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Chapter 6

Thrombogenesis in Atrial Fibrillation

Hanan Ahmed GalalAzzam

Additional information is available at the end of the chapter

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1. Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, which is associated with a high risk of stroke and thromboembolism. Increasing evidence suggests that the thrombogenic tendency in atrial fibrillation is related to several underlying pathophysiological mechanisms. Virchow's triad, a time-honored paradigm that offers mechanistic insights for thrombus initiation and development regardless of origin, does indeed apply to atrial fibrillation thrombogenesis [1,2].

2. Mechanisms of thrombogenesis in atrial fibrillation

More than 150 years ago, Rudolf Virchow proposed a triad of events needed for thrombus formation ie, abnormal changes of the vessel wall, blood flow, and blood constituents [2]. In the 21st century, we now recognize Virchow's triad as: endothelial or endocardial damage or dysfunction (and related structural abnormal changes); abnormal blood stasis; and abnormal haemostasis, platelets, and fibrinolysis (Figure 1). Extensive abnormal changes of these variables are clearly evident in atrial fibrillation. Thus, atrial fibrillation could in fact drive a prothrombotic or hypercoagulable state, by virtue of its fulfillment of Virchow's triad for thrombogenesis [3].

Abnormal changes shown in the vessel wall (eg, atrial tissue changes, endothelial damage and dysfunction), in fl ow (stasis—eg, in the left atrial appendage), and in blood constituents (eg, haemoconcentration, platelets, coagulation cascade activation, infl ammation); all factors contribute to propensity for thrombus formation (thrombogenesis) in atrial fi brillation. vWf=von Willebrand factor.

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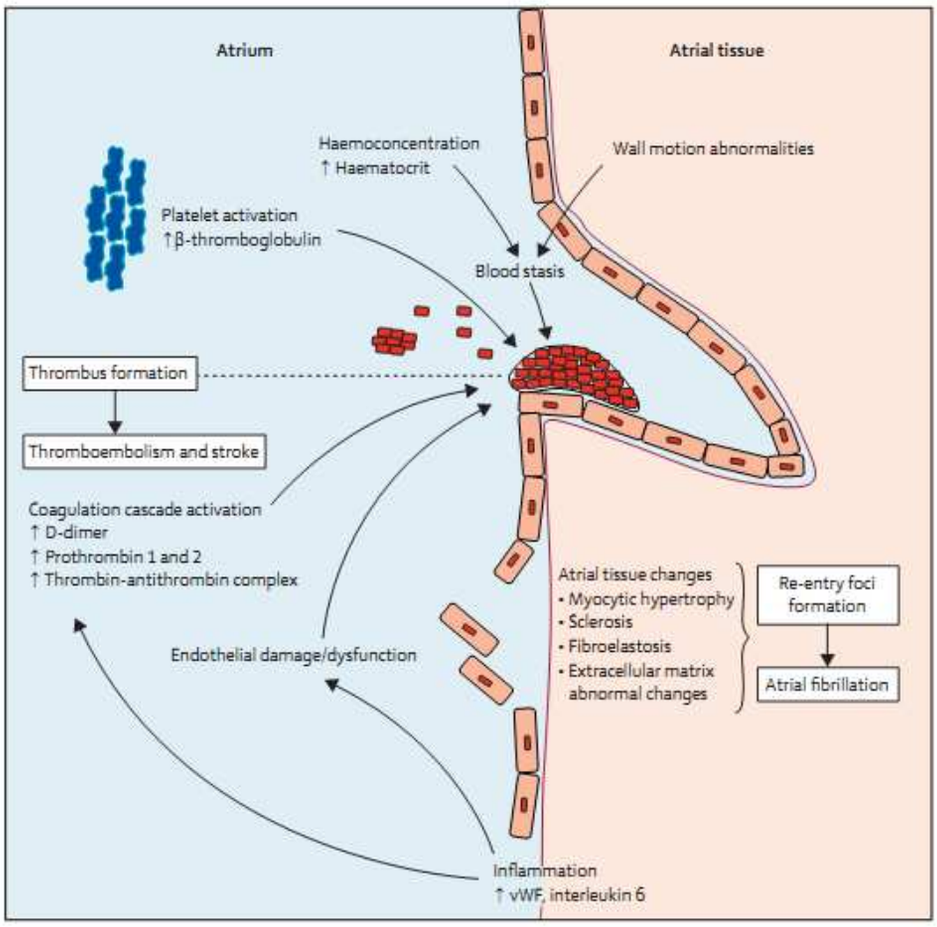


Figure 1. Components of Virchow's triad for thrombogenesis in atrial fibrillation [4](with permission)

2.1. Anatomical and structural considerations:

Attached to each atria is a blind-ended passage known as an appendage. The left atrial appendage (LAA) is long with a narrow inlet, thereby predisposing to blood stasis. Thus, the LAA is the most common site of intra-atrial thrombus formation, not only in atrial fibrillation, but also in patients with sinus rhythm [5,6].

Changes in the dimensions of the left atrium and LAA occur as a consequence of atrial fibrillation, with some correlation to subsequent thromboembolism. Detailed descriptions of endothelial damage in the context of atrial fibrillation are well described and can be visualised by scanning electron microscopy, especially within the appendages. Goldsmith and colleagues [7] have reported more severe endocardial changes in the LAA than in the right-atrial appendages, especially in atrial fibrillation (compared with sinus rhythm) and in mitral stenosis (compared with mitral regurgitation). Similarly, Masawa and co-workers [8] have described a "rough endocardium" with a wrinkled appearance attributable to oedema and fibrinous transformation; small areas of endothelial denudation and thrombotic aggregation have also been noted in patients with atrial fibrillation and cerebral embolism.

Extracellular matrix turnover is a dynamic structure, which continually undergoes a process of structural remodeling [9]. Structural remodelling of the atria could contribute to the hypercoagulable state, by virtue of both enhanced blood stasis and an abnormal endocardium. Structural remodeling of the left atrial appendage to include the pectinate muscles and multiple lobes of the lumen occurs in patients with permanent atrial fibrillation [10]. Morphologic studies have shown larger volumes and luminal surface areas when compared to patients without atrial fibrillation; however, both the absolute and relative surface areas of the pectinate muscles are reduced. In addition, there is significant endocardial thickening with fibrous and elastic tissue (endocardialfibroelastosis) [10].

Several studies have shown that patients with atrial fibrillation have altered amounts of collagen degradation products and impaired matrix degradation, with abnormal plasma concentrations of various matrix metalloproteinases (MMPs), their inhibitors (tissue inhibitor of MMPs [TIMPs]), and various growth factors (eg, transforming growth factor β1) reported [11-13]. These proteins are important in the breakdown of various collagens and hence their regulation is key to ensuring healthy matrix turnover.

Evidence suggests that abnormal changes in the extracellular matrix are not related to the presence of atrial fibrillation in itself, but are probably a consequence of various coexisting comorbidities (eg, hypertension). Nevertheless, MMPs and TIMPs could have a link with the prothrombotic state, as exemplified by a correlation with prothrombin fragments 1 and 2, markers of thrombogenesis [12]. Further studies have identified disruption of other extracellular matrix components, although most have focused on these factors as a cause for the arrhythmia or explanation for remodelling and chamber dilatation [14-17]. One study suggested that some of the changes in MMPs were due to concomitant mitral valve disease [16], whereas another reported changes in the ventricular myocardium, albeit to a lesser extent [17]. Similarly, in patients with ventricular dysfunction (a potent risk factor for atrial fibrillation), various studies have also shown striking atrial structural changes [18,19].

2.2. Abnormal blood stasis

In addition to stasis consequent on the failure of atrial systole, the presence of non-valvular atrial fibrillation seems to promote progressive left atrial (LA) dilatation [20], thus amplifying the potential for stasis. In the presence of mitral stenosis, LA dilatation is increased and leads to further stasis and propensity to thrombosis [21]. The contribution of LA dilatation to thrombogenesis (at least, in non-valvular atrial fibrillation) is indicated by the finding that atrial size corrected for body surface area is an independent risk factor for stroke [22,23].

The contribution of valvular heart disease to thrombogenesis in atrial fibrillation cannot be ignored. In mitral stenosis, up to 75% of patients with cerebral emboli on computed tomography or autopsy are identified to have atrial fibrillation, presumably due to alterations in LA emptying and transmitral flow [24]. By contrast, moderate-to-severe (non-rheumatic) mitral regurgitation seems to reduce the risk of stroke with atrial fibrillation [25]. Defining patients with atrial fibrillation and mitral valve disease who are at the greatest risk of stroke has proved complex. The risk of emboli increases with age and in individuals with a lower cardiac index, but seems to correlate poorly with clinical classification or mitral valve area.

Studies assessing the degree of LA dilatation have also proven inconsistent. However, an initial embolic event is highly predictive for subsequent or recurrent thromboemboli [26].

Abnormal stasis in the LA and LAA can be visualized on TEE with spontaneous echo contrast (SEC) or pulsed-wave doppler during paroxysms of atrial fibrillation [27-30]. In sinus rhythm, aquadriphasic pattern of blood flow can be seen in the LAA, affording minimum blood stasis [31]. This pattern in blood flow is thought to be related to the intimate yet slightly delayed relations between atrial and ventricular passive and active filling. In atrial fibrillation, SEC has been shown to independently predict increased risk of thromboembolism [32].

2.3. Abnormal blood constituents

The main intravascular promoters of thrombogenesis are platelets and the various proteins of the coagulation cascade. In atrial fibrillation, abnormal changes in both these promoters and other blood constituents (eg, inflammatory cytokines, growth factors) are evident, thereby completing Virchow's triad.

2.3.1. Abnormal changes in coagulation

Abnormal haemostasis and coagulation are well described in atrial fibrillation (figure 1,table1). In particular, increased fibrin turnover has been reported in patients with acute onset or chronic atrial fibrillation [33-39]. These changes initially seemed to be unrelated to the cause of atrial fibrillation or structural heart disease [38,39]. However, abnormal concentrations of prothrombotic indices (eg, prothrombin fragments 1 and 2 and thrombin-antithrombin complexes) are more prominent in patients with stroke who have atrial fibrillation than in those who have sinus rhythm [40], as well as in patients with atrial fibrillation and many stroke risk factors (eg, diabetes plus heart failure) compared with either risk factor alone [41-43]. Furthermore, some prothrombotic indices are abnormal in the patients with atrial fibrillation only [44,45] and in those with paroxysmal atrial fibrillation [46]. Notably, some markers have been proposed as suitable candidates to refine various stroke risk stratification schema, many of which are reasonably able to identify patients at low risk or high risk of stroke, but poor at identifying patients at moderate risk [47].

An association between various prothrombotic indices, stasis, and intracardiac thrombus has been described [48,49]. In one study, congestive cardiac failure, a history of recent embolus, and fibrin D-dimer were shown to independently predict the presence of LAA thrombi on TEE, leading the researchers to conclude that D-dimer could be useful in predicting the absence of LAA thrombi [49].

The prothrombotic state also correlates with the degree of LAA dysfunction [50,51]. Furthermore, a relation to TEE indices of stroke risk has been described. For example, SEC that is visible during TEE shows a significant correlation to prothrombin fragments 1 and 2, fibrinopeptide A, and thrombin-antithrombin III complex in non-valvular atrial fibrillation [52,53]. Patients with atrial flutter and impaired LAA function (shown by pulsed-wave doppler) have increased amounts of of D-dimer and â -thromboglobulin[53]. In accordance with clinical data suggesting that mitral regurgitation protects against stroke in atrial fibrillation, a greater degree of mitral regurgitation is associated with reduced coagulation activity as estimated by fibrin D-dimer amounts [54], highlighting the important contribution of stasis.

	Study design	Comment
Gustafsson et al.,[55]	20 AF with stroke; 20 AF without stroke; 20 stroke without AF; 40 healthy controls	↑D-dimer, vWF in NV AF with and without stroke
Kumagai et al., [39]	73 AF; 73 controls	↑D-dimer
Asakura et al.,[56]	83 AF vs healthy controls	↑PF1+2, TATIII
Sohara&Miyahara [57]	13 paroxysmal AF vs healthy controls	NS in D-dimer, TATIII
Lip et al., [38]	87 AF; 158 controls	↑D-dimer, vWF
Lip et al., {58]	51 AF; 26 healthy controls	↑D-dimer
Kahn et al., [36]	75 NV AF with or without previous embolic events; 42 controls with or without previous thrombotic stroke	vWF higher in AF after stroke than controls without stroke and similar to controls after stroke
Heppell et al., [48]	109 AF with or without thrombus in left atrium	↑D-dimer, vWF, TATIII in patients with left atrial thrombus compared with patients without thrombus
Shinohara et al., [51]	45 NV AF	↑D-dimer, TATIII in patients with low LAA velocity vs patients with high LAA velocity
Feinberg (SPAF III) et al., [59]	1531 AF	PF1+2 not associated with thromboembolism
Mondillo et al., [44]	45 AF; 35 healthy controls	↑D-dimer, vWF, s-thrombomodulin
Fukuchi et al., [60]	AF vs without AF	↑vWF in atrial appendage tissue
Conway et al., [[61]	1321 AF	↑vWF in high-risk group for stroke
Kamath et al., [62]	93 AF; 50 healthy controls	↑D-dimer
Vene et al., [63]	113 AF	↑D-dimer in AF with cardiovascular events vs no events
Nakamura et al., [64]	LAA tissue samples of 7 NV AF vs 4 without AF	↑vWF, TF expression
Conway et al., [65]	994 AF	vWF not a significant predictor of stroke and vascular events
Kamath et al., [66]	31 acute onset AF; 93 permanent AF; 31 healthy controls	Haematocrit raised in acute AF; ↑D-dimer in permanent AF, but not in acute AF
Sakurai et al., [67]	28 AFL; 27 controls	↑D-dimer in patients with impaired LAA function
Inoue et al., [42]	246 NV AF; 111 healthy controls	↑D-dimer in NV AF with risk factors, NS in PF1+2
Kumagai et al., [68]	16 AF post mortem	↑vWF mRNA and protein in AF with enlarged atriums
Marin et al., [33]	24 acute onset AF; 24 chronic AF vs 24 coronary artery disease in sinus rhythm; 24 healthy controls	↑D-dimer, vWF, s-thrombomodulin in all AF groups with no significant after cardioversion
Nozawa et al., [69]	509 AF; 111 healthy controls	↑D-dimer, NS in PF1+2
Freestone et al., [70]	59 AF; 40 healthy controls	↑Vwf
Nozawa et al., [71]	509 NV AF	↑D-dimer but not PF1+2 with predictive significance for thromboembolic events
Ohara et al., [43]	591 NV AF; 129 controls	↑D-dimer, PF1+2, platelet factor 4, and â-thromboglobulin in NV AF; D-dimer, prothrombin fragments correlated with accumulation of clinical risk factors for stroke

AF=atrial fibrillation. NV=non-valvular. TATIII=thrombin-antithrombin III complex. AFL=atrial flutter. vWf=von Willebrand factor. LAA=left atrial appendage. TF=tissue factor. NS=non-significant. PF1+2=prothrombin fragments 1 and 2. s-thrombomodulin=soluble thrombomodulin

Table 1. Coagulation abnormal changes in atrial fibrillation [4] (with permission).

2.3.2. Von Willebrand factor (vWf)

Further insight into the hypercoagulable state in atrial fibrillation is provided by studies of vWf, which is a well-established index of endothelial damage and dysfunction. Raised vWf concentrations independently predict presence of LAA thrombus in atrial fibrillation [48]. Furthermore, increased LAA endocardial expression of vWf has been described [60], especially in those with an overloaded appendage, which seems to correlate with the presence of adherent platelet thrombus. Furthermore, increased expression of vWf in the endocardium has been shown to associate with enlarged LA dimensions in mitral valve disease and increased myocyte diameter [68].

Both vWf and tissue factor are overexpressed in the atrial endothelium in patients with atrial fibrillation who have ahistory of cardiogenic thromboembolism—specifically in the endothelial sites containing inflammatory cells and denuded endocardium, which indicate features of persistent myocarditis [64]. Plasma vWf and D-dimer are also positively correlated in patients receiving either aspirin or no antithrombotic treatment, but not in those receiving warfarin [38], further indicating the ability of warfarin to modulate the thrombogenic process.

Furthermore, a positive association between atrial fibrillation and plasma vWf was seen in the Rotterdam study [72]. This relation was most apparent in female patients, which could explain the excess risk of stroke due to atrial fibrillation in women compared with men. Furthermore, plasma vWf amounts were associated with the presence of four independent risk factors for stroke (heart failure, previous stroke, age, and diabetes) and stroke risk stratification schema [61,65]. Follow-up data from this study suggests that vWf concentrations might independently predict subsequent stroke and vascular events [65,73]. However, such applications will probably be hampered by the non-specificity of vWf, concentrations of which are also increased in various other disorders [74,75].

2.3.3. Tissue factor

An understanding of left atrial—left atrial appendage thrombogenesis may have its roots in distinguishing hemostatic and thrombotic clotting. Studies performed by Hoffman and Monroe [76] offer potential mechanistic insight. In a series of wounding experiments, skin punch biopsy tissue was placed on the dorsal skin of C57 black mice. Samples containing the wound specimens were then collected. For comparison, thrombus was provoked in saphenous veins by application of 10% ferric chloride. After complete occlusion, tissue blocks containing the clotted vessels were collected. Histologic evaluation revealed extensive tissue factor staining within saphenous vein thrombi. In distinct contrast, tissue factor staining in hemostatic clots was localized to squamous endothelial cells at the wounds edges—not within the thrombus itself.

The 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 [77,78], to accumulate in high concentrations. Further, and of fundamental teleological rele-

vance, 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 [79,80], 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 [81]. The down regulation of platelet aIIb/b3, in turn, attenuates proaggregatory potential.

2.3.4. Platelets

Many studies indicate a potential role for platelets in the hypercoagulable state (table 2). However, the results of many of these studies have been conflicting, representing the diverse aspects of platelet physiology that have been measured and possibly confounding from interlaboratory assay variability. The available data support the notion that abnormal changes of platelets in atrial fibrillation do exist, but the relation between these measures and increased thrombotic risk remains uncertain, and many of such abnormal changes could simply indicate underlying vascular comorbidities.

Choudhury and colleagues [82] recently showed that patients with atrial fibrillation had far higher amounts of platelet microparticles and soluble P-selectin than healthy controls in sinus rhythm, but no difference was seen between patients with atrial fibrillation and disease-matched controls, implying that the abnormal changes detected were a consequence of the underlying comorbidities rather than atrial fibrillation itself. Increased amounts of β-thromboglobulin, a platelet-specific protein that indicates platelet activation and is released from α-granules during platelet aggregation and subsequent thrombus formation, have been shown in patients with both valvular and non-valvular atrial fibrillation compared with controls in sinus rhythm [51,58,62,83-86]. Substantially higher β-thromboglobulin amounts have been measured in patients with the lowest LAA flow velocities, who had greater left-atrial dimensions [51], suggesting that platelet activation could be enhanced in patients with a greater degree of intra-atrial stasis.

Despite the presence of enhanced platelet activation in atrial fibrillation, any firm clinical evidence indicating that it directly enhances thrombotic risk is lacking. A substudy from the

Stroke Prevention in Atrial Fibrillation III (SPAF-III) trial [59] recorded no association between plasma β -thromboglobulin amounts and subsequent thromboembolic events. By contrast, the population-based Rotterdam study [87] showed that plasma concentrations of soluble P-selectin were predictive of adverse clinical outcomes in elderly patients with atrial fibrillation.

	Patient group	Results
Yamauchi et al., [87]	26 V AF; 73 NV AF; 57 healthy controls	↑ BTG in AF, NS in PF4
Furui et al., [95]	20 AF; 15 healthy controls	BTG increase greater in AF than in controls after treadmill exercise
Gustafsson et al., [55]	20 AF with stroke; 20 AF without stroke; 20 stroke with sinus rhythm; 40 healthy controls	↑BTG, PF4 in NV AF with and without stroke
Sohara et al., [57]	13 paroxysmal AF vs healthy controls	NS in BTG, PF4
Lip et al., [58]	51 AF; 26 healthy controls	↑BTG
Heppell [48]	109 AF with or without thrombus in left atrium	↑BTG, PF4 in patients with left atrial thrombus compared with patients without thrombus
Minamino et al., [86]	25 AF vs healthy controls	↑mP-sel
Shinohara et al., [51]	45 NV AF	↑BTG, PF4 in patients with low LAA velocity vs patients high LAA velocity
Feinberg et al., SPAF III) [59]	1531 AF	BTG not associated with thromboembolism
Minamino et al., [93]	28 AF	↑BTG, mP-sel
Mondillo et al., [44]	45 AF; 35 healthy controls	↑BTG, PF4
Kamath et al., [45]	93 AF; 50 healthy controls	↑BTG, soluble GPV; NS in platelet aggreagation
Conway et al., [61]	1321 AF	sP-sel was independent of risk for stroke
Conway et al., [65]	994 AF	sP-sel not a significant predictor of stroke and vascular events
Atalar et al., [96]	15 paroxysmal AF; 25 chronic AF; 22 healthy controls	Higher BTG, PF4 in chronic AF than in paroxysmal AF and after conversion to sinus rhythm
Nozawa et al., [69]	509 AF; 111 healthy controls	↑BTG, PF4
Sakurai et al., [53]	28 AFL; 27 controls	↑BTG in patients with impaired LAA function
Inoue et al., [42]	246 NV AF; 111 controls	↑BTG, NS in PF4
Nozawa et al., [69]	509 NV AF	BTG, PF4 did not predict thromboembolic events
Choudhury et al., [97]	121 NV AF; 65 healthy controls; 78 disease-matched controls	Similar but raised levels of CD62P, CD63 and sP-sel in AF and disease-matched controls compared with healthy controls
Choudhury et al., [82]	70 NV AF; 46 disease controls; 33 healthy controls	↑PMP and sP-sel in AF and disease controls, but AF not an independent determinant

Atrial fibrillation. V=valvular. NV=non-valvular. AFL=atrial flutter. BTG= β-thromboglobulin. PF4=platelet factor 4. sPsel=soluble P-selectin. mP-sel=matrix P-selectin. GPV=glycoprotein V. LAA=left atrial appendage. NS=non-significant. PMP=platelet microparticles.

Table 2. Studies of platelet function in atrial fibrillation [4] (with permission)

However, Nagao et al., [88] 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 perse. 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 [89-91]. 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 platelet activation seen in this arrhythmia could contribute to thrombogenesis indirectly. For example, increased expression of P-selectin on platelets associated with reduced concentrations of nitric oxide has also been shown to be a risk factor for silent cerebral infarction in patients with atrial fibrillation [92]. Moreover, raised amounts of P-selectin and CD63 have both been associated with the embolic and pre-embolic status of patients with non-rheumatic atrial fibrillation [93]. Or the prominent involvement of platelets in the pathogenesis of atherothrombotic (that is, non-cardiombolic) events [94].

2.3.5. Abnormal changes in fibrinolysis

Few studies have focused on fibrinolytic function in atrial fibrillation. Enhanced fibrinolysis, shown by increased concentrations of tissue-plaminogen activator (t-PA) antigen and t-PA inhibitor (PAI)-1 and reduced amounts of plasmin-antiplasmin complex can be attributable to a pathophysiological response to the prothrombotic state [95,66]. However, the available data are not consistent and conflicting results have also been reported [35]. In the Stroke Prevention in Atrial Fibrillation (SPAF) III study [99], increased concentrations of plasmin-antiplasmin complexes were independently associated with thromboembolic risk factors such as older age (>75 years), recent congestive heart failure, decreased fractional shortening, and recent onset of atrial fibrillation. A significant correlation can be also shown between t-PA amounts and left-atrial diameter in atrial fibrillation [35]. Predictably, anticoagulation leads to some improvement in fibrinolytic markers in rheumatic atrial fibrillation [98].

Increased amounts of t-PA and PAI-1 can indicate the coexistence of confounders, such as hypertension, heart failure, or ischaemic heart disease, all of which can cause endothelial dysfunction, damage, and inflammation. However, studies in patients with atrial fibrillation only confirm that presence of the disorder does modulate these markers. [35,95,99]. Thus, the high amounts of t-PA and PAI-1 in atrial fibrillation could be a consequence of endothelial damage and dysfunction or represent systemic inflammation [100,101]. PAI-1 concentrations are also predictive of successful cardioversion [102], and are independent predictors of the development of atrial fibrillation after cardiopulmonary bypass [103].

It is unclear whether increased amounts of t-PA or PAI-1 in atrial fibrillation are due to endothelial dysfunction, inflammation, fibrinolysis, or vascular disease, or a combination. Nevertheless, abnormal changes in the fibrinolytic system might relate not only to thrombogenesis but also to structural remodelling of the atria, in view of the strong links to extracellular matrix turnover.

2.3.6. Restoration of sinus rhythm

Some evidence suggests that activation of the coagulation system could be adversely affected by cardioversion of atrial fibrillation [104]. Electrical cardioversion has been associated with more prominent activation of the coagulation system than a pharmacological strategy [105]. One study found a positive correlation between the energy delivered for cardioversion to sinus rhythm and plasma D-dimer values on day 7 [105]. Additionally, an extended duration of atrial fibrillation could lead to a more prominent hypercoagulable state (estimated by D-dimer value) after cardioversion[106]. The hypercoagulable state after cardioversion has been seen despite optimum anticoagulation with warfarin [107]. Nevertheless, patients receiving therapeutic low-molecular-weight heparin (LMWH) before cardioversion seem to have reduced hypercoagulability [108].

2.4. What drives the prothrombotic state in atrial fibrillation?

Several mechanisms have been purported to drive then prothrombotic state in atrial fibrillation (figure 2), but recent evidence has focused on the potential role of inflammation and the release of various growth factors.

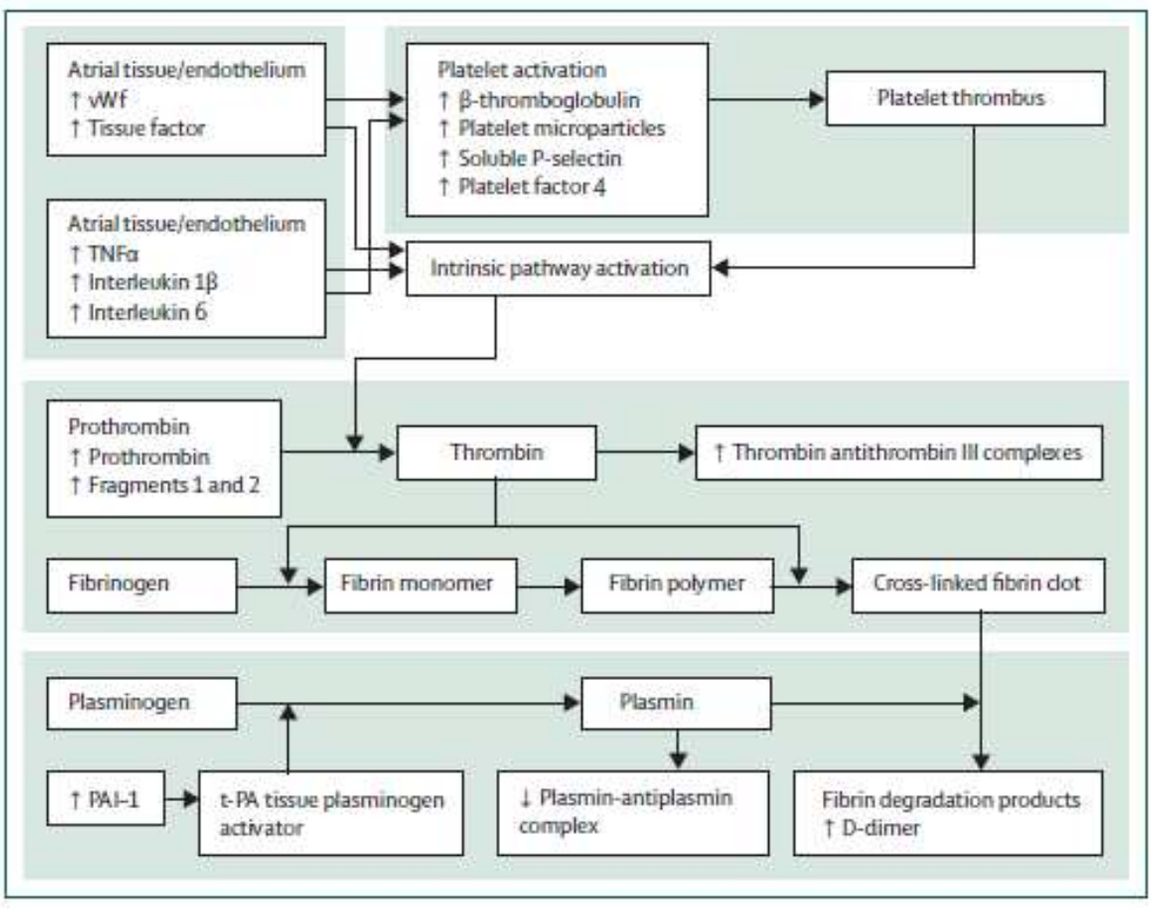


Figure 2. Abnormal changes in coagulation during atrial fibrillation [4] (with permission)

2.4.1. Inflammation

In atrial fibrillation, inflammation might not only result in endothelial damage, dysfunction, or activation, but also be linked directly to thrombogenesis. Increasing evidence has supported a link between inflammation and the initiation and perpetuation of atrial fibrillation [109-113]. Furthermore, abnormal changes in systemic inflammation have been related to prothrombotic indices in atrial fibrillation, suggesting that inflammation could drive the prothrombotic state in atrial fibrillation [109].

Although most cases of atrial fibrillation are associated with various comorbidities, many of which could also enhance the baseline inflammatory state, there may be an underlying direct link between atrial fibrillation and inflammation. Interleukin-6 concentrations are abnormal in atrial fibrillation, with some prognostic implications shown in one study [114]. Many studies have also shown that amounts of high-sensitivity C-reactive protein (hs-CRP) are greater in patients with atrial fibrillation than in controls in sinus rhythm, with a stepwise increase in hs-CRP with the transition from patient groups with an increasing burden (sinus rhythm to paroxysmal then persistent) in atrial fibrillation [115]. Raised hs-CRP amounts consistently correlate with cardiovascular risk, although not with future atrial fibrillation [109].More recently, high hc-CRP amounts were shown to be predictive of mortality and vascular death in atrial fibrillation, but not stroke itself [116].

How is inflammation linked to thrombogenesis in atrial fibrillation? Both CRP and interleukin 6 stimulate tissue factor production from monocytes in vitro [117, 118]. Furthermore, interleukin 6 increases platelet production and sensitivity to thrombin [119], stimulates transcription of fibrinogen [120], and is linked to both endothelial activation and damage [121,122]. However, no link seems to exist between hs-CRP and thrombin-antithrombin complexes [123]. Tissue factor and high stroke risk are also independent associates of interleukin 6, whereas fibrinogen and plasma viscosity are independent associates of hs-CRP amounts [124].

2.4.2. Growth factors

Another potential driver for thrombogenesis could be growth factors. Various pro-angiogenic factors have been identified; concentrations of some of these factors have been shown to alter in atrial fibrillation [70,125,126]. Vascular endothelial growth factor (VEGF) is largely produced by activated platelets [127], and results in upregulation of tissue factor mRNA production and subsequent expression of this compound on the endothelial membrane [128]. VEGF amounts are substantially increased in both persistent and permanent atrial fibrillation, with a corresponding increase in tissue factor [125]. Additionally, raised serum concentrations of transforming growth factor-β1[126] and angiopoetin 2 (but not angiopoetin 1) [70] are also recorded in atrial fibrillation, showing the depth and complexity of modulation of growth factor amounts.

Although the requirements for enhanced angiogenesis in atrial fibrillation are unknown, in view of the intimate association between VEGF and tissue factor, enhanced growth factors could be a crucial driving force behind the hypercoagulable state. Notably, tissue factor acts

as a cofactor to factor VIIa and is widely regarded as the physiological trigger to thrombin formation [129]. But, why are factors such as the angiopoietins involved? Angiopoeitin 1 and 2 are natural co-antagonists and both compete for the same binding site on Tie-2, an endothelial tyrosine kinase receptor. With an excess of angiopoeitin 1, stability of the endothelium is favoured, whereas the converse is true with an excess of angiopoeitin 2 [70]. In these circumstances, the balance could ultimately favour endothelial destabilisation and therefore the action of cytokines such as VEGF.

2.4.3. Extracellular matrix turnover

The relationship between atrial fibrillation and remodeling of the left atrium/arterial appendage is traditionally explained by the absence of contractility and altered flow dynamics. This hypothesis is not entirely fulfilling for several reasons, not the least of which is its inability to substantiate the mechanism of progressive structural change. A contemporary view considers the contribution of coagulation factors and thrombus substrate itself as both initiators and perpetuators of the prothrombotic environment that includes remodeling. Thrombin, a serine protease, beyond its widely recognized role in hemostasis and thrombosis, is directly involved in tissue repair and remodeling through an endothelial mesenchymal transdifferentiation process [130]. Thrombin also exerts an effect on endothelial cell junctions (reviewed in [131], endothelial cell and smooth muscle cell migration and smooth muscle cell proliferation via protease activated receptor (PAR)-1 [132].

Thrombin-induced membrane-type matrix metalloproteinase (MMP)-2 gene transcription and activity [133] may also contribute to structural changes in the atrium/atrial appendage, as may thrombin-augmented fibroblast-mediated collagen gel contraction [134]. Locally generated thrombin has been shown in tissue culture to upregulate tissue factor expression and activity [135].

While thrombin is known to possess a variety of cell regulating capabilities, one must not overlook the contribution

of other coagulation proteases in the remodeling process. Indeed, factor Xa has been shown to promote fibroblast proliferation, migration and differentiation into myofibroblasts through a PAR-2 specific mechanism [136]. Accordingly, the development of oral/direct factor Xa and thrombin inhibitors provides an unprecedented opportunity to investigate fundamental pathological mechanisms in atrial fibrillation.

2.4.4. Nitric oxide

Nitric oxide is synthesized by nitric oxide synthase, which is present in large concentrations in the endothelium. The expression of nitric oxide synthase is regulated by flow-mediated shear stress and is consequently downregulated at sites with low flow velocity [137]. Nitric oxide shows potent antithrombotic effects in arterial endothelium, and nitric oxide released from activated platelets inhibits platelet recruitment to the growing thrombus [138], while also inhibiting expression of PAI-1 [139].

In animal models of atrial fibrillation, the loss of atrial contraction and consequent reduction in shear stress seems to reduce LA expression of nitric oxide synthase with a corresponding decrease in nitric oxide bioavailability and increase in PAI-1 expression [140]. In the LAA, nitric oxide concentrations were also significantly reduced compared with control animals, but this finding did not indicate decreased expression of nitric oxide synthase at this site. Since atrial thrombus is frequently formed in the LAA, this finding still has no adequate explanation.

2.4.5. Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS is now appreciated as key to the pathophysiology of various cardiovascular disease states. The extent of these changes seems to relate predominantly to the reduction in angiotensin-II amounts. Atrial tissue has the capacity to produce and use this hormone with local expression of acetylcholinesterase and angiotensin-II receptors, both of which could be upregulated in atrial fibrillation [141]. RAAS could be mechanistically implicated in initiation and perpetuation of atrial fibrillation [141-143], as well as providing the link to other mechanisms promoting the prothrombotic state in atrial fibrillation.

Angiotensin II has been shown to possess several proinflammatory properties and increases the production of proinflammatory cytokines (eg, interleukin 6 and tumour necrosis factorα [TNFα]), adhesion molecules (eg, vascular-cell adhesion molecule 1), monocyte chemoattractant protein 1, and selectins (eg, P-selectin) [144-146]. Similarly, through release of various chemokines (eg, cytokine-induced neutrophil chemoattractant), angiotensin II can initiate neutrophil recruitment [146]. Expression of angiotensin-II receptors has also been linked with increased atrial cell death and leucocyte infiltration [147]. These data potentially support a complex relation between RAAS, inflammation, and atrial fibrillation.

Additionally, RAAS has been implicated in the activation of various MMPs and thromboxane A2 (a prothrombotic signalling molecule produced by activated platelets). These processes could occur both as a direct effect of angiotensin II and also through induction of interleukin 6 [148]. Furthermore, angiotensin II could accelerate degradation of nitric oxide through production of reactive oxygen species and thereby impair endothelium dependent vasodilatation [149]. Likewise, activation of RAAS increases synthesis of PAI-1, possibly indicating either enhanced endothelial damage or impaired fibrinolysis in atrial fibrillation [150].

3. Conclusion

The mechanisms underlying thrombogenesis in atrial fibrillation are clearly complex and remain only partly understood. Abnormal changes in flow, vessel wall, and blood constituents in atrial fibrillation fulfil Virchow's triad for thrombogenesis, and accord with a prothrombotic or hypercoagulable state in this arrhythmia. That this process is related purely to blood stasis is no longer accepted. Various abnormal changes related both to atrial fibrillation and its comorbidities impart a synergistic effect in maintaining a hypercoagulable state in this condition.

Author details

Hanan Ahmed GalalAzzam

Mansoura university/ Faculty of Medicine, Egypt

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