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Ambient hemolysis and activation of coagulation is different between HeartMate II and HeartWare left ventricular assist devices

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BACKGROUND: Thromboembolic and bleeding events in patients with a left ventricular assist device (LVAD) are still a major cause of complications. Therefore, the balance between anti-coagulant and pro-coagulant factors needs to be tightly controlled. The principle hypothesis of this study is that different pump designs may have an effect on hemolysis and activation of the coagulation system. Referring to this, the HeartMate II (HMII; Thoratec Corp, Pleasanton, CA) and the HeartWare HVAD (HeartWare International Inc, Framingham, MA) were investigated.

METHODS: For 20 patients with LVAD support ($n = 10$ each), plasma coagulation, full blood count, and clinical chemistry parameters were measured. Platelet function was monitored using platelet aggregometry, platelet function analyzer-100 system (Siemens, Marburg, Germany), vasodilator-stimulated phosphoprotein phosphorylation assay, immature platelet fraction, platelet-derived micro-particles, and von Willebrand diagnostic.

RESULTS: Acquired von Willebrand syndrome could be detected in all patients. Signs of hemolysis, as measured by lactate dehydrogenase levels (mean, 470 U/liter HMII, 250 U/liter HVAD; $p < 0.001$), were more pronounced in the HMII patients. In contrast, D-dimer analysis indicated a significantly higher activation of the coagulation system in HVAD patients (mean, 0.94 mg/liter HMII, 2.01 mg/liter HVAD; $p < 0.01$). The efficacy of anti-platelet therapy using clopidogrel was not sufficient in more than 50% of the patients.

CONCLUSIONS: Our results support the finding that all patients with rotary blood pumps suffered from von Willebrand syndrome. In addition, a distinct footprint of effects on hemolysis and the coagulation system can be attributed to different devices. As a consequence, the individual status of the coagulation system needs to be controlled in long-term patients.

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Hemostaseology effects during left ventricular assist device (LVAD) support are complex due to the presence of multiple disease processes, platelet activation, and altered rheologic effects. In addition, acquired von Willebrand (VW) syndrome (VWS) may appear, as may blood stasis within the chambers of the native heart. Further problems

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involve pharmacologic manipulation and its individual patient responses as well as blood exposure to the artificial surfaces. Therefore, bleeding and thromboembolic complications are major causes of morbidity, reoperation, and death after implantation of LVAD, whereas until now, the causal relationship has been poorly characterized.[1]

The HeartMate II (HMII) system (Thoratec Corp, Pleasanton, CA), which was introduced in 2005,[2,3] is an implantable, second-generation axial-flow pump, whereas the HeartWare HVAD (HeartWare International Inc, Framingham, MA), which was launched in 2008,[4] is a third-generation centrifugal-flow pump that is implanted into the pericardial cavity. Both pumps may be used as long-term assist devices.

The increased bleeding tendency in all LVAD patients compared with patients who do not have an LVAD but do receive the same anti-coagulation treatment can be explained, to a certain extent, by the appearance of VWS. All recipients showed VWS after non-pulsatile blood-pump LVAD implantation, demonstrated by reduced or absent high-molecular-weight (HMW) VW factor (VWF) multimer (MM) levels,[5–7] which normalized after heart transplantation.[5,7] Whereas the effects of phenprocoumon and VWS have been studied in detail, little is known concerning platelet dysfunction induced by the use of LVADs.

The main physiologic functions of blood platelets is their role in hemostasis, wound healing, and inflammatory processes.[8] Elevated shear stress, induced jet flow, turbulence, and contact of platelets with foreign surfaces may activate them[9] and lead to the formation of platelet plugs and clots. However, the influence of mechanical damage to platelets, anti-platelet drugs, and VWS on platelet function and plug formation must also be considered.[10]

These complex effects on the balance between the pro-coagulant and anti-coagulant functions of the various platelet factors must be investigated in further detail to optimize therapy concepts for individual patients. In this study, we focussed on the differences in platelet function, microparticle generation, and VWF in continuous-flow axial (HMII) and centrifugal-flow (HVAD) LVADs. Furthermore, differences between the 2 systems were investigated regarding hemolysis and coagulation activation.

Methods

Study design

After approval from the local Ethics Committee, the demographic and clinical data of 20 outpatients who had received elective LVAD implantation (10 with HMII, 10 with HVAD) were evaluated. Routine blood control analysis included Born aggregometry, platelet function analyzer-100 (PFA-100) system (Siemens, Marburg, Germany), the PLT VASP/P2Y12 assay (BioCytex, Marseille, France), hemostasis parameters, clinical chemistry parameters, VWF MM analysis, and microparticles. All laboratory tests that are not described in detail were performed according to the usual procedures and standards.

At the Hannover Medical School, at the time of this study, the long-term oral anti-coagulation regimen for the HMII recipients is phenprocoumon (international normalized ratio [INR] between 2.0 and 2.5), whereas the HVAD device requires the same INR with clopidogrel as an additional anti-platelet agent (3 times a week). One patient in the HVAD group received phenprocoumon only.

Suspicion of serious pump thrombosis arose in 3 different aspects, which can occur concurrently or individually. First, the clinical parameters may indicate LVAD thrombosis (e.g., bloody urine), which may be confirmed by laboratory parameters (increased hemolytic parameters such as lactate dehydrogenase [LDH] and serum free hemoglobin [Hb]) and in the end by the LVAD parameters (increased or not measurable power and eventual concurrently decreased LVAD flow).

Platelet function tests

Light transmittance aggregometry (LTA) was performed as described before.[11] Aggregation parameters were measured with 4 µmol adenosine 5′-diphosphate (ADP), collagen (5 µg/ml), epinephrine (5 µmol), ristocetin (1 mg/ml), and arachidonic acid (0.5 mg/ml) as agonists.

The PFA-100 system was used according to the manufacture's instructions.[12]

VASP/P2Y12 assay

The functional integrity of the purified platelets was verified by the enzyme immunoassay originally described by Geiger et al[13] and performed using the PLT VASP/P2Y12 assay. The ratio of median fluorescence intensity (MFI) of samples incubated with prostaglandin E1 (PGE1) and adenosine diphosphate ($MFI_{PGE1} - MFI_{ADP+PGE1}$)/$MFI_{PGE1}$) was calculated to estimate the ratio of activated vs non-activated platelets. This value was reported as the platelet reactivity index (PRI).

VWF MM analysis

MM analysis was performed by means of sodium dodecyl sulfate–agarose gel electrophoresis with luminescent visualization.[14] The HMW VWF (HMW MM) ratio was calculated to describe the ratio of the VWF MMs of the patients compared with those found in a sample pool.

Microparticles

Platelet-poor plasma was mixed with paraformaldehyde (1:10). Ten microliters of antibody dilution were added to 100 µ1 of the microparticle suspension. Anti-P-selectin (CD62P), anti-CD41, and anti-CD42b antibodies were purchased from AbD Serotec (Oxford, UK).

Statistical analysis

Our statistical analysis was performed using R 2.15.1 software (The R Project for Statistical Computing, www.r-project.org). Comparison of quantitative parameters between groups was performed using the non-parametric Mann-Whitney rank sum test.[15] The statistical analysis of categoric data was performed using Fisher's exact test.