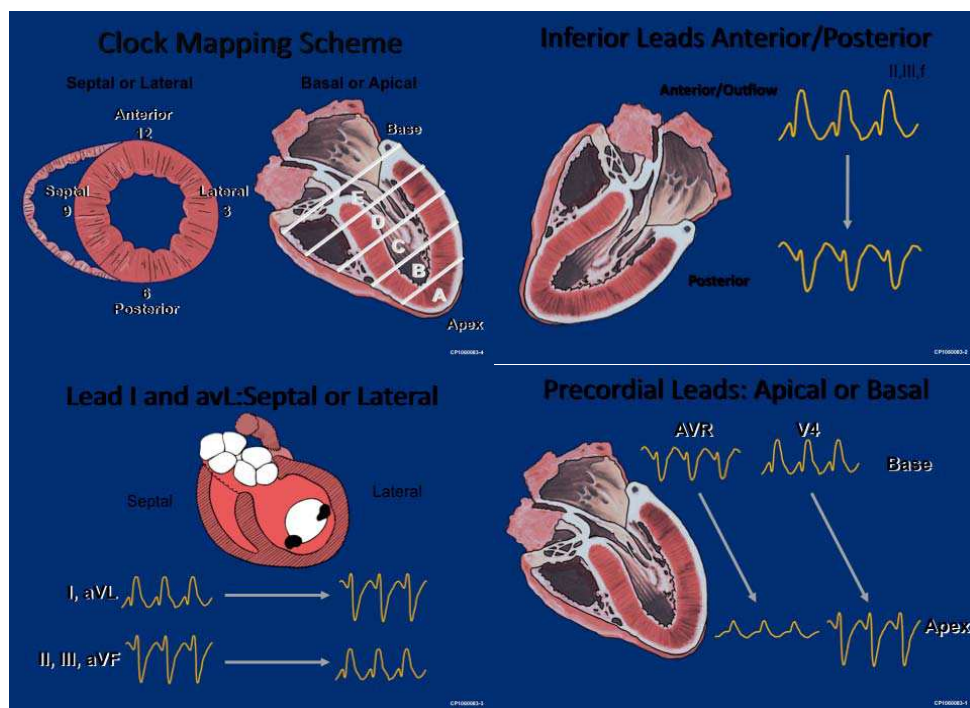


Fig. 3. Schematic for 12-lead EKG analysis of captured VT.

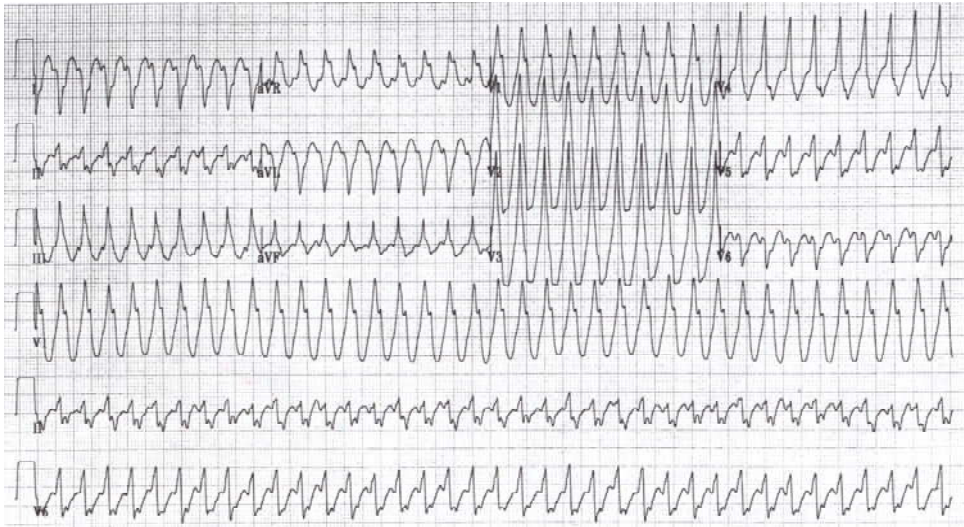


Fig. 4. Monomorphic Ventricular Tachycardia localizing to LV antero-lateral wall.

6.4 Intra-operative cryoablation

LVAD implantation surgery offers a unique opportunity for arrhythmia treatment because of the open access the surgeon is granted to the entire epicardial surface of the heart and the endocardium of the entire left ventricle. In addition, one can proceed with cryoablation with relative impunity on the left ventricle because the LVAD will be in place post-operatively. Given the role of the LVAD in supporting the already failed left ventricle, the preservation and optimization of post-operative left ventricular function does not carry the same supreme importance associated with virtually every other cardiac surgery performed. A common cause of morbidity and mortality in patients with LVADs is RV failure, so care must be exercised to avoid unnecessary ablation on the septum and free wall of the RV, but otherwise one may proceed without excessive concern of damaging healthy myocardium.

The procedure is performed in the same manner as any other LVAD implantation. A median sternotomy is performed followed by pericardiotomy and the preperitoneal pocket is made to accommodate the LVAD pump. Following this, cannulation sutures for cardiopulmonary bypass are inserted, anticoagulation is dosed, cardiopulmonary bypass cannulae are placed, and partial bypass is initiated. Once partial bypass is initiated, epicardial cryoablation is performed using the AtriCure device with the Cryo1 probe. Each pre-identified site of arrhythmogenic substrate is ablated at -70°C for two and a half minutes. If necessary, the malleable Cryo1 probe can be shaped to match the contour of the epicardial surface to facilitate uniform application of the cryothermal energy (see Figure 5). Following epicardial ablation, full bypass is initiated, the aorta is cross-clamped, and cardioplegia is administered. We prefer to perform the endocardial ablation and LVAD placement on the arrested heart, although these procedures can also be done on the empty beating heart. At this point, the left ventricle apex is identified and the coring device is used to create a ventriculotomy for placement of the LVAD inflow cannula. Subsequently, the AtriCure device is again used with the Cryo1 probe for endocardial ablation via the

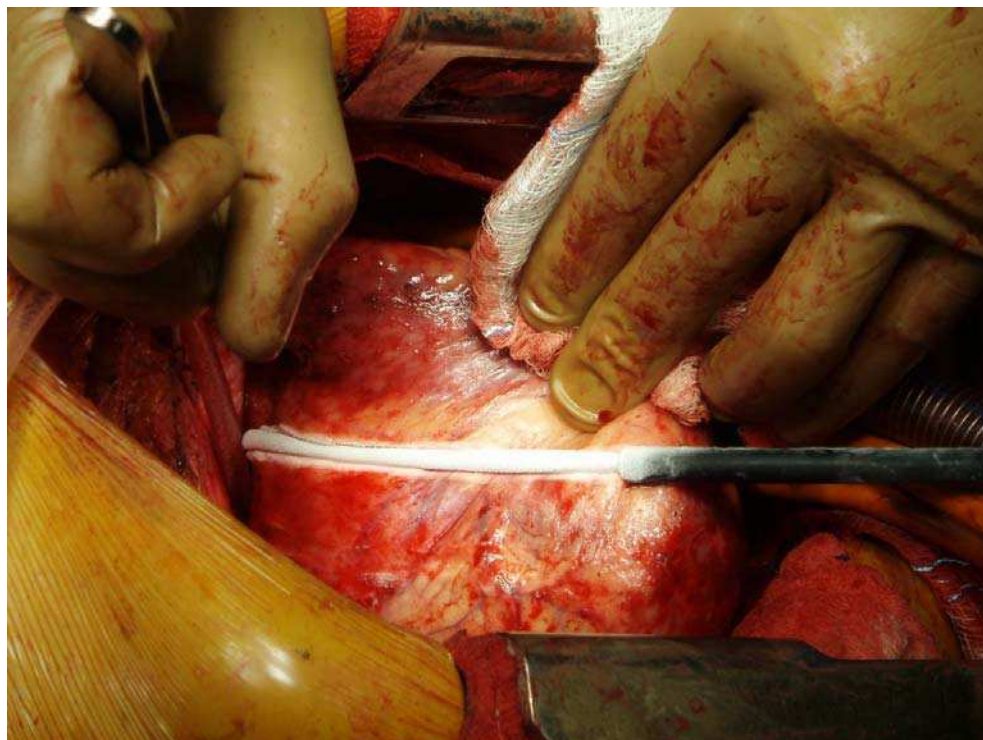


Fig. 5. Epicardial Cryoablation

previously-performed ventriculotomy (see Figure 6). For endocardial ablation in the arrested and non-perfused heart, we opt to reduce cryo time to two minutes, again at -70°C . For effective arrhythmia ablation, care must be taken to ablate the previously identified arrhythmogenic site in addition to creating a surrounding cryoablation tract extending to fixed anatomic sites such as the mitral valve and/or apical LVAD inflow cannula site. Ablation at an arrhythmogenic scar site only, without this extension, could leave the patient prone to recurrent arrhythmias via reentrant conduction around the ablated scar site. Following completion of the endocardial ablation, circumferential stitches are placed at the ventriculotomy, the LVAD inflow cannula is seated, and the remainder of the surgery for standard LVAD placement proceeds as per usual.

7. Results

Since instituting the above protocol for the prevention of post-operative ventricular arrhythmias, we have performed 28 additional HeartMate II LVAD implantations. Of these 28 patients, 9 patients had a history of previous VT/VF and thus underwent pre-operative mapping and intra-operative endocardial and epicardial cryoablation. None of these 9 patients who underwent intra-operative cryoablation have suffered from sustained post-operative ventricular arrhythmias. Of the 21 patients who had no history of pre-operative VT/VF, 3 patients experienced post-operative sustained VT or VF. In all 3 of these cases, the

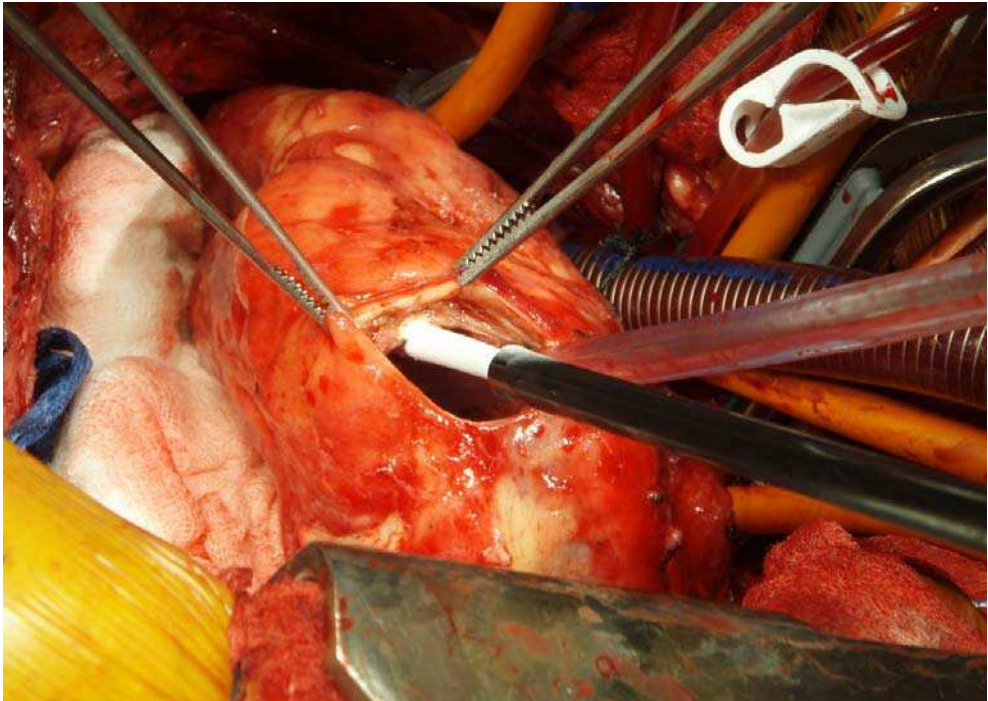


Fig. 6. Endocardial Ablation

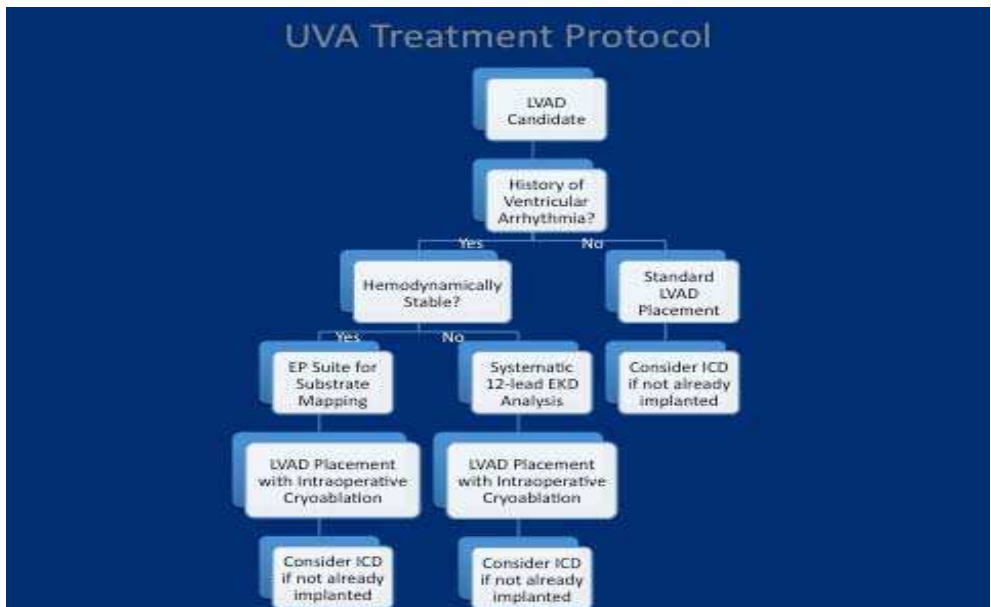


Fig. 7. Treatment Protocol

patients were asymptomatic, the arrhythmias were easily controlled with medical therapy, were not recurrent, and did not require additional intervention. None of the 28 patients required additional catheter-based interventions for arrhythmia control. Prior to instituting this protocol for intra-operative cryoablation, 8 of 23 patients (34.7%) required intervention for recurrent post-operative ventricular tachyarrhythmias. After initiating the protocol 0 of 28 patients required further intervention. It is still too early to know whether and how this procedure has impacted other results; however, it is clear that directed intra-operative cryoablation is useful in decreasing the rates of post-operative ventricular tachyarrhythmias following HeartMate II LVAD implantation.

8. Future direction

The protocol, technique, and results presented above show promise toward the goal of eliminating ventricular tachyarrhythmias following LVAD placement. Admittedly, our experience with this technique is in its infant status and we will develop further refinements as we implant more devices and gain clinical experience managing patients with LVADs and with ventricular tachyarrhythmias. The first question we will have to address is whether to ablate all patients at the time of LVAD implantation, not just those with a prior history of ventricular tachyarrhythmias. Previous studies had demonstrated that the patients who experience problems with post-operative ventricular arrhythmias are not necessarily the same patients with a history of ventricular tachyarrhythmias pre-operatively (Ziv et al., 2005);(Oswald et al., 2010). In the only prospective study to date, Oswald et al. demonstrated that patients with no previous arrhythmia history had an estimated 1-year risk of 24% for appropriate ICD treatment for sustained VT or VF following continuous flow LVAD placement. Other studies have shown similar rates of new ventricular arrhythmias following LVAD placement.

In our experience, although limited, we have not seen any patients with clinically significant VT or VF requiring additional catheter-based therapy in either group. Only time will tell whether this is a sustained finding with our methodology. Notably in the Dor experience, the incidence of post-operative ventricular arrhythmias is less than 2% (Dor et al., 1994). Similar to our approach to cryoablation, in the Dor procedure for ventricular reconstruction for ischemic heart failure, only those patients who have a history of previous sustained VT or VF undergo cryoablation of the border zone surrounding the resected myocardium. In 1994, Dor and colleagues reported on 287 who patients underwent programmed ventricular stimulation prior to subtotal endocardectomy with surgical ventricular reconstruction. 106 patients were found to have inducible (57) or spontaneous (49) ventricular tachycardia pre-operatively; however, ventricular tachycardia was no longer inducible in 92% of patients after operation and only two patients had spontaneous ventricular tachycardia after the operation (Dor et al., 1994). Subsequent studies have replicated this result (Sartipy et al., 2005). It is unclear exactly why the Dor procedure is so successful in limiting the prevalence of post-operative arrhythmias. Logic suggest that the reconstructed ventricle experiences less wall stress and with that, the neurohormonal, mechanical, and hemodynamic conditions which predispose to arrhythmia generation are eliminated. In addition, cryoablation destroys the border-zone ischemic tissue where monomorphic VT may be generated. If this is the case for the Dor procedure, our approach to HeartMate II LVAD implantation with cryoablation may replicate the same results.

Regardless of whether these results bear out over the long term, this chapter should demonstrate that the management and treatment of ventricular arrhythmias in the LVAD population will be an important topic for the heart failure specialist, electrophysiologist, and cardiac surgeon to understand over the coming decades. Destination therapy is here to stay. With over half a million Americans suffering from heart failure, and over 100,000 in NYHA class IIIb or IV heart failure, the pool of patients who may benefit from ventricular assist devices is large. In addition, with over 550,000 people newly diagnosed with heart failure each year and an aging population, all of these numbers stand to expand over the coming years. The benefit of LVAD implantation is clear with large trials now showing two-year HeartMate II survival rates of almost 60% in a population which only ten years ago had a survival rate of 8% with optimal medical therapy (Slaughter et al., 2009);(Rose et al., 2001). With third-generation non-contact bearing devices now approved in Europe and on the horizon in the U.S., LVAD survival and quality of life may soon eclipse the gold standard for heart failure treatment: heart transplant. In order for this to happen, issues such as post-operative ventricular arrhythmias need to be worked out. We believe that following our approach will significantly limit the prevalence of post-operative ventricular tachyarrhythmias, but the nuances of patient selection and procedure performance have room for development. Only with multi-institutional prospective trials will the true answers be known: who to treat, how to map, and where and how to ablate. We hope definitive answers will be known soon and that ventricular arrhythmias in patients with ventricular assist devices will become only a historical footnote. Until then, we push on.

9. References

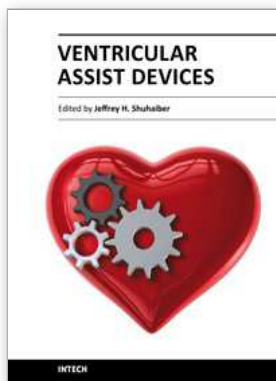
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The assist devices will continue adding a large number of years of life to humans globally and empower the medical society to optimize heart failure therapy. While expensive and cumbersome task, the foundation provided in this book reflects a contemporary product of original research from a multitude of different experts in the field. We hope this cumulative international effort provides the necessary tools for both the novice as well as the active practitioner aiming to change the outcome of these complex patients.

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