Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020

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ABSTRACT

Atrial fibrillation (AF) is characterised by an increased risk of pathological thrombus formation due to a disruption of physiological haemostatic mechanisms that are better understood by reference to Virchow's triad of 'abnormal blood constituents', 'vessel wall abnormalities' and 'abnormal blood flow'. First, there is increased activation of the coagulation cascade, platelet reactivity and impaired fibrinolysis as a result of AF per se, and these processes are amplified with pre-existing comorbidities. Several prothrombotic biomarkers including platelet factor 4, von Willebrand factor, fibrinogen, β-thromboglobulin and D-dimer have been implicated in this process. Second, structural changes such as atrial fibrosis and endothelial dysfunction are linked to the development of AF which promote further atrial remodelling, thereby providing a suitable platform for clot formation and subsequent embolisation. Third, these factors are compounded by the presence of reduced blood flow secondary to dilatation of cardiac chambers and loss of atrial systole which have been confirmed using various imaging techniques. Overall, an improved understanding of the various factors involved in thrombus formation will allow better clinical risk stratification and targeted therapies in AF.

INTRODUCTION

Disruption of normal haemostatic mechanisms can lead to pathological thrombus formation. The mechanism by which this occurs in atrial fibrillation (AF) is complex and multifactorial. Over a century ago, Rudolf Virchow described three main factors involved in thrombus formation as follows: (1) abnormal blood constituents; (2) vessel wall abnormalities and (3) abnormal blood flow.[1] This description, known as Virchow's triad, has withstood the test of time and may be useful to better understand the prothrombotic state in AF (figure 1).

Abnormal blood constituents (hypercoagulability)

Hypercoagulability is principally related to either activation of the coagulation cascade, increased platelet reactivity or impaired fibrinolysis. Each of these factors have been implicated in AF (table 1). In general, the most significant cause for a prothrombotic state relates to activation of the coagulation cascade for which thrombin is a necessary component. Therefore, the rate of thrombin generation may reflect the degree of thrombogenicity, and this can be derived from levels of thrombin-antithrombin complex (TAT) and prothrombin fragment F1 +2 (F1 +2). Other markers of hypercoagulability include von Willebrand factor (vWf) and fibrinogen, which are both directly involved in clot formation. In addition, D-dimer may be used as a marker of fibrin turnover, and platelet activation may be inferred from levels of P-selectin, platelet factor 4 (PF-4) and β-thromboglobulin. Raised tissue plasminogen activator (tPA) levels typically results from secondary fibrinolysis which occurs due to increased clot formation. However, in the presence of raised plasminogen activator inhibitor-1 (PAI-1), most tPA are bounded and remain inactive. Hence, high concentrations of both indices may also suggest impaired fibrinolysis.

Elevated levels of F1 +2 in patients with AF compared with sinus rhythm (SR) have previously been demonstrated.[2 3] Furthermore, patients with chronic AF have increased coagulation factors (factor VIII:C, vWf and fibrinogen), platelet activation (PF-4 and β-thromboglobulin) and secondary fibrinolysis (D-dimer and spontaneous amidolytic activity).[4 5] The introduction of warfarin normalised circulating D-dimer levels, suggesting that warfarin was effective in preventing excessive fibrin turnover. However, the use of warfarin had an apparent lack of effect on levels of fibrinogen and vWf, reinforcing the fact that warfarin does not influence the underlying pathological process in AF.[5] Importantly, the findings suggest that both these biomarkers may be used as a risk indicator for hypercoagulability even in anticoagulated patients with AF. Further clinical studies have confirmed that increased levels of vWF is associated with greater thromboembolic risk.[6 7]

Atrial fibrillation vs comorbidities

Many observational studies investigating the prothrombotic state in AF are confounded by group differences in baseline characteristics which are known to influence haemostasis. Therefore, despite well-defined increases in various prothrombotic indices among patients with AF, it remains unclear whether these are due to AF itself or pre-existing comorbidities.

A study evaluating patients with AF and no other major thromboembolic risk factors ('lone' AF) found that these patients had higher levels of PF-4, β-thromboglobulin, fibrinogen, vWf, D-dimer, tPA and PAI compared with age-matched and sex-matched healthy controls.[8] Lone AF has also been associated with increased levels of P-selectin.[9] Furthermore, Makowski *et al* proved that cardioversion of patients with lone AF resulted in a reduction of platelet reactivity after 4 weeks.[10] These studies suggest that the presence of AF alone is sufficient to promote a prothrombotic state.

In contrast, the Framingham Offspring Study found that higher levels of fibrinogen, vWf and tPA in patients with AF were the result of other cardiovascular risk factors.[11] Additionally, while increased

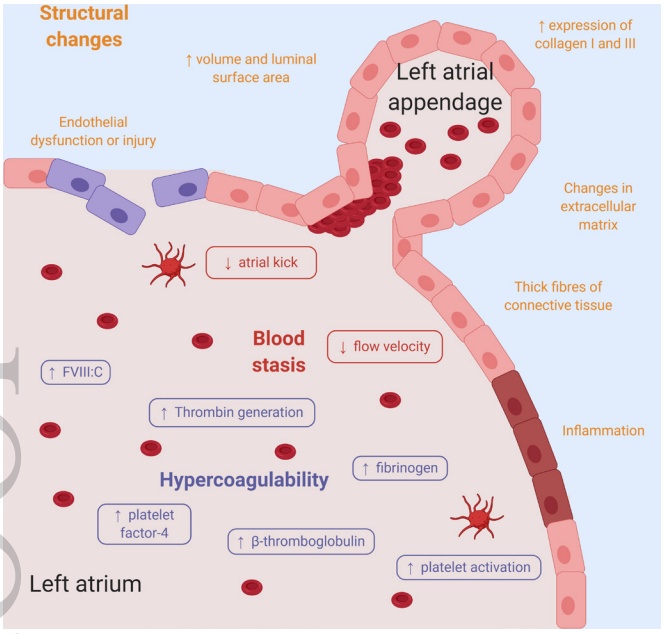

Figure 1 Effects of atrial fibrillation on the various elements of Virchow's triad.

platelet activation is evident in AF, these platelet indices may be accounted for by pre-existing comorbidities (eg, vascular disease).[12] A separate study reported no differences in platelet activation among patients with chronic AF compared with healthy controls, unless they suffered from concomitant diabetes mellitus.[13] However, over half the patients with AF were treated with warfarin which could have attenuated any negative effects of the arrhythmia.

Overall, it is likely that both AF and its associated comorbidities may contribute to a prothrombotic state. This is supported by a previous small study which suggested that successful cardioversion was associated with a significant reduction in selected prothrombotic biomarkers such as D-dimer, but not fibrinogen.[14] However, the effects may only be realised over time as the immediate period following cardioversion is often linked to an increased risk of thromboembolic events due to 'atrial stunning' induced by conversion of AF to SR.[15]

Threshold of AF duration

Having established the contribution of AF to a prothrombotic state, it is important to determine whether there is an arrhythmic threshold required for this to occur. There is limited research in this particular area.

New-onset acute AF of <48 hours was found to generate increased thrombogenesis at least up to 30 days later, despite no further AF recurrence.[16] Another case-controlled study demonstrated that 15 min of AF was sufficient to increase central platelet activation (P-selectin) and thrombin generation (TAT and F1 +2).[17] Akar *et al* found that this happened independent of changes in inflammatory markers (C reactive protein and interleukin-6), suggesting that there are other mechanisms involved. Overall, thrombogenesis may be impacted by the duration of AF per se, although this remains a controversial topic.

Central versus peripheral coagulability

Most studies in AF have focused on assessment of peripheral blood samples. However, as the majority of thrombus formation occurs in the left atrium (LA), specifically the left atrial appendage (LAA), these peripheral samples may not provide an accurate reflection of the prothrombotic state in AF.

Table 1 Effects of AF on hypercoagulability

Study	Study population	N	Relevant findings
Akar *et al*[17]	Paroxysmal AF undergoing catheter ablation	22	AF lasting up to 15 min was independently associated with increased local cardiac P-selectin, TAT complex and prothrombin fragment, and decreased nitric oxide production with no change in inflammatory markers.
Choudhury *et al*[12]	AF	221	Increased platelet adhesion in AF could be accounted for by pre-existing comorbidities. Antithrombotic use was associated with normalisation of platelet adhesion in AF.
Feng *et al*[11]	Community-based cohort	3577	Increased fibrinogen, vWf and tPA antigen in AF were due to concomitant cardiovascular risk factors.
Fu *et al*[9]	Idiopathic AF	90	Increased soluble P-selectin and fibrinogen.
Gustafsson *et al*[4]	Non-valvular AF with and without previous stroke	100	Increased vWf, factor VIII:C, fibrinogen, D-dimer, β-thromboglobulin, PF-4 and fibrinogen/antithrombin ratio.
Krishnamoorthy *et al*[6]	AF, attending outpatient clinics	423	Higher vWF and soluble E-selectin levels in AF were associated with greater risk of composite end point and ischaemic stroke.
Lim *et al*[18]	AF undergoing catheter ablation	87	Increased P-selectin and TAT complex in the left atrium compared with femoral vein.
Lip *et al*[5]	Chronic AF with and without anticoagulation	87	Increased fibrinogen, vWf and D-dimer. Warfarin use was associated with normalisation of D-dimer levels in chronic AF.
Lip *et al*[14]	AF with and without anticoagulation undergoing cardioversion	19	Maintenance of SR following cardioversion in non-anticoagulated AF was associated with decreased D-dimer but no change in fibrinogen. Maintenance of SR following cardioversion in anticoagulated AF was associated with no change in D-dimer or fibrinogen.
Makowski *et al*[10]	Lone AF undergoing cardioversion	36	Maintenance of SR was associated with decreased platelet reactivity as measured by mean fluorescence intensity of CD42b and CD62 on thrombin-stimulated platelets.
Marin *et al*[16]	First onset acute non-anticoagulated AF in whom SR was restored within 48 hours	96	AF lasting <48 hours was associated with increased soluble thrombomodulin, vWf and D-dimer. Successful cardioversion was not associated with changes in soluble thrombomodulin, vWf, D-dimer and echocardiographic indices.
Mondillo *et al*[8]	Lone permanent non-rheumatic AF	80	Increased PF-4, β-thromboglobulin, fibrinogen, vWf, D-dimer, tPA and PAI.
Pinto *et al*[7]	Chronic AF	373	Higher vWF levels in chronic AF were associated with greater ischaemic stroke risk.
Topcuoglu *et al*[3]	Lone AF with acute MCA ischaemic stroke	131	Increased F1 +2. Cardioembolic stroke secondary to AF or other causes was associated with increased TAT compared with those with an atherosclerotic cause.
Turgot *et al*[2]	Non-valvular AF with acute ischaemic stroke	75	Increased F1 +2 and reduced fibrinogen.
Yip *et al*[13]	Chronic non-valvular AF	82	Increased expression of CD62p but only in the presence of concomitant diabetes mellitus.

AF, atrial fibrillation; F1 +2, prothrombin fragment F1 +2; MCA, middle cerebral artery; PAI, plasminogen activator inhibitor; PF-4, platelet factor 4; SR, sinus rhythm; TAT, thrombin-antithrombin complex; tPA, tissue plasminogen activator; vWf, von Willebrand factor.

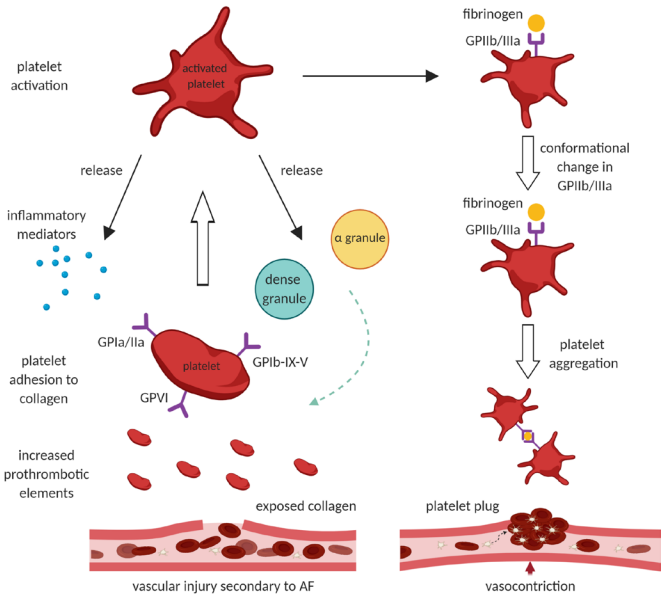

Figure 2 Interaction between vascular injury in atrial fibrillation and the initiation of clot formation in the presence of increased prothrombotic elements Figures are generated using BioRender.

Indeed, a relatively short duration of AF has been associated with increased platelet activation (P-selectin) within the coronary sinus but not in the femoral vein.[17] In addition, peripheral levels of P-selectin were similar between patients with lone AF, patients with AF and multiple comorbidities and controls, despite being markedly raised in the LA of patients from the two former groups.[18] Elevated levels of biomarkers relating to coagulation, fibrinolysis and fibrosis have also been shown in the LA compared with peripheral samples of patients with AF.[19]

Overall, central changes in thrombogenesis may precede those in the peripheral system, which may require a longer duration of AF to become manifest. Therefore, evaluation of prothrombotic biomarkers in blood samples from the LA may be more sensitive for detection of the hypercoagulable state in AF.

Role of platelet activation

Vascular injury in AF (described below) initiates primary haemostasis in the presence of increased prothrombotic elements resulting in vascular spasm, and platelet adhesion, activation and aggregation (figure 2). Rapid vascular spasm involving circular and occasionally longitudinal smooth muscle cells act to reduce blood flow to the area of injury while allowing other haemostatic mechanisms to operate. Despite much evidence to support the role of platelet activation in the prothrombotic state in AF,[4 8–10 17] there are conflicting results reported elsewhere.

In the study by Choudhary *et al*, there was no relation between platelet adhesion and stroke risk in AF, based on the $CHADS_2$ stroke risk scoring system.[12] A substudy from the Stroke Prevention in Atrial Fibrillation III trial also found that increased platelet activation, measured by β-thromboglobulin levels, was not associated with thromboembolism in AF.[20] Furthermore, no differences in biomarkers of platelet activity were demonstrated following acute cardioembolic stroke in patients with AF compared with age-matched and sex-matched healthy controls.[21] However, these studies were performed on peripheral blood samples and may not be reflective of conditions within the LA. Nonetheless, it is perhaps pathophysiologically unsurprising since the clinical use of antiplatelets for stroke prevention in AF has been shown to be ineffective[20] and inferior to oral anticoagulation therapy.[22]

Vessel wall abnormalities (eg, endothelial injury, structural changes)

Certain structural changes in the atria may predispose to the development of AF that subsequently promotes further remodelling.[23] Overall, these alterations contribute to the prothrombotic tendencies observed in AF through a variety of mechanisms (table 2). Histological examination of the LAA found that AF was associated with a significant increase in LAA volume and luminal surface area; reduction in pectinate muscle volume and surface area and marked endocardial thickening with fibrous and elastic tissue.[24] Combined with loss of atrial transport factor ('atrial kick'), these changes may promote abnormal blood stasis (discussed below). The exact relevance of a reduction in

Table 2 Effects of AF on structural changes

Study	Study population	N	Relevant findings
Boldt *et al*[26]	AF	118	Increased collagen I and III.
Climent *et al*[30]	Persistent AF undergoing DCCV	86	Reduced MMP-1. Maintenance of SR following cardioversion was not associated with a change in MMP-1 and TIMP-1.
Goette *et al*[38]	Persistent AF undergoing DCCV	60	Increased endothelial dysfunction as measured by ADMA.
Lim *et al*[18]	AF undergoing catheter ablation	87	Increased ADMA. Maintenance of SR following cardioversion was associated with normalisation of ADMA.
Marin *et al*[29]	Chronic non-anticoagulated AF	48	Reduced levels of MMP-1, and increased TIMP-1 and ratio of TIMP-1 to MMP-1 were due to the combined effects of AF and concomitant risk factors. There was an independent relationship between the MMP/TIMP system and prothrombotic state as assessed by F1 +2.
Masawa *et al*[25]	Cerebral embolism with and without AF (autopsy)	31	Changes in the left atrial endocardium including a granular and wrinkled appearance associated with oedematous and fibrous thickening; mural thrombi and endothelial denudation and thrombotic aggregations.
Nakamura *et al*[41]	Cardiogenic thromboembolism with non-valvular AF	7	Increased endothelial injury as assessed by over-expression of vWf.
Shirani and Alaeddini *et al*[24]	Chronic AF (autopsy)	46	Increased LAA volume, luminal surface area of the bisected LAA and endocardial thickening with fibrous and elastic tissue and reduced transected pectinate muscles.

F1 +2, prothrombin fragment F1 +2; ADMA, asymmetric dimethylarginine; AF, atrial fibrillation; DCCV, direct current cardioversion; LAA, left atrial appendage; MMP-1, matrix metalloproteinase-1; SR, sinus rhythm; TIMP-1, tissue inhibitor of matrix metalloproteinase-1; vWf, von Willebrand factor.

pectinate muscles in AF remains unclear, although it could be speculated that this may encourage thrombus dislodgement.

Masawa *et al* found that morphological changes of a 'rough' endocardium due to a granular and wrinkled appearance with oedematous and fibrous thickening was strongly associated with AF, as these changes were not apparent in those without the condition.[25] Furthermore, the authors demonstrated that the incidence of a rough endocardium was almost universally correlated to the presence of mural thrombi on microscopic investigations. Using, scanning electron microscopy, AF was also linked to increased areas of endothelial denudation and thrombotic aggregations in the LA.[25] The structural changes that occur in AF appears to provide a platform for microscopic thrombi formation that heralds thromboembolic events.

Atrial fibrosis

Extracellular matrix (ECM) is an extensive network of macromolecules (such as collagen, enzymes and glycoproteins) that has an important role in providing physical and biochemical support to surrounding cells. It is one of the most important regulators in cellular and tissue function. However, excessive deposition of ECM leads to fibrosis. A previous study showed AF was associated with LA fibrosis through increased expression of collagen types I and III.[26] This is relevant as LA fibrosis, assessed using late gadolinium enhancement MRI, has been independently linked to thrombus formation in the LAA.[27] In addition, animal models using CREM-transgenic mice which exhibits key characteristics of persistent AF, demonstrate a propensity for development of the arrhythmia and thrombus formation.[28]

Although the correlation of AF and atrial fibrosis is well-established, the underlying mechanisms are poorly understood. Furthermore, it is unclear whether atrial fibrosis is a cause or consequence of AF. However, the process by which atrial fibrosis occurs is likely to involve matrix metalloproteinase (MMP) and tissue inhibitor of matrix metalloproteinase (TIMP). MMPs are involved in the breakdown of ECM while the actions of MMPs are inhibited by TIMP. Therefore, any resultant changes on either of these proteins may negatively impact matrix degradation and promote fibrosis.

Marín *et al* demonstrated lower levels of MMP-1 and higher levels of TIMP-1 among patients with AF compared with controls.[29] However, the findings appeared to be driven by the combined effects of AF and other comorbidities. A major limitation of the study was the relatively short period from diagnosis of AF to enrolment. As a result, more marked abnormalities secondary to AF may not have had sufficient time to manifest. Nevertheless, a subsequent study by the same group found that despite lower levels of MMP-1 and comparable levels of TIMP-1 at baseline among patients with AF compared with healthy controls, maintenance of SR at 1 month following direct current cardioversion was not associated with any change in these variables compared with baseline.[30] In contrast, a systematic review and meta-analysis of 33 studies found that AF was associated with no difference in levels of circulating MMP-1 but elevated levels of atrial tissue MMP-1, circulating and atrial tissue MMP-2, and MMP-9, and reduced levels of circulating TIMP-2.[31] However, many of the included studies were subject to significant publication bias rendering the associations between MMP-2 and MMP-9 in AF uncertain.

Overall, although it is difficult to elucidate the exact effects of AF with its respective comorbidities on the MMP/TIMP system, it does appear that the arrhythmia contributes to atrial fibrosis via different pathways. Furthermore, the hypercoagulable state during AF may promote profibrotic and pro-inflammatory responses.[32]

Role of MMP/TIMP system in coagulation

In vitro studies using human vein and rabbit aorta to demonstrate that thrombin may contribute to the vascular response to injury by activation of latent MMP-2.[33] In return, MMPs may participate in clot formation via the coagulation cascade and platelet activation. A study involving chimeric mice found that inactivation of the MMP-2 gene resulted in hyporeactive platelets and a defective thrombotic response.[34] Furthermore, replacement of MMP-2 restored normal platelet and thrombotic functions. Falcinelli *et al* demonstrated that vascular injury was associated with a significant increase in MMP-2 released by activated platelets that potentiated further platelet activation.[35] Interestingly, aspirin did not influence the expression of MMP-2 despite suppression of serum thromboxane B2 and P-selectin.[35] The study by Marín *et al* further reinforces the link between the MMP/TIMP system and coagulation cascade.[29]

When considering this topic, it is important to recognise that there are various MMPs with potentially differing roles in clot formation. A systematic in vitro comparison of different MMPs under flow conditions demonstrated that inhibition of MMP-1 or MMP-2 suppressed platelet activation, whereas inhibition of MMP-9 or MMP-14 stimulated these processes.[36] Therefore, tight regulation of the MMP/TIMP system is necessary to maintain haemostasis and disruption of these physiological processes in AF may result in abnormal thrombus formation.

Endothelial dysfunction

In addition to the effects of endothelial dysfunction or injury as described above, there is a release of a variety of factors such as tissue factor, vWf and asymmetric dimethylarginine (ADMA) involved in clot formation. ADMA functions as an endogenous inhibitor of endothelial nitric oxide (NO) production and excess ADMA may contribute to endothelial dysfunction.[37] A previous

Table 3 Effects of AF on abnormal blood stasis

Author (ref)	Study population	N	Relevant findings
Ammash *et al*[46]	Non-valvular AF	514	The presence and intensity of spontaneous echo contrast in AF was directly related with levels of vWf antigen and activity which were independent predictors of LAA thrombus after adjustment for $CHADS_2$ score.
Black *et al*[44]	Non-valvular AF undergoing TOE	135	Spontaneous echo contrast in non-valvular AF was independently associated with increased haemotocrit, fibrinogen and LA dimension.
Markl *et al*[43]	AF	75	Complex haemodynamic changes in the LA and LAA including reduced peak and mean velocities, and increased flow stasis.
Vincelj *et al*[42]	Patients undergoing TOE	290	AF was associated with the presence of spontaneous contrast echo.
Wysokinski *et al*[47]	Non-valvular AF	151	Severe spontaneous contrast echo in AF was associated with increased soluble P-selectin.

AF, atrial fibrillation; LA, left atrial; LAA, left atrial appendage; TOE, trans-oesophageal echocardiography; vWf, von Willebrand factor.

study found that patients with AF had higher levels of ADMA compared with those in SR.[38] Furthermore, the normalisation of ADMA levels were observed at 24 hours after successful DCCV, suggesting a direct influence from AF itself. Lim *et al* demonstrated a stepwise increase in ADMA levels from controls to patients with lone AF to patients with AF and comorbidities.[18]

A study in porcine models demonstrated that AF was associated with marked reduction in endocardial NO synthase expression and a corresponding drop of NO levels that resulted in an increased expression of PAI-1 within the LA.[39] Elevated levels of PAI-1 may inhibit fibrinolytic activity, thereby promoting thrombus formation. Furthermore, NO has a role in the inhibition of platelet activation and recruitment.[40] Histological examination of the atria also revealed that AF was associated with overexpression of tissue factor and vWf in conjunction with endothelial injury.[41] The resultant effects on endothelial dysfunction from both AF and its comorbidities may promote a prothrombotic state.

Abnormal blood flow (eg, blood stasis)

Blood stasis is the final component of Virchow's triad that occurs as a direct result of AF and contributes to thrombus formation (table 3). Reduced blood flow within the atria may be seen on echocardiography as an echogenic, smoke-like, swirl (known as 'spontaneous echo contrast'). The incidence of this phenomenon is significantly increased in the presence of AF,[42] which causes sluggish flow to occur as a result of dilatation, increased fibrosis and loss of atrial systole. Use of MRI has demonstrated that AF results in reduced mean and peak LA velocities, and increased LA stasis.[43] Furthermore, these adverse effects extended to include the LAA and were more pronounced in patients with AF during their scan. There was also a graded, negative influence of the CHA_2DS_2-VASc score on these parameters.[43]

Effects of reduced blood flow

There are several mechanisms by which reduced blood flow may contribute to thrombus formation. Spontaneous echo contrast detected on trans-oesophageal echocardiogram in patients with AF was independently associated with increased haematocrit, fibrinogen concentration and LA dimension.[44] These changes may promote thrombus formation through erythrocyte aggregation and by providing fuel to the coagulation cascade.

Abnormal blood stasis in AF may also lead to a prothrombotic state by its effects on vWf. Under normal physiological conditions, vWf is rapidly degraded by ADAM metallopeptidase with thrombospondin type 1 motif 13 (ADAMTS13) into an inactive form. However, the actions of ADAMTS13 is flow-dependent[45] and hence reduced blood flow in AF may disrupt this regulatory process. It has been demonstrated that AF is associated with higher levels of vWf antigen and activity, and that there is a direct relationship between the degree of LA stasis and elevated vWf.[46] Furthermore, these biomarkers were associated with the presence and intensity of spontaneous echo contrast on trans-oesophageal echocardiography, and were independent predictors of LAA thrombus.[46]

In addition, reduced blood flow within the LA in patients with AF has been directly linked to P-selectin levels.[47] However, this effect was only evident for patients with severe blood stasis, as graded by spontaneous contrast echo.

Thromboembolism in atrial fibrillation

A prothrombotic state increases the risk of thrombus formation, thereby occlusion of blood vessels, and localised ischaemia or infarction. In addition to local thrombus formation, blood flow may also be affected by thrombus dislodgement from a distant site ('thromboembolism'). There are various sources from where this thrombus may originate. Although the presence of AF predisposes to thrombus formation in both the arterial and venous circulatory systems, it has traditionally been linked to complications predominantly within the arterial system. This is supported by a recent study demonstrating that while AF was independently associated with an increased risk of pulmonary embolism, the long-term risk of ischaemic stroke was more pronounced (HR 2.45 vs 1.72).[48] Reasons for this are not fully understood but may relate to possible intrinsic differences between the LA compared with the right atrium such as a reduced ability to activate protein C and lower expression of thrombomodulin,[49] both of which have anticoagulant properties. Furthermore, AF appears to be associated with cardiac chamber-specific responses in terms of platelet activation and aggregation,[50] and endothelial dysfunction.[39] The effects of AF on venous thromboembolism, and the temporal relationship between AF and thrombogenesis are discussed in the online supplementary.

CONCLUSION

The mechanisms contributing to a prothrombotic state in AF fulfils Virchow's triad of hypercoagulability, endothelial injury and abnormal blood stasis. Improved understanding of the various factors involved in thrombus formation will allow better clinical risk stratification and targeted therapies in AF. There remains much to be understood in this area.

Take home messages

- Atrial fibrillation (AF) and its associated comorbidities result in a prothrombotic state.
- Thrombogenesis in AF is linked to Virchow's triad of hypercoagulability, vessel wall abnormalities and blood stasis.
- Central changes of hypercoagulability precedes those in the peripheral system.
- Vessel wall abnormalities in AF are related to atrial fibrosis and endothelial dysfunction.
- Blood stasis occurs secondary to cardiac dilatation, increased fibrosis and loss of atrial systole.

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