Von Willebrand Factor, ADAMTS13 and Cardiac Disease

Subjects: Hematology

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This entry briefly describes the involvement of VWF (von Willebrand factor) and ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif-13) in the pathophysiology of cardiac disease.

Keywords: von Willebrand factor ; Cardiac Disease

1. Introduction

Cardiac failure is becoming increasingly common with improvements in therapeutic targets in an aging population [1]. Cardiac failure represents a clinical syndrome with significant morbidity and mortality. The pathophysiology of cardiac failure is a complex mix of structural and functional alterations. However, the exact mechanisms underlying the disease remain poorly defined [2]. Endothelial dysfunction has been identified as one of the components of cardiac failure pathophysiology, whereby disturbances in coronary microcirculation are thought to contribute to cardiac failure and its progression [3][4]. Inflammatory or ischemic endothelial activation results in the release of von Willebrand factor (VWF) from Weibel–Palade bodies held in endothelial cells [5]. VWF is a large, complex protein that has a crucial role in platelet adhesion and aggregation and is involved in both primary and secondary haemostasis [6]. VWF exists in plasma as multimers of increasing size, with the largest (high molecular weight; HMW) expressing the greatest functional activity. A deficiency of VWF is associated with a congenital bleeding disorder called von Willebrand disease (VWD). In addition, the loss of VWF can occur in a variety of acquired conditions [6][7]. Of note, certain cardiac lesions, particularly aortic stenosis, can elongate VWF multimers in the shear field, resulting in proteolytic loss of the highest molecular weight forms, leading to subsequent loss of VWF activity and resultant bleeding [8][9]. VWF activity is controlled through cleavage by a disintegrin and metalloproteinase with thrombospondin type 1 motif-13 (ADAMTS13), also known as VWF-cleavage protease. Elevation of VWF and potential reduction in ADAMTS13 essentially represent biomarkers of endothelial dysfunction, as most recently typified in COVID-19 (Coronavirus Disease 2019) [10].

Plasma VWF levels can be assessed by means of VWF antigen (VWF:Ag) [11][12] and/or a variety of activity assays [6][11][12]. The most common VWF:Ag assays comprise latex-enhanced immunoassays and enzyme-linked immunosorbent assays [11][12]. Activity assays for VWF include measurements of binding to platelet glycoprotein Ib (GPIb), collagen and factor VIII [11]. However, in the main, studies reporting a single VWF parameter report VWF:Ag levels. VWF:Ag levels reflect both active and inactive VWF. There are over 20 different commercial options for the measurement of VWF:Ag, and publications do not always report the method used [10]. ADAMTS13 can also be measured as an antigen assay using enzyme-linked immunosorbent assays [13], or as an activity assay, with FRETS-based assays being common [13], or by using chemiluminescence [14] among other procedures [13]. However, in the main, studies reporting a single ADAMTS13 parameter report activity levels. In total, there are over 20 different commercial options for measurement of ADAMTS13, and publications do not always report the method used [10].

2. Endothelial Dysfunction

Normal vascular endothelium plays a multifaceted regulatory role in blood vessel function, including blood flow, prevention, and the propagation of thrombus at sites of vascular injury and both anti- and pro-inflammatory functions when appropriately stimulated. When the vascular endothelium becomes dysfunctional, this may result in abnormal coronary microcirculatory flow, impairing myocardial perfusion and therefore function [15]. The process may also result in more overt arterial thrombus formation, as seen in cerebrovascular and coronary arterial events [3]. Endothelial dysfunction, represented by circulating endothelial cells, is predictive of major adverse cardiac events and cardiac remodeling in patients after ST elevation myocardial infarction [16]. Endothelial dysfunction has been reported as an independent predictor of morbidity and mortality in patients with cardiac failure [17][18]. Endothelial dysfunction has been associated with a higher rate of cardiovascular events in patients with cardiac failure and a greater risk of atrial fibrillation in patients with

non-obstructive coronary artery disease [19][20]. This may be a result of loss of nitric-oxide dependent vasodilatory signals, proinflammatory states that resulting from cardiac failure, as well as its prothrombotic properties [21].

VWF is a large multimeric glycoprotein selectively expressed in endothelial cells and megakaryocytes, and present in the subendothelial matrix, platelets and plasma. VWF is stored in cigar-shaped vesicles called Weibel–Palade bodies in endothelial cells [22]. Endothelial injury results in stimulation of Weibel–Palade bodies to secrete their contents including VWF into circulation. Due to blood shear, VWF then unfolds, binding the GPIb receptor of platelets to the A1-domain of VWF [23].

The involvement of VWF in local vascular injury and homeostasis lends itself to being a key determinant of endothelial dysfunction, and thus cardiac failure pathogenesis [24]. In a cohort of non-ischaemic, dilated cardiac failure patients with average symptom duration of 19 months, VWF RNA expression by real-time PCR on endomyocardial biopsy was demonstrated to be upregulated, suggesting that over time patients continue to present with progressive endothelial dysfunction despite treatment optimisation [3]. Plasma VWF:Ag levels have also been found to be substantially increased in patients with acute or recent decompensated cardiac failure [25]. If these elevations in VWF are persistent, this may result in a higher risk of thrombosis [26]. Increased plasma VWF:Ag has also been demonstrated as an independent predictor of long-term outcome in these patients [27].

In contrast, animal models have demonstrated that VWF deficiency is protective against atherosclerosis and arterial thrombotic risk [28]. Cohort data from patients with VWD have been conflicting, demonstrating that arterial thrombotic events still occur in patients with VWD. However, these seem to occur with a lower incidence than the general population [29][30]. Additionally, in patients with VWD, the risk of hypertension, a well-known risk factor of cardiovascular events, is reduced [31].

3. ADAMTS13, VWF and Cardiac Dysfunction

The multimeric size of VWF, and therefore its platelet binding activity, is regulated by cleavage by ADAMTS13. As noted above, ADAMTS13 deficiency is most associated with the rare condition of TTP. TTP is a thrombotic microangiopathy caused by severely reduced ADAMTS13 leading to platelet-rich thrombi, thrombocytopenia, and haemolytic anaemia. Acquired TTP after significant endothelial injury is now well recognized but considered a distinct clinical syndrome in the surgical field, particularly in cardiothoracic surgery [32]. The etiology of post-operative TTP may be secondary to autoimmune-mediated antibodies against ADAMTS13 [32][33]. Post-operative TTP following cardiothoracic surgery is associated with high patient morbidity and mortality [33][34]. Additionally, Le Besnerais et al. [34] showed that injecting ADAMTS13 knockout mice with recombinant VWF, leading to a TTP-like state, resulted in reduced left ventricular function, fractional shortening, and reduced cardiac output by day 2 after injection. This was associated with a decreased endothelial response to acetylcholine, indicative of early severe endothelial dysfunction [35].

ADAMTS13 has also been proposed as another biomarker of endothelial damage and dysfunction [36]. Low plasma ADAMTS13 activity has been shown to predict cardiac and cerebrovascular events in patients with established coronary artery disease [37][38][39]. Plasma ADAMTS13 activity has also been associated with myocardial infarct size and cardiac function after a myocardial ischaemic event [40]. Decreased activity of ADAMTS13 with concomitant high VWF:Ag levels has also been demonstrated as an independent predictor of clinical events in patients with cardiac failure [24]. Both VWF levels and ADAMTS13 activity have been correlated in older patients with atrial fibrillation (AF) and an increasing stroke risk calculator scoring system, the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, age 65–74 years, female) [41]. The mechanisms behind cerebral thrombo-embolism in patients with AF are not completely defined. However, it is clear that AF is associated with a prothrombotic state and higher VWF:Ag levels compared to healthy controls [42]. Zhang et al. further demonstrated that elevated VWF:Ag levels were independently associated with an elevated CHA2DS2-VASc score for stroke in patients with and without AF [36]. They also found that, in patients aged 65–74 years, patients with AF had elevated VWF levels and decreased ADAMTS13 activity compared to those without AF. This difference was not seen in patients aged ≥ 75 years, suggesting that AF is one of many factors affecting VWF levels and ADAMTS13 activity, and that age is an important factor affecting endothelial function. Decreased ADAMTS13 activity has also been implicated in the recurrent risk of AF in those undergoing cardioversion [43].

VWF:Ag levels are increased in coronary artery disease, ischaemic stroke, and venous thromboembolism, whereas ADAMTS13 activity levels are reduced [44]. This relationship between VWF and ADAMTS13 can be described as the VWF-ADAMTS13 axis and is indicative of vascular endothelial function [45]. The VWF-ADAMTS13 axis has been shown to

be dysregulated in chronic thromboembolic pulmonary arterial hypertension, whereby increases in VWF, particularly compared to the level or activity of ADAMTS13, are seen, including following invasive intervention [46].

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