Chronic right ventricular pacing, adverse remodelling, and CRT: an ounce of prevention?

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This commentary refers to ‘Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial’, by J.Y.-S. Chan et al., on page 2533

In medicine, it is encouraging when research yields results consistent with our understanding of the operative mechanisms, especially when there is a direct potential impact on clinical practice. Chan et al. have provided us with such a result and a clear message. The 2-year follow-up in the Pacing to Avoid Cardiac Enlargement (PACE) trial confirms that chronic right ventricular (RV) pacing in patients with bradycardia and preserved left ventricular (LV) function leads to sustained and progressive deterioration of LV ejection fraction (EF) and increases in LV volumes. This adverse remodelling process was prevented by pacing with cardiac resynchronization therapy (CRT).

Adverse LV remodelling is a complex maladaptive process involving structural, haemodynamic, histopathological, and genetic changes. The process may be multifactorial and is frequently encountered in patients after loss of myocardium (myocardial infarction), volume overload (valvular insufficiency), or pressure overload (hypertension). It involves both LV hypertrophy and dilatation, and is initially an adaptive response that serves to maintain stroke volume. If persistent and progressive, the process becomes maladaptive and leads to further deterioration of LV function, LV dilatation, and eventually the typical symptoms of heart failure (HF).

It is evident that substantial prolongation of the QRS interval, especially with a left bundle branch pattern, results in a delayed and dyssynchronous LV contraction. This dyssynchrony may be a major contributor that can both initiate and aggravate the process of adverse remodelling. In patients with symptomatic HF, systolic dysfunction, and QRS prolongation, CRT has been shown to be highly efficacious in reducing morbidity and prolonging survival. There is concordance between the reductions in LV volumes, the best indices of LV remodelling, and improvement in clinical outcomes. Acute and chronic RV pacing results in substantial widening of the QRS complex and induces both inter- and intraventricular dyssynchrony. Improvements in measures of dyssynchrony following CRT in patients with HF and previous RV pacing have been demonstrated.

The recently published, focused ESC Guideline Update on devices in heart failure provides a class I recommendation with level of evidence A for CRT, both for patients with systolic dysfunction, New York Heart Association (NYHA) III/IV symptoms, and a QRS >120 ms and for patients with NYHA II symptoms and a QRS >150 ms. The current recommendations for patients with a conventional indication for pacing, systolic dysfunction, and symptomatic HF are class 1 with a QRS >120 ms and class II for patients with QRS <120 ms.

The PACE trial was designed to compare apical RV pacing with CRT in patients with bradycardia and a preserved EF. A total of 177 patients with a conventional indication for a pacemaker and preserved LV function (EF >45%), were, following successful implantation of a CRT device, randomized and programmed to either RV pacing or CRT pacing. The trial evaluated LV function and measurements of remodelling over 12 months at a blinded core laboratory using three-dimensional echocardiography. The results published in the New England Journal of Medicine last year demonstrated significant and substantial reductions in LVEF and increases in end-systolic LV volumes in the RV pacing group during the 1-year follow-up. Evidence of deterioration in LV function was not observed in the group with CRT pacing.

The results of the 2-year follow-up of the PACE trial of Chan et al. are impressive, consistent with the original report, and demonstrate that the deleterious effects of chronic RV pacing on LV function and volumes are sustained and progressive. The co-primary endpoints were LVEF and LV end-systolic volume (ESV). A total of 163 patients (92%), still on their original randomization, were available for follow-up. The reported total

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amounts of paced beats were similar for the two groups (97.9% in the RV paced group and 92.9% in the CRT group; non-significant). By both intention-to-treat and per-protocol analyses, further deterioration in both co-primary endpoints was observed in the group of patients randomized to RV pacing. No evidence of deterioration was seen in the patients randomized to CRT. The between-group difference at 2 years was substantial; 9.9% for LVEF (P < 0.001) and 13 mL for LVEVs (P < 0.001). Pre-specified subgroup analysis confirmed consistency in the results for both endpoints across all subgroups. In the study of Chan et al., figure 1 provides a rapidly digested summary of the time course and magnitude of these deleterious changes.

The reported findings are consistent with previous reports, apart from the PREVENT-HF trial which did not demonstrate differences in LV function over 1 year in a similar population with preserved EF. However, as discussed by Chan et al., this trial was small, with less rigorous echocardiographic assessments and substantial drop-out and crossover for CRT to RV pacing due to failure to implant the LV pacing lead successfully. Ongoing trials address similar hypotheses and should provide additional information as well as evaluate whether the prevention of adverse remodelling by CRT translates into improved clinical outcomes. A recent report compared the degree of reverse remodelling in patients with HF receiving CRT de novo with patients receiving CRT as an upgrade from a previous device [RV pacemaker or implantable cardioverter-defibrillator (ICD)]. The improvements in remodelling, as evidenced by increased LVEF and reductions in systolic and diastolic volumes, were essentially identical for the two groups. It is interesting to note that in the recently reported ESC CRT survey, 29% of 2367 CRT implants in 13 European countries were upgrades from previously implanted RV pacemakers.

The PACE trial provides trial evidence that should be taken into consideration by physicians responsible for the management of patients with a conventional pacing indication. However, there remain several important unanswered questions.

As pointed out in the editorial accompanying the publication of the 1-year results of PACE, RV pacing in patients with sinus node dysfunction without atrioventricular (AV) block is not required and may have resulted in avoidable adverse remodelling in these patients. This is perhaps the most important methodological and ethical criticism of this trial.

The lack of between-group difference on 6 minute walk distance or the quality-of-life tool (SF-36 score) may appear surprising at first. However, these were not patients with symptomatic HF or reduced EF. The 2-year mean EF in the RV group changed from 61.5% at baseline to 53%, but still remained well above conventional cut-off points for preserved systolic function. Clinicians are clearly confident from previous randomized clinical trials that CRT is associated with improvements in symptoms, functional capacity, and clinical outcomes in symptomatic patients with systolic dysfunction.

As the authors acknowledge, the PACE trial was underpowered for analysis of clinical events. The sample size was small and the follow-up short, especially for asymptomatic patients with preserved EF. We are grateful to the local ethical committees for approving the extended follow-up protocol and permitting the investigators to maintain randomization after the 1-year PACE results were presented. Only one patient crossed over to CRT during the extended follow-up due to worsening HF.

So what are the clinical implications? What type of device will you implant in your next patient with bradyarrhycia and a preserved EF? Will you first implant an RV lead and only upgrade to a CRT when there is evidence of adverse remodelling? Routine follow-up at pacemaker outpatient clinics, usually performed by a pacemaker technician, rarely includes an echo. Periodic screening for evidence of early systolic dysfunction would demand increased resources.

Although not addressed in PACE, I imagine these results might affect our management of patients with HF and preserved EF requiring a pacemaker. There is of course some non-trivial, added morbidity associated with CRT implantation as compared with RV pacing, especially with inexperienced operators. What amount of benefit would justify the modest increased risk at implantation as well as the increased costs of a device with shorter longevity?

Obviously, much depends on the pacing indication. Patients with infrequent episodes of bradyarrhycia requiring a back up pacemaker would not be candidates. However, if there is AV block and expectation of pacemaker dependency, a device that results in chronic apical RV pacing will be likely to put your patient at risk for adverse remodelling and it may begin soon after the implantation and progress. However, isolated sinus node dysfunction without AV block may not require an RV lead, and the PACE trial results do not support implantation of a CRT in this population. As with all therapies, the patient’s biological age, functional status, and extent of co-morbidity will enter into the management decision.

Future clinical research must address the major unanswered questions. How should we identify the target population at greatest risk for adverse remodelling following RV pacing and therefore likely to benefit from a CRT device? The impact on health resource utilization would be considerable. Will CRT in patients with bradycardia and preserved systolic function translate into prevention of meaningful adverse endpoints such as hospitalization for HF? If so, it becomes a good investment. Benjamin Franklin put it well: ‘An ounce of prevention is worth a pound of cure.’ In this case, it is about 2 ounces.

**Conflict of interest:** none declared.

**References**


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