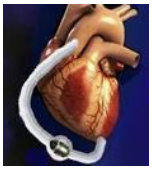

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Peer-Reviewed Review Article

Incidence of Pump Thrombosis in HeartMate II during Destination Therapy

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Abstract

Pump thrombosis occurs during destination therapy (DT) with HeartMate II, a continuous blood flow left ventricular assist device (St Jude, Pleasanton, CA, USA). With adherence to stringent post-operative and long-term anticoagulation a low incidence of pump thrombosis was initially reported during DT. The increased PT incidence during DT that was reported in early 2013 was attributed to lenient anticoagulation. A wide range of pump thrombosis incidence during DT is being reported since the return to stringent post-operative and long-term anticoagulation. We searched PubMed from January 2008 to February 2016 for reports of pump thrombosis during mechanical circulatory support with HeartMate II and focus on the incidence rate of pump thrombosis from DT approval by the Food and Drug Administration to present. Pump thrombosis which may have been initially underestimated continues to complicate DT with HeartMate II despite stringent post-operative and long-term anticoagulation.

Keywords: pump thrombosis, destination therapy, HeartMate II, left ventricular assist device

Introduction

In contrast to initial experience with the HeartMate Extended Vented Electric (XVE; Thoratec, Pleasanton, CA), a pulsatile-flow (PF) left ventricular assist device (LVAD), long-term mechanical circulatory support (MCS) with HeartMate II, a continuous-flow (CF) LVAD (St Jude, Pleasanton, CA), is no longer limited by

device mechanical dysfunction [1, 2]. With textured interior surfaces, HeartMate XVE did not require anticoagulation and was nearly free of pump thrombosis. On the other hand, HeartMate II does require anticoagulation and has a risk of pump thrombosis [3-7].

Destination therapy (DT) with Heart Mate II was approved by the FDA in 2009 [8]. Early DT experience with HeartMate II was associated with a low incidence rate of pump thrombosis [8-10]. However, three high volume DT centers experienced an abrupt increase in pump thrombosis incidence rate in early 2013 [11]. Nowadays, pump thrombosis incidence rate during DT appears to vary greatly from center to center [12-22]. Investigations of pump thrombosis during DT are overwhelmingly of retrospective nature [12-22]. We searched PubMed from January 2008 to February 2016 for reports of pump thrombosis during long-term MCS with HeartMate II and focus on the incidence rate of pump thrombosis from approval of HeartMate II for DT to the latest reports.

Incidence of Pump Thrombosis during Destination Therapy with HeartMate II

Early Experience

The first report of HeartMate II pump thrombosis was published in 2007 [23]. Pump thrombosis occurred 2 months after implantation in a patient after warfarin had been discontinued due to gastro-intestinal bleed. Symptoms improved and power surges receded after intravenous administration of hirudin for 18 days. However, 3 months later return of symptoms and power surges motivated rapid cardiac transplantation. A thrombus was found in the inflow cannula [23].

A low incidence of pump thrombosis was reported in the trial that led to approval of HeartMate II for DT by the FDA [9]. Bleeding was by far the most prevalent adverse event as 108 of the 133 randomized patients to CF-LVAD (82%) required blood transfusion. Pump thrombosis occurred in 5 patients (4%). An even lower pump thrombosis incidence rate was noted in the 281 patients enrolled in the continuous access protocol approved by the FDA for evaluation of HeartMate II [22]. Only 4 of 281 patients (1.4%) experienced primary PT. In contrast, ischemic stroke outnumbered hemorrhagic stroke (11% versus 8%) in the extended access protocol [22]. As detailed later, no mention of PT is made in the third Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) report of the outcome of patients who underwent long-term MCS from June 2006 through September 2010 [8].

From 2006 to 2012 investigators have reported a PT incidence rate that was overall greater than that noted in the landmark HeartMate II trial. Reports from Park et al. and Hasin et al. reveal an increased incidence rate of pump thrombosis with HeartMate II from 4% in 2005-2007 to 6% in 2007-2009 with a peak of 9.3% during the period from 2008 to 2011 [24, 25].

Later Experience

In late 2013 three high volume DT centers reported an abrupt increase in incidence rate of pump thrombosis from March 2011 and culminated in an

incidence rate of 7.5% and 12.4% after 12 and 24 months of support, respectively [11]. The center with the lowest incidence of pump thrombosis before March 2011 had the greatest incidence after March 2011 [11]. The abrupt increase in pump thrombosis incidence rate was retrospectively attributed to a lenient anticoagulation regimen, to forfeiting the use of heparin post-operatively or to both [11]. Facing a high prevalence of bleeding in the post-operative period and during the long-term follow up, DT centers lowered the international normalized ratio (INR) target from 2-3 to 1.5 -2.5 and abandoned the post-operative use of heparin [10, 24]. Modifications of the initial CF-LVAD or in the anticoagulation protocol did not apparently result in an increased rate of pump thrombosis [10, 24]. Over the past 2-3 years DT single centers and registries have reported an extremely variable incidence rate of PT that ranged from 6 to 40% [12-22].

At the University of Pennsylvania Medical Center, 16 of 90 patients (20%) who underwent HeartMate II implantation from January 2011 to March 2014 experienced pump thrombosis which was visually confirmed upon device explantation [13]. From March 2006 to June 2014, 179 patients received a HeartMate II and 21 patients a Heartware at Yale University Medical Center. The indication was DT for 102 patients and BTT in 98 patients [14]. The overall incidence rate of pump thrombosis was 6% [14]. The incidence of pump thrombosis in patients with a HeartMate II for DT was not provided. The majority of pump thrombosis (83%) occurred from 2006 to 2012 with only 3 events over the past 2 years. The decreasing pump thrombosis incidence rate was attributed to implementation of a more aggressive anticoagulation regimen. Sixty four patients underwent first implantation of CF-LVAD at Tampa General Hospital (Tampa, FL) from October 2011 to October 2013 [15]. The CF-LVAD was HeartMate II in 56 patients and Heartware in 8 patients. Pump thrombosis that was confirmed by visualization of the thrombus upon explant occurred in 12.5% of patients. Incidence rate of pump thrombosis was similar with HeartMate II and Heartware. Not all patients received antiplatelet therapy. A greater pump thrombosis incidence rate was noted in patients who did not receive antiplatelet therapy.

Seven of the 18 patients (39%) who were implanted with HeartMate II for DT from January 2010 to December 2013 at our institution experienced pump thrombosis that was confirmed at disassembly of the device at Thoratec (Pleasantville CA) in 6 patients [16]. All 18 patients received standard therapy post implant including antiplatelet therapy and warfarin. The INR target was increased from 2-3 to 2.5-3.5 after the first pump thrombosis event. None of the patients were bridged with heparin post operatively.

Preexisting inflammatory conditions and infectious complications were common in patients with pump thrombosis and rare in patients without pump thrombosis. A recent retrospective evaluation of 276 patients who underwent HeartMate II implantation for DT (N=176) or BTT (N=100) from April 2009 to September 2012 in 27 centers, reported 4 device exchanges for pump thrombosis over an average MCS duration of 8.3 months [17]. Whether pump thrombosis occurred in DT or BTT patients is unclear. One-year survival of DT patients was 70% [17]. Five DT patients suffered an ischemic stroke.

Seven hundred and thirty four patients with first CF-LVAD implantation were enrolled in the Mechanical Circulatory Support Research Network Registry from May 2004 to September 2014 [21]. HeartMate II was implanted in 560 patients and Heartware was implanted in 174 patients. The cumulative risk of pump thrombosis was 14, 24 and 25 % at 1, 3 and 5 years, respectively. The incidence rate of pump thrombosis decreased from 36% before August 2011 to 7.5% after August 2011. A lower INTERMACS profile was the only independent predictor of PT. The type of CF-LVAD was not an independent predictor of pump thrombosis in the multivariable model. The cumulative risk of ischemic stroke was 4, 9 and 10% at 1, 3 and 5 years, respectively. Fifty-five patients underwent echocardiographic ramp testing after HeartMate II implantation at the University of Minnesota (Minneapolis, MN) [26]. Thirteen of the 55 patients (23.6%) experienced PT that was confirmed by visualization of device obstruction. The main findings of above mentioned single centers and registries are summarized in Figure 1.

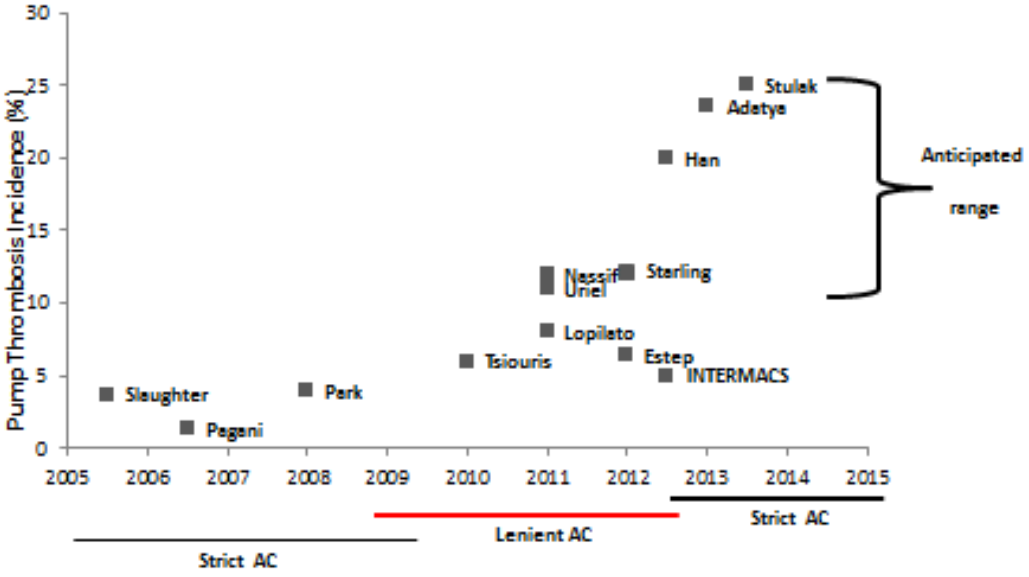

Figure 1 Incidence of pump thrombosis (PT) across studies of long-term mechanical circulatory support with HeartMate II left ventricular assist device. For each study, a mean of the study time period has been used as a time point to depict PT incidence. Studies with outlying PT incidence rates have been excluded [Samson et al [16] and Katz et al [17]. Abbreviations: AC: anticoagulation.

The Interagency Registry for Mechanically Assisted Circulatory Support Data

The INTERMACS reports mention pump thrombosis as an adverse event when it results in a fatal outcome or when it requires pump exchange. The fifth INTERMACS annual report that analyzed patient enrollment and outcomes from June 23, 2006 till June 30, 2012 did not mention any pump thrombosis as adverse event during long-term MCS with CF-LVAD [2]. The report mentions 660 device malfunctions for 5,358 CF-LVAD implantations (12.3%). A similar rate of device malfunction (11.5%) without mention of pump thrombosis is noted in the following quarterly INTERMACS report implants. The issue of pump thrombosis was specifically addressed by INTERMACS in 2014 [3]. Freedom from device exchange or death due to pump thrombosis was reported to have decreased from 99% at 6 months in 2009 to 94% in 2012. INTERMACS revisited the issue of pump thrombosis one year later [4]. The freedom from pump thrombosis at 6 months fell from 98% in 2010 to 92% in 2013 and subsequently improved to 95% through June 2014 [4]. Whether pump thrombosis occurrence effectively decreased is uncertain. A novel analysis of the complete all INTERMACS data using machine learning random forests survival methodology confirmed that the risk of pump thrombosis plateaued in 2013-early 2014 [6]. The novel analysis estimates the current risk for pump thrombosis at 10% that is greater than that initially reported [6].

Mechanistic insight

Pump thrombosis is obviously a complex issue that may result from mechanical and non-mechanical factors [5, 7, 27-29]. As HeartMate II implantation becomes an increasingly performed procedure, cardiothoracic surgeons are fully familiar with correct implant techniques [30]. Inflow cannula misplacement, outflow graft malposition and pump pocket depth may only be responsible for few instances of pump thrombosis [13]. Recent modifications to the HeartMate II surfaces have apparently not affected the incidence rate of pump thrombosis that remained extremely variable.

Non-mechanical potential causes of pump thrombosis have been extensively reviewed [5, 7, 27-29]. Uriel et al. drew attention to non-mechanical pump thrombosis that occurred in 14 of the 177 patients (8%) who underwent HeartMate II implantation at Columbia University Medical Center from January 1, 2009 to November 15, 2012 [12]. The pump thrombosis prevention protocol at Columbia included aspirin, warfarin with an INR target of 1.5 to 2.5 and dipyridamole in patients < 50 years old. An 11% incidence rate of pump thrombosis was reported by the Texas Heart Institute despite the use of an aggressive anticoagulation protocol in patients with HeartMate II implanted from April 2008 to June 2012 [31].

From January 2009 to June 2013 125 patients received a HeartMate II or a Heartware at Tufts Medical Center (Boston, MA) for BTT (N=81), DT (N=33) and bridge to decision (N=11) [18]. All patients received aspirin (325 mg) and warfarin with a target INR 2-3. During a median follow up of 270 days, pump thrombosis occurred in 21 of the 90 patients (23.3%) who received a HeartMate II. After adjusting for age, gender and BTT indication pump thrombosis incidence rate was similar with HeartMate II and Heartware [18]. In a prospective, multicenter

observational study of DT with HeartMate II that enrolled 97 patients, pump thrombosis incidence rate was 6% at 12 months albeit only 70% of patients received both warfarin and antiplatelet therapy post implantation [19].

Two hundred and sixty four patients underwent HeartMate II implantation from January 2009 to June 2013 at the University of Washington School of Medicine (St Louis, MS) [20]. Hundred patients did not receive erythropoiesis stimulating agent, while and 121 received it. Pump thrombosis was confirmed by direct observation of an obstructive thrombus in the pump or suspected for severe hemolysis. Over a mean follow up period of 14.2 months, pump thrombosis incidence rate was 12% in patients not receiving erythropoiesis stimulating agent and 23% in patients receiving it [20].

After the 2014 report of an abrupt PT increase and the return to aggressive anticoagulation the incidence rate of PT appears to vary greatly from center to center. Overall, many centers nowadays observe an incidence rate of PT ranging from 10 to 20% [12, 13, 15, 18, 20-22]. Thus, the return to an aggressive anticoagulation protocol has not been accompanied by a declining rate of pump thrombosis.

An issue that has been less addressed is the underestimation of pump thrombosis in early reports of MCS with HeartMate II. Several oversights may have led to early underestimation of HeartMate II pump thrombosis. First, most centers which contributed to the approval of HeartMate II for DT by the FDA had previous experience with HeartMate XVE [9]. With uniquely textured surfaces HeartMate XVE was associated with an extremely low rate of PT during prolonged MCS. The physical examination adage “You find what you look for” may have led to pump thrombosis underestimation. Second, DT related implants increased from 28.5% in 2011 to 44% in 2014 and BTT implants remained stable at 30%, the incidence rate of pump thrombosis seems to have increased with the longer duration of MCS associated with DT [32]. Third, pump thrombosis can masquerade as an arterial embolic event and particularly as ischemic stroke that is a not infrequently reported adverse event during long-term MCS with HeartMate II. Akin et al. reported such instance in a patient after HeartMate II implantation [33]. Finally, with HeartMate II being increasingly implanted for DT, patients may not have been as thoroughly screened for comorbid conditions that may contribute to pump thrombosis as are BTT patients. Malignancies, chronic inflammatory disorders, connective tissue diseases, autoimmune disorders and hypercoagulable states are known to increase the risk of thrombus formation [16].

Treatment of suspected pump thrombosis is beyond the scope of the present review. However prevention/avoidance of PT is undoubtedly the undisputed goal of DT. Prevention of pump thrombosis requires long-term antiplatelet therapy with 81-325 mg of aspirin and unremitting anticoagulation. Warfarin is the only available oral anticoagulant known to prevent formation of red clot within the device [7, 30]. A target INR of 2.5-3.5 may be preferable to that of 2-3 as recommended by current guidelines [34]. Temporary administration of fractionated heparin is recommended when INR is < 2. Plasma LDH level should be obtained with each INR determination. An unexplained abrupt increase in INR warrants computerized

tomography angiography/echocardiography ramp study and possibly thrombolytic therapy.

Competitive and reversible inhibition of thrombin with dabigatran is not as effective as warfarin in suppressing mechanical heart valve thrombosis [35]. As probably occurs with mechanical heart valves, thrombin is generated in response to exposure of blood to the artificial surface of the CF-LVAD [7]. Unfortunately adherence to warfarin low with only 40.2% of patients with atrial fibrillation having warfarin readily available ≥ 80% of the time based on fill date and the days of supply on pharmacy claims [36]. Medication refill adherence is likely to underestimate warfarin non-adherence in patients with CF-LVAD who are closely monitored and unlikely to be left without warfarin prescriptions. Warfarin treatment in patients with CF-LVAD requires compulsive attention to time in the therapeutic range. Patient's adherence to medications and diet is the key factor of pump thrombosis.

Future Directions

Early detection of pump thrombosis during HeartMate II support remains Achilles heel. Apart from inflammatory conditions and malignancies, recurrent sub-therapeutic anticoagulation state and device related mechanical factors contribute to pump thrombosis (16). Regularly scheduled measurements of serum lactate dehydrogenase (LDH) levels appear more suitable for the detection of pump thrombosis than serial echocardiography. Serum LDH levels increase after HeartMate II implantation and thereafter tend to remain stable. Elevated LDH levels (>600U/L) have been noted in patients with clinical and echocardiographic evidence of pump thrombosis. However, absence of data on correlation between early rise in LDH level and thrombus formation makes early detection of pump thrombosis difficult. Review of confirmed cases of pump thrombosis may reveal relationship between the extent of increase in LDH level and the development of pump thrombosis. Furthermore, it is likely that we may not find "one-size-fit-for-all' LDH level which should lead to the early detection of pump thrombosis. Instead, serial LDH level measurements may help establish a trend for a given patient and deviations should prompt further investigation. Knowing the increase in LDH levels should alert clinicians to pump thrombosis "in progress" and may allow early use of fractionated heparin to stop/slow the thrombus propagation.

Meanwhile, the design of HeartMate 3 ((St Jude, Pleasanton, CA, USA) aimed at improving its hemocompatibility over that of previous devices by incorporating a magnetically levitated rotor with wide blood-flows paths and an artificial pulse. The HeartMate 3 device still requires aggressive anticoagulation with intravenous heparin as soon a chest tube drainage allows (<50ml/h for 3 hours) and aspirin plus Coumadin as soon as the patient can take oral medications. The target international normalized ratio (INR) is 2-3. Preliminary European experience in 50 patients enrolled at 10 centers indicates that mechanical circulatory support (MCS) with HeartMate 3 is not associated with device thrombosis at 6 months (37). The absence of the device thrombosis at 6 months after implantation of HeartMate 3 is extremely promising. However, it clearly needs to be confirmed in a larger cohort

on a longer MCS duration. The ongoing MOMENTUM3 trial will provide more definitive information. The enrollment is expected to end in the middle of 2016 (38).

Conclusion

In summary, pump thrombosis has been and continues to remain a major adverse event during destination therapy. Pump thrombosis may have been initially underestimated. Aggressive monitoring of anticoagulation and hemolysis is the sine qua non of pump thrombosis prevention.

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