Impact of Rate and Rhythm on Atrial Thrombogenesis in Atrial Fibrillation
Which Takes Priority?

We read with interest the clinical study by Lim et al. (1) in which rapid atrial rate and atrial fibrillation (AF) both resulted in increased platelet activation and thrombin generation in humans, but AF additionally induced endothelial dysfunction and inflammation. They concluded that although the rapid atrial rate increased the thrombogenic risk, AF might further potentiate this risk. Nevertheless, we consider that there are several controversial aspects that could reduce the value of this conclusion.

In their study, they enrolled both paroxysmal and persistent AF patients. In fact, the extent and the source of inflammation might be different across all types of AF. Kamath et al. (2) found that abnormal platelet activation in patients with permanent AF was not consistently observed in those with paroxysmal and persistent AF. Also, a recent study by Scridon et al. (3) found higher left atrial vascular endothelial growth factor levels in paroxysmal AF, but not in persistent AF. Furthermore, we wonder how long have these patients with persistent AF been in sinus rhythm following cardioversion? The inflammatory status in persistent AF following cardioversion has not been clearly established. Electrical cardioversion of the patients with persistent AF did not significantly alter levels of von Willebrand factor, soluble P-selectin, or fibrinogen, despite maintenance of sinus rhythm at 3 months (4). Contrary to these results, Kamath et al. (2) demonstrated a significant decrease in plasma soluble P-selectin levels in patients with persistent AF who remained in sinus rhythm at 2 weeks and 2 months following successful cardioversion. This inconsistency merits further investigation. Therefore, a limited number of patients combined with variable types of AF made the evaluation of inflammatory status in the present study less accurate.

A rapid atrial rate and rhythm disturbances are 2 characteristics of AF. The main finding in the present study that AF additionally induced endothelial dysfunction and inflammation is another controversy. In fact, the impact of rhythm on thrombogenesis in AF is still controversial. The increased asymmetric dimethylarginine (ADMA) levels and reduced mRNA expression of ventricular and aortic endothelial nitric oxide synthase (eNOS) by rapid atrial pacing in the study by Goette et al. (5) were mainly due to the rapid atrial rate. Although there was no difference in ventricular rate between the AF and atrial pacing groups, it should be noted that the atrial rate was statistically much higher in the AF group than the atrial pacing group (293.1 ± 58.0 vs. 150.0 ± 0 beats/min, p < 0.01). Therefore, it was much more possible that the higher atrial rate in the AF group caused additional induced ADMA and platelet-derived inflammation (sCD40L). At least until now, we could not perceive of any convincing evidence that the abnormal rhythm contributed atrial thrombogenesis in AF. The conclusion that AF additionally induced endothelial dysfunction and inflammation in the present study seems misleading to some extent. Although the mechanisms of atrial thrombogenesis in AF have been well documented (6,7), the individual impact of rate and rhythm is still inconclusive. Nevertheless, Lim et al. (1) enlightened all of us in this field.

**References**


Reply

We thank Dr. Zhang and colleagues for their comments and interest in our work (1). Previous studies on prothrombotic markers such as platelet activation in atrial fibrillation (AF) patients have yielded conflicting results. This could be due to several factors. First, different sampling sites—we have found from previous studies and this study that atrial sampling yielded abnormal platelet activation and increased thrombogenesis that was not reflected in
peripheral samples (1,2). Second, patients may have presented in sinus rhythm or different durations of AF before blood sampling. Our study was performed within a pre-defined period of baseline and 15 min, demonstrating acutely elevated prothrombotic markers with rapid atrial pacing and AF induction (1). Third, the type of AF and underlying patient comorbidities could influence the patient’s baseline prothrombotic state. Higher levels of inflammatory markers have been described in patients with higher AF burden (3). Furthermore, patients in AF within 24 h of sampling had higher C-reactive protein levels than those in sinus rhythm (3). These findings suggest the contribution of the arrhythmia itself to the patient's inflammatory state. Although patients with paroxysmal and persistent AF were recruited in our study, all patients were in sinus rhythm for ≥48 h before the study. The prothrombotic changes observed were significant compared with each individual patient’s baseline state, indicating that the acute changes were in addition to the patient’s underlying type of AF or comorbidities.

Studies of AF patients post-cardioversion have similarly yielded varying results, probably due to the influence of the aforementioned factors. In our study, none of the patients with persistent AF underwent cardioversion within 3 months before the study.

It is possible that the further effects observed in the AF group were due to its higher atrial rates, as discussed in the study limitations (1). Previous animal studies that demonstrated up-regulation of asymmetric dimethylarginine (ADMA) and decreased nitric oxide levels have utilized rapid atrial pacing models to simulate AF (4,5). However, to prevent inadvertent induction of AF in the atrial-paced group in our study, the degree of rapid atrial pacing was limited. We agree that further questions remain as to the extent and relative contribution of rapid atrial rates and abnormal rhythm to thrombogenesis in AF.

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