The phenomenon of early recurrence of atrial fibrillation

Between 1994 and 1999, the number of abstracts on atrial fibrillation submitted for presentation at the Congress of the European Society of Cardiology rose from approximately 100 to more than 400, representing an increase to over 5% of the total number of submitted abstracts. This impressive rise in interest and research activity, both basic and clinical, has largely been driven by the emergence of two major concepts. The first is that an increasingly recognized and growing number of patients have atrial fibrillation initiated, and possibly maintained, by an ectopic focus of repetitive atrial activity and tachyarrhythmia. The second concept is that fibrillation of atrial myocardium itself causes changes in cellular electrophysiology that, at least in animal models, have the effect of further increasing the tendency to fibrillation, and that there is reversal of this electrophysiological remodelling after a period of sinus rhythm. The first of these two concepts relates to the triggers for initiation of the arrhythmia and the second to the myocardial substrate predisposing to and maintaining the arrhythmia.

Early recurrence of atrial fibrillation

The phenomenon of early recurrence of atrial fibrillation following successful cardioversion is a clinical setting in which both of these important and intriguing concepts are implicated and may interact. This interface between these topical concepts coupled with increasing use of internal electrical cardioversion, the catheters for which enable recording of atrial electrograms, provide the motive and the means for study of this phenomenon which has acquired its own acronym — ERAF (early recurrence of atrial fibrillation). The study in this issue[3] has investigated use of internal defibrillation catheters not only for cardioversion and electrophysiological measurement but also as a means of pacing the atria, to attempt suppression of early recurrence of atrial fibrillation.

Although there is a very broad spectrum of arrhythmia-free duration in patients with recurrent atrial fibrillation, it is clear that the most vulnerable period for reinitiation is immediately after reversion to sinus rhythm. If ERAF is considered to represent simply an early example of the same phenomenon as ‘late’ recurrence of atrial fibrillation, a finding that pacing prevents or delays early recurrence of atrial fibrillation in a subset of patients is perhaps not surprising as there are several sizeable studies showing the benefit of atrial pacing in other clinical settings such as sick sinus syndrome and bradycardia-dependent and refractory atrial fibrillation. But there is evidence to suggest that early recurrence is characterized by a markedly exaggerated tendency of clinical importance and merits particular attention. However, the extent to which early recurrence of atrial fibrillation is due either to enhanced frequency...
of atrial ectopic activity as potential triggers or to enhanced vulnerability of the remodelled recently defibrillated atrium to the effects of the atrial ectopy remains uncertain.

Studies on early recurrence of atrial fibrillation have shown a prevalence of 16–36%, but this is in part determined by the definition of early. In their earlier study,[4] the authors of the paper in this issue found that of 64 patients with atrial fibrillation of at least 1 month’s duration, 81% had successful internal cardioversion, of whom 31% had early recurrence of atrial fibrillation within 5 min. In their small study in this issue[3] early recurrence of atrial fibrillation was defined as occurring within 2 min of cardioversion. In showing that of the 12 with early recurrence of atrial fibrillation out of the 45 internally cardioverted patients, pacing suppressed early recurrence of atrial fibrillation in five (42%) and delayed it in the remainder, this is the first systematic study to show efficacy of pacing in early recurrence of atrial fibrillation. But is the pacing effective through modifying the trigger or the substrate?

Triggers and substrate

With respect to the myocardial substrate predisposing to atrial fibrillation, if in humans the time course of reversal of atrial fibrillation-induced electrical remodelling is similar to that in the well characterized animal models,[2] in which intracellular calcium overload is in large part responsible for the remodelling, this would explain the incidence of relapse of atrial fibrillation being highest immediately and subsiding with time, and the reduced incidence by administration of agents such as verapamil that block the intracellular calcium overload. Indeed, Tieleman et al.[5] showed that of the 57% of patients with relapse of atrial fibrillation during the first month after cardioversion, 63% of them occurred within the first 5 days, and that being on calcium channel blockers preceding the cardioversion was the only significant variable-related to maintenance of sinus rhythm.

With respect to the triggers for atrial fibrillation, there is evidence that any tendency to atrial ectopic activity is exaggerated in the early period following cardioversion. In the previous study by Tse et al.[4], 91% of the episodes of early recurrence of atrial fibrillation were triggered by atrial premature complexes, and in six patients repeated episodes of early recurrence of atrial fibrillation occurred with the same P-wave morphology and coupling interval. Atrial ectopics that triggered atrial fibrillation were more premature than those that did not. After repeated early recurrence of atrial fibrillation, sotalol infusion (1.5 mg. kg⁻¹ over 30 min) decreased sinus rate and the frequency and prematurity of the atrial premature beats, and prevented further early recurrence of atrial fibrillation in 83%. Interestingly, five episodes (9%) in two patients had preceding bradycardia with no atrial ectopy, and maintenance of atrial rate (by atropine in one and right atrial pacing in one) prevented further recurrences. Similarly, in the study in this issue[3], the atrial ectopics that triggered early recurrence of atrial fibrillation were of a significantly shorter coupling interval than those that did not. Pacing at 500 ms intervals decreased the density, and prolonged the coupling interval, of atrial ectopic beats in the entire group, and in the subgroup in whom early recurrence of atrial fibrillation still occurred, pacing delayed the onset.

Enhanced atrial ectopy post cardioversion plays an important role in early recurrence of atrial fibrillation. In studies of the various manoeuvres aimed at provoking elusive atrial ectopy when trying to map and ablate it, DC cardioversion of atrial fibrillation deliberately induced by pacing has been shown to provide a subsequent period with enhanced ectopic tendency. In this setting, however, the question remains as to whether the atrial ectopic beats post cardioversion are necessarily the triggering mechanism for the clinical episodes of atrial fibrillation in such patients.

There is evidence, therefore, that both factors, triggers and substrate, contribute to the phenomenon of early recurrence of atrial fibrillation, and may interact in a dynamic manner. In the study by Tieleman et al.[5] the more premature the atrial ectopy, the shorter the time to relapse. The finding that patients with the longer-coupled atrial ectopic beats relapsed later would be consistent with the concept of progressive reversal of the remodelling of the atria (and prolongation of the shortened refractoriness) after return to sinus rhythm, accounting for the interval before long-coupled atrial ectopic beats began to encroach on the ‘window of dispersion of refractoriness’ and reinduce reentry and atrial fibrillation.

Pacing and early recurrence of atrial fibrillation

Taken together, studies in this area would add support to the hypothesis that atrial pacing after cardioversion acts by modifying the triggering event, but that the remodelled substrate remains adequately sensitive to the remaining triggers in some to have early recurrence of atrial fibrillation. If, as has been
suggested, the likelihood of early recurrence of atrial fibrillation recedes very rapidly after the first few minutes following cardioversion as a result of the rapid early phase of reverse remodelling of atrial myocardial electrophysiology, to pace the atria rapidly during this period, such as the 300 ms intervals as in the study in this issue[3], may actually attenuate this reverse remodelling and perpetuate the proarrhythmic state. This may explain the lack of incremental benefit of pacing if excessively rapid[3].

What can be concluded about pacing in early recurrence of atrial fibrillation? Is the evidence so compelling that we should consider cardioverting all patients internally in order that they can all be paced for a period after initial success? From the study in this issue, in that only 12 patients fulfilled the inclusion criteria of having repeatable early recurrence of atrial fibrillation after two successive shocks, broad generalizations for clinical practice cannot be drawn. What also cannot be established from this study is whether post cardioversion right atrial pacing in all patients would actually provoke atrial fibrillation in a proportion of patients who would not otherwise have had early recurrence of atrial fibrillation. It would not take many of the remaining 33 non-EARF patients to have atrial fibrillation reinitiated by routine use of pacing to annihilate the benefits. The tiered strategy of atrial pacing and then intravenous sotalol for early recurrence of atrial fibrillation adopted in this study resulted in a 96% success rate of a single session of internal cardioversion. It remains to be proven whether such an impressive outcome can be achieved in larger studies.

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References

CRP: does it stand for Coronary Restenosis Prediction?

See page 1152 for the article to which this Editorial refers

CRP: does it stand for Coronary Restenosis Prediction?

Of course not! CRP stands for C-reactive protein which is one of the acute phase reactants, a non-specific marker for inflammation. C-reactive protein activates the complement system and neutrophil adhesion. C-reactive protein also attracts complement within the coronary plaque by adhering to phosphorylcholine groups that become exposed by enzymatic degradation of tissue-deposited LDL[1]. C-reactive protein is thus thought to be involved in the development and progression of atherosclerotic lesions. Perhaps in a more consistent way than fibrinogen, serum amyloid type A or other markers of inflammation, increased plasma levels of C-reactive protein were shown to be associated with increased risk of coronary disease as well as with a worse prognosis in patients with either stable or unstable angina.

The study by Gottsauener-Wolf et al[2] was performed in a small group of stable patients undergoing elective coronary stenting. C-reactive protein levels were normal prior to the procedure but increased after stenting, irrespective of the antithrombotic/antiplatelet therapy. However, in 11 patients later shown by follow-up angiography and QCA to have developed in-stent restenosis, post-procedural C-reactive protein elevations were significantly higher and lasted longer (peak at 96 h after stenting vs at 48 h in patients without later restenosis). The authors thus concluded that a prolonged inflammatory