

The endothelium and thrombotic risk in heart failure

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Chronic heart failure (HF) is increasingly recognised as a syndrome which confers a considerable prothrombotic risk. Whilst the annual incidence of venous thromboembolism is about 0.1% in general population, prospective observational studies have shown that thromboembolic events would occur in 1.7–2.7% of patients with HF each year (1). Indeed, a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials reported that the annual incidence of thrombotic events (including strokes, pulmonary emboli and peripheral emboli) in patients with ventricular dysfunction and sinus rhythm was 1.8% in men and 2.4% in women (2). Furthermore, patients with HF generally suffer more severe strokes that are associated with high mortality rate (3).

However, even this high prevalence of thromboembolic events may just represent the tip of the iceberg. Indeed, more than 30% of patients with HF, irrespective of its aetiology, may experience 'silent' asymptomatic thromboembolic strokes detected by brain magnetic resonance imaging (4).

In addition to the risk of venous thromboembolism, patients with HF also have a high (and often underestimated) risk of arterial thrombosis. The risk of sudden cardiac death, often attributable to acute arterial thrombosis, is 6- to 9-fold higher in those with HF compared to the general population (5). In the Assessment of Treatment with Lisinopril and Survival (ATLAS) study, fresh coronary thrombus was found in more than 30% of such sudden death cases (6). Both acute myocardial infarction and unstable angina are independent risk factors for death in patients with congestive HF (7).

Why does HF confer a prothrombotic state? HF is associated with abnormalities of flow (low cardiac output, impairment of intracardiac haemodynamics, dilated cardiac chambers, stasis of blood in peripheral vascular beds, etc), vessel wall (endothelial damage/ dysfunction), and abnormalities of blood constituents (abnormalities of platelets and haemorrhheology). Thus HF fulfils all of Virchow's triad of characteristics of a prothrombotic state, which promote the risk of thrombosis and unsurprisingly, the risk of thromboembolic complications rises accordingly the degree of left ventricular contractility impairment (2). Given that endothelial dysfunction is commonly seen in HF pathophysiology, the contribution of the endothelium to thrombosis may be especially important in patients with HF.

Endothelium and thrombogenic alterations in heart failure

The prominent antithrombotic characteristics of healthy endothelial cells are changed dramatically in the damaged or dysfunctional endothelium (8) (Fig. 1). Indeed, endothelial abnormalities are typical amongst patients with HF and represent one of the major pathophysiological pathways implicated in the development and progression of HF. For example, impaired flow-mediated dilation, increased numbers of circulating endothelial cells shed off vascular wall, raised plasma levels of von Willebrand factor (vWF, a marker of endothelial damage) are all consistently reported in patients with HF irrespectively of its aetiology (i.e. whether ischaemic or non-ischaemic) (9). Persistent exposure to various cytokines, chemokines and proinflammatory stimuli shifts the balance towards a prothrombotic endothelial cell phenotype. Endothelial damage as assessed by plasma vWF levels is even predictive of adverse outcomes in patients with HF (10).

Endothelial impairment results in dysregulation of all major elements of coagulation system. Endothelial activation shifts the balance in favour of platelet aggregation and clot formation through the suppression of anticoagulant mechanisms and stimulation of procoagulant pathways. In the vessel wall, for example, tissue factor (TF) is constitutively expressed in vascular smooth muscle cells and fibroblasts leading to rapid initiation of coagulation when the vessel is damaged. As endothelial cells do not express TF under physiological conditions, cellular TF is normally isolated from the circulation by the endothelial monolayer (11).

Inflammatory cytokines are abundant in patients with HF (e.g. tumour necrosis factor- α , interleukin-1 β) and these modify endothelial physiology and may trigger endothelial expression of TF (12, 13). Active endothelial production of TF results in downstream activation of factor Xa and leads to cleavage of prothrombin to form active thrombin. Indeed, the cytokine-mediated expression of TF by endothelial cells and inflammatory cells acts as one of the primary initiators of thrombosis in different pathological conditions (14). In acute HF, elevation of TF levels are significantly correlated with inflammatory burden and is much

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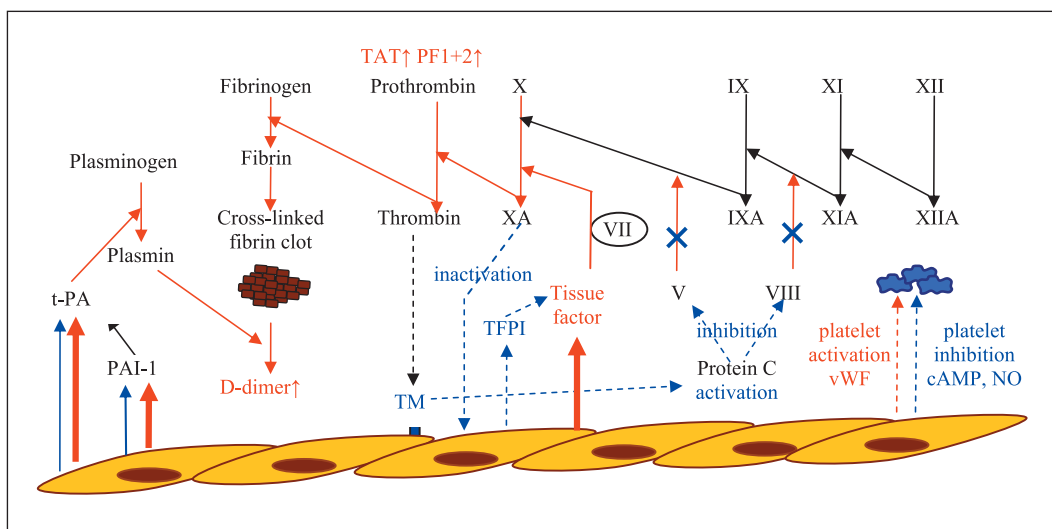


Figure 1: Regulation of haemostasis by the vascular endothelium. cAMP, cyclic adenosine monophosphate; NO, nitric oxide; PAI-1, plasminogen activator inhibitor type 1; PFI+2, prothrombin fragments 1+2; TAT, thrombin-antithrombin III complex; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; t-PA, tissue-type plasminogen activator; vWF, von Willebrand factor. Blue lines reflect activities of normal endothelium, red lines show changes associated with dysfunctional endothelium.

higher in those who died during a six-month follow-up period (15). TF has also been demonstrated to be a predictor of poor prognosis in chronic HF (16).

Activation of thrombin also promotes development of thrombosis via fibrin formation, as well as a number of fibrin-independent effects. Indeed, thrombin may activate platelets, thus enhancing their surface expression of P-selectin and increasing production of platelet activation factor. Through protease-activated receptors presenting on endothelial cells, thrombin also contributes endothelial cell activation, triggers vWF release, possible TF production, changes of endothelial cell shape and increases endothelial cell permeability (17). All together, these changes all promote inflammation and a procoagulant state.

Indeed, thrombin activity is substantially increased in patients with HF as demonstrated by elevated plasma levels of thrombin-antithrombin complex and prothrombin fragments 1+2 (18). In a follow-up of 214 subjects with HF, thrombin-antithrombin complex levels were significantly associated with increased risk of death, even after adjustment for other prognostic factors (e.g. age, gender, traditional cardiovascular risk factors, New York Heart Association Classification, systolic left ventricular function, renal failure, haemoglobin) (19). Of note, these prothrombotic markers can be significantly reduced by the administration of warfarin (20). However, the clinical utility of long-term anticoagulation has not been confirmed as yet in large clinical trials, for example WATCH (21), and results of the ongoing WARCEF trial are awaited.

Platelet abnormalities in HF are also well described and are at least partly attributable to the endothelial cell impairment (23, 24). Indeed, a dysfunctional endothelium initiates the expression of platelet-activating factor which promotes platelet adhesion to endothelial cells and up-regulates production of vWF (24). The latter is constitutively expressed and stored in Weibel-Palade bodies within endothelial cells and physiologically facilitates the binding of platelets to exposed extracellular matrix components of damaged vascular wall. Impaired endothelial cells also release excessive amounts of vWF, further promoting platelet adhesion and activation. Also, patients with HF have increased concentrations of β -thromboglobulin, platelet surface P-selectin and

CD63P (25). More recently, endothelium-derived fractalkine was also found to be a contributor to platelet adhesion and activation (26).

In this issue of *Thrombosis and Haemostasis*, Jug et al. further expand our knowledge on the endothelium-dependent procoagulant pattern in HF (27). They also study implications of the fibrinolytic system on the prognosis in HF and show an independent prognostic impact of the circulating t-PA levels on prognosis. Given that the latter is largely produced by vascular endothelium and is also known as a marker of endothelial malperformance we are provided by further evidence of significant and multi-facet roles of these cells in the pathogenesis of HF. It is also arguable that a marker of thrombus dissolution (i.e. t-PA) rather than conventional 'prothrombotic' marker (such as prothrombin fragments or PAI-1) were predictive of adverse events in HF. What may this mean? One may speculate that whilst prothrombin levels can be considered as markers of 'probability' of thrombotic events, high t-PA concentrations in HF may more directly reflect activity of more 'persistent' thrombotic burden in this condition. If such assumption is true, then t-PA may potentially become a clinical marker of prognosis in HF.

The multi-faced endothelium: What do not we know?

The assessment of endothelial effects on the thrombogenic status in HF perhaps needs to be expanded to include endothelial progenitor cells (28). Although several studies have shown changes in mobilisation and functionality of endothelial progenitors in HF, implications of these cells is still to be determined (29). Additionally, major qualitative differences exist between macro- and micro-vascular endothelial cells (30). The latter have distinct morphology, pattern-specific expression of adhesion molecules and vary in their responsiveness towards agonists (30). For example, endothelial cell thickness varies from $<0.1 \mu\text{m}$ in capillaries to $1 \mu\text{m}$ in the aorta. In stable conditions, TFPI is primarily associated with the microvascular endothelium, while protein C receptor is predominantly expressed on the luminal

surface of large vessels, and vWF is not only expressed by macrovascular but also lung microvascular endothelial cells (31–33). eNOS activity is also higher in the endothelium of arteries from the renal medulla compared with glomeruli and peritubular capillaries (34). Admittedly, only limited data are available on the performance of the microvascular endothelium in HF.

Moreover, ethnicity is known to affect the risk of HF development. For example, it has been shown that patients of South Asian origin more often (for about 40%) suffer from coronary artery disease with higher mortality rate when compared to white population (35). Epidemiological and pathophysiological differences between patients with HF from different ethnic groups have also been demonstrated (36). Patients of South Asian origin bear higher risk of HF and are (on average) younger compared to white Europeans with HF (37). Indeed, endothelial damage/dys-

function may be an important contributor to the ethnicity-related adverse outcomes in HF. Of note, eNOS gene polymorphisms among South Asian population are associated with the risk of arterial hypertension and aneurysmal subarachnoid haemorrhage (38, 39). Even healthy South Asians have diminished endothelial activity and reduced endothelial progenitor cell numbers and function, but increased C-reactive protein levels when compared with White Europeans (40, 41). However, the role of ethnicity in the pathophysiology of HF is still grossly understudied with limited data available on possible ethnic differences in endothelial activity in relation to the risk of thrombotic and thromboembolic complications. More studies are clearly warranted to shed further light on pathophysiological nuances of the prothrombotic risk in patients with HF.

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