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The Thrombogenic Role of Platelets in Valvular Atrial Fibrillation

Hanan Ahmed Galal Azzam
*Mansoura University, Faculty of Medicine,
Egypt*

1. Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, which is associated with a high risk of stroke and thromboembolism. The association of atrial fibrillation and valvular heart disease results in a substantial stroke and thromboembolic risk, with a 17-fold greater risk than unaffected controls (Wipf & Lipsky, 1990).

Important insights into the pathophysiology of thrombus formation (thrombogenesis) in atrial fibrillation can be made by reference to the different components of Virchow's triad for thrombogenesis, that is, abnormal blood flow, abnormal blood constituents and vessel wall abnormalities (Brotman et al., 2004).

There have been many studies which have focused on risk factors for thrombogenesis in atrial fibrillation. However, the studies exploring the presence of a hypercoagulable state in atrial fibrillation (Lip1995; Lip et al., 1995) have concentrated on various clotting factors, and markers of endothelial damage or dysfunction, rather than on platelets per se. In this chapter, we present an overview of the thrombogenic role of platelets in valvular atrial fibrillation.

2. The platelet physiology

2.1 The platelet structure

Platelets were recognized as a distinct blood element in the late 19th century (and not white blood cells) (Bizzozero, 1882). Platelets are anucleated cells arising from cytoplasmic fragmentation of megakaryocytes in the bone marrow, and have a typical diameter of ~2-3 μm . Platelets circulate in a discoid form and their average lifespan in humans is ~10 days (Hanson & Slichter, 1985). However, following activation, they undergo dramatic changes in shape and ultrastructure; the membranes become ruffled with cytoplasmic projections and the granules are centralized and discharged (Spaet, 1974; White, 2008). Normal human platelet count is ~150,000-400,000/ μl , though spontaneous bleeding resulting from reduced (but functionally normal) platelets is unusual at levels >10,000/ μl (Slichter, 2004).

Despite their lack of a nucleus, platelets are actively involved in a broad range of physiologic and pathologic processes. Platelets contain a variety of mediators that regulate hemostasis and thrombosis as well as a myriad of other functions including recruitment of other cells (chemotaxis), vasomotor function, cell growth, and inflammation, among others. Relevant constituents for thrombosis are present both on the cell membrane and in the cytoplasm, mainly within platelet granules. The platelet membrane, which consists of a

typical bilayer of phospholipids, contains membrane glycoproteins that interact with various ligands, either soluble ligands that activate the platelets, or fixed ligands within the vessel wall or on other cells through which the platelets adhere to these structures. One unique feature of the platelet is that its plasma membrane contains a network of numerous invaginations into the platelet interior, connected to the exterior through small pores (White et al., 1999; White & Clawson, 1980), known as the open canalicular system (OCS).

Dense granules	Nucleotides Adenine: ATP, ADP Guanine: GTP, GDP Amines Serotonin Histamine Bivalent cations
α -granules	Adhesion molecules Platelet endothelial cell adhesion molecule-1 (PECAM- 1/CD31) Fibrinogen von Willebrand factor (vWF) Thrombospondin-1 (TSP1) Vitronectin, Fibronectin Mitogenic factors Platelet-derived growth factor (PDGF) Vascular endothelial growth factor (VEGF) Transforming growth factor- β (TGF- β) Membrane proteins P- selectin CD40L Glycoprotein IIb/IIIa (GPIIb/IIIa, α IIb β 3 integrin, CD41/CD61) Coagulation factors Fibrinogen, Plasminogen, Protein S, Kininogens Factors V, VII, XI, XIII Protease inhibitors C1 inhibitor Plasminogen activator inhibitor-1 (PAI-1) Tissue factor pathway inhibitor (TFPI) Matrix breakdown Hydrolytic enzymes MMP - 2, MMP - 9 Leucocyte recruitment Chemokines: PF4, RANTES, β - thromboglobulin, ENA-78, SDF - 1 α
Lysosomes	Glycosidases Proteases Cationic proteins

Table 1. Contents of the three different granule subpopulations (α -granules, dense granules, and lysosomes) of platelets (modified from Rendu & Brohard-Bohn, 2001).

This feature imparts upon the platelet a much greater surface area than would normally be found on such a small cell. Platelets contain a second channel system, derived from megakaryocyte smooth endoplasmic reticulum, known as the dense tubular system (DTS). The DTS stores calcium and a variety of enzymes involved in platelet activation; in contrast to the OCS, the DTS does not associate with the plasma membrane (Ebbeling et al., 1992; Rendu & Brohard-Bohn, 2001). Three main populations of platelet granules (alpha granules, dense granules, lysosomes) serve as secretory vesicles, releasing components to the extracellular fluid and also serve to direct molecules to the plasma membrane in a process of exocytosis (table 1) (Rumbaut & Thiagarajan, 2010).

2.2 The platelet function

Although platelets have an important role in the normal haemostatic response, they probably contribute to several diverse processes beyond hemostasis and thrombosis, including promoting inflammatory and immune responses, maintaining vascular integrity, and contributing to wound healing (Smyth et al., 2009).

The contribution of platelets to hemostasis is different in arteries and veins. In the venous system, low-flow rates and stasis permit the accumulation of activated coagulation factors and the local generation of thrombin largely with a less prominent contribution from platelets. Venous thrombi contain platelets, but the dominant cellular component consists of trapped erythrocytes. In the arterial circulation, higher flow rates limit fibrin formation by washing out soluble clotting factors. Platelets, which work best at higher shear rates, help to form a physical barrier against further blood loss and, at the same time, provide a surface on which thrombin is generated and fibrin can accumulate (Brass, 2010).

The formation of a stable platelet plug following vascular injury is often described as occurring in three distinct stages: (1) initiation, (2) extension, and (3) stabilization (Figure 1). Initiation by collagen fibrils (within the vessel wall which become exposed to the circulation when the endothelial cell monolayer is breached, forming a complex with von Willebrand factor (VWF) and glycoprotein (GP) I_b on the platelet surface binds to the VWF A1 domain) produces a platelet monolayer that supports the subsequent adhesion of activated platelets to each other. Extension occurs when additional platelets adhere to the initial monolayer and become activated. Thrombin, ADP, and thromboxane A₂ (TxA₂) play an important role in this step, activating platelets via cell surface receptors coupled to heterotrimeric G proteins. ADP is secreted from storage sites within platelet-dense granules. TxA₂ is synthesized from arachidonic acid released from platelet membrane phospholipids when platelets are activated. TxA₂ formation in platelets is dependent on cyclooxygenase-1 (COX-1). The local generation of thrombin is facilitated by activated platelets that provide a surface on which clotting factor complexes can be assembled once phosphatidylserine has moved to the platelet surface from the inner leaflet of the plasma membrane. Intracellular signaling downstream of agonist receptors activates integrin $\alpha_{IIb}\beta_3$ (GP IIb-IIIa), making cohesive interactions between platelets (ie, aggregation) via fibrinogen possible. Stabilization refers to the later events of platelet plug formation that help to stabilize the platelet plug and prevent premature disaggregation, in part by amplifying signaling within the platelet. Examples include outside-in signaling through integrins and signaling through receptors whose ligands are located on the surface of adjacent platelets. The net result is a hemostatic plug comprised of activated platelets embedded within a cross-linked fibrin mesh, a structure stable enough to withstand the shear forces generated by flowing blood in arterial circulation (Brass, 2010).

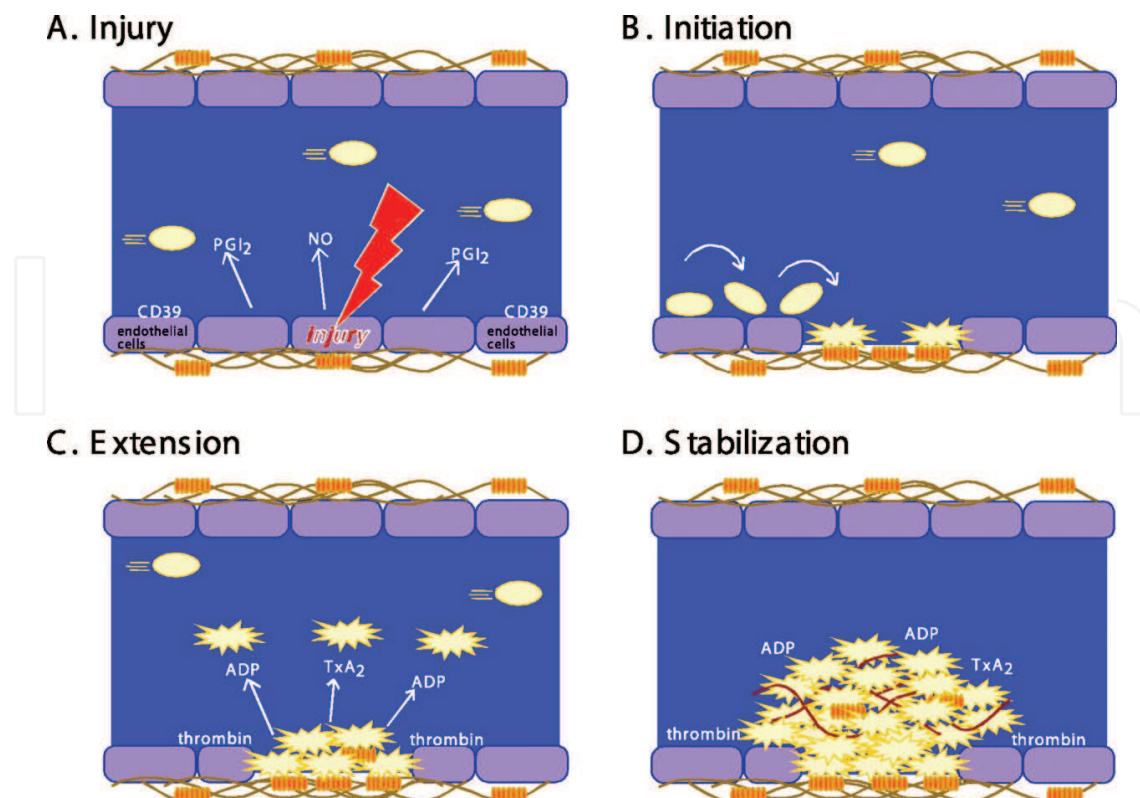


Fig. 1. Stages in platelet plug formation. A classical model. (A) Prior to vascular injury, platelet activation is suppressed by endothelial cell-derived inhibitory factors. These include prostaglandin PGI₂ (prostacyclin), nitric oxide (NO), and CD39, an ADPase on the surface of endothelial cells that can hydrolyze trace amounts of ADP that might otherwise cause inappropriate platelet activation. (B) Initiation. The development of the platelet plug is initiated by thrombin and by the collagen-VWF complex, which captures and activates moving platelets. Platelets adhere and spread, forming a monolayer. (C) Extension. The platelet plug is extended as additional platelets are activated via the release or secretion of TxA₂, ADP, and other platelet agonists, most of which are ligands for G protein-coupled receptors on the platelet surface. Activated platelets stick to each other via bridges formed by the binding of fibrinogen, fibrin, or VWF to activated α IIb β 3. (D) Stabilization. Finally, close contacts between platelets in the growing hemostatic plug, along with a fibrin meshwork (shown in red), help to perpetuate and stabilize the platelet plug. This model is being revised as new observations (described in the text) of the behavior of individual platelets within the hemostatic plug add additional refinements (Brass, 2010 ,with permission).

3. The assessment of platelet activation

In general, the quantification of platelet abnormalities can be performed using a wide variety of measures, such as platelet volume, aggregometry (Gabassov et al., 1989), excretion of metabolites (FitzGerald et al., 1988), flow cytometry (Corash, 1990) to detect various platelet antigens, and by the measurement of increased plasma levels of platelet products, such as platelet factor 4, beta thromboglobulin (Chen & Wu, 1980; Ikeda et al., 1997), the soluble adhesion molecule P-selectin (Blann et al., 1997), soluble CD40L (Choudhury et al., 2007) and matrix metalloproteinase-1 (Martin et al., 2003) (Table 2). However, some

measures (such as platelet volume) are less useful or practical. Furthermore, the choice of method may depend on the nature of the study. For example, measurement of large numbers, say, in epidemiological studies may require the use of plasma markers rather than the more specialized, time-consuming techniques such as flow cytometry (Kamath et al., 2001).

1) Platelet aggregation in response to
ADP Collagen Epinephrine Thrombin Thromboxane or arachidonic acid
(2) Measurement of platelet release products
In plasma: Beta thromboglobulin Platelet factor 4 Soluble P-selectin Soluble CD40L Matrix metalloproteinases In urine: Thromboxane
(3) Measurement of platelet surface antigens
Flowcytometry: GP IIb/IIIa P selectin (CD63) Platelet microparticles CD40L

Table 2. Assessment of platelet activation.

4. The thrombogenesis in atrial fibrillation

The association between atrial fibrillation and the risk of stroke and thromboembolism has long been recognized. Approximately one in three patients with atrial fibrillation not receiving anticoagulants will develop an ischemic stroke in their lifetime, with roughly two-thirds being cardioembolic and one-third being atherothrombotic. Cardioembolic strokes are more disabling than atherothrombotic strokes, with a higher early mortality rate (Bejot et al., 2009; Lip & Lim, 2007).

Evidence suggests that the thrombogenic tendency in atrial fibrillation is related to several underlying pathophysiological mechanisms, which can be discussed in relation to Virchow's triad for thrombogenesis (fig 2). Abnormal changes in flow are evident by stasis in the left atrium, and seen as spontaneous echocontrast. Abnormal changes in vessel walls—essentially, anatomical and structural defects—include progressive atrial dilatation, endocardial denudation, and oedematous or fibroelastic infiltration of the extracellular matrix. Additionally, abnormal changes in blood constituents are well described, and include haemostatic and platelet activation, as well as inflammation and growth factor changes (Choudhury & Lip, 2004; Watson et al., 2009). These changes result in the prothrombotic or hypercoagulable state in this arrhythmia.

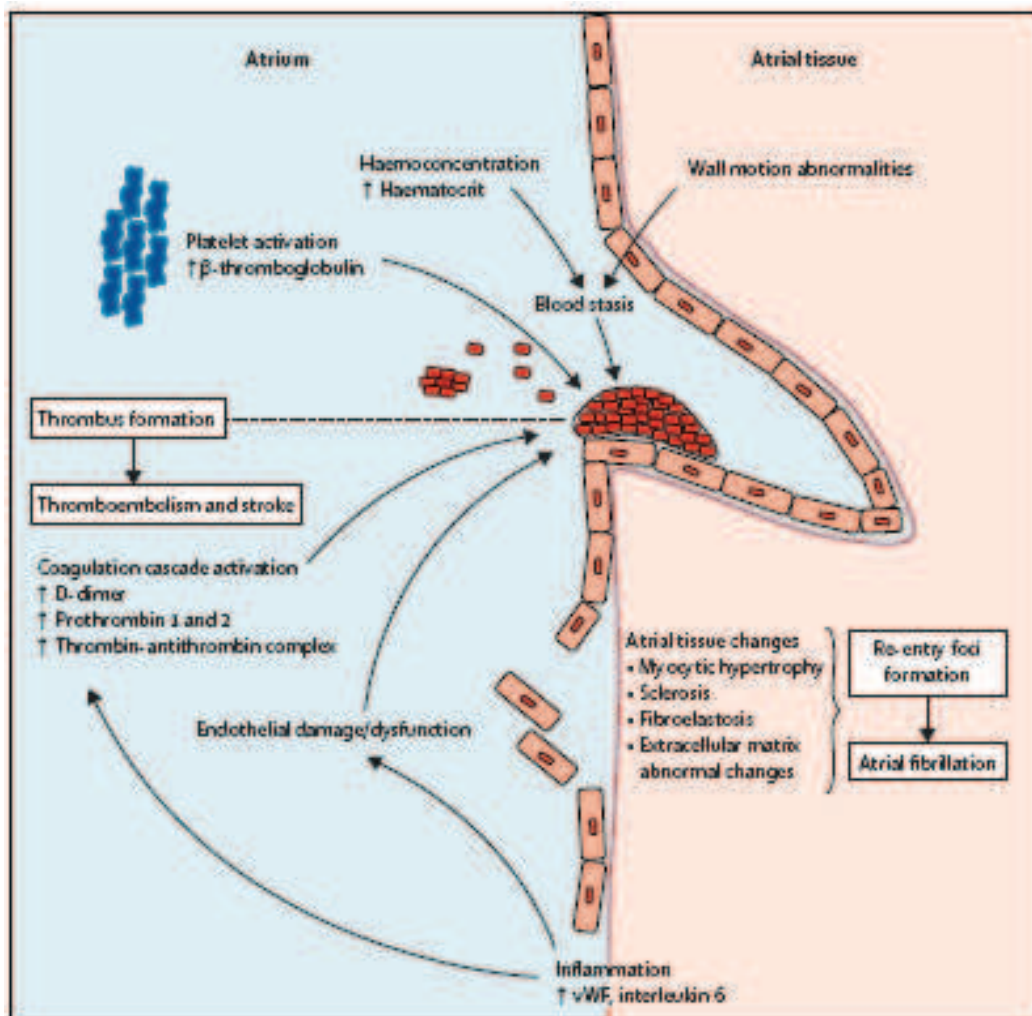


Fig. 2. Components of Virchow's triad for thrombogenesis in atrial fibrillation. Abnormal changes shown in the vessel wall (eg, atrial tissue changes, endothelial damage and dysfunction), in flow (stasis—eg, in the left atrial appendage), and in blood constituents (eg, haemoconcentration, platelets, coagulation cascade activation, inflammation), all factors contribute to propensity for thrombus formation (thrombogenesis) in atrial fibrillation. vWf=von Willebrand factor (Watson et al., 2009, with permission).

An understanding of left atrial—left atrial appendage thrombogenesis may have its roots in distinguishing hemostatic and thrombotic clotting. Studies performed by Hoffman et al., 2006 offer potential mechanistic insight and their experimental findings suggest that a large volume of blood must flow over an injured surface, such as the left atrial—left atrial appendage endocardium in a person with atrial fibrillation for significant tissue factor, derived from both circulating cells and microparticles (George, 2008; Lechner & Weltermann, 2008), to accumulate in high concentrations. Furthermore, hemostasis occurs rapidly, with tissue factor of local origin determining the rate of thrombus development. The cell-based model of coagulation translates well to left atrial—left atrial appendage thrombogenesis and supports a primary role for tissue factor-based thrombin generation, with a secondary role being played by platelets. While the results of clinical trials (Connolly et al., 2006; Healey et al., 2008) and meta-analyses are consistent with this hypothesis, several biological constructs potentially provide a mechanistic platform as well.

The integrated complexity of coagulation in general and platelet-dependent thrombin generation in particular is becoming evident. One of the most interesting and clinically relevant observations over the past decade is the concomitant interdependence and independence of platelet activation and thrombin generation. The former is best considered in the context of primary hemostasis and possibly arterial thrombosis-both highly dependent on platelet activation, platelet aggregation and thrombin generation (in concentrations sufficient to provoke further platelet activation). In the latter instance, platelet subpopulations with distinct intracellular calcium signaling properties yield procoagulant domains (Munnix et al., 2007). The down regulation of platelet $\alpha\text{IIb}/\text{b}_3$, in turn, attenuates proaggregatory potential.

5. The role of platelets in valvular atrial fibrillation

The risk of stroke and thromboembolism is a major complication of atrial fibrillation. The risk of thrombogenesis with atrial fibrillation increases over five-fold in the presence of rheumatic heart disease, especially mitral valve stenosis. Rheumatic heart disease is observed in 15% of Western atrial fibrillation patients, but this is even a larger problem worldwide (Bejot et al., 2009). This increase in thrombogenic risk with valvular heart disease could in part be explained by activation of platelets and the coagulation system.

5.1 Mitral stenosis

Platelet activation appears to play an important role in the initial step of thrombus formation in patients with rheumatic mitral stenosis (Kranidis et al., 1993). Evidence has been shown that shear stresses in turbulent flow occur as a result of stenotic valves induce platelet activation (Stein & Sabbah, 1976; Yu et al., 1978).

Many studies have demonstrated that platelet activation, evaluated by measuring the secretory substance of platelets as beta-thromboglobulin (BTG), Platelet factor 4 (PF4) and soluble P-selection, occurs in the peripheral blood of patients with rheumatic mitral stenosis and atrial fibrillation (Chen et al., 2004; Kataoka et al., 1994; Yetkin et al., 2003).

Chen et al., 2003 demonstrated that in patients with moderate to severe mitral stenosis, increased regional left atrial platelet P-selection expression detected by flow cytometry had a significantly direct relationship with the severity of mitral stenosis. Also, they found that the fraction of peripheral venous platelets expressing P-selection in patients with chronic lone atrial fibrillation did not differ from that of healthy volunteers who were in sinus rhythm and this result provided one possible basic mechanism to clarify the ineffectiveness of aspirin in preventing thromboembolism in patients with non valvular atrial fibrillation according to previous large clinical trials (Petersen et al., 1989; The Stroke Prevention in Atrial Fibrillation Investigators, 1993).

The role of the CD40-CD40L axis in patients with atherothrombotic diseases has generated interest as this molecule may play a pivotal link among platelets (Henn et al., 2001; Langer et al., 2005; Slupsky et al., 1998), inflammation (Anand et al., 2003; Henn et al., 2001), the endothelium (Slupsky et al., 1998; Zhou et al., 1998), coagulation (Slupsky et al., 1998; Zhou et al., 1998) and, ultimately, thrombosis. The triad of functional activity of CD40L in atherosclerotic models, high content in platelets, and mobilization during platelet thrombosis provide a readily testable hypothesis and places platelet-derived CD40L as a possible important mitigating factor in atrial fibrillation. In patients with moderate to severe mitral stenosis and atrial fibrillation, the plasma soluble CD40L levels were found to be higher than healthy controls or patients with lone atrial fibrillation (Chen et al., 2005).

Azzam & Zagloul, 2009 demonstrated that patients with rheumatic mitral stenosis and atrial fibrillation have enhanced platelet activation, assessed by elevated platelet microparticles in the plasma which have a significantly direct relationship with the severity of mitral stenosis. Platelet microparticles are generated from activated platelets and may not only be a marker of platelet activation but also a pathophysiological mediator leading to thrombosis (Niuwland & Struck, 2002).

Correction of mitral stenosis by performing percutaneous transluminal mitral valvuloplasty (PTMV) not only confers significant beneficial haemodynamic effects but also seems to affect platelet activation. Yetkin et al., 2003 reported that soluble P-selection and BTG levels which are markers of platelet activation decreased significantly after PTMV, indicating a reduction in platelet activity. Zaki et al., 2000 also shown significant decrease in prethrombotic state 30 min. after PTMV by measuring BTG, PF4 in patients with a left atrial pressure <10mm HG after PTMV. Also, Chen et al., 2005 found that PTMV rapidly reduced platelet activity in patients with moderate-to-severe mitral stenosis, consequently rapidly reducing soluble CD40L released from platelets. On the contrary, Goldsmith et al., 2000a reported that increased levels of soluble P-selection immediately post procedure and at 24h, in association with increased venous von Willebrand factor levels at 24h after PTMV are in keeping with the increase in platelet activation and endothelial dysfunction following PTMV. These changes may contribute to the increased risk of thromboembolism following the procedure and suggest the need for adequate antiplatelet and anticoagulant therapy following PTMV. These studies therefore suggest that the degree of platelet activation corresponds inversely with the mitral valve orifice area and the more severe the mitral stenosis, the greater is the degree of platelet activation. Furthermore, damage or disease of the atrial wall, including endocrinal damage secondary to valve disease, may contribute to further thrombogenesis.

5.2 Mitral valve prolapse

Mitral valve prolapse has been linked with systemic thromboembolism, especially in young women (Barnett et al., 1980), and transient ischemic attacks or partial strokes occurring as a complication of mitral valve prolapse accounted for 40% of these cases in patients aged under 45 years. Mechanisms for this appear to be related to clot or platelet aggregates originating from the rough surface of prolapsed mitral valves or from the traumatized adjacent left atrial surface (Jeresaty, 1985). Indeed, thrombi have been found on the leaflets of patients with mitral valve prolapse who died of cerebral embolism (Lewis, 1988). There are also reports of shortened platelet survival and increased platelet coagulant activity in patients with cerebral embolism and mitral valve prolapse (Lewis, 1988).

On the other hand, recent population based and case-control studies demonstrated no increased frequency of mitral valve prolapse among patients with stroke or transient ischemic attacks, including young patients (Gilon et al., 1999; Orenica et al., 1995; Petty et al., 1994). In addition, patients with mitral valve prolapse who had strokes were similar in age to the general stroke population, and many had other risk factors for strokes, including atrial fibrillation (Gilon et al., 1999; Nishimura et al., 1985; Orenica et al., 1995). Also, some studies on the platelets have failed to demonstrate an association of platelet activation with pure mitral valve prolapse alone (Tse et al., 1997), suggesting that if the predisposition of mitral valve prolapse to thromboembolism were true, it may well operate via a mechanism other than platelet activation alone. Perhaps the severity of mitral regurgitation in mitral valve prolapse may be a factor as reported by Martini et al., 1996 who studied the platelet

and coagulation activation in patients with mitral valve prolapse and suggested that mitral valve prolapse is not responsible per se for blood clotting activation, but in patients with severe mitral insufficiency an increase in thrombin generation can occur. These alterations in hemostatic system may represent a mechanism by which mitral regurgitation increases the risk of thromboembolic events in patients with mitral valve prolapse.

5.3 Mitral regurgitation

Mitral regurgitation appears to have variable effects on platelet activation and the risk of thromboembolism, which is dependent on the underlying status of the mitral valve and whether or not there is coexisting atrial fibrillation. Some studies have shown an increase in platelet activation in patients with severe mitral regurgitation (Tse et al., 1997) in association with mitral valve prolapse, when compared to patients with mitral valve prolapse and mild to moderate mitral regurgitation, which was independent of age and left atrial size. However, other studies failed to demonstrate the same effect (Martini et al., 1996), but instead report increased activation of the coagulation system and thrombin generation in these patients.

For example, Karatasakis *et al.*, 1995 showed that significant mitral regurgitation correlates with a lower incidence of spontaneous echo contrast, thrombi and embolization in patients with rheumatic mitral valve disease. Similar studies by Hwaang *et al.*, 1994 and Movsowitz *et al.*, 1993 confirmed similar findings. In patients with non-valvular atrial fibrillation, moderate to severe mitral regurgitation seems to protect against stroke especially in patients with left atrial enlargement (Nakagami et al., 1998). Also, Kranidis et al., 2000 demonstrated that mitral regurgitation has a protective effect on the development of left atrial thrombus in patients with rheumatic valve disease and atrial fibrillation. Furthermore, the presence of mitral regurgitation appears to reduce intracardiac thrombus in patients with dilated cardiomyopathy (Maze et al., 1989).

Nevertheless, there are limited data relating these clinical observations to the degree of platelet activation or thrombogenesis. However, Goldsmith *et al.*, 2000b reported an intraoperative study of patients with severe mitral regurgitation, where soluble P-selectin levels (as an index of platelet activation) were significantly lower within the left atrium compared to peripheral vein levels, indicating reduced platelet activation in association with the 'stirring' effect of the (severe) mitral regurgitation jet.

Does moderate to severe mitral regurgitation increase the risk of thromboembolism in mitral valve prolapse but paradoxically decrease the risk in rheumatic mitral valve disease and/or non-valvular atrial fibrillation? To answer this question, further studies are needed which would clarify the influence of mitral regurgitation on platelet activation in mitral valve prolapse, rheumatic mitral valve, and non-valvular atrial fibrillation.

5.4 Aortic valve disease

Haemodynamic studies have shown that diseased cardiac valves, whether stenosed or incompetent, create regions of increased turbulence and shear stresses that are large enough to damage the vascular endothelium and cellular blood elements, leading to abnormal haemorheology, platelet activation, and endothelial dysfunction (Stein & Sabbah, 1976). For example, the intensity of turbulence in patients with pure aortic stenosis may be 10 times greater than normal while the intensity of turbulence in patients with pure aortic regurgitation may be three times greater than normal (Stein & Sabbah, 1976).

Goldsmith et al., 2000c measured plasma concentrations of soluble P-selectin (a marker for platelet activation), von Willebrand factor (a marker for endothelial cell dysfunction) and fibrinogen (as an index of haemorheology and a clotting factor), in 61 patients with moderate to severe aortic valve disease in sinus rhythm, and reported that patients with aortic valve disease had higher mean plasma fibrinogen, von Willebrand factor and soluble P-selectin levels, which were not significantly different between patients with aortic stenosis or regurgitation.

Also, Prohaska et al., 2008 studied the platelet function in 660 patients considered for isolated coronary artery bypass graft (CABG) surgery, and in 421 patients considered for single aortic valve replacement (AVR). Platelet function was monitored preoperatively using the platelet function analyzer device (PFA-100), and reported that due to disturbed flow and shear exposition following an initial activation, the platelets are partially degranulated, shed microparticles, and might become involved in the pathogenesis of microvascular dysfunction and thrombotic events in patients with aortic valve disease. Furthermore, Dimitrow et al., 2009 determined markers of thrombin generation (thrombin-antithrombin complex, prothrombin fragment 1+2), platelet activation (soluble CD40 ligand, beta-thromboglobulin, P-selectin) in seventy-five patients with aortic stenosis, and reported that mean concentrations of thrombin and platelet markers were higher approximately two-fold in patients than in controls and maximal gradient as an index of turbulent flow associated with activation of coagulation and platelets.

6. The role of platelets in non- valvular atrial fibrillation

Whilst abnormalities of clotting markers are well recognized in non-valvular atrial fibrillation, abnormal platelet activation has also been reported in these patients (Lip, 1995; Yamauchi et al., 1986). However, Kamath et al., 2002 found that platelet markers (plasma beta-thromboglobulin, soluble glycoprotein V) and coagulation markers (fibrin D-dimer) were higher in atrial fibrillation compared to healthy controls with no significant abnormalities of platelet aggregation in response to standard platelet agonists, again casting doubt on the extent and significance of platelet activation in atrial fibrillation- which they have previously reviewed (Kamath et al., 2001). Choudhury et al., 2008 assessed platelet activation using 4 different aspects of platelet pathophysiology: 1) platelet surface expression of CD62P (P-selectin) and CD63 (a lysosomal glycoprotein) (by flow cytometry); 2) mean platelet volume (MPV) (by flow cytometry); 3) plasma levels of soluble P-selectin (sP-selectin, enzyme-linked immunoadsorbent assay); and 4) total amount of P-selectin per platelet (pP-selectin) ("platelet lysis" assay). They concluded that there is a degree of excess of platelet activation in atrial fibrillation compared with "healthy control subjects," but no significant difference between atrial fibrillation patients and "disease control subjects" in sinus rhythm. Platelet activation may differ according to the subtype of atrial fibrillation, but this is not in excess of the underlying comorbidities that lead to atrial fibrillation. Platelet activation in atrial fibrillation may be due to underlying cardiovascular diseases, rather than due to atrial fibrillation per se. Also, Choudhury et al., 2007 suggested that there is an excess of platelet activation in AF patients compared to healthy control subjects, as measured by sCD40L and sP-selectin levels. However, there was no excess of platelet activation in atrial fibrillation patients compared to disease control subjects. This would support the argument that platelet activation in atrial fibrillation patients is more related to the associated vascular diseases than to the arrhythmia itself. Furthermore patients with

atrial fibrillation have been noted to have impaired matrix degradation, with abnormalities in matrix metalloproteinase-1 (MMP-1) and its inhibitor, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), although these again were not independently associated with the presence of atrial fibrillation on multivariate analysis (Marin et al., 2003). However, an independent relationship was noted between the MMP/TIMP system and the prothrombotic state (assessed by prothrombin fragments 1 and 2 levels). From the available data, it seems that increased interstitial fibrosis in atrial tissue is more likely due to underlying comorbidities, like hypertension, ischemic heart disease, or uncontrolled heart failure (circumstances associated with high risk to develop atrial fibrillation), rather than the presence of the arrhythmia itself.

The heart rate does not seem to be related to the extent of platelet activation in atrial fibrillation (Yamauchi et al., 1986). Therefore, heart rate control therapy itself is unlikely to offer significant benefit in terms of reducing thromboembolic risk in atrial fibrillation. Nevertheless, exercise may increase platelet activation in atrial fibrillation (Furui et al., 1987). For example, Furui et al., 1987 report an increase in platelet sensitivity to ADP aggregation and the level of beta thromboglobulin in the plasma in 20 patients with lone atrial fibrillation in comparison with age-matched controls when exercising at up to 85% of predicted maximal heart rate. However, Li Saw Hee et al., 2001 did not demonstrate any significant increase in soluble P-selectin levels amongst patients with atrial fibrillation exercised to exhaustion. One reason for the difference in findings between the studies by Furui et al., 1987 and Li Saw Hee et al., 2001 may be the choice of markers of platelet activation, and hence, different pathophysiological release mechanisms. Furthermore, there does not appear to be any significant diurnal variation in abnormal platelet activation in atrial fibrillation, as reflected by changes in soluble P-selectin levels (Li Saw Hee et al., 2000), but this may simply reflect the high thrombogenic state associated with chronic atrial fibrillation.

The extent of platelet activation in non-valvular atrial fibrillation may be related to the other features of the left atrium. For example, an enlarged left atrium and reduced left atrial appendage flow velocity has been correlated with increased platelet activation by (Shinohara et al., 1998). The study by Shinohara et al., 1998 reported a significant difference in platelet activation amongst patients with nonvalvular atrial fibrillation with a low left atrial appendage velocity (<40 cm. s⁻¹) when compared to patients with a high left atrial appendage velocity ≥40 cm. s⁻¹. The patients with a low atrial appendage velocity also had a significantly higher prevalence of spontaneous echo contrast and left atrial thrombus, suggesting a relationship between platelet activation and pre-embolic events if atrial fibrillation was accompanied by abnormal flow dynamics within the left atrium. Using scanning electron microscopy, we have recently demonstrated atrial endocardial cell damage, which was most commonly seen in the left atrial appendage amongst patients with mitral valve disease and atrial fibrillation (Goldsmith et al., 2000d). The interaction between activated platelets or clotting factors and the damaged endocardium may in part contribute to thrombogenesis within the left atrium.

Whether the peripheral venous levels of markers of platelet activation and thrombogenesis truly and wholly reflect left atrial levels of coagulation and platelet activation in non-valvular atrial fibrillation is not exactly clear. Li Saw Hee et al., 1999 demonstrated that there was no significant difference in the markers of platelet activation and thrombogenesis between the atria and the periphery vein amongst patients with atrial fibrillation due to mitral stenosis. Peverill et al., 1996 found that the markers of coagulation activity in similar

patients were no different between the left atrium and the periphery in the absence of left atrial spontaneous echo contrast. However, levels were significantly raised in the left atrium when compared to the periphery in the presence of left atrial spontaneous echo contrast, irrespective of the underlying rhythm. Similarly, Yamamoto *et al.*, 1995 demonstrated a significant difference in the levels of some markers of coagulation between the left atrium and the periphery, namely, thrombin-antithrombin III complex and fibrinopeptide A in patients with mitral stenosis, but failed to demonstrate the same with respect to another marker of platelet activation, namely, beta-thromboglobulin.

7. Platelet activation and thromboembolic risk in atrial fibrillation

Perhaps a continuum exists between normal platelet function, 'statistically' abnormal platelet function and overt thrombosis in patients with cardiovascular disease and stroke. Thus the abnormal platelet activation in atrial fibrillation, as summarized in the evidence above, may represent a 'pre-embolic' status in non-valvular atrial fibrillation (Pongratz *et al.*, 1997). Indeed, platelet activation seems to occur even before the occurrence of spontaneous echo contrast in patients with atrial fibrillation (Heppell *et al.*, 1997) and is correlated with both spontaneous echo contrast (Pongratz *et al.*, 1997) and left atrial thrombus (Heppell *et al.*, 1997) in atrial fibrillation.

For example, Pongratz *et al.*, 1997 demonstrated that the amount of circulating platelets expressing P-selectin was significantly higher in the patients with spontaneous echo contrast or left atrial thrombus in comparison with patients without either of these, or healthy controls. The study by Heppell *et al.*, 1997 reported that plasma levels of beta thromboglobulin were independently associated with left atrial thrombus whether or not spontaneous echo contrast was present. Studies in canine models have also demonstrated that platelet activation is significantly associated with silent cerebral infarction in atrial fibrillation (Minamino *et al.*, 1998).

However, other clinical studies have demonstrated platelet activation in atrial fibrillation but failed to relate the former to the risk of thromboembolism. Thus, even though platelet activation appears to be significantly correlated with spontaneous echo contrast and left atrial thrombus, it does not seem to be convincingly correlated with stroke (or transient ischaemic attack) in nonvalvular atrial fibrillation. For example, the study by Gustafsson *et al.*, 1990 showed that patients with atrial fibrillation and stroke had no greater platelet activation than patients with atrial fibrillation without stroke, whilst patients with sinus rhythm and stroke had no greater platelet activation than controls in sinus rhythm without stroke; patients with non-valvular atrial fibrillation without stroke had significantly more platelet activation than individuals with stroke in sinus rhythm. Whether platelet activation contributes to stroke/transient ischaemic attack in atrial fibrillation is not clear, and whether it can be used as a predictor of risk of stroke in atrial fibrillation in addition to other parameters, such as hypertension and left ventricular dysfunction still needs to be clarified.

Thus, the available evidence suggests that thromboembolism in atrial fibrillation is probably due to enhancement of various components of the coagulation system due to stasis of blood in the inordinate and irregular atria, rather than to platelet activation *per se* (Nagao *et al.*, 1995). The relative role of coagulation versus platelet activation in the pathogenesis of thrombogenesis in patients with atrial fibrillation can roughly be inferred from the results of antithrombotic drug interventions that have been tested in randomized clinical trials. Among non-valvular atrial fibrillation patients, the relative risk reduction (RRR) for stroke

that is achieved with moderate intensity oral anticoagulant [international normalized ratio (INR)=2-3] compared to placebo is approximately 65%, as opposed to the 20% RRR achieved with aspirin versus placebo (Hart et al., 2007; Lip & Lim, 2007). Consistently, moderate intensity oral anticoagulant produces a RRR for stroke of 40% compared to aspirin, and of 30% compared to aspirin +clopidogrel (Hart et al., 2007). Interestingly, among medium-high risk non-valvular AF patients not eligible to make warfarin, aspirin+ clopidogrel was superior to aspirin alone for stroke prevention (Connolly et al., 2009).

Taken together, these results indicate that inhibition of coagulation remains the mainstay in preventing atrial fibrillation -related thrombogenesis. The lesser but significant role of platelets- best inhibited by a combined antiplatelet drug regimen - is presumably related to the prominent involvement of platelets in the pathogenesis of atherothrombotic (that is, non-cardiombolic) events (Lip et al., 2009).

8. Conclusion

The thrombogenic role of platelets in atrial fibrillation is clearly complex and remain partly understood. Definitive answers to the questions of whether platelet activation contribute towards stroke in atrial fibrillation or is it just an associated factor? Does a reduction in platelet activation beneficially influence thromboembolic risk in atrial fibrillation? are far from simple and compare with the somewhat equivocal benefits of antiplatelet drugs in atrial fibrillation in clinical trials. Future directions in this field should involve further clarification of the role of different aspects of platelet activation in atrial fibrillation.

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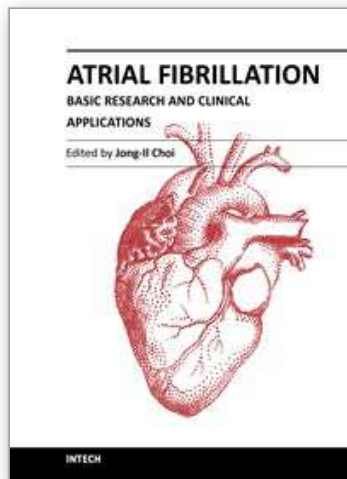
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Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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