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Antithrombotic therapy in ventricular assist device (VAD) management: From ancient beliefs to updated evidence. A narrative review☆

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ABSTRACT

Platelets play a key role in the pathogenesis of ventricular assist device (VAD) thrombosis; therefore, antiplatelet drugs are essential, both in the acute phase and in the long-term follow-up in VAD management. Aspirin is the most used agent and still remains the first-choice drug for lifelong administration after VAD implantation. Anticoagulant drugs are usually recommended, but with a wide range of efficacy targets. Dual antiplatelet therapy, targeting more than one pathway of platelet activation, has been used for patients developing a thrombotic event, despite an increased risk of bleeding complications. Although different strategies have been attempted, bleeding and thrombotic events remain frequent and there are no uniform strategies adopted for pharmacological management in the short and mid- or long-term follow up. The aim of this article is to provide an overview of the evidence from randomized clinical trials and observational studies with a focus on the pathophysiologic mechanisms underlying bleeding and thrombosis in VAD patients and the best antithrombotic regimens available.

1. Introduction

Depending on the definition applied, the prevalence of heart failure (HF) is approximately 1–3% in the adult population, rising to 8–10% for subjects aged 75 years or older [1, 2]. In patients acutely hospitalized, HF is still associated with very poor medium-term prognosis, with all-cause death being approximately 20% and all-cause re-hospitalization rate up to 50% at 1-year follow up [3].

Permanent implantable ventricular assist devices (VADs) are a consolidated alternative to heart transplantation (HTx) for ineligible patients with end-stage HF (destination therapy). VADs are currently implanted also in patients on waiting list for HTx (as bridge to transplantation) or needing evaluation for candidacy in order to achieve end-organ recovery (bridge to candidacy) [1].

VADs can be categorized based on their mechanism of blood propulsion. First generation VADs were pulsatile devices mimicking the natural heart flow dynamic, whereas second- and third-generation devices provide continuous flow (with axial or centrifugal design) [4].

Despite technological improvements (greater durability and easier placement) with the continuous flow design, bleeding and thromboembolism, as well as pump thrombosis, remain frequent complications that may affect the long-term outcome of patients on VAD [5–7]. Indeed, only 30% of patients remain free from bleeding or thromboembolic complications after 1 year from VAD implantation [8].

The event rate per patient-year is ≈0.40 and 0.06 for non-gastrointestinal and gastrointestinal major bleeding [9], 0.04 to 0.09 for pump thrombosis [10], and 0.08 for hemorrhagic or ischemic stroke [9]. The clinical consequences of thrombotic and bleeding complications can be devastating, with ischemic and hemorrhagic stroke remaining among the most common causes of death in these patients (adjusted hazard ratio 6.1; 95% CI, 4.6–7.9) [11]. Even if an increase in pump thrombosis reported in previous studies [12–14] has been mitigated in recently published trials [15, 16], pump thrombosis may be a vexing problem because of older patients and longer duration of life after implantation. Device manufacturers usually suggest the use of a specific antiplatelet or anticoagulant agent, without any strong evidence

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supporting their indication. Therefore, the antithrombotic therapy in patients with VADs is still evolving to better face the fine balance between bleeding and thrombosis.

The aim of the present review is to summarize the available evidence about the pathophysiological mechanisms contributing to bleeding and thrombosis in VAD patients, the managements that are usually adopted and the future lines of research.

2. Search strategy

Databases including PubMed, OVID, SCOPUS, CINAHL, Cochrane and Web of Science were searched from database inception through to 28 March 2018, using the predefined search terms "assist device", "thrombosis", "bleeding", "antiplatelet therapy", "anticoagulation", "antithrombotic management" using Boolean logic operators (AND) and (OR), with exploded headings. Search of the literature was performed without predefined "timeframe" for published articles. No language and study type limits were applied. Reference lists of selected publications were also analyzed for additional linking studies.

3. Pathophysiology of thrombosis and bleeding in LVAD patients

Thrombus formation is a dynamic process that is regulated by components of the hemostatic system, which, under physiological conditions, form blood clots that limit blood loss from damaged vessels [15]. Platelet reactions with the solid surfaces of damaged blood vessels depend on the presence of plasma von Willebrand Factor (vWF) activity [17]. vWF is a multimeric glycoprotein manufactured by the endothelial cells, where it is constitutively released into the circulation and stored into the Weibel-Palade bodies, from where it can be rapidly released upon stimulation [17, 18]. vFW is stored also in the α-granules of megakaryocytes/platelets, from which it is released only upon platelet activation [17, 18]. vWF circulates in the plasma and it is critical for primary hemostasis, being essential for platelet adhesion to the subendothelium of damaged blood vessel, platelet activation and platelet aggregation [19]. Furthermore, it is required to control the formation of vascular network [19].

Rheological variables play a role in thrombus formation, by affecting the ability of platelets to hook up to adhesive proteins that are exposed on the vessel wall (platelet adhesion) or are bound on the surface of other platelets (platelet aggregation) [17]. Shear stress is defined as the force for area unit between the blood laminae. The normal physiologic range of fluid shear stress within the cardiovascular system is 15 to 40 dyne/cm^2 (1.5–4 Pa) [20]. Under physiologic shear stress, vWF undergoes a conformational elongation from a globular state to an extended chain conformation with exposure of binding sites for the platelet glycoprotein complex GpIb/IX/V and various subendothelial constituents [21]. The interaction of vWF with platelet GPIb/IX/V causes platelet activation, secretion of ADP, activation of the GpIIb-IIIa receptor and platelet aggregation. However, the same conformation elongation exposes the disulfide bonds of vWF multimers, site of enzymatic degradation cleavage of large, active vWF multimers into small, nonactive vWF fragments by the vWF protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [22–25]. Therefore, the pathogenesis of bleeding and thrombosis depends on the imbalance between these pro-hemostatic and anti-hemostatic factors.

3.1. Thrombosis

Each VAD has a specific mechanism of blood propulsion, able to produce different hemodynamic profiles associated with changing degrees of pulsatility, turbulence and shear stress. The shear stress that is generated within VADs ranges between 20 and 500 Pa [26, 27].

Shear stress acts as chemical agonists, showing dose and time-response characteristics. The elongated vWF formed under conditions of high shear stress becomes procoagulant through accumulation of contact pathway factors. Accordingly, placement of VADs has been associated with persistent generation of activated contact proteins (FXIa and its co-localized activator FXIIa), that accumulate on the vWF as they form under pathological flow [28] and are absorbed to the surface of VADs via the *Vroman* effect (according to the original theory, the small molecules are the first to be absorbed on a surface, but they are gradually stifled by proteins with greater affinity) [29]. The threshold evoking a specific response in terms of platelet adhesion and aggregation may change over time depending on the specific interactions between platelets and solid surface and the exposition time [17].

Platelet aggregation induced under supraphysiologic shear stress, as usually occurred in patients with VAD, has peculiar characteristics [30–33]. Thrombelastographic analyses have demonstrated that contact protein pathway activation results in a thrombus that develops strength at a significantly faster rate and that takes significantly longer to lyse than thrombi generated by tissue factor initiated coagulation, by more efficient activation of the thrombin-activatable fibrinolysis inhibitor [34]. It is well known that vWF stress-stimulated aggregation is little affected by inhibition of cycloxygenase by acetylsalicylic acid, whereas it is inhibited by fibrinolytic agents [35,36].Therefore, ideally, agents acting on ADP activity (as $P2Y_{12}$ inhibitors), blocking GP Ib or GP IIb/IIIa or acting on the fibrinolytic system might be suitable therapeutic target to decrease thrombosis rate in VAD patients.

In experimental studies analyzing platelet-rich plasma under conditions of high shear stress, >50% of activation and aggregation caused by the interaction of vWF with platelet GP Ib could be inhibited by blocking the action of $P2Y_{12}$ [37].

Similarly, studies in vitro have demonstrated that, under supraphysiologic shear stress, phosphodiesterase (PDE) 3 inhibitors suppress the platelet thrombus formation initiated by the interaction of the platelet receptor GPIb/V/IX with the vWF [38]. The only selective PDE-3 inhibitor available is cilostazol. Several observations conducted in vitro have confirmed the favorable profile of cilostazol in reducing platelet activation under both constant and dynamic device-related conditions [33, 39, 40]. However, as recently reported, FDA has contraindicated the use of cilostazol for patients with any degree of heart failure [33, 41]. Dipyridamole is both a PDE-3 and -5 inhibitor, but studies in vitro have revealed its decreased activity on platelet inhibition under conditions of high shear stress [33].

Finally, a further mechanism leading to thromboembolic complications in VAD patients could be the heat stress. Investigations in this field have revealed hemoconcentration, activation of coagulation with decreased clotting time and increased clot strength and thrombin and D-dimer release [42]. Heat stress may act promoting activation of several inflammatory pathways and inducing the release of chemical agonists as epinephrine. This explains why in this context inhibition of the cyclo-oxygenase enzymes by acetylsalicylic acid, decreasing production of prostaglandins and other inflammatory mediators, is of potential benefit [43].

3.2. Bleeding

On the opposite site of the coin, shear stress may have a role in bleeding diathesis. Acting on the weaker disulfide bonds of vWF multimers, shear stress could tear apart vWF monomers. In parallel, supraphysiologic shear stress is the major mechanism leading to enzymatic degradation cleavage of large, active vWF multimers into small, nonactive vWF fragments by the vWF protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [30]. As a result, an acquired vWF deficiency develops, thus significantly affecting sprouting angiogenesis. vWF is a ligand for the integrin αvβ3, involved in the regulation of the directionality of cellular migration [22]. Furthermore, vWF drives the formation of Weibel-Palade bodies, which stores regulators of angiogenesis and inflammation including angiopoietin-2.