

## COMMENTARY

## Hypercoagulability and haemodynamic abnormalities in atrial fibrillation

Non-valvular atrial fibrillation confers a substantial risk for stroke and thromboembolism which is estimated to be between 4.5% and 12% per year depending on associated risk factors.<sup>1,2</sup> Recent studies have established the value of warfarin as thromboprophylaxis in atrial fibrillation; however, this treatment carries with it the inconvenience of regular monitoring of anticoagulation intensity and the risk of bleeding.<sup>1,2</sup> Attention has therefore focused on the development of alternative, safe, and convenient antithrombotic regimens, and appropriate thromboembolic risk stratification. For example, a low intensity fixed dose warfarin-aspirin regimen has certain attractions for convenience, but the recent third Stroke Prevention in Atrial Fibrillation study demonstrated the lower efficacy of this regimen compared with conventional, adjusted dose, warfarin therapy.<sup>3</sup> Careful risk stratification has also been advocated to ensure that patients with atrial fibrillation at high risk of stroke and thromboembolism receive warfarin, while low risk patients are at least treated with aspirin. A strategy of prescribing warfarin to every patient with atrial fibrillation, irrespective of risk stratification, may increase risk of bleeding, particularly intracranial haemorrhage, and cause unnecessary inconvenience to patients.<sup>4</sup> Most risk stratification can be performed on clinical criteria alone, with some refinement of risk stratification using echocardiography.<sup>2</sup> However, other developments to assist thromboembolic risk stratification are needed; one area may be the study of various haemostatic and clotting indices that suggest a hypercoagulable state.

As long as 150 years ago, Virchow<sup>5</sup> postulated three components for thrombogenicity: abnormalities in the blood vessel wall, blood flow, and blood constituents. These three basic postulates appear to be fulfilled in patients with atrial fibrillation. Clinical and echocardiographic criteria may help identify the first two of Virchow's basic postulates for thrombogenesis—abnormalities of vessels and blood flow, such as heart valve disease and cardiac impairment. It is also well recognised that atrial fibrillation confers a hypercoagulable state, satisfying the third of Virchow's postulates.<sup>6</sup> The hypercoagulable state in chronic atrial fibrillation appears to be independent of the underlying aetiology or any structural heart disease, including left atrial size or left ventricular function.<sup>7-9</sup> Patients with paroxysmal atrial fibrillation have also been shown to demonstrate abnormalities of haemostasis<sup>10,11</sup> related to the duration of a paroxysm of atrial fibrillation and whether the patient was in atrial fibrillation at the time of sampling.<sup>11</sup> Patients who are started on anticoagulation<sup>7,12</sup> or cardioverted from atrial fibrillation to sinus rhythm<sup>13,14</sup> demonstrate significant changes in markers of haemostasis, suggesting a reduction in the hypercoagulable state.

The phenomenon of spontaneous echo contrast has

been shown during paroxysms of atrial fibrillation, indicating atrial stasis.<sup>15</sup> The relation of various haemostatic markers and the risk of stroke or thromboembolism to the presence of spontaneous echo contrast is further evidence for a correlation between a hypercoagulable state and intra-atrial stasis.<sup>16-20</sup> Blood stasis within the left atria is also detected by atrial appendage dysfunction<sup>21,22</sup> and this appears to be an additional contributory factor to thrombus formation.

In this issue of *Heart*, Heppell *et al*<sup>23</sup> further evaluate the relation between haemostatic and haemodynamic parameters to the presence of left atrial thrombus in non-rheumatic atrial fibrillation. They initially found abnormalities in haemostatic markers in patients with left atrial thrombus compared with those without thrombus, consistent with the association between thrombogenesis and these markers. Furthermore, these abnormalities were significantly associated with haemodynamic abnormalities, as indicated by peak left atrial appendage velocity (but not peak mid-left atrial or mitral valve outflow velocity), and the presence of spontaneous echo contrast on transoesophageal echocardiography, suggesting intra-atrial blood stasis. The close association between haemostatic and haemodynamic abnormalities in atrial fibrillation are again consistent with Virchow's triad.

However, transoesophageal echocardiography is not 100% sensitive for the detection of intracardiac thrombi, and the presence of haemostatic abnormalities associated with likely haemodynamic appearances of stasis (spontaneous echo contrast, reduced left atrial appendage velocity, etc), further strengthens the case that risk stratification of stroke or thromboembolism could be further refined using indices of hypercoagulability. The value of haemostatic markers as risk stratification in patients with atrial fibrillation requires further study. We need to know—for example, whether an abnormal marker of a hypercoagulable state, such as high fibrin D-dimer, will predict stroke, thromboembolism or death in patients with atrial fibrillation.<sup>6</sup> Lack of prognostic data in patients with chronic atrial fibrillation raises the question of whether these abnormalities of haemostasis in patients with atrial fibrillation are a "cause or effect" phenomenon.

Prognostic value of some haemostatic markers is provided by evidence that some markers are predictive of mortality, progression of arterial disease, and cardiovascular events, from studies in normal healthy men and patients with peripheral vascular disease. For example, high plasma fibrin D-dimer (but within the "normal" range) predicts both arterial thrombotic events<sup>24-26</sup> and postoperative thrombosis.<sup>27</sup> Other haemostatic markers, such as plasma fibrinogen and von Willebrand factor also have prognostic implications in patients with ischaemic heart disease and hypertension, being associated with pro-

gression or severity of disease and cardiac events.<sup>28 29</sup> These abnormalities in haemostatic markers are therefore suggestive of a continuum that exists between health, "statistically" increased haemostatic abnormalities such as a prethrombotic or hypercoagulable state, and "overtly" increased clotting in acute thrombosis (or sometimes in acute extravascular fibrin formation, as follows injury or surgery).<sup>6</sup>

Nevertheless, there have been concerns whether peripheral measurements of various haemostatic markers are equivalent to levels of similar markers within the left atrium.<sup>30 31</sup> Indeed, a recent report suggests that increased regional left atrial coagulation activity—for example, in mitral stenosis, occurs in the presence of left atrial spontaneous echo contrast in either sinus rhythm or atrial fibrillation, and is associated with normal systemic coagulation activity.<sup>30</sup> Nevertheless, some of these studies have been performed in relatively small numbers of patients, some of whom were in sinus rhythm or atrial fibrillation, and had treatments with various antithrombotic regimens (including aspirin, warfarin, and heparin), and the precise relation between left atrial and systemic coagulation activities are still unresolved. In cardiovascular disease, the process of thrombogenesis is also unlikely to be confined to the left atrium.

Where do we go from here? The evidence is fairly clear for the presence of a hypercoagulable state in atrial fibrillation<sup>6</sup> and increasing evidence such as that by Heppell *et al*<sup>23</sup> point towards a relation between intra-atrial stasis and the haemodynamic abnormalities associated with atrial fibrillation. Ideally, we should ascertain whether various markers of haemostasis are predictive of stroke and thromboembolism in patients with atrial fibrillation, which would therefore complement clinical and echocardiographic risk stratification for thromboembolism. However, the value of haemostatic markers in assessing prognosis in many cardiovascular disorders (including atrial fibrillation) requires further, larger studies. Based on recent clinical trials, most patients with chronic atrial fibrillation should now be considered for prophylactic oral anticoagulation therapy, and so it may no longer be ethical to undertake a prospective study of the predictive nature of haemostatic abnormalities in patients with atrial fibrillation without any oral anticoagulant therapy. Perhaps such studies could be performed in patients with atrial fibrillation whose risks of thrombosis or bleeding do not justify anticoagulant prophylaxis. The relation of haemostatic markers to existing risk stratification could be further clarified—for example, by relating levels of these markers to other clinical and echocardiographic risk factors in large populations of patients with atrial fibrillation. These indices of hypercoagulability may be useful in the evaluation of new antithrombotic treatment regimens, for example, aspirin-warfarin combinations,<sup>2</sup> low dose warfarin,<sup>32</sup> ticlopidine or clopidogrel, for patients with atrial fibrillation. The value of these markers in assisting the monitoring of anticoagulation intensity needs to be fully established.

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