Prothrombotic markers in atrial fibrillation: what is new?

See page 1741 for the article to which this Editorial refers

Atrial fibrillation is the commonest sustained arrhythmia[1,2]. Stroke and peripheral thromboembolism account for much of the mortality and serious morbidity associated with atrial fibrillation, and are common in all forms of atrial fibrillation. There is a 4–5% annual incidence of stroke in patients with non-rheumatic atrial fibrillation and 17% in patients with rheumatic atrial fibrillation. Furthermore, atrial fibrillation accounts for 15–20% of all ischaemic strokes[3,4]. Most strokes in atrial fibrillation are due to embolization of thrombus from the left atrium, particularly from the left atrial appendage[5]. Asymptomatic cerebral infarction may often be demonstrated using computerized tomography in patients with chronic atrial fibrillation, and thus the incidence of embolic stroke in chronic atrial fibrillation may be higher than previously recognised[5].

The mechanism by which atrial fibrillation increased this risk is unknown. Altered flow patterns in the atrial appendage are thought to be involved, but intravascular thrombosis at other sites often involves abnormalities of the endothelium or of the blood.

Several studies have investigated the possibility of the existence of a hypercoagulable state that could contribute to thromboembolism in atrial fibrillation (including the current study published in this issue by Lip et al[5]). Plasma levels of prothrombin fragment F1+2 and thrombin-antithrombin III are more frequently elevated in patients with atrial fibrillation and mitral stenosis than in patients with atrial fibrillation alone[8,9]. The circulating concentrations of von Willebrand factor, factor VIII, fibrinogen, D-dimer, beta-thromboglobulin and platelet factor 4 are significantly increased in patients with non-valvular atrial fibrillation compared to stroke patients in sinus rhythm and healthy controls[9,10], and left atrial thrombus is associated with raised peripheral blood levels of fibrinopeptide A and D-dimer, a degradation product of fibrinogen. However, it is uncertain to what extent each of the above factors contributes to thrombus formation in the fibrillating atrium.

These findings reflect thrombin-mediated fibrin formation and degradation of fibrinogen, respectively,
but do not inform us of the mechanism of thrombus formation. It is possible that stasis, a hypercoagulable state, and endothelial damage or dysfunction may all contribute to thrombus formation in atrial fibrillation.

Previous works focused on markers of hypercoagulability in certain groups of atrial fibrillation patients. No study to date has compared the thrombogenic risk in paroxysmal atrial fibrillation (PAF) with persistent and permanent atrial fibrillation patient groups and controls. The study in this issue\(^7\) has done just that and also assessed prothrombotic markers in the group with persistent atrial fibrillation before and after cardioversion. Furthermore this study also compared markers of endothelial cell dysfunction (von Willebrand factor), platelet activation (P-selectin) as well as an index of haemorrhology and a clotting factor (fibrinogen).

Von Willebrand factor has two primary roles in haemostasis. First, it functions in primary haemostasis by binding both to platelets via the glycoprotein (Gp) Ib platelet-surface receptor and to exposed subendothelial matrix via as yet poorly defined collagen type. This has the effect of bringing platelets into contact with exposed subendothelium and initiating the primary haemostatic process. It also mediates in platelet–platelet binding, von Willebrand factor is synthesized by endothelial cells and megakaryocytes and is either secreted constitutively or stored within the Weibel-Palade Bodies, from which it is secreted in response to injury, endothelial dysfunction or exposure to thrombin. Thrombin is known to induce the endothelium to express von Willebrand factor, and also to stimulate platelets and monocyte adhesion to the endocardium.

P-selectin is an endothelial cell surface glycoprotein, which may be of great importance in the early adhesion of leukocytes to the endothelium. Animal studies have also demonstrated increased expression of P-selectin and intercellular adhesion molecule-1 (ICAM-1) on left atrial appendage endothelium with pacing induced atrial fibrillation as early as 8 h\(^{11}\). In another study in the canine model, plasma nitrite and nitrate (Nox) levels were significantly decreased and the levels of P-selectin on platelets and of neutrophil/platelet conjugates were significantly increased after the onset of atrial fibrillation. In vitro experiments demonstrated that the inhibition of NO synthesis increased the expression of P-selectin on platelets. The irregular heart rate that is characteristic of atrial fibrillation appeared to blunt NO synthesis. The increased expression of P-selectin on platelets associated with the reduced NO levels was a risk factor for silent cerebral infarction in patients with atrial fibrillation\(^{12}\). Human fibrinogen is a large glycoprotein, which is an important determinant of both the rheological characteristics of blood flow and of platelet aggregability. Fibrinogen is also an essential component of the blood coagulation system, being the precursor of fibrin (by the action of thrombin). Thrombin is a central molecule in coagulation is also involved in inflammation. Notably, thrombin induces endothelial neutrophil adhesion, P- and E-selectin expression, and chemokine production.

However, upon activation of the endothelium with agonists such as thrombin, the Weibel-Palade bodies (which is the home of von Willebrand factor and P-selectin) fuse with the plasma membrane, and P-selectin is rapidly translocated to the endothelial cell, where it tethers circulating leukocytes and positions them for activation by endothelial-bound platelet activating factor\(^{13,14}\).

White et al\(^{15}\) showed that induced atrial fibrillation is accompanied by a substantial increase (up to 80%) in atrial pressure. In addition, it is well known that persistent atrial fibrillation is accompanied by a significant dilation of the atria. Increased atrial volume and/or filling pressures enhance atrial stretch, a condition that is associated with endothelial dysfunction\(^{16,17}\). Endothelial dysfunction plus changes in the flow pattern within the atria and its appendages result in stagnation and hence thrombin generation. Over 90% of atrial thrombi in non-valvular atrial fibrillation are situated in the left atrial appendage\(^{5}\).

It is thought that this is due to the relative stasis of blood that occurs at this site during the writhing and uncoordinated contractions that occur in the atria in atrial fibrillation. The predilection of thrombus formation to the left atrial appendage may be due to the fact that left atrial appendage is effectively a blind pouch with an irregular curved shape and a narrow orifice; also it is heavily trabeculated.

A previous report has demonstrated that the left atrial appendage area is larger in patients with an apparent left atrial appendage thrombus, whether they are in atrial fibrillation or sinus rhythm\(^{18}\). Similarly, it has been found in patients in atrial fibrillation or sinus rhythm, that reduced or absent left atrial appendage inflow and outflow velocities and a low left atrial appendage ejection fraction are associated with left atrial appendage ‘spontaneous contrast’ and thrombus formation\(^{18,19}\). Low peak left atrial appendage filling and emptying velocities have also been associated with a history of systemic embolism\(^{18,19}\).

Following cardioversion and restoration to sinus rhythm, atrial fibrillation patients exhibit depressed atrial mechanical function for a variable period of time; this is also reflected in left atrial appendage

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function. Left atrial appendage ‘spontaneous contrast’ and decreased inflow and outflow velocities have been shown to develop after successful cardioversion of atrial fibrillation\[18,19\]. This has important implications for prophylactic anticoagulant therapy administration in the post-cardioversion period. Several studies have shown that the left atrial appendage may also be a source of thrombus in patients in sinus rhythm\[18,19\]. The contribution of the endothelium to thrombus formation in the left atrial appendage is unknown. In a recent study\[20\] we have demonstrated that von Willebrand factor was significantly expressed in the atrial appendages in atrial fibrillation patients. The left atrial appendage with the highest levels of von Willebrand factor confirmed the predilection of thrombus to this site.

Randomized clinical trials have demonstrated that anticoagulation with warfarin results in a significant reduction in stroke rate and mortality in patients with atrial fibrillation. It is notable that in these trials anticoagulated patients were highly selected (in three of the North American warfarin–placebo trials, only about 10% were ultimately randomized). In those assigned to warfarin therapy, withdrawals occur at rates of up to 38% per year\[21\]. In warfarin-treated patients, approximately 50% of the strokes occurred in individuals who had inadvertent therapeutic lapses, or required temporary or permanent cessation of therapy\[21–23\] a finding that parallels experience in patients with valvular prosthesis\[24,25\].

More than 50% of the atrial fibrillation population is aged 75 or older\[23\] and it has been estimated that 20% or more have a contraindication to warfarin therapy\[26\]. This not only reflects under-prescribing of warfarin therapy to patients who are eligible, but also a high incidence of contraindications in patients who are at risk of thromboembolism. Thus, although warfarin is effective in reducing the incidence of stroke, in practice it is often difficult to treat patients continuously and effectively in the recommended manner. Therefore alternative forms of therapy are needed for the prophylaxis of thromboembolism in these patients. Furthermore, knowing which group is at high risk is also of great importance in planning management.

A study is therefore needed to assess the thromboembolic risk in the different groups of atrial fibrillation patients to help in planning their effective prevention.

The study of Li-Saw-Hee et al.\[7\] demonstrated for the first time that the three groups of atrial fibrillation (PAF, persistent and permanent) differ in their prothrombotic state. Permanent atrial fibrillation was associated with significantly high levels of the three markers studied (von Willebrand factor, P-selectin and fibrinogen), persistent with normal levels and PAF with normal levels of P-selectin but high levels of von Willebrand factor and fibrinogen.

These important findings have some differences when compared with previous studies. The difference could be due to the type of markers chosen, or the duration of atrial fibrillation or even the number of patients studied. This study has the advantage that the markers chosen could not be affected by prior usage of warfarin therapy or aspirin as is the case in previous studies\[27,28\]. On the other hand in the study of Li-Saw-Hee et al.\[7\], despite what could be a short duration of follow-up after cardioversion (3 months) in persistent atrial fibrillation, the return of atrial systole and the lack of changes in the prothrombotic state following cardioversion are an indication of normalization of atrial function.

There are conflicting reports on the risk of thromboembolism after cardioversion. Some workers reported an increase in the prothrombotic state after cardioversion. This is thought to be related to left atrial mechanical dysfunction following cardioversion, which may result in stasis\[29,31\]. One study suggested\[32\] early activation of haemostatic indices even after pharmacological cardioversion, while another\[33\] reported an improvement in the levels of fibrin D-dimer following successful cardioversion. However, the latter study could be affected by the concomitant intermittent usage of heparin or warfarin.

The ‘normal’ levels of indices of endothelial dysfunction and platelet activation compared to controls in persistent atrial fibrillation reported by Li-Saw-Hee et al.\[7\] is intriguing. It is difficult to know whether the duration of atrial fibrillation, the small number of patients studied or the lack of other cardiovascular risk factors could have influenced these results. Duration of atrial fibrillation has an important effect on the prothrombotic state\[34\]. However, even atrial fibrillation of short duration, such as 48 h could increase the thromboembolic risk. We do not know whether the study by Li-Saw-Hee et al.\[7\] have other cardiovascular risks, which could influence their results. Although this information might be available, it is difficult to separate the effects because of the small number of patients studied in each group. The results reported by Li-Saw-Hee et al.\[7\] may suggest that patients with persistent atrial fibrillation and low baseline levels of prothrombotic markers have a low risk of thromboembolism post-cardioversion. However, a large study is needed to address these important findings, as it will have an important clinical implication.

It is also difficult (as stated by authors) to quantify the duration and frequency of PAF as many of the
patients could have asymptomatic paroxysms and it is often impossible to time precisely the first episode with PAF.

Transoesophageal echocardiography was not used in Li-Saw-Hee et al."s[7] study. If transoesophageal echocardiography had been used this might have given a different picture in that there may have been an echo contrast or ‘smoke’ in the left atrial or left atrial appendage prior to or post cardioversion, which would have reflected local activation of haemostatic factors. However, the authors aim was the correlation between improvement of left atrial function and the changes in the prothrombotic markers. In contrast, none of the previous studies have related changes in haemostatic markers to the return of atrial systole and this study is of value in this regard.

Nevertheless this study has confirmed the presence of a hypercoagulable state in patients with permanent atrial fibrillation who are fully anticoagulated with warfarin (2.0–3.0).

One previous study suggested that patients with PAF associated with intermediate levels of thrombogenic risks between chronic atrial fibrillation and sinus rhythm[35], while another suggested that PAF might have a similar risk to chronic atrial fibrillation, especially if associated with risk factors[36]. However, the finding by Li-Saw-Hee et al."[7] that PAF resulted in high levels of von Willebrand factor and fibrinogen but not P-selectin suggests that the haemodynamic effect of PAF is related to haemorheology and endothelial dysfunction rather than platelet activation, an important finding if confirmed in a large study.

Finally, despite the small number of patients studied in each group, this study is important because it is the first to investigate three groups of atrial fibrillation as well as control subjects in one study. Furthermore, this study has found a hypercoagulable state in both PAF and permanent atrial fibrillation, an important clinical finding, especially in the case of permanent atrial fibrillation as ‘this was present despite adequate therapy with warfarin’. If these findings are reproduced in a large study it will have important clinical implications in planning the long-term management of these patients.

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References

Electron beam CT scanning: finding more than calcium

See page 1748 for the article to which this Editorial refers

There is nothing quite like the prospect of getting something for nothing to arouse interest. The article by Hunold et al.[1] therefore deserves close scrutiny.

The first prototype computed tomography scanner was installed in 1972, at the Atkinson Morley Hospital in London, developed by Sir Godfrey Hounsfield. This machine started an era of imaging that now allows high-resolution three-dimensional data from humans to be analysed in exquisite detail. Acquisition of data from humans to be analysed in exquisite detail.

Because of the frequently unheralded nature of acute coronary syndromes, the detection of coronary plaque that is not flow limiting, but is vulnerable to rupture or erosion is an important but as yet unattainable goal. Detection and quantification of calcified coronary atheroma may be a first step, for while such atheroma may act as a marker for other more active lesions.

A patient having an electron beam tomography scan for coronary calcium simply lies in the scanner, and scans are triggered by the patient’s electrocardiogram. Intravenous contrast is not given. The scanner acquires a series of 3 mm thick datasets sequentially from the level of the left pulmonary artery down to the diaphragm. This dataset can be reconstructed to give tomograms of a range of diameters. When assessing coronary calcium a 26 cm field of view is employed, but the raw data can be used to generate a larger diameter image to encompass the entire lower two thirds of the thorax with no additional scanning required. In order to optimally visualize the coronary arteries and calcification (and the rest of the mediastinum) it is usual to review the images on a fairly narrow window setting (e.g. a level of 0 or 50

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