Plasma von Willebrand factor, fibrinogen and soluble P-selectin levels in paroxysmal, persistent and permanent atrial fibrillation

Effects of cardioversion and return of left atrial function


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Background Atrial fibrillation is associated with increased risk of stroke and thromboembolism, possibly by conferring a prothrombotic or hypercoagulable state. However, it is unclear whether or not this differs in the clinical subgroups of chronic atrial fibrillation patients, that is, in those with paroxysmal, persistent or permanent atrial fibrillation. We therefore hypothesized that: (i) there are differences in the prothrombotic state between these patients; and (ii) reduction in indices of hypercoagulability would follow elective electrical cardioversion of persistent atrial fibrillation and the return of left atrial function.

Patients and Methods We studied 69 patients with chronic atrial fibrillation: 23 with paroxysmal atrial fibrillation (16 males; mean age 65 years ± SD 13); 23 with persistent atrial fibrillation (16 males; 65 years ± 13), with a mean duration of atrial fibrillation of 3 months (range 2 to 6 months); and 23 with permanent atrial fibrillation (16 males; 67 years ± 10). Blood results were compared to 20 age- and sex-matched healthy controls. The patients with persistent atrial fibrillation then underwent elective DC cardioversion, with Doppler echocardiographic examinations and bloods tests performed prior to cardioversion, and at 3 and 12 weeks afterwards. The prothrombotic state was quantified by measurement of plasma levels of fibrinogen, soluble P-selectin (an index of platelet activation) and von Willebrand factor (a marker of endothelial dysfunction).

Results Permanent atrial fibrillation was associated with significantly raised levels of von Willebrand factor ($P=0.0067$) and fibrinogen ($P=0.0001$) but not soluble P-selectin ($P=0.472$); and persistent atrial fibrillation with normal levels of fibrinogen, von Willebrand factor and soluble P-selectin when compared to healthy controls (all $P=ns$). Stepwise multiple regression analyses demonstrated that the presence of atrial fibrillation was an independent predictor of abnormal von Willebrand factor, fibrinogen and soluble P-selectin levels. Electrical cardioversion of the patients with persistent atrial fibrillation did not significantly alter levels of von Willebrand factor ($P=0.766$), soluble P-selectin ($P=0.726$) or fibrinogen ($P=0.50$) despite maintenance of sinus rhythm and a significant return of left atrial systolic function (as quantified by the presence of A wave on Doppler echocardiography) at 3 months.

Conclusion There were significant differences in the prothrombotic state when patients with paroxysmal and permanent atrial fibrillation are compared to matched patients with persistent atrial fibrillation or controls in sinus rhythm. Cardioversion of persistent atrial fibrillation did not significantly alter indices of hypercoagulability even after 3 months maintenance of sinus rhythm, despite the return of atrial systole.

Key Words: Atrial fibrillation, electrical cardioversion, haemostatic markers, left atrial function.
Introduction

Atrial fibrillation is associated with increased risk of stroke and thromboembolism\(^{10}\), but these patients are unlikely to be a homogeneous population. For example, one proposed clinical definition of atrial fibrillation divides these patients into acute-onset and chronic atrial fibrillation; the latter are further divided into paroxysmal and sustained\(^{11,2,3}\). Sustained atrial fibrillation is further divided into persistent and permanent atrial fibrillation. Paroxysmal atrial fibrillation is episodic atrial fibrillation occurring intermittently and usually spontaneously terminating within 48–72 h, whist persistent atrial fibrillation is sustained atrial fibrillation that can be successfully cardioverted, and permanent atrial fibrillation is sustained atrial fibrillation that is either resistant to, or not appropriate for, cardioversion\(^{2,3}\). The differentiation between these clinical categories is dependant upon the history given by the patient, ECG documentation of the current episode and the duration of the last episode of atrial fibrillation. Although this classification is helpful, there is considerable inter- and intra-patient variability in the temporal pattern or atrial fibrillation episodes and therapy must thus be individualized. It is nevertheless still unclear whether there is a difference in thromboembolic risk between these patient subgroups.

Cardioversion of atrial fibrillation, especially if persisting >48 h, is known to be associated with cerebral, systemic and pulmonary embolic events, which are minimized by warfarin\(^{11,2,3}\). Nevertheless, the mechanism and pathogenesis of thromboembolic episodes after restoration of sinus rhythm in these patients is not wholly understood. Part of the mechanism is thought to arise as a result of stasis caused by the delayed return of atrial systole and left atrial mechanical dysfunction or ‘sunning’ caused by the switch to sinus rhythm after long-standing atrial fibrillation, following cardioversion (even in the absence of atrial thrombus)\(^{6,7}\). There is some evidence that the prothrombotic state associated with atrial fibrillation might be involved in contributing towards the risk of thromboembolism following cardioversion, but reports are conflicting. For example, Oltrona et al.\(^{9}\) suggested that there was early activation of a haemostatic mechanism soon after cardioversion, with an increase in fibrinopeptide A and thrombin-antithrombin complex levels. This is in contrast to the findings by Lip et al.\(^{9}\) who found a significant reduction in plasma fibrin D-dimer levels at 14 days after cardioversion of atrial fibrillation patients without prior oral anticoagulant therapy.

We hypothesized that: (i) there are differences in the prothrombotic or hypercoagulable state between patients with paroxysmal, persistent and permanent non-valvular atrial fibrillation; and (ii) changes in indices of hypercoagulability following elective electrical cardioversion of patients with persistent atrial fibrillation may be related to return of left atrial function (A waves on Doppler study). We measured plasma von Willebrand factor (a marker of endothelial cell dysfunction\(^{10}\)), fibrinogen (an index of haemorheology and a clotting factor\(^{11,13}\)) and soluble P-selectin (an index of platelet activation\(^{12}\)) as these three markers are not affected by full oral anticoagulation with warfarin (INR 2·0–3·0) prior to cardioversion. Furthermore, these markers are not affected by prior aspirin usage\(^{11,14}\).

Patients and Methods

Over a period of 4 months, we initially recruited 43 consecutive patients with persistent atrial fibrillation who underwent elective DC cardioversion. Persistent atrial fibrillation was defined electrocardiographically on at least two occasions, either at hospital or outpatient clinic review and again prior to elective DC cardioversion, at least 6 weeks apart. All patients were fully anticoagulated (target INR 2·0–3·0) for a minimum of 3 weeks pre-cardioversion and for 3 months post-cardioversion. All were treated with either sotalol or amiodarone to maintain sinus rhythm post-cardioversion. Only 23 patients (mean age 65 years, SD 13) completed the study and remained in sinus rhythm at the 3 month visit, which we decided to use as our (very) strict definition of persistent atrial fibrillation for this study, that is, patients who could be successfully cardioverted and could be maintained in sinus rhythm. The other 20 patients were totally excluded from the present analysis, either because the procedure was unsuccessful or they had reverted back to atrial fibrillation within 3 months.

These 23 patients with persistent atrial fibrillation were age- and sex-matched with 23 patients with paroxysmal atrial fibrillation, who were defined as patients with documented paroxysms of atrial fibrillation lasting ≥10 beats on 24 h Holter monitoring, and 23 other patients with permanent atrial fibrillation, where atrial fibrillation was present for ≥1 year and cardioversion was considered inappropriate or was previously unsuccessful. These 23 patients with persistent atrial fibrillation were an entirely separate group from the initial 43 patients undergoing cardioversion. All patients with permanent atrial fibrillation and 16 (out of 23) patients with paroxysmal atrial fibrillation were fully anticoagulated with dose-adjusted warfarin achieving an International Normalized Ratio (INR) of 2·0–3·0. Exclusion criteria were other acute causes of atrial fibrillation (for example, thyrotoxicosis, pneumonia or other infections), acute cardiovascular or cerebrovascular events (myocardial infarction, congestive heart failure, stroke, etc.) occurring within 3 months, valvular heart disease (that is, we only studied non-valvular atrial fibrillation), malignancy, connective tissue disease, infectious or inflammatory conditions and chronic renal/hepatic disease.

Healthy control subjects were drawn from among healthy hospital staff and from those who were attendees at hospital for hernia repair, varicose veins or minor operations. All were free of diabetes, and were without
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any signs or symptoms of cardiovascular, cerebrovascular, neoplastic or connective tissue disease. The project had the approval of the research Ethics Committee of the West Birmingham Health Authority and written informed consent was obtained from each participant.

**Echocardiography**

Echocardiographic examinations were performed immediately prior to the procedure, and at 3 and 12 weeks after successful cardioversion. All measurements were made during quiet respiration with the patient lying in the left lateral position. Transthoracic echocardiographic two-dimensional imaging and guided pulsed wave Doppler recordings were obtained using a Hewlett-Packard Sonos 100 echocardiography machine (Hewlett-Packard, Arondale, U.S.A.) with a 2.5 MHz phased array transducer. Transmitral Doppler inflow velocities were recorded from the apical four-chamber view with the sample volume positioned between the tips of the mitral leaflets. Peak velocities of early fillings (E) wave and atrial filling (A) wave were determined and reported in cm.s⁻¹. The inter- and intra-observer variability was <5% for these measurements.

**Laboratory**

Citrated plasma was obtained from venous blood by centrifugation at 2500 rpm for 15 min at 4 °C. Aliquots were stored at −70 °C to allow batch analysis. Soluble P-selectin and von Willebrand factor were measured by ELISA using commercial reagents (R&D Systems, Abingdon, U.K. and Dako-Patts, Ely, U.K.). The unit for von Willebrand factor is IU . dl⁻¹ and was standardized by reference to von Willebrand factor from the National Institute for Biological Standards and Controls, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, U.K. Other indices (units: ng . ml⁻¹) were standardized by recombiant product supplied by the manufacturer. Intra-assay coefficients of variation for all ELISA assays were <5%, inter-assay variances were <10%. Plasma fibrinogen (g . l⁻¹) was measured by the Clauss technique on a Pacific Haemostasis (Hunterville, N Carolina, U.S.A.) coagulometer with bovine thrombin from Alpha Laboratories (Eastleigh, Hants, U.K.).

**Statistical analysis**

Results are expressed as mean ± standard deviation (SD) or median (IQR, interquartile range). Data between patients and controls was analysed by t-testing and one-way ANOVA or the Mann–Whitney U test and Kruskal–Wallis test, with Tukey’s post-hoc analysis, as appropriate. Sequential data pre- and post-cardioversion were analysed by Friedman’s repeated measures analysis of variance. Correlations were performed by Spearman’s rank correlation method. Stepwise multiple regression analyses were performed to determine independent predictors for plasma soluble P-selectin, von Willebrand factor and fibrinogen levels, using age, sex, left atrial size, left ventricular dimensions (diastole, systole), presence of underlying medical disease, smoking status and the presence of atrial fibrillation. All statistical calculations were performed on a microcomputer using a commercially available statistical package (Minitab release 11, Minitab Inc, PA, U.S.A.). A value of P<0·05 was considered significant in all statistical analyses.

**Results**

**Clinical characteristics**

We studied 69 patients with chronic non-valvular atrial fibrillation: (i) 23 had paroxysmal atrial fibrillation (16 males; mean age 65 years, SD 13); (ii) 23 had persistent atrial fibrillation (16 males; mean age 65 years, SD 13), with a mean duration of atrial fibrillation of 3 months (range 2 to 6 months); and (iii) 23 had permanent atrial fibrillation (16 males; mean age 67 years, SD 10). The patients with paroxysmal atrial fibrillation were in sinus rhythm at the time of study. These patients were compared to 20 age- and sex-matched healthy controls in sinus rhythm (Table 1). At the 3-month follow-up visit after cardioversion, all of the patients with persistent atrial fibrillation were in sinus rhythm, and no thromboembolic episodes had occurred. Patient demography and associated medical conditions are summarized in Table 1. There were no significant differences in mean age, sex ratio, or smoking status between atrial fibrillation patients and controls.

**Cross-sectional analyses**

There were no significant differences in mean age, sex ratio, associated medical history and echocardiographic parameters (left atrial size, left ventricular dimensions and fractional shortening) between patients with paroxysmal, persistent and permanent atrial fibrillation. Permanent atrial fibrillation was associated with significantly raised levels of von Willebrand factor, fibrinogen and soluble P-selectin compared to patients with persistent and paroxysmal atrial fibrillation, and controls (Tukey’s post-hoc analysis, all P<0·001). Patients with paroxysmal atrial fibrillation had significantly elevated levels of plasma von Willebrand factor and fibrinogen (Tukey’s post-hoc analysis, von Willebrand factor P=0·0067 and fibrinogen P=0·0001) but not soluble P-selectin levels (P=0·472), when compared to controls. Patients with persistent atrial fibrillation had similar
Table 1  Demographic data for patients with atrial fibrillation and healthy controls in sinus rhythm

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Paroxysmal AF</th>
<th>Persistent AF</th>
<th>Permanent AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>20</td>
<td>23</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>63 ± 9</td>
<td>65 ± 13</td>
<td>65 ± 13</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>Males/females</td>
<td>17:3</td>
<td>16:7</td>
<td>16:7</td>
<td>16:7</td>
</tr>
<tr>
<td>Left atrial diameter (cm)</td>
<td>—</td>
<td>3.7 ± 0.8</td>
<td>4.0 ± 0.7</td>
<td>4.2 ± 0.8</td>
</tr>
<tr>
<td>Left ventricular diastolic dimension (cm)</td>
<td>—</td>
<td>5.0 ± 0.4</td>
<td>5.0 ± 0.5</td>
<td>5.2 ± 1.0</td>
</tr>
<tr>
<td>Left ventricular systolic dimension (cm)</td>
<td>—</td>
<td>3.9 ± 0.4</td>
<td>3.7 ± 0.7</td>
<td>4.0 ± 1.0</td>
</tr>
<tr>
<td>Left ventricular function FS (%)</td>
<td>—</td>
<td>25.8 ± 7.9</td>
<td>21.6 ± 5.2</td>
<td>24.4 ± 9.4</td>
</tr>
</tbody>
</table>

Numbers, except for age and echocardiographic data, expressed as mean ± SD.

A history of hypertension is defined as a physician-confirmed diagnosis, based on recorded untreated blood pressure of >160/95 mmHg on ≥2 occasions, and/or concomitant treatment with antihypertensive agents. A history of ischaemic heart disease is based on previous documented myocardial infarction or angina, abnormal coronary angiography or revascularization procedure (angioplasty or coronary artery bypass surgery). Previous stroke and diabetes are defined using standard criteria and have been documented in clinical records by a specialist physician.

Table 2  Indices of thrombogenesis in patients with atrial fibrillation and healthy controls in sinus rhythm

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Paroxysmal AF</th>
<th>Persistent AF</th>
<th>Permanent AF</th>
<th>P value (ANOVA or Kruskal–Wallis test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble P-selectin (ng . ml⁻¹)</td>
<td>34 (30–46)</td>
<td>36 (32–44)</td>
<td>51 (37–63)</td>
<td>210 (162–284)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>von Willebrand factor (IU . dl⁻¹)</td>
<td>101 ± 30</td>
<td>130 ± 34</td>
<td>106 ± 26</td>
<td>143 ± 47</td>
<td>0.018</td>
</tr>
<tr>
<td>Fibrinogen (g . l⁻¹)</td>
<td>2.5 ± 0.6</td>
<td>3.3 ± 0.7</td>
<td>2.7 ± 0.8</td>
<td>3.1 ± 0.9</td>
<td>0.077</td>
</tr>
</tbody>
</table>

All indices expressed as mean ± SD except for soluble P-selectin (median, IQR).

One-way ANOVA for von Willebrand factor and fibrinogen levels, with Tukey’s post-hoc analysis; Kruskal–Wallis test for soluble P-selectin levels, with Tukey’s post-hoc analysis after log-transformation.

levels of plasma fibrinogen, von Willebrand factor and soluble P-selectin, when compared to controls (Tukey’s post-hoc analysis, all P=ns) (Table 2).

Effect of elective DC cardioversion of patients with persistent atrial fibrillation

There were no significant changes in the three markers studied despite successful DC cardioversion and maintenance of sinus rhythm at 3 months (Friedman’s repeated measures ANOVA, soluble P-selectin P=0.726, von Willebrand factor P=0.766, fibrinogen P=0.500) (Table 3). There was a return of atrial contractility using Doppler echocardiography, as shown by the progressive increase in A wave velocity (Friedman’s repeated measures ANOVA, P<0.0001).

Correlations between haemostatic markers and atrial function

There were no significant correlations between the change in von Willebrand factor, fibrinogen or sPsel levels, and the change in Doppler A wave velocity (all P=ns) in the patients who were cardioverted. There was a significant correlation between the change from baseline to week 3 in plasma fibrinogen and von Willebrand factor levels (r=0.599, P<0.05). There were no other significant correlations between the change in various measured indices and the change in Doppler parameters between baseline and weeks 3 or 12 (P=ns, data not shown).

Stepwise multiple regression analyses

Using stepwise multiple regression analysis, independent predictors for plasma soluble P-selectin levels were the presence of atrial fibrillation (R²=53.6), which interacted with the left ventricular fractional shortening (R² for both=57.7). Similarly, stepwise multiple regression analysis demonstrated that the presence of atrial fibrillation (R²=17.2) was the only independent determinant of von Willebrand factor levels, whilst atrial fibrillation (R²=7.51) interacting with associated cardiovascular disease (R² for both=13.4) were independent predictors for plasma fibrinogen levels (all P<0.05).
Table 3  Levels of von Willebrand factor, fibrinogen, soluble P-selectin and Doppler echocardiography in patients with persistent atrial fibrillation following successful DC cardioversion

<table>
<thead>
<tr>
<th></th>
<th>Pre-cardioversion</th>
<th>3 weeks post-cardioversion</th>
<th>3 months post-cardioversion</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble P-selectin (ng . ml⁻¹)</td>
<td>51 (37-63)</td>
<td>45 (37-76)</td>
<td>52 (34-80)</td>
<td>0·726</td>
</tr>
<tr>
<td>von Willebrand factor (IU . dl⁻¹)</td>
<td>106 ± 26</td>
<td>104 ± 33</td>
<td>115 ± 25</td>
<td>0·766</td>
</tr>
<tr>
<td>Fibrinogen (g . l⁻¹)</td>
<td>2·7 ± 0·8</td>
<td>2·8 ± 0·7</td>
<td>2·5 ± 0·8</td>
<td>0·500</td>
</tr>
<tr>
<td>Doppler echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A waves (cm . s⁻¹)</td>
<td>0</td>
<td>0·58</td>
<td>0·85</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>E waves (cm . s⁻¹)</td>
<td>0·6 (0·53-1·24)</td>
<td>0·69 (0·53-1·09)</td>
<td>0·90 (0·53-1·24)</td>
<td>0·420</td>
</tr>
</tbody>
</table>

(All indices expressed as mean ± SD, except for soluble P-selectin, A and E waves (median, IQR) Friedman’s ANOVA for pre-, 3 weeks and 3 months post-cardioversion.)

Discussion

This study is limited by its cross-sectional nature, but demonstrates that abnormalities in the prothrombotic or hypercoagulable state may be present in permanent and paroxysmal atrial fibrillation, rather than in patients in persistent atrial fibrillation. Using stepwise multiple regression analyses, atrial fibrillation also emerged as an independent determinant of plasma soluble P-selectin, von Willebrand factor and fibrinogen levels. Some studies have demonstrated an improvement of indices of thrombogenesis after successful cardioversion, but have been confounded by concomitant intermittent usage of heparin or warfarin that influences some markers, such as fibrin D-dimer. In the present study, we have examined the effect of electrical cardioversion on the other two aspects of the prothrombotic state in atrial fibrillation, namely endothelial dysfunction (von Willebrand factor) and platelet activation (soluble P-selectin), and have chosen markers that are not significantly influenced by warfarin or aspirin.

Nevertheless, a longer period of follow-up in sinus rhythm may be required before any significant changes in these markers are seen, but by 3 months we would have expected normalization of abnormal indices since atrial systole had fully returned. We do accept that these markers may also reflect more generalized vascular disease, heart disease or hypertension, rather than atrial fibrillation per se, although previous work has shown that the prothrombotic state in atrial fibrillation is independent of underlying structural heart disease or aetiology (as reviewed by Lip), and our patient subgroups were broadly comparable with respect to underlying aetiology and echocardiographic data. Finally, we did not perform transoesophageal echocardiography in our patients with persistent atrial fibrillation prior to electrical cardioversion, but looked, in particular, for spontaneous echocontrast, as the main aim of our study was to correlate the improvement of left atrial function with the changes in prothrombotic markers. In view of the small numbers studied, quantification of the duration and frequency of paroxysms of atrial fibrillation in patients with this condition was not an objective of this study.

Atrial fibrillation is associated with a significant morbidity and an increased risk in thromboembolic stroke. Our study confirms the presence of abnormal haemorheology, platelet activation and endothelial dysfunction in patients with permanent atrial fibrillation who had been fully anticoagulated with warfarin (achieving INR 2.0–3.0) with significantly elevated levels of fibrinogen, soluble P-selectin and von Willebrand factor, respectively. Our patients with paroxysmal atrial fibrillation also exhibited similar abnormal levels of fibrinogen and von Willebrand factor, but not soluble P-selectin, suggesting that the haemodynamic effects of paroxysmal atrial fibrillation (as opposed to persistent atrial fibrillation) does not result in (statistically) significant platelet activation, and that the prothrombotic state in paroxysmal atrial fibrillation may be more related to haemorheology and endothelial dysfunction, rather than platelets. However, patients with paroxysmal atrial fibrillation may have a similar stroke risk compared to chronic atrial fibrillation, especially if risk factors are present (as reviewed by Lip). Indeed, we have previously reported that paroxysmal atrial fibrillation was associated with intermediate levels of intravascular thrombogenesis, such as fibrin D-dimer and fibrinogen, when compared to chronic atrial fibrillation and sinus rhythm. Similarly, Sohara et al found that abnormal prothrombotic factors are present in paroxysmal atrial fibrillation.

Interestingly, our patients with persistent atrial fibrillation were found to have ‘normal’ levels of the indices of endothelial dysfunction and platelet activation compared to controls. This would be consistent with our (very) strict definition of persistent atrial fibrillation for the purposes of this study, who were the subgroup which could be converted to (and successfully maintained in) sinus rhythm. Our observations suggest that patients with persistent atrial fibrillation, who are likely to have been in atrial fibrillation for a much shorter duration...
than those with permanent atrial fibrillation, have abnormalities in prothrombotic markers which are perhaps more comparable to patients in sinus rhythm — indeed, the present study suggests that these patients may even be at lower prothrombotic risk when compared to paroxysmal or permanent atrial fibrillation, although the possibility that this risk changes with time (that is, when persistent atrial fibrillation becomes permanent atrial fibrillation) remains. This hypothesis is supported by Sohara et al.[18], who found that abnormalities of prothrombotic factors can be related to the duration of atrial fibrillation and whether patients were in atrial fibrillation, although only 11 of their patients had a duration of atrial fibrillation which was >12 h. The present study and that of Sohara et al.[18] raises the hypothesis that the degree of hypercoagulability in atrial fibrillation may be closely related to the duration that the patient may have been in atrial fibrillation, and that a significant prothrombotic only occurs in atrial fibrillation patients when atrial fibrillation becomes more 'permanent'. Further studies relating the duration of atrial fibrillation to prothrombotic markers in larger numbers of patients would confirm the association(s), if any.

Thromboembolism after restoration of sinus rhythm is thought to be related to stasis caused by left atrial mechanical dysfunction following cardioversion, even in the absence of pre-existing atrial thrombus[6,7,19]. Nevertheless, the restoration of sinus rhythm is not always immediately associated with the return of effective atrial contraction. There is conflicting evidence about the role of haemostatic mechanisms in contributing towards the risk of thromboembolism after cardioversion. The study by Oltrona et al.[3] suggested that there was early activation of haemostasis soon after pharmacological cardioversion, with an increase in thrombin–antithrombin complex (TAT) and fibrinopeptide A levels immediately after cardioversion, which decreased at 1-month follow-up. The study by Lip et al.[9] of 19 patients with atrial fibrillation undergoing electrical cardioversion, where seven were not anticoagulated with warfarin prior to the cardioversion, demonstrated a significant reduction in plasma fibrin D-dimer levels (an index of thrombogenesis) at 14 days after cardioversion in the atrial fibrillation patients without prior oral anticoagulant therapy. There was no change in the (normalized) fibrin D-dimer levels in the atrial fibrillation patients who had been fully anticoagulated with warfarin pre- and post-cardioversion. This present study therefore confirms our previous observations that fibrinogen levels are not significantly influenced by electrical cardioversion[9]. None of these studies have related changes in haemostatic markers to the return of atrial systole, and furthermore, the patients studied by Oltrona et al.[8] were fully anticoagulated at follow-up and they measured markers which could potentially be influenced by warfarin. Importantly, these previous studies have not carefully defined the subgroups of atrial fibrillation, as in the present study, who appear to have different hypercoagulable states at baseline.

Despite restoration of sinus rhythm and return of left atrial function (as shown by the presence of A waves) up to 3 months post-cardioversion, there were no significant changes in fibrinogen, soluble P-selectin and von Willebrand factor levels. Furthermore, the recovery of left atrial systole, as indicated by the change in A wave on Doppler echocardiography, did not correlate with the changes in the levels of soluble P-selectin, von Willebrand factor and fibrinogen. However, the levels of these markers in patients with persistent atrial fibrillation at baseline did not differ significantly from controls in sinus rhythm, and if we postulate that cardioversion would 'normalize' abnormal prothrombotic factors, the lack of gross abnormalities at baseline makes it difficult to detect any significant change in these markers. One could nevertheless hypothesize that a patient with persistent atrial fibrillation with normal fibrinogen, von Willebrand factor or soluble P-selectin is at low risk of thromboembolism post-cardioversion, but only a prospective study can address this question; based on current management guidelines[3], it would not be ethical to undertake such a study without any antithrombotic therapy.

In conclusion, there were significant differences in the prothrombotic state when patients with paroxysmal and permanent atrial fibrillation are compared to matched patients with persistent atrial fibrillation or controls in sinus rhythm. Furthermore, patients with persistent atrial fibrillation were found to have similar levels of von Willebrand factor, fibrinogen and soluble P-selectin, when compared to healthy controls in sinus rhythm; cardioversion of these patients did not significantly alter these indices, even after 3 months maintenance of sinus rhythm, despite the return of atrial systole.

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References

Chronic atrial fibrillation (AF) is associated with increased risk of thromboembolic events, particularly stroke. The pathophysiological mechanisms underlying these effects are complex and not fully understood. Several studies have explored various aspects of this disease. Here, we provide an overview of the literature, focusing on the effects of AF on platelet function and coagulation.


