The ‘Happy Ending Problem’ of cardiac pacing? Cardiac resynchronization therapy for patients with atrial fibrillation and heart failure after atrioventricular junction ablation

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This editorial refers to ‘Benefit of cardiac resynchronization therapy in atrial fibrillation patients vs. patients in sinus rhythm: the role of atrioventricular junction ablation’ by A.M. Ferreira et al., on page 809.

The ‘Happy Ending Problem’ in mathematics is the following statement: Any set of five points in the plane in a general position has a subset of four points that form the vertices of a convex quadrilateral.

A particular analogy can be drawn between this so-called unsolved problem in mathematics and the still unsolved problem of treatment of patients with heart failure (HF) associated with atrial fibrillation. Patients with HF and atrial fibrillation represent a subgroup of patients that encounters additional difficulties when compared with patients in sinus rhythm (SR). Most available studies, which include this subgroup of patients, suggest a beneficial effect of cardiac resynchronization therapy (CRT) on the outcome (Table 1).1–8 However, most studies in the field of CRT excluded this particular patient population. Moreover, studies until now have contained 95% of the patients in SR. Despite this, a few well-conducted studies have addressed this problem. Unfortunately, some studies have caused a certain amount of confusion because of controversial data. This controversy arises as a result of errors in the study design, interpretation, and the low inclusion rates. The above-mentioned analogy in mathematics clearly points out another difficulty in decision-making in this multifactorial problem. The five points in this geometrical problem can represent at least five independent factors, which could influence future recommendations. Furthermore, these factors could have a potential effect on the outcome: the effect of atrioventricular (AV) node ablation and pacing, the effect of the pacing site on cardiac function, a diminished atrial function (lack of atrial kick), the effect of rhythm regularization, and the presence of additional drug therapy.

Ferreira et al.9 address this rather difficult problem. The unique feature of this study is that it compares three groups of patients: patients undergoing CRT implantation in SR, in atrial fibrillation without AVJ ablation, and in atrial fibrillation with AVJ ablation. Although the authors failed to address all the above-mentioned important issues, some clear confirmation can be obtained by analysing their data. The number of patients included in this paper is sufficient for a single centre study, but definitely far beyond the optimal statistical power targeting such an important issue. Moreover, this number was achieved during a relatively long period of >6 years. As treatment standards, including the practice of resynchronization therapy, have changed significantly during this period, some data should be interpreted with caution. The results are rather confirmatory in terms of the value of CRT in patients with HF associated with atrial fibrillation. The fact that patients after AVJ ablation respond to CRT in the same way as patients in SR is an important message. To understand the complexity of this otherwise important issue, we can also look at this data in a wider perspective.

Heart failure and atrial fibrillation: epidemiology and therapeutic options

The likelihood of a patient with HF developing atrial fibrillation is strongly correlated with the patient’s New York Heart Association (NYHA) functional class. Although the prevalence of atrial fibrillation is 0.4% of the general population, its prevalence in NYHA I functional class patients...
Pacing and left ventricular performance: right ventricular pacing and alternative pacing sites after atrioventricular junction ablation

Interestingly enough, there are a large number of studies available investigating left ventricular performance after AVJ ablation. These studies provide no clear conclusions on this issue, and these results can also be confusing. The studies have shown harmful effects of right ventricular (RV) pacing on patients with structural heart disease. The DAVID trial enrolled patients who had an indication for automatic implantable defibrillator therapy but no indication for pacing. Right ventricular apical pacing had a deleterious effect on the combined endpoint of death or hospitalization.10 Right ventricular pacing indeed can result in structural changes similar to changes associated with left bundle branch block, such as paradoxical septum motion, increased mitral regurgitation, perfusion defects, and reduction of left ventricular ejection fraction. Biventricular pacing or left ventricular pacing can overcome most of the above-mentioned disadvantageous haemodynamic effects and therefore seems to be a therapeutic alternative for these patients.

The role of cardiac resynchronization therapy in patients with heart failure and atrial fibrillation

Feasibility and efficacy of CRT in this patient population is clearly suggested by early and recent studies (Table 1), although only a few studies addressed this issue directly. Gasparini et al. described the follow-up of more than 600 patients in whom 162 were in atrial fibrillation. Although surprisingly low number of patients passed the arbitrary used value of 85% biventricular capture for adequate pacing, those who did showed similar improvement in comparison with patients in SR.4 In this respect, the paper of Ferreira and colleagues is somewhat confirmatory. Furthermore, this was also seen in the study of Delnoy et al. Interestingly enough, the latter authors stressed the importance of >90% biventricular capture.7 In most publications, 85% is used as a standard value and therefore there is an obvious need to further investigate this important issue. Nevertheless, one of the main advantages of AVJ ablation is that hypothetically it provides almost 100% pacing in most patients (Table 2).11–13 Moreover, device programming is an important issue in this patient category. As the potential detrimental effect of RV pacing is prevented by the use of biventricular pacing, the optimal target heart rate should be selected in order to provide the best long-term cardiac output. This may require individual tailoring. As of now, no clear recommendation can be made for the optimal setting based on the currently available study data.

Biventricular pacing to prevent deterioration of left ventricular function

In patients with a bradycardia pacing indication, or after AV node ablation for atrial fibrillation, an increasing number of physicians implant a biventricular pacing system. At this point, another unique study should be mentioned. In the PAVE study, patients with chronic atrial fibrillation associated with medically refractory rapid ventricular rates were randomized to CRT or RV pacing after AVJ ablation. The unique aspect of PAVE should be emphasized, because it allowed the inclusion of patients either with or without normal left ventricular function.14 The outcome for patients with preserved left ventricular function did not differ from the RV pacing and CRT groups. Nevertheless, patients with symptomatic HF benefited more from CRT than from RV pacing after AVJ ablation.14 This suggests that the

### Table 1 Former cardiac resynchronization therapy studies allowing the inclusion of patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Pacing rate %</th>
<th>Follow-up (months)</th>
<th>Main finding</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR/AF</td>
<td>na/na</td>
<td>12</td>
<td>Favourable results of CRT in HF + AF patients</td>
<td>2002</td>
</tr>
<tr>
<td></td>
<td>67/64</td>
<td></td>
<td>Benefit of CRT in HF + AF patients</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>30/30</td>
<td>Reduction of AF incidence by biventricular pacing in HF patients</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>36/36</td>
<td>Similar benefit of CRT in HF patients with AF or SR</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td>263</td>
<td>167/96</td>
<td>Similar benefit of CRT in HF patients with AF or SR</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td>673</td>
<td>511/162</td>
<td>New-onset of AF did not diminish the impact of CRT</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>813</td>
<td>409/404*</td>
<td>CRT occur shorter AF duration and right atrial remodelling</td>
<td>2007</td>
</tr>
</tbody>
</table>

*CRT/medical therapy, SR, sinus rhythm; AF, atrial fibrillation; CRT, cardiac resynchronization therapy; na, not available; HF, heart failure.
real target population of CRT after AVJ ablation is the symptomatic HF population.

This initial analogy was named ‘Happy Ending Problem’ by the famous mathematician Erdos. The ‘Ending’ he had envisaged was his subsequent marriage to Esther Klein, who had previously challenged him with this so-called unsolved mathematical problem.

Whether AVJ ablation and biventricular stimulation will result in a happy marriage is still uncertain and this subject still requires some additional investigation. Specific well designed and adequately powered studies are necessary. For example, AVERT-AF reporting to be finished this year will increase our current knowledge. In conclusion, this paper does not provide us the ultimate result we needed to formulate clear recommendations. In contrast, it draws attention to the fact that despite the high number of patients suffering from the combination of atrial fibrillation and HF, only a few dedicated studies are available and most of our knowledge is obtained from studies where subgroup analysis was performed.

Conflict of interest: none declared.

References


Table 2 Studies including atrial fibrillation patients who underwent cardiac resynchronization therapy and atrioventricular node ablation

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Subgroups SR/AF + AVNA/AV – AVNA</th>
<th>Pacing rate % SR/AF + AVNA/AV – AVNA</th>
<th>Follow-up (months)</th>
<th>Main finding</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leon et al.</td>
<td>20</td>
<td>–/20/–</td>
<td>–/100/–</td>
<td>6</td>
<td>Benefit of biventricular upgrade in patients with HF + AF + AVN ablation</td>
<td>2002</td>
</tr>
<tr>
<td>Molhoek et al.</td>
<td>60</td>
<td>30/17/13</td>
<td>na/100/82</td>
<td>6</td>
<td>Greater benefit of CRT in HF + AF patients with AVN ablation</td>
<td>2004</td>
</tr>
<tr>
<td>PAWE</td>
<td>184</td>
<td>–/103/84</td>
<td>–/100/100</td>
<td>6</td>
<td>Improvement by biventricular pacing vs. RV pacing in HF + AF + AVN ablation</td>
<td>2005</td>
</tr>
<tr>
<td>OPSITE</td>
<td>56</td>
<td>–/56/–</td>
<td>–/100/–</td>
<td>12</td>
<td>Benefit of rhythm regularization by AVN ablation in HF + AF</td>
<td>2005</td>
</tr>
<tr>
<td>Kies et al.</td>
<td>74</td>
<td>–/51/23</td>
<td>–/100/81</td>
<td>6</td>
<td>Benefit of CRT + AVN ablation vs. – AVN ablation in HF + AF patients</td>
<td>2005</td>
</tr>
<tr>
<td>Gasparini et al.</td>
<td>162</td>
<td>511/114/48</td>
<td>na/100/88.2</td>
<td>48</td>
<td>Long-term benefit of CRT in HF + AF patients if AVN ablation was performed</td>
<td>2006</td>
</tr>
</tbody>
</table>

*aCRT in AF + AVN ablation/RVP in AF + AVN ablation; SR, sinus rhythm; AF, atrial fibrillation; CRT, cardiac resynchronization therapy; na, not available; HF, heart failure; and AVNA, atrioventricular node ablation.*