of platelets with long-term administration of fibrinogen receptor antagonists has proved unsafe\cite{10}, there may be much to gain by redirecting our efforts towards more effective inhibition of coagulation. More specific, effective and safe versions of heparin\cite{11} or novel factor Xa inhibitors\cite{12} may provide improved control of coagulation.

The study also points to the fact that patients in clinical trials are not homogeneous. Here for example, the patients with elevated markers had more events. There is a great need to be able to identify such patients, so that only those likely to gain will be exposed to increasingly complex antithrombotic regimens. While the assays used in this study may prove useful, the complexities surrounding sampling and measurement may limit their application. Potential sources of individual variation that could be exploited in order to identify these patients include genetic polymorphisms and aspirin resistance, defined as continued platelet aggregation to ADP despite treatment with aspirin. Such variation in the population may not only predict risk, but also the response to treatment. Studies linking genetic markers to drug response are already underway\cite{13}.

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References


A novel use of cardiac pacing to improve cardiac function, quality of life and (hopefully) survival in patients with heart failure and permanent atrial fibrillation

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Atrial fibrillation and heart failure are frequently associated. For example, the Framingham Heart study\cite{11} showed that patients with heart failure have a relative risk for developing atrial fibrillation, ranging from 4.5 for men to 5.9 for women, and about 20–40% of the patients included in heart failure studies have atrial fibrillation\cite{2,3}. Many heart failure

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patients still experience debilitating symptoms and die prematurely despite ‘optimal’ medical therapy. There is a need for adjunctive therapy. New non-pharmacological therapies using pacemaker technology have been developed in recent years addressing this need. These include AV junction ablation and pacing, resynchronization pacing, and resynchronization pacing associated with ICD implant. Their use in clinical practice needs the unique cooperation of electrophysiologists and heart failure pharmacotherapists.

Rate control

Acute studies have shown that irregular RR intervals are associated with a negative haemodynamic effect, which is independent of heart rate and that this effect is reversed by regularization of the rhythm. In a recent clinical trial, the PIAF study, the control of heart rate had a similar effect on quality of life as maintenance of sinus rhythm and caused fewer hospitalizations. Two important randomized controlled trials (AFFIRM and RACE) that have given consistent results have been recently announced. The AFFIRM study randomized 4060 elderly patients to medical management of atrial fibrillation. The primary study end-point, total mortality, was slightly lower in the rate-control arm, although the trend was not quite statistically significant. At an average of 3.5 years of follow-up, there were 306 deaths in the rate-control arm vs 356 in the rhythm-control arm. Outcomes were approximately the same for the two groups in the secondary end-point, ischaemic stroke. The RACE trial compared medical therapy to control heart rate with electrocardioversion of rhythm. The difference between primary end-points was small. The rate of death or severe cardiovascular incident was 17.2% among the 256 patients in the rate-control trial arm vs 22.6% among the 266 patients in the electrocardioversion rhythm-control arm. Cardiovascular mortality rates were 7.0% for the rate-control arm and 6.7% for the rhythm-control arm; heart failure rates were 3.5% and 4.5%, respectively. The subgroup of patients with hypertension in particular did not do well with electrocardioversion for rhythm control; the rate of mortality, thromboembolism, or other severe complication was approximately 19% for rate-control therapy vs approximately 31% for rhythm control. Thus, in conclusion, the above trials showed that rate control is not inferior to rhythm control. A trend toward an even better outcome for rate control therapy is consistent in all studies but it needs further evidence.

The control of heart rate achievable with pharmacologic therapy is imperfect and, in many patients, difficult to obtain. Ablation and pacing therapy offer a theoretical perfect control of heart rate and consequently the expected results should be superior to those observed with drug therapy. Indeed, an improvement in cardiac performance and quality of life has been confirmed in a few clinical not uncontrolled studies. One recent randomized controlled study, showed that the long-term clinical effects of ablation and pacing therapy were superior to those obtained with drug therapy. The improvement was greater for the specific symptoms of the arrhythmia, such as palpitation and effort dyspnea, than for the indexes of general health-related quality of life; cardiac performance (evaluated by means of echocardiographic and exercise indexes) remained stable during follow-up.

The aim of the PAF2 trial was to evaluate the effect of antiarrhythmic drug therapy on long-term maintenance of normal sinus rhythm after ablation and pacing therapy and to evaluate its clinical efficacy. In brief, 141 patients affected by severely symptomatic paroxysmal atrial fibrillation were randomized, after successful AV junction ablation and DDDR pacemaker, to antiarrhythmic drug therapy or to no antiarrhythmic drug therapy. Despite the drug arm patients having a 57% reduction in the risk of developing chronic atrial fibrillation, the study was unable to show any clinical benefit in patients treated with antiarrhythmic therapy in addition to that already obtained with ablation and pacing alone and, in contrast, in some patients, serious adverse clinical events, as evidenced by the higher number of episodes of heart failure and hospitalization, were observed. Thus, the perfect control of ventricular rhythm provided by ablation and pacing seems to be the most important objective to be obtained and probably minimizes the importance of preserving atrial contraction. Again, the results of the PAF2 study are very consistent with those of the above mentioned drug studies. In conclusion, rate control therapy obtained either by medication or by AV junction ablation is a very attractive alternative to rhythm control therapy.

It is commonly accepted that pacing from the apex of the right ventricle is not optimal since it provides non-physiologic asynchronous contraction which results in a decrease in cardiac performance. This suggests that the beneficial haemodynamic effect of regularization of heart rhythm may be counteracted by the adverse haemodynamic effect of non-physiological right ventricular pacing. Pacing from the apex of the right ventricle causes an electrocardiographic pattern of left bundle branch block which is similar to that of patients with spontaneous left bundle branch block. In one study performed in...
patients with otherwise normal hearts, the presence of left bundle branch block was associated with a significant deterioration of cardiac function of about 10%-20%. In the recent years, some acute haemodynamic studies have demonstrated that biventricular pacing or left ventricular pacing are able to improve haemodynamic performance in patients with severe heart failure and left bundle branch block, by means of the correction of left ventricular asynchrony which is caused by the intraventricular conduction delay[19–22]. These data form the background for the use of ventricular re-synchronization pacing in patients with heart failure who undergo ablation and pacing therapy. This issue remains largely to be proven by a prospective controlled ongoing trial[23].

Ventricular re-synchronization

There is increasing evidence of the favourable effect of cardiac re-synchronization pacing in patients with heart failure and intraventricular conduction delay who are in sinus rhythm. A number of trials have been performed on this point. Some were observational studies of a series of patients undergoing biventricular pacing[24,25]. Other trials involved randomization to biventricular pacing or no pacing — single-blinded — as in the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial[26], or double-blinded — as in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial[27,28]. It should be emphasized that some of this is preliminary data, which may change after the follow-up is completed. However, it is clear that there is a high degree of consistency in the data so far available from trials.

Very little is known about patients with permanent atrial fibrillation. An acute haemodynamic study by Etienne et al.[20] showed similar haemodynamic benefits in both sinus rhythm and atrial fibrillation, and more recently, Leclercq et al.[29] showed a sustained positive effect of permanent biventricular pacing with sinus rhythm and atrial fibrillation. In the latter study, patients with atrial fibrillation tended to benefit more than patients in sinus rhythm, perhaps due to the double correction of both left ventricular asynchrony and irregular heart rate. In a small controlled study[30], left ventricular pacing was better than right ventricular pacing in improving quality of life, exercise capacity, cardiac function and in reducing the magnitude of mitral regurgitation both in patients with sinus rhythm and atrial fibrillation.

In this issue, the results of the first randomized clinical study are reported[31]. These are the results of the atrial fibrillation arm of the MUSTIC study. It was a randomized, single-blind, cross-over, controlled study aimed to assess the value of bi-ventricular pacing in 59 patients with advanced heart failure and chronic atrial fibrillation. The primary end-point was the 6-min walked distance, secondary end-points were peak oxygen uptake, quality of life, hospitalizations, patients’ preferred study period and mortality. The predefined analysis was based on the intention-to-treat principle. Because of the higher than expected drop-out rate (42%), only 37 patients completed the cross-over phases. This fact and patient heterogeneity at baseline greatly limited the statistical power of the study. As a result, the intention-to-treat analysis showed no statistically significant difference in either primary or secondary end-points between the two pacing modalities. However, in the on-treatment analysis, the mean walked distance increased significantly by 9-3% on biventricular pacing; similarly, peak oxygen uptake increased by 13%, hospitalizations decreased by 70% and 85% of the patients preferred the biventricular pacing mode. The average magnitude of the effect is modest, although very helpful, in terms of clinical improvement. The situation is almost certainly one in which some patients show marked clinical benefit, balanced by other patients with very little benefit. Moreover, the effect of biventricular pacing could have been underestimated because of other study limitations which are correctly discussed in the article, i.e. a number of withdrawals for technical difficulties, the ‘artificial’ inclusion criteria of a paced QRS duration >200 ms, the inclusion of several patients who had already had a pacemaker implanted for bradyarrhythmia indications, the imperfect rate control in some non-ablated patients, the possible confounding effect of AV junction ablation, etc. For all these reasons, the authors correctly conclude that further randomized studies are required to definitely validate this therapy in patients with atrial fibrillation. Nevertheless, this is an important cornerstone study on the foundation of device therapy for heart failure whose results must be put in the right perspective since they follow the trend of all other studies. After the MUSTIC study the question is no longer whether re-synchronization is useful in atrial fibrillation patients, but rather when and how to offer this therapy to patients with atrial fibrillation.

The following are areas of interest for future studies:

- How to measure LV dyssynchrony and how to verify the effect of re-synchronization? The widely used criteria is that of the presence of left bundle branch block with wide QRS. The criteria of a paced QRS >200 ms was used in MUSTIC. In a recent study,
improvement in tissue Doppler imaging (or tissue velocity imaging) measurements of the synchrony of LV segment contraction was associated with clinical improvement, exercise time improvement and LV ejection fraction improvement, whereas patients without improved measurements showed no benefit from biventricular pacing[32].

- How to select candidates for CRT? Who benefit more? Potentially all patients with heart failure and chronic atrial fibrillation could benefit from rate control with AV junction ablation and re-synchronization pacing to avoid the deleterious effect of right ventricular pacing. On the other hand we know from the literature[33] that predictors of poor outcome after AV junction ablation are ejection fraction \(<30\)\%, moderate to severe mitral regurgitation or lack of acute improvement immediately after ablation; these patients could benefit more from re-synchronization pacing.

- Left ventricular pacing or biventricular pacing? Some recent acute and follow-up studies suggest that left ventricular pacing was associated with almost equivalent improvement of subjective and objective parameters to that of the more complex (and expensive) biventricular model[15,20,30,34,35].

**Rate control plus re-synchronization pacing**

In conclusion, the combination of two new therapies, namely AV junction ablation and left ventricular (or biventricular) pacing seems to have a potential additive beneficial effect in the patients with atrial fibrillation and heart failure. Two different populations of patients can be identified who may benefit from this therapy: patients with a conventional indication for AV junction ablation because of an uncontrolled high ventricular rate in whom the adjunct of left ventricular (or biventricular) pacing is expected to increase the results of ablation; and the patients with a ‘conventional’ indication for left ventricular (or biventricular) pacing because of left ventricular de-synchronized contraction (generally due to the presence of left bundle block) in whom the rate control obtained by the AV junction ablation is a pre-requisite for left ventricular pacing, other than having haemodynamic benefit per se.

**Future directions**

Many patients with heart failure die from sudden death. Medications are not preventing sudden death. ICDs do it better. The need for implementing re-synchronization therapy with a back-up ICD is here. Even if the Contak-CD trial[36] failed to prove a significant benefit with biventricular pacing plus ICD vs no therapy in patients different from those in whom there were conventional indications for ICD therapy, the recent MADIT 2 trial[37] showed that, in patients with a prior myocardial infarction and advanced left ventricular dysfunction with an ejection fraction \(<30\)\%, prophylactic implantation of a defibrillator improved survival and should be considered as a recommended therapy.

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Surrogate markers to monitor efficacy of anticoagulants or antiplatelet drugs in atrial fibrillation

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Thromboembolic events are an important possible sequel of atrial fibrillation (AF). In a cross-sectional study Kamath et al. examined the effects of anti-thrombotic (dose-adjusted warfarin) or antiplatelet therapy (75–325 mg aspirin q.d.) on coagulation markers (D-dimer) and on platelet activation markers (beta thromboglobulin [β-TG] and soluble glycoprotein V [sGPV]).

D-dimer levels were about two-fold higher in patients with AF as compared to controls, β-TG levels were 40% higher and sGPV levels were 40–80% higher in AF patients. As compared to warfarin-treated patients, D-dimer levels were three–four-fold higher in AF patients. As compared to warfarin-treated patients, D-dimer levels were three–four-fold higher in AF patients.