

The MicroMed DeBakey VAD—Part II: Impact on the Hemostatic Systems

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The implantation of a left ventricular assist device (LVAD) may serve as a bridge to transplantation or lead to recovery of the failing heart (1–3). However, because of limitations in the availability of donor organs, the permanent implantation of an LVAD as an alternative for heart transplantation may be an option in the future.

With the development of smaller, lighter, more durable systems that are completely implantable, important steps in the development of systems for permanent use have already been made. The MicroMed DeBakey™ LVAD (MicroMed Technology, The Woodlands, TX) incorporates features that make it attractive, not only for bridging but also for permanent implantation. However, most VAD systems are associated with the risk of development of thromboembolic events and, therefore, require potent anticoagulation involving the risk of bleeding complications. In consequence, peripheral thromboembolism and stroke largely contribute to the morbidity and mortality following implantation of a VAD (4,5). Therefore, in addition to the above-mentioned features, improved biocompatibility is a major goal in the development of new VADs.

This review gives a survey of alterations of the coagulation system, the inflammatory response, and the degree of hemolysis following implantation of the MicroMed DeBakey LVAD.

ANTICOAGULATION PROTOCOLS AND COAGULATION SYSTEM

In the approximately 100 MicroMed DeBakey™ LVADs that have been implanted worldwide to date, anticoagulation was based on the protocols of the individual centers and only in a minority of patients were alterations in the hemostatic systems investigated more closely (6).

Noon et al. reported the use of intravenous unfraction-

ated heparin (UFH) to an International Normalized Ratio (INR) to 2.0–2.5 or subcutaneous low molecular weight heparin (LMWH) followed by coumadin, aspirin, and clopidogrel (7). Wieselthaler et al. used a similar protocol with intravenous UFH until the patients were stabilized, followed by coumadin, aspirin, and dipyridamole (8). Koster et al. reported a protocol in which heparinization was restarted 6–12 hours after surgery to achieve a target activated clotting time (ACT) of between 160 and 180 s. Antiplatelet agents were simultaneously administered according to the in vitro-induced platelet aggregation test using the method of Born. The test was performed with ADP 20 $\mu\text{mol/L}$, epinephrine 100 $\mu\text{L/L}$, collagen 190 $\mu\text{g/mL}$, and arachidonic acid 500 $\mu\text{g/mL}$. The target value for ADP and epinephrine-induced platelet aggregation was 30–50% and <40% for arachidonic acid. A decrease of the aggregation to a value of 70–90% was regarded as sufficient for collagen-induced platelet aggregation. After removal of all drainage tubes, the anticoagulation was switched to coumadin. Depending on the results of the platelet aggregation tests, this medication was combined with antiplatelet agents. Antiplatelet therapy was initiated with aspirin, beginning with 50 mg/d and rising to 200 mg/d as a maximum dosage. If patients did not respond to this therapy, dipyridamole (400–1000 mg/d) was given (6).

Using this protocol, Koster et al. investigated changes in the coagulation system for the period of 6 weeks after implantation and compared the values to those of patients after implantation of a Novacor LVAD (6). The group investigated Factor XIIa (FXIIa) as a marker of contact activation, β -thromboglobulin (β -TG) and platelet factor 4 (PF4) as markers of platelet degradation and activation, thrombin/antithrombin (TAT) complexes and D-Dimers as markers of thrombin generation and thromboses, and plasmin/ α 2antiplasmin (PAP) complexes as markers of fibrinolysis. With the exception of the PAP levels in the Novacor group, all parameters were elevated in both groups. No significant difference was observed with respect to the generation of thrombin. The levels of β -TG, PF4, FXIIa, and PAP were significantly increased in the axial flow LVAD group.

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As platelet aggregation was adjusted to comparable values in the two groups, these data suggest a strong degradation of the platelets by the MicroMed DeBakey LVAD. Moreover, the elevated values for D-Dimer, TAT, and FXIIa reflect a powerful activation of the plasma coagulation system and, therefore, an increased risk for thromboembolism. In particular, the data for FXIIa are noteworthy because it was expected that, because of the smaller nonendothelial surface of the MicroMed DeBakey LVAD, contact activation would be reduced.

This strong activation of the plasma coagulation system was accompanied by increased fibrinolysis. The reason for this observation remains unclear, but maybe this moderate hyperfibrinolysis protected the patients from thromboses because of the activated plasma coagulation system.

However, it must be emphasized that these data were only collected in a small group of six patients using an anticoagulation protocol that was based on experience with pulsate VADs. Moreover, no clinical evidence of thromboembolic events was noted. Additional data are necessary for a better differentiation of the effects of the patients' condition and the VAD itself.

INFLAMMATORY RESPONSE

Limited data with regard to changes of the inflammatory system after implantation of the system are available. Loebe et al. reported on six consecutive patients following implantation of a MicroMed DeBakey LVAD in which markers of the inflammation cascade were assessed (9). The course of tumor necrosis factor alpha (TNF), C3a, C5a, interleukin 6 (IL6), and neutrophil elastase (NE) were measured twice a week and compared to that in patients following implantation of a pulsatile Novacor (Baxter) LVAD. Both groups were comparable in their clinical course, in particular with regard to the duration of ventilation, time on the ICU, and anticoagulation protocol. In both groups, the values for all measured parameters were elevated during the period of the investigation. While TNF, C3a and NE revealed no significant differences between the two groups, the values obtained for C5a and IL6 were significantly increased in the MicroMed DeBakey group.

Although both parameters play pivotal roles in the systems of inflammation and coagulation, the clinical impact of these findings, in particular with regard to the values obtained for TNF, NE, and C3a, remains uncertain. It was discussed that these increases of the marker of the inflammatory system have to be attributed to changes in the coagulation system, especially the contact activation and fibrinolytic systems. However, the limited data available from patients with a MicroMed DeBakey LVAD do not permit a definitive statement regarding this question. Despite the comparable clinical outcome of the patients, the

differences of these values may have to be attributed more to the clinical condition of the patient than to changes in homeostasis induced by the LVAD itself. Further investigations are needed to elucidate this problem.

HEMOLYSIS

The currently available data showed no significant elevation of the mean plasma free hemoglobin levels (8,10). Therefore, it can be concluded that hemolysis plays only a minor role after the implantation of the MicroMed DeBakey LVAD.

PERSPECTIVES

Although more than 100 MicroMed DeBakey LVADs have been implanted, knowledge of the device's effects on the hemostatic system is limited. However, it appears that the axial-flow impeller device does not lead to clinically relevant hemolysis but causes significant platelet damage. Because the platelet system plays a central role in the plasma coagulation system and inflammatory response, it is conceivable that most of the changes observed in these systems must be attributed to this injury of the platelets. The reason for this lack of biocompatibility remains unclear. However, it is most likely that platelet injury is caused by mechanical trauma attributable to contact with the impeller.

Improvements of the device are in progress: A *CARMEDA* heparin coating of the device is held to contribute to an increase in its biocompatibility. However, because of the relatively small artificial surfaces of the device, effects of this modification may be limited.

Another more promising option may be the development of sophisticated strategies for platelet stabilization. Recently, Thompson proposed an elaborated anticoagulation protocol for the MicroMed DeBakey LVAD using additional techniques for monitoring coagulation, such as thrombelastography, and emphasizing the necessity to stabilize platelet membranes (11). New classes of potent antiplatelet agents, such as the platelet glycoprotein IIb/IIIa antagonists, may play a pivotal role with regard to this issue.

Further studies are necessary to elucidate to what extent such more sophisticated anticoagulation strategies are able to reduce the effects on the hemostatic system and whether progress of the MicroMed DeBakey LVAD toward increased biocompatibility is required.

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