Acute Infective Endocarditis

Subjects: Infectious Diseases
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Infective endocarditis (IE) is a potentially fatal disease with a mortality rate of over 20%, largely unmodified over recent decades. Mechanisms of IE pathogenesis are still incompletely understood but involve bacteria, host immune responses and the coagulation system.

Keywords: prognosis ; embolism ; D-dimers ; aPTT ; biomarkers

1. Introduction

Vegetations, the pathologic hallmark of IE, consist of a fibrin mesh wherein platelets and bacteria are embedded. Vegetations form as a consequence of a pathological thrombo-inflammatory reaction and underlie the progression of the disease and its complications, including heart valve destruction and septic embolic events [1][2]. The first step in vegetation formation encompasses an abnormal immune thrombotic reaction with subsequent bacterial entrapment [3][4]. Among major IE causative pathogens, *Staphylococcus aureus* directly promotes coagulation, generating thrombin-like activity by staphylocoagulase and von Willebrand factor (vWF)-binding protein, making up staphylothrombin [5]. Staphylothrombin mediates the conversion of fibrinogen to fibrin and initiates platelet (PLT) aggregation [6]. Intriguingly, the inhibition of staphylothrombin by dabigatran was safe and effective in reducing coagulation activation, time to blood culture clearance and metastatic foci of infection in *S. aureus* bacteremia, including IE [7].

These data strongly suggest it could be beneficial to monitor and modulate coagulation in IE. Among coagulation parameters, D-dimers have been previously identified as a marker able to provide important insights into the infection-related coagulation abnormalities [8][9][10]. Three studies have evaluated the prognostic role of D-dimers in IE. Turak and colleagues suggested that high D-dimers levels on admission could identify IE patients at increased risk for in-hospital mortality [11]. Lin et al. found D-dimers as a prognostic factor of in-hospital adverse events and six-month mortality [12], while Xu et al. found that higher plasma D-dimers levels were predictive of ischemic stroke in 173 patients with IE [13]. However, use of coagulation markers in the prediction of IE prognosis has not yet entered into clinical practice [14].

2. Coagulation and Inflammation

Coagulation and inflammation are closely linked, and a prothrombotic tendency is often observed in acute infectious diseases [4][15]. In the present study, we evaluated the association of hemostasis parameters with the severity and prognosis of IE. Being inexpensive routine tests, easy to obtain in every hospital, coagulation parameter assessments could improve the clinical management of IE.

Derived from one of the largest single-center cohorts of IE where hemostasis has been studied, our data suggest that coagulation parameters are strictly tied to the course and outcome of the disease. D-dimers were independently associated with in-hospital mortality, whereas aPTT was a predictor of 1-year mortality. In addition, higher levels of D-dimers and shorter aPTT, both signaling a pro-coagulant state, translated into a higher risk of embolic events. In contrast, the significance of PLT and fibrinogen levels remains unclear from our data.

Among coagulation parameters, D-dimers have received the most interest, and their use in clinical practice is well established. Our results corroborate previous data suggesting a predictive value of D-dimers for the short-term prognosis of IE and the prediction of embolism [11][12][16][17] and septic embolic stroke [13]. Consistently, Meini et al. recently found that very high levels of D-dimers signaled a worse in-hospital outcome in patients with acute, severe infections [8].

Interestingly, aPTT levels also showed predictive value for IE outcomes. Their association with 1-year mortality needs to be elaborated as, to the best of our knowledge, no prior similar data exist. Apparently, a shorter aPTT implies a prothrombotic state that associates with IE embolic complications and staphylococcal etiology. Whether this relates to factor VIII or vVF levels remains to be studied. In contrast, longer aPTT may be associated with other forms of

coagulopathy that signal a reduced chance of survival. PT-INR and aPTT are modified by anticoagulant treatment in patients with prosthetic valves or atrial fibrillation, and it is well known that PVE and arrhythmias imply a worse IE outcome and a higher incidence of embolism [18][19][20]. Overall, it is interesting to note that common coagulation parameters may provide more clinically relevant information in IE than other parameters that are more complex to obtain, such as homocysteine [21] and prothrombotic genetic polymorphisms [22].

Etiology also appeared to have an impact on coagulation function in IE. *S. aureus* was significantly associated with higher D-dimers levels and shorter aPTT, confirming and further supporting previous data about the role of *S. aureus* in the coagulation imbalance in IE [5][6]. Further investigation of the role of staphylothrombin inhibition by direct anticoagulants in *S. aureus* IE [7] seems warranted.

Comorbidities were common in our cohort, and a CCI ≥ 4 was associated with specific changes in hemostasis parameters. Since previous studies highlighted the negative effect of comorbidities on IE outcome [23][24][25], we hypothesize that changes in coagulation function could represent one possible link between these two factors.

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