ACTIVATION OF COAGULATION AND FIBRINOLYTIC PATHWAYS IN PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES

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Left ventricular assist devices have provided successful supportive therapy for patients awaiting cardiac transplantation for extended periods of time. Although thromboembolic events have complicated support with these devices, the HeartMate left ventricular assist device developed by Thermo Cardiosystems, Inc., Woburn, Massachusetts, was specifically designed with a textured blood-contacting surface to minimize this risk. Clinical experience with this device has been encouraging, inasmuch as minimal thromboembolic complications have occurred despite the absence of anticoagulation. The coagulation and fibrinolytic pathways in these individuals were investigated to better understand the hematologic status of patients treated with the Thermo Cardiosystems device. Despite apparently normal prothrombin and activated partial thromboplastin times, as well as platelet counts, evidence of significant thrombin generation and fibrinolysis was present. To eliminate underlying cardiac failure as the responsible factor for these abnormalities, we made similar measurements in patients with end-stage heart failure who were not supported by an assist device or anticoagulation. These measurements revealed no evidence of thrombin generation or fibrinolysis. These data demonstrate that patients supported with a left ventricular assist device, while successfully sustained without systemic anticoagulation, nevertheless have evidence of activation of coagulation. These phenomena appear to be related to the presence of the device rather than to the underlying cardiac abnormalities. Although procoagulant and fibrinolytic pathways are apparently balanced in these patients, these data underscore the potential for the development of bleeding or thrombosis in clinically relevant settings. (J Thorac Cardiovasc Surg 1996; 112:1090-7)

Cardiac transplantation has become the accepted standard of care for patients with end-stage heart failure. The ever-widening gap between the number of potential cardiac transplant recipients and the

number of available donor organs,[1-3] however, has necessitated the development of intermediate or "bridging" devices designed to sustain the patient awaiting an appropriate donor heart. The success of these pumps has prompted a movement toward their use as a permanent form of cardiac replacement.[4-8] One of the critical factors limiting the use of left ventricular assist devices (LVADs) in the past has been a reported rate of thromboembolic complications of 30% or greater, as well as a significant perioperative coagulopathy.[9-12]

Compared with the early LVADs, whose surfaces were mainly smooth, the HeartMate LVAD developed by Thermo Cardiosystems, Inc., Woburn, Massachusetts, was designed with specific features intended to minimize the potential for thromboembolic complications.[13-17] Specifically, this LVAD, containing a textured surface, was designed to facilitate the formation of a tightly adherent "pseudo-

Table I. *Demographic profile of patients having LVADs*

	Age (yr)	Sex	Diagnosis	Length of LVAD treatment (days)	Type of LVAD pump*
1	52	F	Idiopathic CM	335	Pneumatic
2	65	M	Ischemic CM	46	Pneumatic
3	51	M	Ischemic CM	139	Pneumatic
4	19	M	Idiopathic CM	35	Electric
5	61	M	Ischemic CM	101	Electric
6	17	M	Idiopathic CM	65	Electric
7	61	M	Ischemic CM	100	Electric
8	58	M	Ischemic CM	70	Electric
9	58	M	Ischemic CM	68	Pneumatic
10	48	M	Ischemic CM	221	Electric
11	68	M	Ischemic CM	56	Pneumatic
12	39	F	Subacute MI	49	Pneumatic
13	56	M	Ischemic CM	9	Pneumatic
14	51	F	Subacute MI	7	Pneumatic
15	65	M	Ischemic CM	33	Electric
16	59	F	Ischemic CM	35	Pneumatic
17	65	M	Ischemic CM	33	Pneumatic
18	52	M	Idiopathic CM	25	Pneumatic
19	51	M	Ischemic CM	11	Pneumatic
20	30	M	Idiopathic CM	5	Pneumatic

CM, Cardiomyopathy; *MI*, myocardial infarction.
*HeartMate LVAD; Thermo Cardiosystems, Inc., Woburn, Massachusetts.

neointima" on the blood-contacting surfaces, a strategy aimed at reducing the risk of thromboembolism by eliminating direct contact between the device and circulating blood.[17] A thromboembolic rate of less than 2% has been associated with the use of this device in patients receiving no or minimal forms of anticoagulation.[18]

To better understand the hematologic profile that underlies this low thromboembolic risk and to more fully understand the long-term physiologic implications of its use, we analyzed measurements of thrombin generation and fibrinolysis in patients supported by the HeartMate LVAD.

Patients and methods

Patients. Twenty patients in clinically stable condition with implanted Thermo Cardiosystems HeartMate LVADs and 12 other patients in clinically stable condition with New York Heart Association class IV heart failure were entered into this study during the period extending from June 1995 through November 1995. The study was conducted in accordance with the rules and regulations of the Institutional Review Board of Columbia University College of Physicians and Surgeons. Among the patients supported with an LVAD, 14 had pneumatically driven LVADs and the other six had electrically driven LVADs. The mean age of the patients with an LVAD was 51.7 years (range 17 to 65 years) and the mean duration of LVAD treatment was 83 days (range 5 to 335 days). No patients in the LVAD group were receiving heparin, warfarin sodium, or other systemic anticoagulant therapy.

Five patients were receiving aspirin (325 mg by mouth every day) (Table I). The 12 patients with class IV end-stage heart failure were selected for inclusion in this study because they were not receiving systemic anticoagulation. Their mean age was 54 years (range 33 to 65 years). All patients in this group were receiving aspirin (325 mg by mouth every day).

Values for a normal control population were obtained from the clinical laboratories at Columbia Presbyterian Medical Center for prothrombin time, activated partial thromboplastin time, levels of platelets and fibrinogen, fibrinogen (fibrin) degradation products (FDPs), and D-dimers. These values were obtained by examining blood samples of 30 normal volunteers. Normal values for thrombin-antithrombin complex (TAT), prothrombin activation peptide (F_{1+2}), and soluble thrombomodulin were provided by the manufacturers from which the enzyme-linked immunosorbent assay (ELISA) kits were obtained. These values were derived by analysis of plasma samples from 120 clinically stable volunteers. Levels of F_{1+2} are a specific reflection of the effects of factor Xa on prothrombin and thus are a marker of thrombin generation and activation of coagulation.[19-20]

Materials. After peripheral blood had been obtained in accordance with the aforementioned protocols, complete blood count, prothrombin time, activated partial thromboplastin time, fibrinogen levels, and FDPs were obtained from the clinical laboratories of Columbia University College of Physicians and Surgeons according to standard methods. ELISAs for TAT and F_{1+2} were obtained from Behring Diagnostics, Inc. (Westwood, Mass.), and ELISA kits for D-dimers and soluble thrombomodulin were obtained from American Diagnostica (Greenwich,
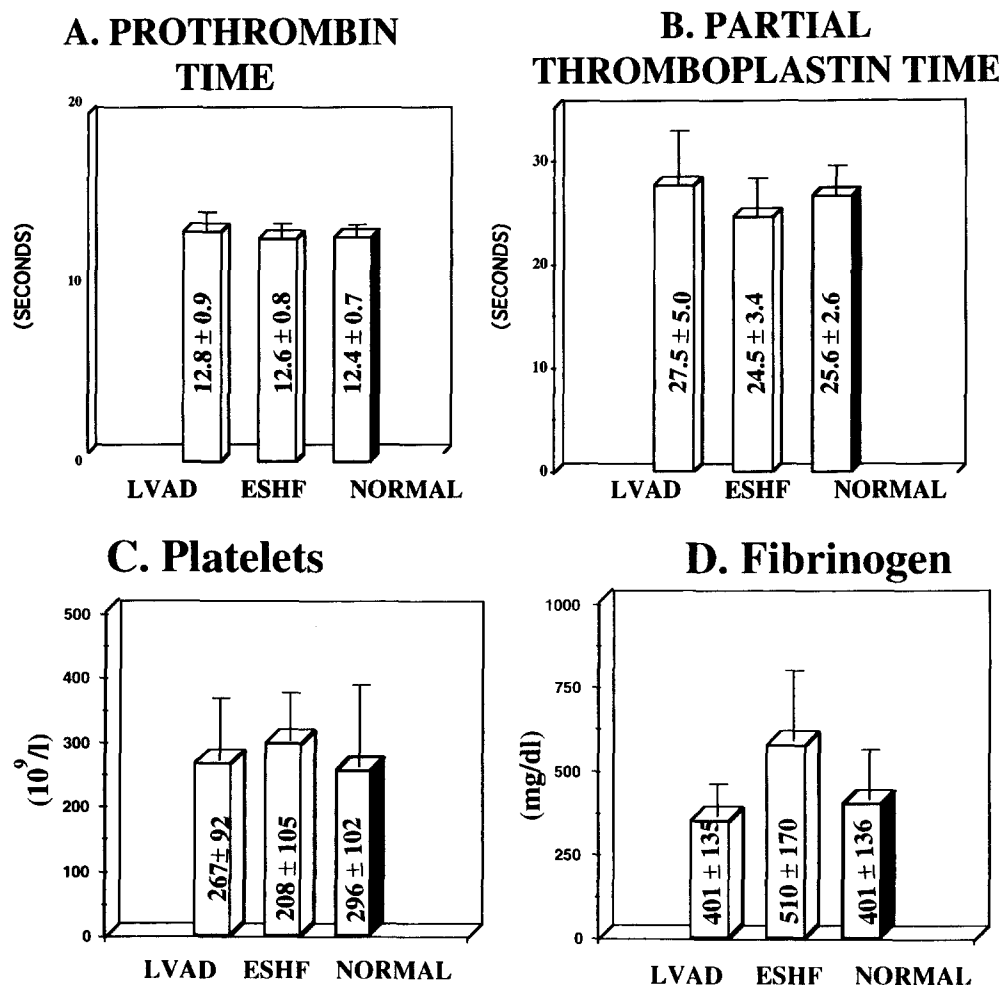
Fig. 1. Assessment of routine coagulation parameters in patients with LVADs and patients with end-stage heart failure (ESHF). Plasma was obtained by peripheral venipuncture from the patients with LVADs or end-stage heart failure as described in the text. Parameter (normal control) values were obtained from the clinical coagulation laboratory of Columbia Presbyterian Medical Center. Mean values ± standard deviation for prothrombin time, activated partial thromboplastin time, and levels of platelets and fibrinogen are depicted within the *bar graphs*. No significant differences were noted except that patients with end-stage heart failure had higher levels of fibrinogen than patients with LVADs and normal control subjects ($p < 0.02$).

Conn.). All ELISAs were performed according to the manufacturers' instructions.

Statistical analysis. Data were analyzed with SAS System software (SAS Institute, Inc., Cary, N.C.). The Kruskal-Wallis test (χ^2 approximation[21]) and the nonparametric analog of the analysis of variance were used to test the differences in means across the three groups (LVAD, end-stage heart failure, and normal). If the Kruskal-Wallis test showed significant differences, then a nonparametric multiple comparisons test was applied to determine among which groups statistically significant differences existed.[22, 23] Differences were considered significant if the probability value (p value) for comparison was less than 0.05.

Results

As previously described, plasma was obtained from patients at random times during LVAD therapy which corresponded to our study period. The mean length of LVAD implantation at the time of blood sampling was 87 days (range 5 to 335 days). The patients were all in clinically stable condition when they were tested. Blood sampling was performed in the morning in all cases, but no samples were obtained with the patient fasting. As stated previously, no patients were receiving oral or intravenous anticoagulant therapy. Five of the patients
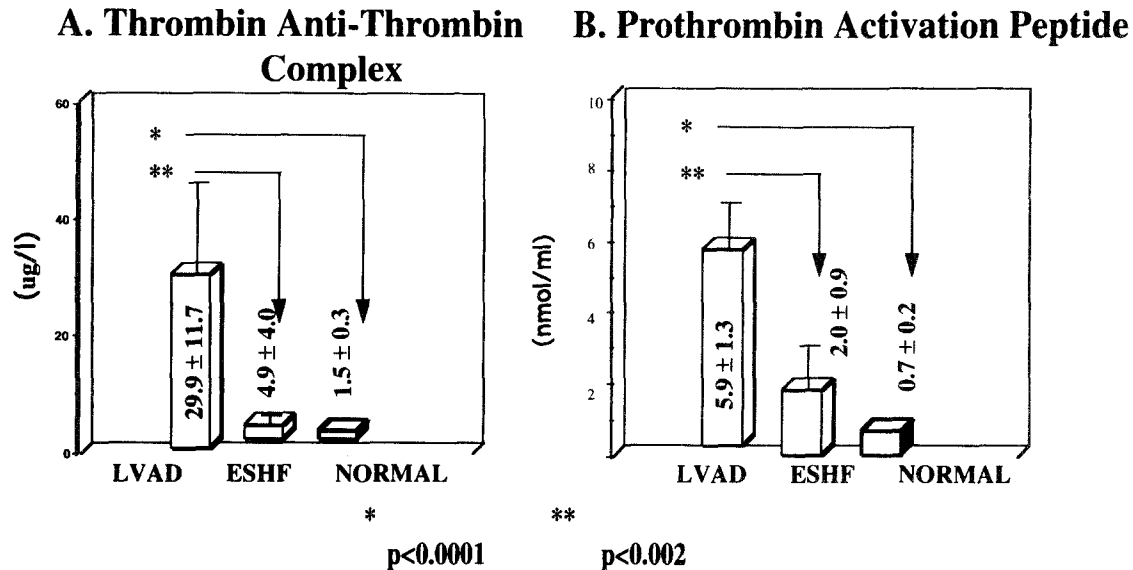
Fig. 2. Assessment of thrombin generation in patients with LVADs and in patients with end-stage heart failure (ESHF). Peripheral blood was obtained as described in the text and plasma was assayed as described for F_{1+2} and TAT. Mean values $\pm$ standard deviation are shown within the bar graphs. Levels of F_{1+2} and TAT were significantly higher in patients with LVADs than in patients with end-stage heart failure and than the normal control values ($p < 0.002$ and $p < 0.0001$, respectively).

were receiving aspirin at a dosage of 325 mg one time a day. Normal population control values were obtained from our clinical laboratories or from the manufacturers of the respective assay kits used in these experiments. Plasma was also obtained from patients with class IV heart failure to eliminate the presence of heart failure as a cause of the observed coagulation abnormalities. These samples were similarly taken in the morning, but not with the patient fasting. All of these patients were receiving aspirin (325 mg orally every day), but none was receiving anticoagulant therapy.

Our initial studies revealed that there were no significant differences between patients supported by an LVAD and the normal population with respect to platelet count, prothrombin and partial thromboplastin times, and levels of plasma fibrinogen. Comparison with patients in end-stage heart failure also failed to reveal any significant differences in any of these studies (Fig. 1).

To evaluate more subtle indices indicative of activation of the procoagulant pathway, we measured levels of TAT and F_{1+2}. Evaluation of these markers of thrombin generation revealed that patients supported with an LVAD had statistically significantly higher levels of TAT ($p < 0.0001$) and F_{1+2} ($p < 0.0001$) than the control population (Fig.

2). Similarly, these markers of thrombin generation were significantly higher in patients with an LVAD than in patients with end-stage heart failure ($p < 0.002$). There were no discernible differences between patients with pneumatically driven or electrically powered LVADs with respect to markers of thrombin generation, nor were differences detected in LVAD patients receiving aspirin compared with those receiving no antiplatelet therapy (data not shown).

To investigate whether enhanced fibrinolysis accompanied activation of the procoagulant pathway, we evaluated patients for the presence of D-dimers and FDPs. Compared with the normal control population and patients with end-stage heart failure, patients with an LVAD had significantly higher levels of plasma D-dimers and FDPs ($p < 0.0001$ and $p < 0.0001$, respectively) (Fig. 3). Levels of D-dimer and FDP in patients with an LVAD were similarly elevated irrespective of the type of LVAD or treatment with aspirin (data not shown).

We examined levels of soluble thrombomodulin as an additional marker of endothelial disturbance potentially caused by the effects of microemboli generated in the coagulopathy associated with LVAD therapy. Soluble thrombomodulin, most likely made and released by the endothelium,[24] was

A. D-Dimers

B. Fibrinogen Degradation Products

* p<0.0001   ** p<0.002
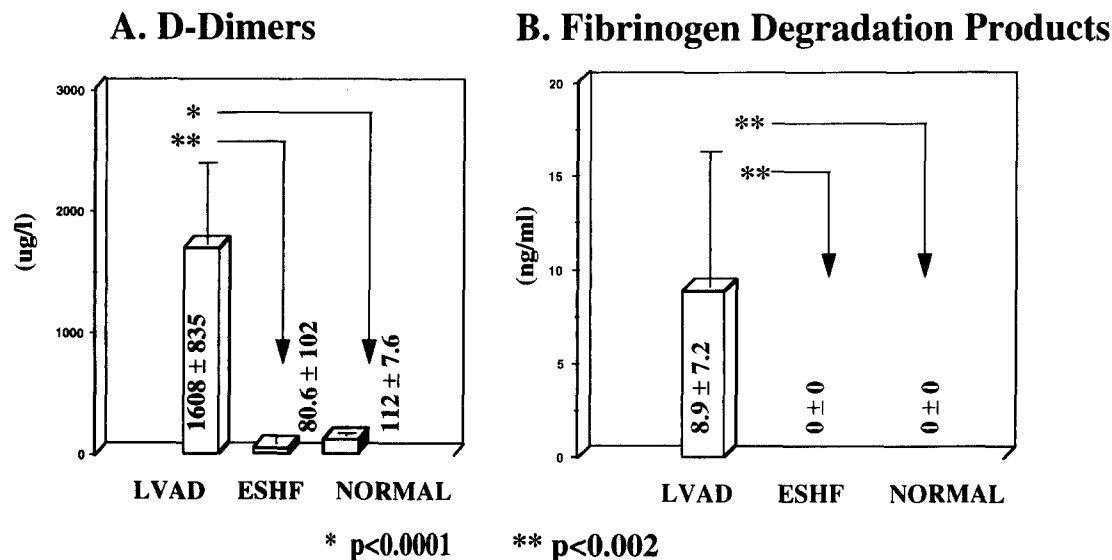
Fig. 3. Assessment of activation of fibrinolysis in patients with LVADs and patients with end-stage heart failure *(ESHF)*. Peripheral blood was obtained as described in the text and plasma was assayed as described for levels of D-dimers and FDPs. Mean values ± standard deviation are shown within the *bar graphs*. Levels of D-dimers were significantly higher in patients with LVADs than in patients with end-stage heart failure and than the normal control values ($p < 0.002$ and $p < 0.002$, respectively). Levels of FDPs were significantly higher in patients with LVADs than in patients with end-stage heart failure and than the normal control values ($p < 0.0001$ and $p < 0.0001$, respectively).
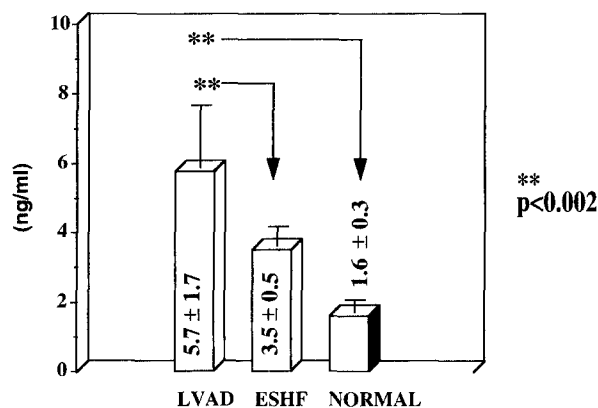

Fig. 4. Elevation of soluble thrombomodulin in patients with LVADs: a possible marker of endothelial perturbation. Peripheral blood was obtained as described in the text and plasma was assayed as described for levels of soluble thrombomodulin. Mean values of soluble thrombomodulin ± standard deviation are shown within the *bar graphs*. Levels of soluble thrombomodulin were significantly higher in patients with LVADs than the normal control values ($p < 0.002$). There was no significant difference in levels of soluble thrombomodulin in patients with LVADs and patients with end-stage heart failure sustained without anticoagulation.

at a higher concentration in the plasma of patients with an LVAD than in normal subjects ($p < 0.002$) (Fig. 4). Increased plasma soluble thrombomodulin is likely to result from endothelial perturbation caused by a number of factors including sustained activation of coagulation and fibrinolytic pathways, altered blood flow, or other vascular changes consequent to the presence of the LVAD.
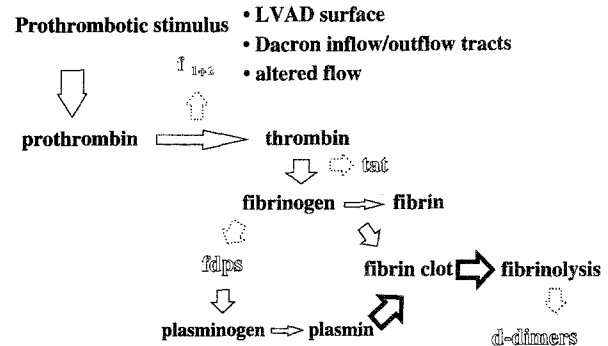
Discussion

Our data indicate that patients with Thermo Cardiosystems HeartMate LVADs have significant activation of coagulation with secondary fibrinolysis, despite both apparent clinical stability and "normal" screening values of routine hemostatic parameters such as platelet count, prothrombin time, and activated partial thromboplastin time. Soluble thrombomodulin, derived from an integral membrane protein constitutively expressed by endothelium,[24] is likely to be shed or proteolyzed as a result of endothelial perturbation, perhaps related to the presence of the LVAD or to microemboli associated with activation of coagulation (Fig. 5). From a clinical standpoint, the extent of activation of the
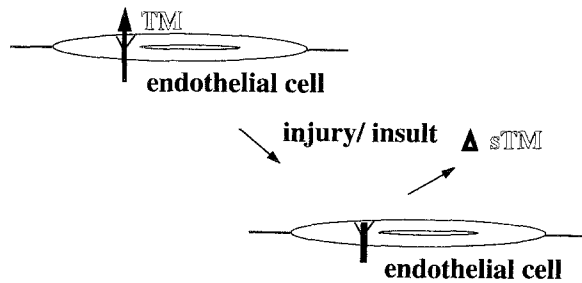
Fig. 5. Soluble thrombomodulin. We postulate that soluble thrombomodulin, likely derived from the integral membrane protein constitutively expressed by the endothelium, is shed and/or proteolyzed as a result of endothelial perturbation caused by the presence of the LVAD. Such inciting causes as the presence of microemboli in a procoagulant milieu, altered flow characteristics with cellular activation, and/or other vascular factors associated with the LVAD itself are likely contributory factors.

Fig. 6. Coagulation cascade/fibrinolysis. As demonstrated by our studies, evidence exists for significant thrombin generation (as reflected by increased levels of TAT and F_{1+2}) and fibrinolysis (increased levels of D-dimers and FDPs) in patients with LVADs compared with values for the normal control population and values for patients with end-stage heart failure not supported by LVAD or anticoagulant therapy. The mechanism(s) underlying the generation of a procoagulant state are not yet clear. For example, it is not known whether activation of the intrinsic and/or extrinsic pathways of coagulation underlie these findings. *Closed arrows* are indicative of the procoagulant pathway resulting in the formation of a fibrin clot. *Open arrows* follow the fibrinolytic pathway. *Dotted arrows* and *open font* signify the markers of these pathways reported in this study.

thrombin-generating and fibrinolytic pathways appears balanced in these patients; our earlier studies demonstrated low (2%) thromboembolic complication rates associated with the use of this LVAD.[18] Furthermore, clinical experience does not demonstrate a bleeding or thrombotic diathesis in the nonstressed or nonsurgical setting.[4-8, 14-18]

The causes underlying these hemostatic abnormalities are of considerable interest. Such LVAD-specific causes as the textured polyurethane surface, the titanium housing, and the Dacron inflow/outflow lines need to be considered. Other causes, such as altered flow characteristics and the presence of preexisting clots in the diseased ventricles, must also be investigated. Our data do not suggest that these findings are a direct result of the surgical implantation procedure of the LVAD, inasmuch as hemostatic findings remain abnormal at least up to day 335 of LVAD therapy (see Figs. 1 to 4). In this context, Livingston and colleagues[25] have shown that in the perioperative period, patients with an LVAD consistently have significantly higher markers of thrombin generation (TAT and F_{1+2}) and fibrinolysis (D-dimers and FDPs) than do patients who have had coronary bypass grafting.[25] Our pilot studies, in which we prospectively examined patients having LVADs, do not demonstrate that these perioperative findings are sustained, because the overt indices of thrombin generation and fibrinolysis are acute and procedure-related. In fact, pilot studies in two patients examined to date have revealed that markers of thrombin generation/fibrinolysis are significantly elevated during the operation, return to

near-normal values by days 5 to 7 after the operation, and then rise in a time-dependent manner, peaking at approximately day 35 of LVAD therapy, an effect that is subsequently sustained (data not shown).

Indeed, these data suggest that a specific characteristic of the LVAD itself is responsible, at least in part, for these observations. In this context, we and others have demonstrated considerable cellular entrapment by this device in studies of explanted LVADs.[26-30] Flow cytometry studies have demonstrated that the majority of these cells are myeloid/monocytic in origin. In addition, a smaller percentage of the cells are pluripotential hematopoietic cells, which can be induced to differentiate in culture to mature hematopoietic cells.[30] Menconi and colleagues[29] found that the surface of explanted LVADs contained adherent mononuclear cells, platelets, and myofibroblasts intermingled with areas of compact fibrinous material, as well as areas of collagenous tissue. Similarly, Salih and colleagues[26] found the surface of the explanted LVAD polyurethane membrane to consist of fibrinous and cellular layers. The layer atop the membrane was composed

of a compact fibrin coating, as well as numerous mononuclear cells and spindle-shaped cells. An intermediate middle layer consisted of cells resembling fibroblasts and fewer mononuclear cells than were observed in the inner layer. The outermost layer, at the biomaterial/tissue interface, contained a foreign body reaction with numerous multinucleated giant cells. Sections of tissue islands removed from the titanium surface revealed organized fibrous and collagenous tissue with few cellular areas, except for occasional mononuclear cells. Whereas Salih and colleagues found no evidence of endothelial cells on the surface of the LVAD, other studies have disputed this. Specifically, Frazier and colleagues[27] found evidence for the presence of endothelial cells on the pseudointimal lining of the textured LVAD surface. Using antibodies to von Willebrand factor, they demonstrated positive immunoreactivity in certain cells on the lining, suggestive of the presence of endothelial cells. (Of course, platelet material may also be responsible for this positive immunostaining for von Willebrand factor.) The significance of defining the presence of endothelial cells in this setting cannot be overstated, because their presence may suggest the potential for restoration of normal control of the vascular procoagulant and anticoagulant pathways.

Consistent with the hypothesis that the LVAD surface itself contributes to the multiple biologic phenomena observed in the course of its use, studies have revealed that this lining is metabolically active. Menconi and associates[29] showed by ribonucleic acid hybridization analysis that the colonizing cells actively expressed genes encoding proteins for cell proliferation markers, cell adhesion molecules, cytoskeletal structures, and extracellular matrix components.

Taken together, these data suggest that the cells lining the LVAD surface are not biologically inert. In this context, we postulate that the mononuclear cells, platelets, and pluripotential stem cells initially trapped by the polyurethane surface, titanium housing, or Dacron grafts[25-30] may become activated, thus leading to the generation of a local proinflammatory/procoagulant state. We further postulate that this mechanism is responsible, at least in part, for triggering and subsequently sustaining activation of the coagulation and fibrinolytic cascades (Fig. 6). In fact, our recent pilot studies have demonstrated that peripheral blood-derived mononuclear cells adhere almost immediately to representative sections of the LVAD polyurethane surface and that,

within days, these mononuclear cells appear to differentiate into mononuclear phagocyte–type cells with epithelioid changes consistent with their activation. Further studies are ongoing to demonstrate whether these cells produce mediators such as cytokines and tissue factor, which could certainly contribute to the initiation and propagation of procoagulant events, culminating in the generation of thrombin.

In conclusion, patients with the Thermo Cardiosystems HeartMate 1000 IP LVAD have evidence of enhanced thrombin generation with fibrinolysis. Thus, despite the apparent clinical stability of patients having an LVAD, as well as a low incidence of clinically apparent or subclinical microemboli, our results identify the presence of a coagulopathy with the potential to exacerbate bleeding or clotting complications in clinically relevant settings, for example, operation, infection, or inflammatory stress. The current balance appears to result in a favorably low thromboembolic rate; however, studies to determine the mechanisms triggering perturbation of the procoagulant and fibrinolytic pathways in patients having an LVAD are essential to identify targets of potential therapeutic intervention in these patients if necessitated by the development of hemostatic complications associated with long-term use of this device.

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