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De-airing method of an axial flow left ventricular assist device influences post-operative lactate dehydrogenase levels: a possible explanation for some episodes of pump thrombosis

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Abstract

Background

Pump thrombosis (PT) is a relatively uncommon but serious complication of a left ventricular assist device (LVAD). We believe that de-airing of the HeartMate II (HMII) with the pump turned on and a clamp across the outflow graft may lead to early thrombus formation due to heat generation on the bearings.

Methods

Patients who underwent HMII implantation from November 2012 to February 2016 were retrospectively reviewed. Patients were separated into two groups depending on the timing of removing the clamp from the outflow graft. Patients in Group 1 underwent de-airing by turning on the pump with the vascular clamp on the outflow graft and patients in Group 2 were completely de-aired with the pump off and the pump was only activated after removing the clamp.

Results

There were 45 patients in Group 1 ("clamp on") and 33 patients in Group 2 ("clamp off"). Five patients had PT in Group 1 but none in Group 2 (p=0.07). Average LDH levels in the early postoperative period were similar (404±168 IU/L vs 425±267

IU/L; p=0.71). However, average LDH levels in the late postoperative period were significantly higher in Group 1 (388±214 IU/L vs 313±73 IU/L; p=0.045).

Conclusion

De-airing a running HMII with the outflow graft clamped increases LDH levels, suggesting that the bearings may act as a nidus for early thrombus formation caused by the lack of heat dissipation. Delaying pump activation until removal of the clamp on the outflow graft may affect the incidence of PT after HMII implantation. This may have potential importance in any VAD where there are mechanical bearings or other areas susceptible to heat generation.

Keywords: HeartMate II, LVAD, thrombosis

Introduction

Left ventricular assist devices (LVADs) have transformed the manner in which patients with end-stage cardiomyopathy are managed. However, their use is not without risk. One particularly troublesome event is pump thrombosis which can manifest with embolization, recurrent heart failure or hemolysis. Pump thrombosis is relatively uncommon, with a rate of 2 - 4 % seen in the HeartMate II (HMII) bridge to transplantation and destination therapy trials [1, 2]. Recently, there has been increased attention to the issue of pump thrombosis, which was highlighted in the article by Starling et al. [3]. This demonstrated a pump thrombosis rate of 8.4% over a period of 3 months in three centers. Multiple factors have been identified as potential risk factors for thrombosis of a left ventricular assist device (LVAD), including device-specific factors, patient-related factors, surgical implantation techniques, and post-operative management.

In response to the article by Starling et al., we reevaluated all aspects of the management of patients undergoing LVAD implantation at our hospital for changes in patient management that could explain a potential rise in the rate of pump thrombosis. The only significant change identified in surgical technique, pump management or post-operative care was the method of pump de-airing prior to separation from bypass. Beginning in 2007, one author (JE) would routinely de-air prior to powering the pump, and the pump was only activated after de-airing was complete and the outflow graft was unclamped. As more pumps were implanted and discussions amongst clinicians allowed for cross-fertilization of ideas and techniques, the de-airing method was changed such that the pump was activated with the clamp across the outflow graft with a de-airing hole in the graft. This could speed the de-airing process and possibly decrease the potential for air embolization. This technique was adopted and used on all HMII patients without apparent short-term consequences beginning approximately in 2010. With the reports of increased pump thrombosis, the concern developed that this method of de-airing was a potential source for pump thrombosis due to heat generation on the inflow and outflow bearings when the pump was spinning in a pool of relatively stagnant blood, with subsequent protein denaturation and deposition on the bearings. As such, the de-airing method was changed back such that the HMII LVAD was never activated until de-airing was completed and the clamp across the outflow graft was removed.

Over the past several years, it has become apparent that elevations in lactate dehydrogenase (LDH) are an early marker of thrombosis, and as such, LDH is typically followed routinely in patients on LVAD support [4]. Even in the absence of other signs of potential pump thrombosis (hemolysis, pump power elevations, embolic events), a rise in LDH may lead to additional testing or a change in the anticoagulation regimen for a given patient.

The aim of this study was to compare two de-airing methods and evaluate the impact on the incidence of pump thrombosis and LDH levels.

Methods

Patients

All patients who underwent primary LVAD implantation with HeartMate II (Abbott Laboratories, Illinois, USA) by a single surgeon at a single institution from November 2012 to February 2016 were enrolled in the study. The method to de-air the pump was switched between March 2014 and May 2014. Data was collected retrospectively reviewing medical charts, which was approved by the institutional review board. Patients were separated into two groups depending on the timing of removal of the vascular clamp from the outflow graft. Patients in Group 1 underwent de-airing by turning the pump on with the vascular clamp on the outflow graft and patients in Group 2 were completely de-aired with the pump off and activating the pump only after removing the clamp.

Surgical procedure and anticoagulation management

The only difference in surgical procedures between two groups was the timing of vascular clamp removal from the outflow graft. In the typical case, sternotomy is performed, followed by creation of the LVAD pocket and tunneling of the driveline. Heparin is then given. After cannulation, the outflow graft anastomosis is completed with a side-biting vascular clamp. The patient is then placed on bypass support. The inflow cannula connector is placed using a “cut-then-sew” technique. The LVAD inflow cannula is secured and actively vented. Once de-airing seems to be complete, the LVAD is connected to outflow graft and the LVAD and left ventricle are further de-aired through a 20-gauge hole in the outflow graft between the pump and the clamp on the outflow graft, using transesophageal echocardiography to assess the completeness of de-airing. In Group 1, this was performed with the pump on. In Group 2, the pump was off. The patient is weaned from bypass support while further de-airing occurs with a pressurized left ventricle. The clamp is then removed after making sure there was no air bubbles coming through the 20-gauge hole. In Group 2, the pump is activated at this point. In both groups, pump speeds are increased as tolerated. Protamine is given to reverse the heparin. Blood products are only administered for significant anemia, or coagulopathy with bleeding. Activated coagulation factors were avoided in all patients. The LVAD is secured into the pocket. Low pump speeds were avoided whenever possible. All implantation recommendations concerning pump pocket size and location, inflow cannula positioning and pump anchoring (PREVENT surgical recommendations) were followed in both groups [5]

Heparin bridging was routinely used, and typically started on the first post-operative day unless bleeding was present. Warfarin was started when the patient

was tolerating an oral diet, and adjusted for an International Normalized Ratio (INR) of 1.8-2.2. Aspirin 325 mg was administered daily once tolerating an oral diet. The INR and/or aspirin dose were decreased if there was GI bleeding. Additional antiplatelet agents were added or the INR goal increased if there was an unexpected significant rise in LDH, or worrisome elevations in pump power. A single person (JE) was involved in the decisions to change anticoagulation regimens in all patients.

Study design

The incidence of pump thrombosis within 3 months after implantation was compared between two groups. LDH levels were averaged over postoperative day (POD) 1 to 1 month (30 days) for the early postoperative period and 1 month to 3 months (31 to 90 days) for the late postoperative period. These average LDH levels were compared between two groups. Primary outcome was pump thrombosis requiring replacement of the LVAD pump. Secondary outcome was bleeding or thromboembolic complication.

Pump position was assessed by the criteria described by Adamson et al [6] and validated in the PREVENT Trial substudy on pump position [7]. Extreme pump position was defined as the following:

a. Pocket depth $\geqslant$ 8 cm or $\leqslant$ 19 cm, or

b. Inflow cannula angle relative to pump $\geqslant 46^\circ$, or

c. Inflow cannula angle relative to vertical $\geqslant 0^\circ$ or $\leqslant 39^\circ$

Angles were measured on the scout image of the post-operative CT scan (if available) or on a chest radiograph that showed the entire body of the pump.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared with Student's t-test. Categorical variables were evaluated by chi-square test or Fisher's exact test as appropriate. P values of less than 0.05 were deemed statistically significant. Statistical analysis was performed using the R statistical software package version 3.2.2 (R foundation, Vienna, Austria).

Results

There were 45 patients in Group 1 (the pump started with the clamp on) and 33 patients in Group 2 (the pump started with the clamp off). Table 1 shows baseline characteristics of the patients. Ischemic cardiomyopathy was significantly more common in Group 1 (p=0.015). The patients in Group 1 received significantly more intraoperative blood transfusions (3.0±3.1 versus 0.8±1.3, p<0.0001). All other factors including liver function, anticoagulation/antiplatelet and pump speed were not significantly different. None of the patients had perioperative issues suspected to be caused by air embolization.

Table 1: Characteristics of patients whose LVAD was started with the clamp on or off

	Clamp ON (Group 1)	Clamp OFF (Group 2)	P value
Number	45	33	
Age (years)	60.9±10.2	57.3±10.4	0.14
Male	36 (84%)	24 (73%)	0.27
Height (cm)	177±9	179±11	0.52
Weight (kg)	189±39	200±50	0.29
BMI	27.2±4.9	28.2±6.1	0.42
Ischemic cardiomyopathy	21 (47%)	6 (19%)	0.015†
INTERMACS	2.8±0.4	2.7±0.5	0.42
Atrial fibrillation	20 (44%)	9 (27%)	0.16
Hypertension	35 (78%)	21 (67%)	0.21
Diabetes	20 (44%)	11 (33%)	0.36
Deep vein thrombosis	0 (0%)	3 (9%)	0.18
Cerebrovascular disease	5 (11%)	6 (18%)	0.51
GFR (units)	50.2±10.7	52.6±10.6	0.34
Total bilirubin (mg/dL)	0.94±1.03	0.97±0.83	0.88
AST (IU/L)	39.8±42.9	32.5±33.5	0.42
LDH (IU/L)	274±97	340±365	0.36
Redo operation	10 (22%)	6 (19%)	0.78
IABP	6 (13%)	4 (12%)	0.99
ECMO	2 (4%)	2 (6%)	0.99
TVR	7 (16%)	3 (9%)	0.51
AVR	5 (11%)	0 (0%)	0.07
MAP (discharge) (mmHg)	83.7±9.8	86.8±8.5	0.17
Antiplatelet≥2	7 (16%)	5 (15%)	0.99
Bridged w/ heparin	41 (91%)	33 (100%)	0.13
Pump speed (ICU)	8933±267	8903±312	0.65
Pump speed (discharge)	9118±253	9232±244	0.06
Pump speed (30 day)	9123±249	9219±240	0.10
INR (discharge)	2.26±0.57	2.29±0.60	0.88
INR (30 day)	2.13±0.66	2.16±0.79	0.87
PRBC (OR)	3.0±3.1	0.8±1.3	<0.0001†
PRBC (postop)	4.9±5.8	4.0±5.9	0.5

BMI: body mass index; GFR: glomerular filtration ratio; AST: Aspartate transaminase; LDH: lactate dehydrogenase; IABP: intraaortic balloon pump; ECMO: extracorporeal membrane oxygenation; TVR: tricuspid valve repair; AVR: aortic valve repair/replacement; MAP: mean arterial pressure; PRBC: packed red blood cells; †: statistically significant

Table 2 shows the outcome of the patients. There were five patients who required pump replacement because of pump thrombosis in Group 1. Four of them occurred within 3 months after initial implantation and required pump replacement. The last case was delayed thrombosis and resulted in a large stroke and the subsequent death of the patient. No patient in Group 2 had pump thrombosis. The difference in the incidence of pump thrombosis was not statistically significant (p=0.07). Average LDH levels in the early postoperative period (postoperative day 1 to 30) were 404±168 in group 1 and 425±267 in group 2 (p=0.712). However, average LDH levels in the late postoperative period (postoperative day 31 to 90) were significantly higher in Group 1 (388±214 IU/L vs 313±73 IU/L; p=0.045) (Figure 1).

Table 2. Outcomes

	Clamp ON	Clamp OFF	P value
Early LDH (IU/L)	404±168	425±267	0.71
Late LDH (IU/L)	388±214	313±73	0.045†
Pump thrombosis	5	0	0.07

Early LDH: postoperative day 1 to 30; Late LDH: postoperative day 31 to 90
LDH: lactated dehydrogenase
†: statistically significant

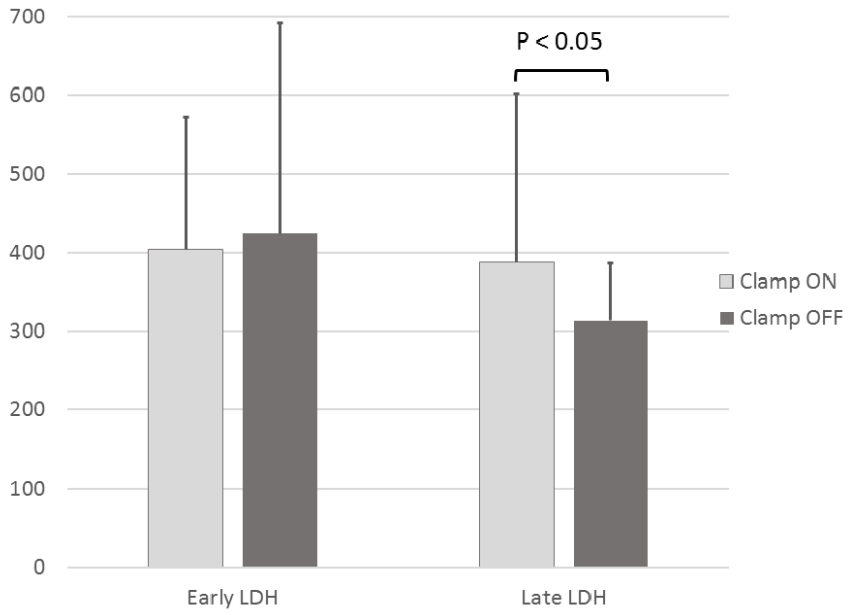

Figure 1. Starting the pump with a clamp ON/OFF on the outflow graft and LDH levels

Extreme pump position was present in 12/45 (27%) of patients de-aired with the pump on and in 12/33 (36%) of patients de-aired with the pump off and was almost exclusively due to a shallow pocket (< 8cm) (9/45 with pump on and 11/33 in pump off). Three patients in Group 1 (pump on) had an inflow cannula angle relative to vertical with an angle $\geqslant 0^{\circ}$. In Group 2 (pump off), two patients had an angle $\leqslant 39^{\circ}$ (one patient in this group also had a shallow pump pocket). Patients with extreme pump position were distributed throughout the study, negating the possibility of a learning curve. Table 3 shows the average values for pump position for each group. Among the five patients with pump thrombosis, three had a normal pump position, one had a shallow pocket (68 mm) and one had an inflow cannula -7° relative to vertical. Even though three of the parameters had a p-value $\geqslant 0.05$, two of these parameters (depth of pump pocket and pump angle relative to the spine) favored Group 1.

Table 3: Pump placement characteristics

	De-air with pump on	De-air with pump off	P value
Pocket depth (mm)	99.3[91.8, 128.9]	91.7 [76.9, 117.4]	0.05
Outflow cannula angle related to pump body (°)	103.0 [99.0, 107.0]	107.0 [100.0, 113.0]	0.08
Pump angle relative to spine (°)	88.0 [84.0, 97.0] (mean 90.8)	88.0 [78.0, 92.0] (mean 85.5)	< 0.01
Inflow cannula angle relative to pump body (°)	66.0 [64.0, 75.0]	70.0 [64.0, 75.0]	0.01
Inflow cannula angle relative to vertical parallel to spine (°)	20.0 [14.0, 31.0]	20.0 [18.0, 28.0]	0.11

Data is presented as median values [IQR]

There was no difference between preoperative ejection fraction, post-operative ejection fraction, preoperative left ventricular end-diastolic diameter (LVIDd) or post-operative LVIDd between the groups. Overall, there was an increase in the ejection fraction of 5 percentage points after implantation of the LVAD, and a decreased in the LVIDd of 1 cm, as would be expected with unloading of the hearts.

Discussion

Pump thrombosis is a serious complication of LVAD support, and usually requires pump replacement or urgent heart transplantation. It is associated with a high incidence of other complications such as embolization and mortality. After an initial period of relatively low rates of pump thrombosis, there was a perceived increase at some centers. This led to a national discussion and further investigation into the question and possible causes.

One possibility for this increase is that the bearings act of the HMII as a nidus for thrombus deposition either during the implantation procedure, or shortly thereafter. While there may be numerous potential causes for this deposition, one concern is that it may occur during the de-airing process of the LVAD. When de-airing the LVAD with the pump on and a clamp across the outflow graft, there is no flow through the pump, and a diminished capacity to dissipate the heat generated by the pump motor and by the friction of the bearings at either end of the rotor. In a study looking at a 'zero-flow' situation in short-term centrifugal pumps, a temperature change of approximately 5ºC was seen after only 90 seconds [8]. Heat generation in a pump is higher than normal when there is increased load on the pump [9], a situation that can easily occur with outflow occlusion. The heat generation described in these studies likely underestimates the maximal heat seen in the HeartMate II under a 'zero-flow' scenario, as the temperature at the contact point between the two bearings has not been measured, and is likely to be significantly higher than the temperature of the blood itself. Heat dissipation occurs primarily through two mechanisms – thermal radiation into the surrounding tissues and removal as blood flows through the device [9]. When there is no blood flow through the pump, one of the main mechanisms of heat removal is nullified, leading to increased temperatures within the body of the LVAD in general, and at the point of the bearings specifically [10]. Protein degradation can begin to occur at temperatures between 43-45ºC [11], temperatures easily obtainable under the de-airing scenario described. This heat generation is associated with a drop in platelet count, likely due to adhesion of the platelets to the heated surface, and to a 66% increase in the amount of material adherent to the heated surfaces [10]. Heat generation is felt to be one of the factors involved in initiating the sequence of fibrin deposition that ultimately leads to local thrombus formation and pump thrombosis [12].

In our current study, the patients whose pump was started with a clamp on (Group 1) tended to have higher incidence of pump thrombosis, although it was not statistically significant. The reason it did not reach statistical significance is likely to be relatively small patient population and rarity of the event. They also had significantly higher LDH levels in the late postoperative period (31 to 90 days after implantation). It is possible that the timing of clamp removal affected the incidence of pump thrombosis. Furthermore, that patients in Group 2 did not have a higher incidence of suspected air embolization including stroke or right ventricular failure from incomplete de-airing. Therefore, it would be prudent to say we should not run the pump with the outflow graft occluded. The reason that there was no difference in early postoperative LDH is probably because there were other factors like tissue injury, liver damage or transfusions that could affect LDH levels in the early postoperative period.

There were a few events that occurred between approval of the HeartMate II pump and the perceived rise in the rate of pump thrombosis, each with the potential to contribute to this increase. Data demonstrated that patients on HeartMate II support could be managed without heparin bridging [13]. There was an increased recognition of LDH as an early marker of pump thrombosis [14]. There were modifications in the HeartMate II technology, with the introduction of a modified, sealed outflow graft. In addition, there was the rise of competing technology, such

as the HeartWare HVAD. Each could have led to the rise in pump thrombosis in different ways.

In the HeartMate II trials, bridging with heparin was recommended. Subsequently, Slaughter et al published data suggesting that heparin bridging was not necessary in the HMII as there was an increased risk of bleeding associated with bridging and no appreciable increase in embolic or thrombotic events in the absence of bridging [13]. While it is difficult to quantitate, there seemed to be a change in the practice at many VAD centers in relation to heparin bridging following the publication of this data, although our policy on heparin did not change over that time period.

LDH has become an accepted method for monitoring the amount of hemolysis produced by an LVAD. As pump thrombosis is usually associated with an increase in the LDH, it has become a proxy for early pump thrombosis such that many centers will increase the frequency of monitoring, increase anticoagulation or do additional testing if there is a significant rise in LDH. The increased use of LDH as a marker seems to have occurred around 2012-3 when there were increased numbers of presentations at national meetings. More attention to rises in LDH may have led to the increased recognition and diagnosis of probable pump thrombosis where it may not have been otherwise suspected.

The timing of the spike in pump thrombosis published by Starling et al. [3] coincided with the release of the gelatin-impregnated outflow graft on the HeartMate II, and was felt by some to be the source of the increased rate of thrombosis. However, a study that analyzed the rate of suspected cases of pump thrombosis nationwide comparing gelatin-impregnated to non-impregnated outflow grafts found that there were more queries regarding potential pump issues that occurred over a relatively short period of time and occurred in pumps both with and without the modified outflow grafts [15].

The final factor that comes into play is the rise of competing technologies. The HeartWare HVAD system was approved by the FDA for use in patients awaiting transplantation in late 2012. It is possible that as clinicians gained experience with other devices such as the HVAD, they altered their techniques and management of patients with the HeartMate II. With the lack of bearings and contact points, de-airing of the HVAD (and later with the HeartMate 3) is theoretically not likely to generate as much heat and thus not serve as a nidus for protein deposition that could be seen with the HeartMate II device.

It is clear that there is no single cause of pump thrombosis, and there is likely a rate of thrombosis that is inherent to each system which cannot be eliminated. It seems unlikely that the perceived spike in pump thrombosis was related to the modification in the HeartMate II outflow graft. It most likely resulted from a change in patient selection, implantation technique, anticoagulation management, and/or recognition of thrombosis events. We propose that running the HMII LVAD pump with the outflow graft occluded was one of the factors that may have caused some cases of pump thrombosis.

This study has several limitations. First and foremost, the patients were divided into two groups that were implanted during two different periods of time. It is possible that there were other changes in patient selection or management that

occurred over this time that were not recognized. Secondly, the conclusions are based primarily on LDH values and not on actual episodes of pump thrombosis. This was done since thrombosis is an infrequent event. However, there was a trend towards a higher rate of thrombosis in the patients who underwent implantation in Group 1, but it did not reach statistical significance. Finally, without knowledge of how many surgeons de-air with each technique and their personal rates of pump thrombosis, it is difficult to make generalizations in the applicability of the data to other programs.

In conclusion, running the HeartMate II LVAD pump with the outflow graft clamped may increase the incidence of pump thrombosis. Release of the outflow graft clamp before starting the pump may reduce this risk. While the approval of new bearingless pumps such as the HeartMate 3 will likely lead to decreased usage of the HeartMate II, the lessons learned from this study may be applicable to future pumps that have bearings where heat dissipation is important.

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