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# Editorial

## Atrioventricular junction ablation and pacemaker in patients with heart failure and permanent atrial fibrillation

Gabriele Lupi, Michele Brignole

Department of Cardiology and Arrhythmologic Center, Ospedali Riuniti, Lavagna (GE), Italy

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Address:

Dr. Michele Brignole

Dipartimento  
di Cardiologia  
Ospedale di Lavagna  
Via Don Bobbio, 5  
16033 Lavagna (GE)  
E-mail:  
brignole@omninet.it

Atrial fibrillation is the most common sustained cardiac arrhythmia, and heart failure is a frequent precursor of this condition. Epidemiological studies have shown that these diseases are frequently associated. Indeed, the Framingham Heart Study<sup>1</sup> 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 15-20% of the patients included in heart failure studies have atrial fibrillation<sup>2</sup>. Conversely, it is common knowledge that atrial fibrillation *per se* can precipitate congestive heart failure in the absence of cardiac disease.

Many patients with heart failure complain of severe symptoms despite optimal medical treatment; in addition, some patients with heart failure and atrial fibrillation show less than optimal heart rate control, which, associated with the irregular rhythm typical of this arrhythmia, can further worsen ventricular function. Therefore, non-pharmacological treatments have been developed in order to ameliorate symptoms and ventricular function in patients with heart failure and atrial fibrillation. We will discuss the potential role of atrioventricular junction ablation and pacing therapy, with special reference to previous experiences and ongoing investigations.

### Management of atrial fibrillation

As a rule, pharmacological therapy remains the initial therapy of choice in patients with atrial fibrillation; this is also true in the setting of heart failure. The aim of

therapy is to restore and preserve sinus rhythm, and to control the ventricular rate during paroxysm or when atrial fibrillation has become permanent. However, especially in patients with heart failure, antiarrhythmic drugs are relatively inefficacious in maintaining sinus rhythm and carry a substantial risk of adverse effects<sup>3</sup>. Theoretically, when drugs have failed, non-pharmacological therapies which aim to preserve or restore sinus rhythm should be the optimal choice; however, strategies such as the endocardial ablation of atrial fibrillation foci, atrial defibrillation or atrial pacing are still under investigation and their role has not yet been fully defined<sup>4</sup>. Conversely, the control of fast and irregular ventricular rates achieved by means of "ablate and pace" therapy is a well established treatment for patients affected by atrial fibrillation.

**Atrioventricular junction ablation and conventional pacing.** In patients with atrial fibrillation, radiofrequency ablation of the atrioventricular junction is unable to eliminate the electrophysiologic substrate of the disease; therefore, "ablate and pace" is a palliative treatment, by means of which an old disease is replaced by a new, less uncomfortable disease.

In expert hands, the procedure is highly effective in producing complete atrioventricular block (more than 95% of cases), with very low periprocedural complication (2%) and procedure-related death rates (< 0.1%)<sup>5</sup>.

Randomized controlled trials<sup>6,7</sup> have clearly demonstrated that patients with

symptomatic paroxysmal atrial fibrillation not controlled by medical therapy do better after ablation, achieving quality of life scores similar to those of asymptomatic patients.

Less clear are the effects in patients with chronic atrial fibrillation and heart failure. From a pathophysiological point of view, it is well known that irregular sequences of R-R intervals are associated with a negative hemodynamic effect which is independent of the heart rate<sup>8</sup>; moreover, a hemodynamic study by Daoud et al.<sup>9</sup> showed that an improvement in cardiac output could be achieved by regularizing the rhythm. In the PIAF study<sup>10</sup>, the effect of adequate control of heart rate was similar to that of the maintenance of sinus rhythm and caused fewer hospitalizations.

The perfect rate control achieved by "ablate and pace" constitutes the rationale for this therapy in patients with permanent atrial fibrillation and heart failure. Indeed, the beneficial effect of ablation has been confirmed in small groups of patients enrolled in preliminary non-controlled studies<sup>11-14</sup>.

A randomized controlled study<sup>15</sup> compared the long-term clinical effects of "ablate and pace" versus drug therapy in patients who had manifest heart failure and chronic atrial fibrillation. The results of this study showed that patients who underwent ablation enjoyed a statistically significant improvement in the specific symptoms of atrial fibrillation such as palpitation and effort dyspnea, but only a trend (not significant) towards an improvement in the quality of life compared with medically treated patients. Moreover, ablation and pacing was not superior to drug therapy in improving the objective parameters of cardiac and functional performance. Thus, patients treated with ablation feel better, probably owing to the optimal rhythm regularization, but their cardiac performance is unaffected. Therefore, at present, clinicians are not mandated to choose "ablate and pace" in patients with permanent atrial fibrillation and heart failure<sup>16</sup>.

**Atrioventricular junction ablation and synchronization pacing.** A major concern regarding ablation and conventional pacing is that the procedure implies permanent pacing from the apex of the right ventricle. It is commonly accepted that stimulation at this site causes non-physiological asynchronous ventricular contraction<sup>17-19</sup>; therefore, the hemodynamic benefits stemming from the control of irregular RR sequences might be counteracted by the negative effects of the non-physiological pacing.

Some acute hemodynamic studies have demonstrated that both biventricular pacing and left ventricular pacing alone are similarly able to improve the hemodynamic performance in patients with severe heart failure and an intraventricular conduction disorder, by correcting the left ventricular asynchrony<sup>20-23</sup>.

In a few clinical studies, synchronization therapy has proved to be effective for sinus rhythm patients.

The results of a large multicenter registry (the InSync Study) showed a clinical benefit from biventricular pacing, as expressed by an intra-patient improvement in NYHA functional class, by the distance covered in a 6-min walk-test and by results of a questionnaire investigating the quality of life<sup>24</sup>. More recently, the results of an intra-patient cross-over comparison study, the MUSTIC study<sup>25</sup>, have demonstrated that in patients with systolic dysfunction, sinus rhythm and a wide QRS (> 150 ms) atrio-biventricular pacing improves the quality of life and physical performance. To date, the positive results of some other ongoing studies (PATH CHF trial, MIRACLE study, CONTACT study) have only been announced at international congresses, but they have not yet been published.

A few small-sized studies, showing the effects of biventricular or of left ventricular pacing alone, have addressed the topic of biventricular or left ventricular pacing in patients with atrial fibrillation. An acute hemodynamic study by Etienne et al.<sup>21</sup> showed similar hemodynamic benefits both in sinus rhythm and in atrial fibrillation, and more recently, Leclercq et al.<sup>26</sup> showed a sustained positive effect of permanent biventricular pacing in patients with drug-refractory heart failure and intraventricular conduction disorders; the patients with atrial fibrillation benefited more than those in sinus rhythm, owing to the adjunctive effect on rhythm regularization obtained with atrioventricular junction ablation.

In a controlled study<sup>27</sup>, the acute and medium-term effects of left ventricular pacing on quality of life scores, exercise capacity and non-invasive parameters of cardiac performance were evaluated in 13 patients affected by severe drug-refractory heart failure and bundle branch block; 7 patients had permanent atrial fibrillation and underwent atrioventricular junction ablation at the time of pacemaker implantation. Left ventricular pacing induced a significant improvement in the left ventricular ejection fraction, Minnesota Living with Heart Failure Questionnaire score, NYHA functional class and 6-min walking test in comparison with sinus rhythm or right ventricular pacing; no substantial difference between the outcome observed in patients in sinus rhythm and that observed in subjects with atrial fibrillation was found. Thus, in a small selected population with drug-refractory heart failure, left ventricular pacing proved superior to right ventricular pacing in ameliorating the subjective and objective indexes of cardiac function. Therefore, in patients with atrial fibrillation biventricular pacing or left ventricular pacing alone seems to be as effective as in patients with sinus rhythm.

### Ongoing studies

The results of these studies, which showed a non-optimal effect of conventional right ventricular pacing

and promising new models of stimulation (biventricular or left ventricular pacing) raise the question of which is the optimal site to pace in patients with permanent atrial fibrillation undergoing atrioventricular junction ablation; in fact, the heart rate regularization and synchronization pacing might have additional effects both in patients with a conventional indication to "ablate and pace" therapy and in patients with an indication to synchronization therapy owing to the presence of a ventricular asynchrony. To answer this question, an international trial, the OPSITE study<sup>28</sup>, has recently been undertaken. This study is a prospective randomized cross-over comparison of three different modes of pacing for patients with permanent atrial fibrillation: right ventricular apical pacing, left ventricular pacing via the coronary sinus and biventricular pacing. The study population will include both patients with permanent atrial fibrillation in whom a clinical decision has been made to undertake "ablate and pace" therapy and patients with drug refractory heart failure and a left bundle branch block pattern or a non-specific intraventricular conduction delay (QRS  $\geq$  150 ms) in whom a clinical decision has been made to undertake left ventricular synchronization pacing (consistent with a previous diagnostic work-up decision for biventricular pacing). The primary endpoints are the quality of life and exercise capacity in the medium-term period; the secondary endpoints are the acute and medium-term non-invasive evaluation of cardiac performance, subgroup analysis of the quality of life and exercise capacity for patients with a baseline ejection fraction  $<$  40% and for those with a baseline ejection fraction  $>$  40%, and the effects of atrioventricular junction ablation on the quality of life and left ventricular ejection fraction.

At the end of this study we will be able to evaluate whether the perfect rate regularization obtained with atrioventricular junction ablation associated with pacing in the optimal site of stimulation can improve not only specific symptoms, but also the quality of life and cardiac performance.

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