Platelet Dysfunction in Outpatients With Left Ventricular Assist Devices

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Background. **Thromboembolic and bleeding complications in outpatients with a left ventricular assist device are common and can be detrimental. A meticulous balance between anticoagulant and procoagulant factors is therefore crucial. However, in contrast to routinely performed plasmatic coagulation tests, platelet function is hardly ever monitored although recent reports indicated platelet dysfunction. We therefore differentially evaluated platelet function with four commonly used point-of-care devices.**

Methods. **In a cross-sectional design platelet function was assessed in 12 outpatients and 12 healthy matched volunteers using thrombelastography platelet mapping, thromboelastometry, platelet function analyzer, and a new whole blood aggregometer (Multiplate).**

Results. **Phenprocoumon produced an international normalized ratio of 3.5. It was associated with a twofold prolongation in the thromboelastometry clotting time ($p < 0.001$). Platelet function under high shear was severely compromised: collagen adenosine diphosphate closure times were 2.5-fold longer in patients than in volunteers ($p < 0.001$), and 50% of patients had maximal collagen adenosine diphosphate closure time values. Although antigen levels of von Willebrand factor were 80% higher in patients ($p < 0.001$), von Willebrand factor–ristocetin was subnormal in 5 of 12 patients. Ristocetin-induced aggregation was also threefold higher in volunteers ($p < 0.001$), indicating an additional functional defect of platelets affecting the glycoprotein Ib–von Willebrand factor axis. The von Willebrand factor multimer pattern in patients also appeared abnormal.**

Conclusions. **Multimodal antiplatelet monitoring showed markedly impaired platelet function in patients with a left ventricular assist device. Platelet dysfunction under high shear rates and abnormal ristocetin-induced aggregation is only partly attributable to low von Willebrand factor activity. These findings resemble the acquired von Willebrand syndrome that is associated with microaggregate formation and enhanced bleeding.**

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The need for mechanical circulatory devices to minimize end-organ damage and to provide rehabilitation potential for individuals awaiting heart transplantation becomes more important as the incidence of heart failure is still rising on account of refined medication [1]. Furthermore, heart transplantation still remains a limited treatment option for patients with end-stage heart failure because of the scarcity of donor organs [2]. In these instances, and when heart transplantation is not considered opportune, left ventricular assist devices (LVADs) are increasingly implanted as destination therapy.

Foreign surfaces of LVADs, altered rheologic conditions, and blood stasis within the chambers of the native heart induce activation of coagulation [3] and require adequate anticoagulation to prevent thromboembolic events [4]. Most often, a combination of platelet inhibitors and a vitamin K antagonist is prescribed for this purpose [5]. Whereas clinicians routinely measure the effect of warfarin (Coumadin) derivatives on plasmatic coagulation, they rarely measure the effect of platelet inhibitors on platelet function. Severe perioperative bleeding and also spontaneous hemorrhage have been reported in LVAD patients that cannot completely be explained by the anticoagulation regimen alone. It has been suspected that platelet dysfunction does play a role here. We thus hypothesized that platelet dysfunction may be present in LVAD patients owing to high shear forces at the artificial surfaces. Shear stress, ie, stress, which is applied parallel or tangential to the face of a material, is sensed by ligand-bound extracellular domains of integrins and converted to functional cellular responses such as the activation of platelets. Hereby, high shear–induced platelet plug formation is dependent on a functioning von Willebrand factor–glycoprotein Ib (vWF–GpIb) axis.

To date, however, there is no routine monitoring procedure for platelet inhibition, and platelet function

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Abbreviations and Acronyms

ASPItest = aspirin test
CADP-CT = collagen adenosine diphosphate closure time
CEPI-CT = collagen epinephrine closure time
GpIb = glycoprotein receptor Ib
LVAD = left ventricular assist devices
PFA-100 = platelet function analyzer-100
TEG = thrombelastography
vWF = von Willebrand factor
vWF:Ag = von Willebrand factor antigen
vWF:RiCO = von Willebrand factor ristocetin

has not even been systematically evaluated in this patient population. Different platelet function tests currently on the market (ie, thrombelastography [TEG], rotation thromboelastometry, and the platelet function analyzer-100) have been used for this purpose to a variable extent by centers that have an active LVAD program. The three devices mentioned above use whole blood, which is a more physiologic approach as compared with studying platelet suspensions. The complementary use of these point-of-care tests allows assessment of the underlying pathophysiology of platelet dysfunction. However, with the exception of single case reports they have not been used simultaneously and test results have not been compared with each other. We therefore determined platelet function in LVAD outpatients with the help of the above mentioned and widely used four point-of-care tests including the newly developed Multiplate, a whole blood aggregometer. In addition, we also tried to elucidate the cause of the suspected dysfunction.

Material and Methods

Study Design

After institutional review board approval, written informed consent was obtained from all subjects. In this observational study platelet function of 12 outpatients after elective LVAD implantation was evaluated by the following frequently used point-of-care tests: TEG, rotation thromboelastometry, platelet function analyzer-100, and Multiplate. Additionally, blood from healthy volunteers without a history of previous bleeding or thrombosis recruited from hospital staff, matched for age and sex, was analyzed to define laboratory specific ranges for normal values. Blood samples were taken from fasting patients and volunteers during the morning hours. All measurements were done within 4 hours after blood sampling. All LVAD outpatients were anticoagulated with 100 mg of aspirin orally (Aspirin; Bayer, Vienna, Austria) once daily and phenprocoumon (Marcoumar; Roche, Basel, Switzerland; desired international normalized ratio, 2.5 to 3.5).

Thrombelastography Platelet Mapping Assay

Thrombelastography (Haemoscope, Skokie, IL) enables monitoring of hemostasis as a whole dynamic process, rather than isolated end points. Global assessment of hemostatic function is made from whole blood, documenting the interaction of platelets with the protein coagulation cascade from the time of the initial platelet–fibrin interaction, through platelet aggregation, clot strengthening, and fibrin cross linkage to eventual clot lysis. The "signature" of generated tracings can give information on clotting factor activity, platelet function, and any clinically significant fibrinolytic process within 20 to 30 minutes. The platelet-mapping assay that measures the presence of aspirin requires heparin to suppress thrombin and 10 μL of ActivatorF (Haemoscope) to replace thrombin in converting fibrinogen into fibrin and arachidonic acid as platelet agonist [6, 7]. ActivatorF consists of the snake venom reptilase that converts fibrinogen to des-A-fibrin and activated factor XIII, which crosslinks the fibrin monomers. Heparinized blood as well as ActivatorF is also necessary for the determination of fibrin to clot strength. In contrast, when kaolin is used as an activator, citrated blood is needed.

For quantification of TEG variables, the time from sample placement in the cuvette until the tracing amplitude reaches 2 mm represents the rate of initial fibrin formation and is related to plasma clotting factor and circulating inhibitor activity (intrinsic coagulation); the greatest amplitude on the TEG trace is a reflection of the absolute strength of the fibrin clot—a direct function of the maximum dynamic properties of fibrin and platelets.

Rotation Thromboelastometry

Rotation thromboelastometry (Pentapharm, Munich, Germany) is related to, but in some aspects different from, classical TEG. In rotation thromboelastometry a ball bearing guides the firmness sensor, which makes the analysis less susceptible to mechanical stress, movement, and vibration. Just before running the assay, citrated blood samples were recalcified with 20 μL of $CaCl_2$ 0.2 mol/L. To assess activation and inhibition of coagulation sensitively we did not add an exogenous agonist to the test system (no agonist thromboelastometry) [8]. The following variables were analyzed: coagulation time, clot formation time, and maximum clot firmness. To functionally assess the fibrinogen of the samples, the clotting was determined using tissue factor activation of clotting after addition of an unknown amount of platelet inhibitor cytochalasin D, which the company would not disclose (fibrinogen thromboelastometry). Both tests, no agonist and fibrinogen thromboelastometry, were performed in samples from both patients and volunteers.

The Platelet Function Analyzer-100

The platelet function analyzer-100 (Dade Behring, Marburg, Germany) measures in vitro platelet plug formation in whole blood under high shear stress. It determines the closure time needed for a platelet plug to form after activation of platelets by pathophysiologically rele-