Anticoagulation assessment

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Bleeding and thromboembolism are serious adverse events that have been associated with the use of ventricular assist devices (VADs). Historically, anti-thrombotic therapy was recommended in treatment protocols and included the early postoperative use of intravenous heparin as a transition to warfarin and aspirin therapy. Hence, anticoagulation therapy is in itself an additional risk factor for the onset of hematological complications. These include hypercoagulability with consequential arterial and venous thrombosis as seen in heparin-induced thrombocytopenia (HIT) syndrome, and intracerebral or gastrointestinal bleeding due to over-anticoagulation. The aim of our efforts is to determine the optimal anticoagulation for individual patients (*Video 1*).

Over 150 years ago, the German pathologist, Rudolf Virchow, postulated that thrombus formation and propagation resulted from abnormalities of blood flow, the vessel wall, and blood components. These three factors are known as Virchow's triad-that is, abnormalities of hemorheology and turbulence at vessel bifurcations and stenotic regions; abnormalities in the endothelium, such as atherosclerosis and associated vascular inflammation; and abnormalities in coagulation and fibrinolytic pathways.

Through investigating the physiology of coagulation, we now understand the phenomena of primary and secondary hemostasis, both of which are impaired in VAD patients. In the 1960s, two groups proposed a model of coagulation, portraying it as a series of pathways in which activation of one clotting factor leads to the activation of another, eventually resulting in a 'burst' of thrombin generation. The extrinsic pathway may be monitored by measuring prothrombin time (PT), and the intrinsic pathway by assessing activated partial thromboplastin time (aPTT). Dynamic assessment of clot formation via both pathways is possible by thromboelastography performed by rotational thromboelastometry (ROTEM) devices (EXTEM, INTEM).

The evolution of knowledge of the process of hemostasis in cell-based models of coagulation has accordingly shifted the primary focus of research from protein components to cellular participants. In 2001, Hoffman and Monroe proposed a cell-based model of hemostasis (1). This allowed us to visualize the extrinsic and intrinsic pathways of coagulation as having distinct roles, as they act on different cell surfaces at different stages of the hemostatic process. Understanding thrombus formation on the VAD surface became even more complex, as a diversity of additional factors contributing to the activation of coagulation were discovered.

However, Virchow's triad must still be strongly considered in the clinical implementation of VAD support. The three factors play a significant role in flow stagnation around the VAD cannulae or deceased myocardium, exposure to foreign surfaces (VAD cannulas and pump body), and acute changes in coagulation balance (over-anticoagulation with intravenous agents, platelet deficiency, HIT syndrome and hypercoagulability). As a result, VAD patients have an increased risk of HIT serological conversion after VAD insertion, compared to regular cardiac surgical patients (2).

Early hematological consequences of VADs can be seen through the additive effects of cardiopulmonary bypass and left VAD insertion, which lead to platelet activation, elevation of markers of in vivo thrombin generation, fibrinogen cleavage and fibrinolytic activation. Other consequences include activation of the contact system-dependent fibrinolytic system and resultant consumption of contact factors through fibrinolysis, and increased levels of plasmin-a2-antiplasmin complexes (thrombin-antithrombin III complexes, PF4 and b-thromboglobulin following

surgery).

A Von Willebrand (vWF) factor study performed at our institution showed that impairment of vWF-dependent platelet function was observed on post-operative day seven and advanced during the time of support. As a result, all factors contributing to bleeding and thrombosis are considered when deciding the main strategy and choice of anticoagulation at our institution (3).

Such factors include pro-thrombotic diseases (known thrombophilia, atrial fibrillation, intra-aortic balloon pump, large myocardial infarction, ongoing infection, active tumors) and pro-bleeding states (liver failure, low platelet count and dysfunction, anti-platelet therapy immediately before surgery, continuous venovenous hemodiafiltration therapy or dialysis).

Furthermore, with common coagulation parameters (aPTT, INR, PLT count, fibrinogen level, AT III, D-Dimers), ROTEM and multiplate results may help to guide specific coagulation therapies, especially in the first hours following VAD placement. Such therapies may include coagulation factor concentrates, fibrinogen substitution, platelet concentrate, anti-thrombin III substitution, tranexamic acid therapy. It is important to assess the results of ROTEM concurrently with other coagulation parameters and anticoagulant doses.

Multiplate (whole blood aggregometry) provides real-time data on platelet aggregation activated by thrombin (TRAP), arachidonic acid (ASPI, effect of aspirin) and ADP (effect of clopidogrel or prasugrel). Dividing patients into two groups according to their risk may help to choose the starting doses of anticoagulants and intensity of dose escalation. Those with a higher thrombotic risk require a higher anticoagulant starting dose (heparin, 5 U/kg/hr or argatroban, 0.1 mcg/kg/min) [after 6-8 hours after intensive care unit (ICU) arrival]. Others with a higher bleeding risk may be evaluated every 4-6 hours up to 24 hours postoperatively and be required to start with a lower dose (heparin 2 U/kg/h or argatroban 0.05 mcg/kg/min).

Following ICU arrival, immediate action should include correction of acidosis, body temperature and Ca^{2+}. With stable technical and hemolysis parameters patients can tolerate even lower anticoagulation levels in case of non-surgical bleeding. Close monitoring (every 2-4 hours) may also be beneficial. If any increases in energy consumption or hemolysis parameters are observed, therapy must be escalated with consideration of the risk of pump thrombosis.

Antiplatelet agents can be started at a low dose, following recovery of platelet numbers and function (Multiplate test). After recovery of hepatic & renal functions, improvements in nutritional status (albumin), and clearance of systemic infections, oral anticoagulants can be initiated (warfarin or phenprocoumon) and carefully titrated to achieve a VAD-specific international normalized ratio (INR) range. We facilitate the education of patients with INR-self-measurements, which enable them to keep INR levels within given target ranges (4,5).

In the later postoperative period, VAD dependent fibrinolysis becomes less important, leading to a shift towards coagulation with sustained prothrombin and PLT activation. Other observed sequelae include an acquired vWF syndrome, apical cannula malposition, flow pattern disturbances, low-flow or pump-stop episodes (suction events, ventricular tachycardias, implantable cardioverter-defibrillator shocks, driveline disconnection) and infection.

Modern VADs and improvements in our understanding of complex interactions between VAD and patient have resulted in a low incidence of bleeding/thromboembolic events. Optimal anticoagulation protocols have promoted a balance between bleeding and thromboembolism. Initially, higher anticoagulation level with subsequent de-escalation may result in long-term stroke/bleeding-free support. A tailored regime involving all risk factors in decision-making process (infection, HIT syndrome, avWF disease, age, sex, comorbidities, inflow-cannula related factors, etc.) is crucial in avoiding serious adverse events.

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