Ventricular pacing: a promising new therapeutic strategy in heart failure. For whom?

See page 1246 for the article to which this Editorial refers

At present long-term therapy for heart failure is entirely targeted to the modulation of neurohormonal systems, in particular the renin-angiotensin-aldosterone and the autonomic nervous systems. No therapy specific to the heart is available. Resynchronization of ventricular activity by electrical pacing might be such a therapy, but for whom? For a few selected patients or for many? And how can potential responders be recognized? These are obviously very important questions and are not specific to ventricular pacing. We must recognize that our therapeutic approach to heart failure is rather empiric. For instance, we do not use specific criteria to select patients to be treated with widely accepted classes of drugs such as ACE-inhibitors and beta-blockers. It is somewhat paradoxical that we base the prognostic stratification of our heart failure patients on a set of functional parameters which does not include neurohormonal variables, whereas the drugs we use are mainly neurohormonally active. However the definition of indicators outlining the potential responders to pacing therapy is particularly important because this therapy requires an invasive, disturbing procedure, is costly and is irreversible. We cannot be approximate; negative or even neutral effects would not be easily tolerated. Moreover the available clinical evidence shows that treated patients have extremely heterogeneous responses, at least acutely1–2, which underlines the need for accurate selection of candidates for the treatment. Thus the question of how to select the patients is of primary importance.

The rationale of pacing interventions is that inter- and intra-ventricular conduction delays which can occur in advanced heart failure, desynchronize the mechanical activity of the ventricles thus affecting their pump performance. In fact three major types of myocardial asynchrony can occur in heart failure patients. One is a progressive loss of integrity of the myocardial collagen matrix, typical of the familial cardiomyopathies but common to all dilated cardiomyopathies. The myocardial fibrillar collagen weave ensures structural integrity of adjoining myocytes and provides the means by which myocyte shortening is translated into overall left ventricular pump function. Disruption of the collagen network by altering the QRS and loss of mechanical efficiency. Another type of ventricular asynchrony is intraventricular conduction delay, generated by bundle branch blocks which most frequently impair conduction through the left bundle branch. A further type of ventricular asynchrony is that of regional wall motion abnormalities typical of ischaemic heart disease. Uncoordinated ventricular contraction alters regional workload and stress. The region of early activation contracts against minimal load, rapid early systolic shortening does not translate into pressure because the rest of the

myocardium is still inactive; late-activated regions have to face considerable systolic pre-stretch and are subjected to disproportionate load and stress. Much of the ventricular myocardial work is wasted in powerless activity and in transferring ejection from one portion of the chamber to another. In terms of overall ventricular mechanics, this results in a prolongation of the ventricular pre-ejection time, a shortening of the ejection and relaxation times, a reduction of ejection fraction, and an increase in mitral regurgitation.

The therapeutic approach to such desynchronized ventricular activity is to attempt to resynchronize the ventricles by modifying their activation sequence. Of course this cannot entirely compensate for intraventricular desynchronization but it can, at least in some patients, improve the ventricular mechanical efficiency. Thus, to select candidates for resynchronization therapy we should use criteria that are indicators of marked ventricular desynchronization. There are two families of such indicators: electrical, i.e. QRS and QT duration, and mechanical. The former are simpler, routinely available and easily standardized. This is the reason why the severity of disease (in terms of NYHA functional class) and a broad QRS are the usual inclusion criteria of heart failure patients in studies dealing with ventricular pacing.

According to this background, Farwell et al.[3], in this issue tried to answer an important public health question: how many people with heart failure are appropriate candidates for ventricular pacing? Importantly, to analyse the matter they did not examine a database of cardiac patients, but rather looked at consecutive patients admitted to a large General Hospital, during one year. By adopting evidence of dilated cardiomyopathy, a NYHA class III or IV, and a QRS duration greater than 120 ms as selection criteria, about 10% of heart failure patients (including those with atrial fibrillation) resulted as being appropriate candidates for ventricular pacing. Taking into account the huge population affected by heart failure worldwide, as the authors note, this represents a large number of patients. The authors also underline how critical the choice of the QRS length suitable for ventricular pacing is; restricting the indication to treatment to >150 ms would reduce the candidates to this therapy by over 50%. The authors think that adherence to this restrictive guideline ‘would exclude a significant number of patients who might benefit from this form of therapy’. On the basis of the present clinical evidence this is an unfounded assumption. It is, however, true that at present we lack a rationale for choosing a definite QRS length cut-off point. What we do know from previous research is that QRS duration broadens as the severity of left ventricular failure worsens and that the QRS complex is an independent marker of increased risk of death in heart failure patients[4-8].

However, what struck me, is that this is not true in the series reported by Farwell et al.[3] In this population the one-year mortality rate was identical (28%) in patients with QRS greater than or equal to 120 ms or less than 120 ms. Surprisingly enough, the authors do not comment at all on this important finding; they assume that ‘biventricular pacing’ will be beneficial both in terms of mortality and quality of life in heart failure patients and focus the question on how many would benefit from the treatment. The lack of association between QRS duration and mortality contradicts all the other reports on this matter. Recently Shamim et al.[6] analysed the prognostic power of ECG parameters in heart failure patients assessed in the heart failure unit of the Royal Brompton Hospital in London, and found that intraventricular conduction delay is a powerful independent predictor of mortality. A graded increase in mortality with an increase in QRS duration was noted, without any evidence of a threshold effect at any QRS value. Three year mortality rates were 20% for patients with a QRS less than 120 ms, 36% for those with a QRS between 120 and 160 ms, and 58% for a QRS >160 ms. The area under the receiver operating curve, which is a measure of the overall ability of the test to predict mortality, was rather high, 0.73.

Why are the results of Shamim et al.[6] and those of Farwell et al.[3] so different? A glance at the characteristics of the populations studied may help to answer this question. The mean age of the patients included in Shamim’s investigation was 60 years, all had stable heart failure and all were in sinus rhythm; patients receiving antiarrhythmic agents, those with any important non-cardiac disease and those unable to undergo exercise testing were excluded. One year mortality was 16%. In Farwell’s study no patients were excluded, the mean age of the subjects was 79 years, half were female, and although only 28% of the patients were in NYHA class III–IV, one year mortality was 29%. Obviously the populations studied in the two investigations were completely different. Interestingly, Shamim’s study group fits rather well with the general characteristics of the population usually enrolled in clinical trials, while Farwell’s study group is more similar to populations described in community studies or in national surveys of heart failure patients. The recently reported US National Hospital Discharge Survey[9] showed that of the 2.5 million heart failure patients discharged from US hospitals in 1995, 48% of males and 63% of females were aged 75 years or older. Males and females were
equally represented. In a survey performed in France\(^\text{[18]}\), the median age of hospitalized heart failure patients was 78 years with 63% of the cases being over 75 years old. The male/female ratio was about 1:1. The Scottish National Registry\(^\text{[11]}\) provides similar data: the mean age of hospitalized patients was 76 years. Again the number of males and females was similar. In contrast, in randomized controlled trials the mean age of subjects enrolled is usually between 60 and 65 years, typically the male/female ratio is about 4/1 and the general characteristics of the patients are quite different from those seen in the community (Table 1). This is obviously due to the selection imposed by the interplay of inclusion–exclusion criteria but not only to that. The findings of the Italian national heart failure database, which includes more than 11 000 outpatients consecutively enrolled in the last 5 years by about 140 cardiology centres, are similar to those observed in the trials’ populations: the mean age of patients is 63 years, 80% are males and the annual mortality is around 16%. It is evident that this is the profile of heart failure patients seen in cardiology centres, which is markedly different from the profile of heart failure patients seen in the community. Because the randomized, controlled trials dealing with heart failure are carried out by cardiologists, they enroll the patients that they see in their units, who represent a small subset of the universe of heart failure patients: about 5% in Scotland, 16% in the U.S.A., 20% in Italy. An interpretation of the strong prognostic significance of QRS duration in heart failure patients observed by Shamim et al.\(^\text{[16]}\), as opposed to the lack of any prognostic relevance in Farwell’s study\(^\text{[23]}\), may be that in selected, relatively young, cardiac patients without relevant co-morbidities, in whom functional abnormality of the heart is the core of their disease, an indicator of ventricular desynchronization such as QRS broadness is clinically and prognostically important, whereas in old patients, in whom the heart failure syndrome portends different clinical and prognostic characteristics, it is not. If this is true, Farwell and co-workers’ translation of the selection criteria used in small trials of selected patients to the universe of heart failure patients, in order to evaluate how many people might benefit from ventricular pacing, is based on faulty assumptions.

Actually, I feel that it is too early to pose such a question. I join John Cleland\(^\text{[12]}\) in saying that ‘the techniques for ventricular resynchronization are in their infancy. The hypothesis that atroventricular and ventricular asynchrony are important contributors to cardiac dysfunction is attractive, plausible and testable’, but it is still an hypothesis. Several trials are in progress to validate it. If ventricular pacing (either biventricular as Farwell and co-workers seem to support or left ventricular as others suggest) is proven to be effective in randomized, controlled trials, the process of incorporating this new therapeutic strategy into clinical practice will start and it is easy to predict that it will not be a simple process, for several reasons including the technical difficulties and the cost. Given the large heterogeneity of individual responses to this treatment\(^\text{[1,2]}\) the definition of simple indicators allowing identification of potential responders from among the universe of heart failure patients will be of vital importance. To this purpose it is essential that the randomized trials are designed in such a way as to obtain not only statistically significant results in terms of morbidity–mortality, but also to permit subgroup analyses allowing identification of the characteristics of the responders and non-responders. Meta-analyses of pooled data will be of particular importance because, as a consequence of the high cost of the devices, the sample sizes of the projected trials are not very large. I would like to be confident that commercial companies will have the intellectual integrity to make their data available to such analyses. However, even if this is the case, it will not be enough. Outcome studies will be necessary to follow and guide the

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**Table 1**

<table>
<thead>
<tr>
<th>Characteristics of HF patients</th>
<th>Randomized controlled trials</th>
<th>Community setting</th>
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<tbody>
<tr>
<td>Mean age (years)</td>
<td>60–65</td>
<td>75–80</td>
</tr>
<tr>
<td>Gender: male, female</td>
<td>4/1</td>
<td>1/1</td>
</tr>
<tr>
<td>LV ejection fraction &gt;40%</td>
<td>Exclusion criterion</td>
<td>30–40%</td>
</tr>
<tr>
<td>Unstable ischemic heart disease, hypertension</td>
<td>Exclusion criteria</td>
<td>Frequent</td>
</tr>
<tr>
<td>Creatinine ≥2–2.5 mg %</td>
<td>Exclusion criterion</td>
<td>17–34%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>~20%</td>
<td>~40%</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>Exclusion criteria</td>
<td>Very frequent</td>
</tr>
<tr>
<td>Target drug dose</td>
<td>Usually reached</td>
<td>Usually lower</td>
</tr>
<tr>
<td>Compliance</td>
<td>Optimal</td>
<td>Poor</td>
</tr>
<tr>
<td>Observation period</td>
<td>1–3 years</td>
<td>Lifelong</td>
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</tbody>
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incorporation of the therapeutic procedure into the real world[13], populated by old, fragile subjects who constitute most of the universe of heart failure patients.

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References


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Beta-blockers, ventricular arrhythmias, and sudden death in heart failure: not as simple as it seems

See page 1259 for the article to which this Editorial refers

The recent experience with beta-blockers in randomized trials in patients with chronic heart failure has been nothing short of remarkable. Four out of the five currently completed trials were stopped prematurely because of highly significant reductions in mortality [USCP (United States Carvedilol Programme), CIBIS II (Cardiac Insufficiency Bisoprolol Study), MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Heart Failure), and COPERNICUS (Carvedilol Prospective Randomised Cumulative Survival Trial)[1–3]. The fifth, BEST (Beta-blocker Evaluation Survival Trial), did not show a reduction in all-cause mortality and interpretation of this discrepant finding awaits the publication of full details of the study[4]. All of the three fully published trials reported a substantial reduction in the risk of sudden death (by 55% in USCP; 44% in CIBIS II, P=0.0011 and 55%, P=0.0002 in MERIT-HF)[1–3]. It is, therefore, tempting to see the report of Cice et al. in the current issue as offering mechanistic support for the effect of beta-blockers on sudden death in chronic heart failure[6]. There are, however, a number of problems with this interpretation.

Cice et al.[6] report an ‘on treatment’ rather than ‘intention to treat’ analysis, excluding 20/155 (13%) of patients who did not complete the double-blind phase of the study. Secondly, ‘within group’ rather and ‘between group’ comparisons were made. Both these limitations reduce the certainty that carvedilol really did reduce ventricular arrhythmias in their patients. Indeed, even though beta-blockers are widely perceived to have an antiarrhythmic action, supporting data from properly controlled trials are sparse[7–9].

Even if we do accept that carvedilol really did reduce the prevalence of ventricular premature beats