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Allosensitization and the Ventricular Assist Device: Dual Evolution of Technology

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1. Introduction

Heart failure is a growing worldwide phenomenon, affecting more than 10 million people between the U.S. and Europe [1]. The quality of life for advanced heart failure patients is poor, with repeat hospitalizations and high rates of mortality. With the aging of the general population the number of people experiencing heart failure will rise. Cardiac transplantation has been the goal for some patients, but the growth in number of available donors has not kept pace with the number of potential recipients, and optimal candidates are carefully selected. As a result the search for alternative therapies to support a failing heart, in particular the development of ventricular assist devices (VAD) has been a focus of research for more than 30 years.

Because refractory heart failure frequently involves failure of the dominant left ventricle, early devices were designed to assume the work of the left ventricle. The intent was to improve overall blood flow to the body and organs, reducing some symptoms and secondary end organ failure. Early devices were used primarily as a bridge to transplantation (BTT) to assist patients waiting for a suitable organ. The technology has continued to advance over the last decade and many such devices are in use as stand alone, or destination therapy. The use of VADs has been associated with immune dysregulation and allosensitization, which can be an impediment to transplantation.

This chapter will review the evolution of assist devices in relation to alloimmunity, specifically antibodies to human leukocyte antigens (HLA). The development of antibodies to HLA antigens is caused by exposure via pregnancy, transplantation, and blood transfusion. The

level and specificity of alloantibodies is detected by screening against a panel of typed cells or antigen bound to a solid surface, and is reported as panel/percent reactive antibodies (PRA). Different test methods have yield different sensitivity with cell-based (complement dependent cytotoxicity; CDC) being least sensitive and solid phase being most sensitive.

2. Role of alloantibody in acute rejection and chronic allograft vasculopathy

The rapid evolution of effective immunosuppressant drugs has significantly decreased the frequency and severity of acute cellular rejection following cardiac transplantation, but the incidence and effective treatment of antibody mediated rejection (AMR), especially over the long term remains problematic. AMR was first described in 1987 by Herskowitz [2] as arteriolar vasculitis associated with poor outcome. Patients at increased risk are multiparous women and patients with alloantibody against donor antigens detected both pre- and post-transplant. Diagnosis requires clinical graft dysfunction, pathological evidence (endothelial swelling, presence of C4d positive staining on biopsy), and detectable donor specific antibody. Available treatments include plasmapheresis, intravenous steroids, intravenous immunoglobulin, and monoclonal antibodies directed against antibody producing cells (e.g. Rituximab targets CD20).

Acute AMR with high titer antibody damages graft tissue by activation and fixation of complement. The cascade induces coagulation and the terminal event results in the membrane attack complex which injures vascular endothelium. Severe AMR can result in death. Lower titer alloantibody associated with chronic AMR activates endothelial intracellular signaling cascades [3] inducing cell proliferation manifested ultimately as transplant vasculopathy and deterioration of graft function. Ho [4] recently reported results of a large cohort (n=950) of transplants with long term follow-up including biopsies and HLA antibody testing. Development of AMR had significant impact on long term graft survival (16% versus 63% in the AMR negative group at 12 years). In most cases the recipient demonstrated antibody directed against donor HLA antigens. Importantly those who developed antibody more than one year after transplant had the worst outcomes.

Since recipients who demonstrate pretransplant anti-HLA antibodies have higher risk of graft dysfunction, preventing allosensitization is important. However, the use of ventricular assist devices has a history of association with high alloantibody titer. Minimizing the incidence of antibody induction is of prime importance. Table 1 summarizes existing literature of allosensitization among VAD implanted patients. There is a trend toward decreasing allosensitization over time, concurrent with evolution of device from pulsatile to axial flow, evolution of antibody testing from cell-based to solid phase, and an increasing use of leukoreduced blood products.

Author	Study period	Center	Device	n=	PRA>10% (method)	% male	Blood modification
Massad, M et al 1997	1992-1995	Cleveland	HeartMate pulsatile	53	65% (CDC)	87.0%	Few leukoreduced
John R et al, 2003	1992-99	New York	HeartMate pulsatile	105	66% (CDC)	78.1%	Not reported
Drakos, S et al 2007	1993-2002	Utah	HeartMate pulsatile	71	53.7% (CDC)	91.5%	Lower among leukofiltered
McKenna D, et al 2002	1995-2000	Minneapolis	not reported	29	28%	83.0%	Few leukofiltered
Pagani F et al 2000	1996-2000	Michigan	HeartMate pulsatile	38	28% (CDC)	67.6%	Most leukofiltered
George I, et al 2008	1999-2006	New York	HeartMate pulsatile	36	28% (CDC)	83.0%	Most leukofiltered
Arnaoutakis, et al 2011	2004-2009	UNOS	HM XVE pulsatile	673	25.3% (multiple)	84.8%	Not reported
Kumpati, G et al 2004	1991-2000	Cleveland	HM/Novacor pulsatile	231	<5% (CDC)	84.0%	Filtration >1995
Baran, D et al 2005	1989-2002	New Jersey	Novacor pulsatile	26	27% (CDC)	96.2%	Not reported
Kirsch, L et al 2007	1985-2006	Brussels	Novacor pulsatile	27	18.5% (CDC)	65.5%	Not reported
George I, et al 2008	1999-2006	New York	HeartMate II/ DeBakey	24	8% (CDC)	83.0%	Most leukofiltered
Grinda, J et al 2005	199-2004	Paris	DeBakey- axial	14	0% CDC/ELISA	100.0%	All leukoreduced
Drakos, S et al 2009	not reported	Utah	HeartMate II axial	11	9% (CDC/bead array)	63.6%	Most leukofiltered
Coppage, M et al	2009	New York	Mixed multiple	55	8% (CDC/bead array)	85.0%	All leukoreduced

Table 1. Literature on allosensitization among recipients of assist devices.

3. Volume displacement pumps

Early devices were designed to mimic the pulsatile flow of a native heart [5]. These devices include the Thoratec “HeartMate I XVE/1P” and the Abiomed “BVS5000/AB5000.” Due to the mechanical nature of these devices reliability was an issue. This first generation of pumps had large surface area that contacted both tissue and blood, and were associated with multiple reports of coagulopathy, immune dysregulation, and allosensitization. In 1997 Massad [6] reported that LVAD (HeartMate) patients were at increased risk for development of antibodies to HLA. While less than 5% of the 53 patients observed had PRA greater than 10% as measured in the CDC assay prior to VAD placement, 66% developed antibody after receiving a VAD.

The overall mean PRA increased significantly from 2.1% to 33.5% during VAD support, although a decrease was observed over time. One source of sensitization to HLA antigens is transfusion, and this group also reported an average of 148 units of blood products on the HeartMate, although the association was limited to transfusion associated with the LVAD and not remote blood product support. During the next few years, other groups also reported that VAD implantation was associated with allosensitization [7-9].

In contrast Stringham [10] reported on a small population (n=6) of recipients who survived VAD implantation without transfusion of blood or platelets. Three of the patients had no history of and did not develop anti-HLA antibody up to transplantation at days 33-50. The other three patients all became highly sensitized with PRA >90% between 30 and 90 days after the VAD surgery. They speculate three potential causes. First, all of the patients did receive fresh frozen plasma (FFP) after separation from the cardiopulmonary bypass, and FFP may contain soluble HLA antigens. Second, two of the three had experienced previous cardiac surgery accompanied by transfusion. They argue that the cardiac dysfunction leading up to VAD placement may have induced a state of immune anergy that was broken when improved cardiac function was restored. This association is not supported by the previously reported Massad[6] study that demonstrated no correlation between remote cardiac surgery with transfusion and later sensitization. Finally, they postulate that immunogenic component(s) of the LVAD cause development of antibody directed against or cross-reactive with HLA antigens. The same group [11] later presented a larger cohort of HeartMate recipient (n=71) analyzing the effect of leuko-reduced blood products, but found no significant effect. Our laboratory [12] reported a series of 55 VAD recipients, most of whom had received a pulsatile device. Our center only uses leuko-reduced, irradiated, and ABO matched blood products and we observed minimal allosensitization.

Drakos [13] undertook a study to determine risk factors contributing to allosensitization. They reviewed records of 75 patients, most of whom received the HeartMate I. The most significant factor identified was a history of prior sensitization to HLA antigens, followed by female gender. Neither of these findings is surprising. Pregnancy is a common sensitizing event, and the presence of HLA allosensitization predisposes to increased antibody production upon re-exposure to antigen. This same group [14] investigated the use of prophylactic intravenous immunoglobulin, commonly used in desensitization strategies, in prevention of HLA sensitization. Patients received either no IVIG or 10g per day of IVIG for 3 days after VAD implantation. The groups were of equal size (25 and 26 respectively), but were not randomized. No statistically significant difference in PRA was observed between the groups, and the overall rate of sensitization (defined as PRA >10%) was over 30% for both.

Several reports addressed the issue of allosensitization stratified by the type of device. The early reports compared the pulsatile pumps with one another. Baran [15] assessed sensitization in a series of 23 patients who received the Novacor (Worldheart, Ottawa) device prior to transplant as opposed to the HeartMate for which previous high PRA had been reported. They note that the HeartMate I was made of textured titanium that develops a neointimal lining that averts the need for systemic anti-coagulation. However, the existence of this lining was suggested to induce immune up-regulation associated with increased PRA. The Novacor had

a smooth blood-contacting surface that would not develop a neointimal lining. Of the 23 patients, 13 had less than 5% change in PRA, five had increases of up to 30%, and five experienced a decrease in PRA as tested in the CDC assay. Post-transplant courses were not significantly different between the BTT and non-BTT groups with similar rates of rejection and transplant vasculopathy. Another group [16] undertook a propensity matched study of 231 patients who received either the HeartMate I (n=166) or Novacor (n=55) device. In contrast to Baran [15], this group observed no differential rate of sensitization in a much larger patient population. However, they did report a general rapid, but small increase in PRA in the immediate post-VAD implantation period that decreased over time. In this study, the predictors of sensitization include female sex (pregnancy is a common source of allosensitization) and total number of blood transfusions. The overall level of sensitization of this population was lower than previous reports, with peak PRA <50%, possibly due to their predominant use of leukoreduced blood products.

Gonzalez-Stawinski [17] reviewed early and late rejection as well as HLA sensitization in a series of 119 recipients who were bridged to transplant with 3 different types of VAD, but all were volume displacement. Not surprisingly, higher PRA and positive flow cytometry crossmatch was associated with increased level of rejection on biopsy at 30 days and 2 years post-transplant, but long term outcome was not addressed. However, Joyce [18] surveyed the International Society of Heart and Lung Transplant (ISHLT) registry and divided the cardiac transplant group (n=11,457) into 3 groups including LVAD used, not used, or unknown. Virtually all of the VAD recipients receive pulsatile devices. In this large dataset, the presence of VAD was a significantly higher ($p<0.0001$) predictor of sensitization as defined by PRA>10%. Importantly, rates of rejection, measured by comparing drug treated events from transplant to 1 year follow up were not different between recipients who bridged with a VAD and those who did not. Likewise there were no significant differences in mortality at 1 or 2 years between the groups.

4. Axial flow pumps

The second generations of assist devices are smaller and contain an impeller that spins to deliver blood through the circulatory system [5]. These pumps are much smaller in size, but the impeller moves at 6000 rpm to 15000 rpm, which may cause hemolysis and platelet activation contributing to general immune activation.

Grinda[19] reported Anti-HLA sensitization for a group of 21 patients who were implanted with the DeBakey axial flow VAD. For this study PRA was measured by both the CDC and solid phase assays. None of their patients developed detectable anti-HLA antibodies during the course of VAD support with mean duration 87 days (range 21-224). This group also uses only leukoreduced blood products. Their findings were supported by a later report from George[20] who compared sensitization observed among patients who received one of two axial flow devices (HeartMate II and DeBakey n=24) with the pulsatile (HeartMate I n=36) device. Alloantibody was tested in all patients by the CDC method, and sensitization was

defined as a PRA of $>10\%$. The actual percent PRA was not reported. They observed a significantly higher rate of sensitization for recipients of the HeartMate I pulsatile device (28%) compared with either axial device (8% $p<0.01$). In both groups the number of allosensitized decreased over time and was lower at the time of heart transplant than as measured after VAD placement. The presence of sensitization did not affect short-term survival in either the axial or pulsatile group.

5. Radial flow devices

The third generation of VADs provides radial or centrifugal flow. In general, they are slightly larger than the axial flow devices, but their design makes them especially suited to long term cardiac support. For that reason these devices are ideal for use as a destination or permanent therapy. Allosensitization would therefore not be an impediment to future therapy. There is one report [21] of successful cardiac transplantation of a small cohort of recipients who had been implanted with HeartWare (Heartware International, USA) or VentriAssist (Ventracor, Ltd, Australia) centrifugal devices. Thirteen patients were transplanted with a one year survival of 91%. While no allosensitization or crossmatch data are presented, one may infer that alloantibody was not a obstruction to transplantation. Conversely, there is a report [22] regarding the Evaheart (Medical USA, Inc) that demonstrates significant platelet activation using centrifugal VAD and two different coatings (carbon versus 2-methoxyethylolylphosphoryl choline) in a bovine model. While platelet activation does not itself lead to allosensitization, platelet activation and microaggregates were also associated with coagulopathy and ultimately allosensitization in some of the earlier models. As of this writing, no specific reports of anti-HLA antibody associated with the use of radial flow VADs exist.

6. Immune dysregulation associated with VADs

The development of ventricular assist devices provided extended time for patients who were waiting for a compatible heart to become available. The theory and technology has steadily improved over the last 2 decades. Devices are smaller and have a reduced contact with the body's blood and tissue, thus making them less immunogenic. This fact is reflected in the data reviewed here. In the late 1990s and early 2000s, the pulsatile devices were most common, and reports documenting the risk of allosensitization stem from VADs began during this period. The relatively large surface area and composition of materials made for greater contact with tissue and blood, and in addition to reports of allosensitization came reports of general immune dysregulation [23, 24] and coagulopathy [25, 26].

Recipients of the early smooth textured VADs were at increased risk for hemorrhage and later for thromboembolism [27, 28]. Later devices incorporated a textured surface on which developed a neointimal cellular lining. Although the risk of thromboembolic events declined, the cellular lining introduced new complications. These cells were demonstrated to be

primarily resting monocytes and activated macrophages[23]. These cells help to maintain an inflammatory state, and were shown to augment production of cytokines (especially of TH2 pathway) and coagulation factors [23]. John [29] studied markers of endothelial and coagulative activation in 21 LVAD recipients (HeartMate II) and noted significant baseline activation of both systems in the immediate postoperative period, with elevated levels remaining to 180 days. Rothenburger [30] also demonstrated that T and NK cell populations decreased and the level remained depressed for over 100 days. At the same time B cell numbers increased as did IL-6 and CRP. Hyper-reactivity of B cells was postulated as VAD recipients demonstrated elevated antiphospholipid antibodies in addition to the risk of anti-HLA antibodies. A more recent study [31] demonstrated the presence of natural antibodies in transplant candidates with VAD. Taken as whole, cardiopulmonary bypass surgery and implantation of a ventricular assist device induces systemic inflammation and humoral amplification[32] including coagulation and complement cascades.

Not surprising given immune dysregulation and the introduction of a foreign body, infection is a nearly universal threat for device-related morbidity. The literature for infectious complications is extensive and will not be reviewed here. The presence of microorganism(s) or fungi, however, contributes to humoral amplification.

7. Immunomodulatory effects of transfused blood products

Our group has observed that soluble immune modulatory factors (sCD40L, IL-8, and RANTES) are present and biologically active in platelet concentrates [33-35] and non-leukoreduced red cells, and to a lesser extent this may be true of FFP as well. We hypothesize that intravenously administered blood components (including FFP), administered as a bolus (as opposed to being produced in a paracrine manner) access the lymphatic system where immune effectors reside, and modulate their responses. This complements previously reported systemic alterations and immune dysregulation involving B cells following VAD implantation [23, 30, 36]. Prior to the general acceptance of universal leukoreduction, a prime indication of this effect on B cell immunity was the production of anti-HLA antibodies. MHC molecules are immunogenic and provide a stimulus for an antibody response. Anti-HLA responses became a focus regarding the hazards of blood transfusion in VAD patients. Immunomodulatory factors present in blood transfusion, especially those that contain white cells or platelets, contribute to a systemic TH2 response, including non-specific activation of B cells and up-regulation of immunoglobulin production [37].

8. Evolution of antibody testing systems

As the technology and understanding of device technology has evolved over the years, so has the science of histocompatibility testing. The practice standard until the last decade was the complement dependent cytotoxicity (CDC) test, often augmented by anti-human globulin

(AHG) to detect low levels of or non-complement fixing antibody. Most of the early reports describe the use of some form of CDC assay, but the addition or exclusion of AHG impacts the sensitivity and specificity of the test. It may allow identification of low level alloantibody, but is also more prone to false positive detection. In the late 1990s, solid-phase assay began to be adapted. The first generation was enzyme-linked immunosorbent assays (ELISA). ELISA assays include HLA antigen bound to a solid, generally plastic surface. These tests are more sensitive than cell based assay, and also include the use of AHG. Newell[38] reported that IgG antibodies detected in the ELISA assay of serum from VAD patients were actually anti-albumin antibodies, a reagent commonly used in ELISA assays. The positive reactions converted to negative when sera were pre-incubated with albumin-coated beads. Similarly, serum from VAD patients tested in our laboratory [12] exhibited reactivity in ELISA assays, but reactivity occurs even in wells that do not contain HLA antigen, indicating false positive reactions.

The up-regulation of humoral immunity described for VAD recipients may include specific (e.g. anti-albumin), non-specific (e.g. natural anti-ABO), and memory (e.g. anti-HLA from pregnancy) antibody responses. Our group has also reported the formation of circulating immune complexes of ABO antigen and their corresponding antibodies in patients who received ABO unmatched platelets [39, 40]. We believe that any or all of these phenomena may interfere with immune assays, especially those that use an anti-immunoglobulin (second-step) reagent such as ELISA, and flow or AHG crossmatch. Recently, however, bead based anti-HLA antibody tests were introduced. In our hands these have proved to be both sensitive and specific, although, like other solid-phase assays they use an anti-human immunoglobulin secondary step. The beads used in these assays are particulate in nature and more rigorous wash steps to remove low avidity antibody may be used to limit weak or non-specific reactions. However, some kits employ recombinant HLA antigen that has an increased propensity for denaturing due to alternate glycosylation and peptide loading. There are multiple reports of “natural” antibody that reacts with HLA antigen [41, 42] and also to denatured HLA antigens [43] that have little or no clinical relevance to allotransplantation. Awareness of the strengths and weaknesses of the various assays that are employed in determining anti-HLA sensitization is vital to accurate interpretation of the data they provide.

A final confounding factor in assessing the role of anti-HLA antibody in ventricular assist devices is how allosensitization is defined. Much of the cardiothoracic literature defines allosensitized as having a PRA > 10%, meaning the candidate has antibody against 10% of the HLA antigens expected among the local organ donor pool. Conversely, this means that the candidate does NOT have antibody to 90% of HLA antigens, and has a 90% likelihood of finding a compatible donor. The histocompatibility community generally does not consider a person highly sensitized unless they demonstrate antibody against more than half of a standard panel. Thus centers who reported rates of sensitization of 30-60% may have simply been using a definition that encompasses patients who should not be so classified. In this light the phenomenon of allosensitization might not exist under a more stringent definition.

In summary, the introduction of a foreign device via major cardiopulmonary bypass surgery is not an immunologically benign event. Patients have systemic complications going into the surgery secondary to cardiac failure. Some of these improve with the introduction of the VAD

and improved blood circulation, but inflammation, infection, and coagulopathy are consistent causes of morbidity and mortality in this population. Continued improvements of the devices to those that are smaller and have continuous flow are less invasive and are more reliable for long term use. Literature around use of the early, large, pulsatile devices pointed to allosensitization to HLA antigens as posing an impediment to using the VAD as a bridge to transplantation. Over the years, our understanding of immune events and the systems used to tests for allosensitization have also evolved. In addition many centers have implemented policies for using leukoreduced blood products. While the development of anti-HLA antibodies is a clear risk for some recipients (e.g. multiparous women, previous sensitized recipients), the phenomenon is not as widespread as once assumed.

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