Peri-infarct pacing to prevent left reverse remodelling: an unvalidated concept?

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Online publish-ahead-of-print 27 October 2015

The management of acute ST-segment elevation myocardial infarction (STEMI) has evolved considerably in recent decades. Modern treatment includes STEMI network activation, antithrombotic drugs, and rapid early revascularization (mainly by mechanical reperfusion).1,2 Cardioprotective interventions aimed at reducing the extent of myocardial necrosis have been evaluated in basic and clinical research with negative or minimal effects.1,2 After myocardial injury, left ventricular (LV) remodelling of the infarct zone and the circumferential residual viable myocardium leads to thinning and dilatation of the affected myocardium and hypertrophy of the viable myocardium. This process of LV remodelling impairs LV function, enlarges the left ventricle, and has a major effect on the patient’s outcome in terms of quality of life, heart failure, and survival. Therapies that may attenuate or reverse the process of LV remodelling might have a favourable effect on the prognosis of patients with STEMI. In this issue of the journal, Stone et al. report the results of a clinical trial that assessed a new concept for preventing or attenuating LV remodelling after a myocardial infarction, namely peri-infarct pacing.3 Chronic cardiac pacing is not only indicated for patients with bradycardia but, as in most patients implanted with a cardiac resynchronization device, also for haemodynamic purposes.

Previous studies in normal hearts using magnetic resonance imaging have shown that electrical pre-excitation reduces local loading characteristics while increasing them in remote and late activated regions.4 The hypothesis of the potential efficacy of peri-infarct pacing to prevent LV remodelling after myocardial infarction was first evaluated in animal studies. In ischaemic and surrounding tissue, an increase in wall stress is observed, which could be reduced by pacing. Shuros et al. showed, in a myocardial infarction model in swine, that ventricular pre-excitation with 8 weeks of pacing in the border regions significantly reduced regional strain and decreased heart weight and LV and left atrial dimensions compared with no pacing.5 Although not significant, cardiomyocyte apoptosis was lower in the pacing group. In a rabbit model of myocardial infarction that compared different pacing modalities (no pacing, right ventricular pacing, and biventricular pacing) with a sham-operated group without myocardial infarction, only biventricular pacing (with the LV lead positioned away from the apical infarction) prevented systolic and diastolic LV dilatation and the reduction in fractional shortening.6

The feasibility of biventricular pacing in patients with recent myocardial infarction was reported in a small pilot dual-centre randomized study.7 Eighteen patients with myocardial infarction within the previous 30–45 days with an LV ejection fraction (LVEF) ≤30% and QRS duration ≤120 ms and conventional medical therapy were randomized to receive a biventricular intracardiac cardioverter defibrillator (ICD) (treatment group) or a dual ICD (control group). In the biventricular group, the LV lead was positioned, if possible, in a lateral vein close to the lateral edge of the infarction. The goals of the study were to assess the safety of delivering biventricular pacing in this population and the effect of biventricular pacing on the LV volume at 1 year. Most of the patients (15/17 who were implanted) had a myocardial infarction. Out of eight successful biventricular implantations, the lead was positioned near the myocardial infarction in seven. LV end-diastolic and end-systolic volumes did not change in the biventricular group, but increased in the control group. However, the difference was only significant for LV end-diastolic volume and not for LV end-systolic volume, which is widely accepted as the best criterion to evaluate LV reverse remodelling in cardiac resynchronization therapy (CRT) trials. Importantly, no differences were observed for LVEF or various clinical endpoints [New York Heart Association (NYHA) class, quality of life, and 6-min walk test]. With a sample size of only 17 patients, the study needs to be considered as hypothesis-generating at best, and its
lack of power precluded the assessment of differences in clinically relevant endpoints, particularly the safety of the invasive technique.

The concept of peri-infarct pacing to prevent LV remodelling has been further evaluated, by the same group, in a larger randomized clinical trial including 80 patients with an anterior myocardial infarction, a high concentration of peak creatine kinase, QRS < 120 ms, and LVEF ≤ 35% with ≥ 30% wall motion abnormality. In the Prevention of Myocardial Enlargement and Dilation Post Myocardial Infarction Study (MENDMI), the treatment group received a biventricular ICD 2–14 days (much sooner than the pilot study) after myocardial infarction with a peri-infarct LV lead placement and the control group received a single- or dual-chamber ICD. In 39/42 patients in the pacing group, an LV lead was successfully implanted, but 7 patients (19%) were excluded during follow-up because of loss of LV capture, which limited the power of the study. Interestingly, there was also a discrepancy between the evaluation of LVEF by the investigators and the core laboratory, the mean values being 28% and 36%, respectively. A significant reduction in wall motion abnormality was observed in the biventricular pacing group compared with the control group, but this had no effect on the primary endpoint (the change in LV end-diastolic volume from baseline to 12 months). Similarly, LV end-systolic volume and LVEF remained unchanged, and no difference was observed for NYHA class, quality of life, brain natriuretic peptide, hospitalization rate, or survival. Of note, 26% of the patients with biventricular pacing had an adverse event related to the LV lead. One of the limitations of this study to validate the concept was that there was no proof of real pre-excitation of the left ventricle.

Despite these neutral study results, the investigators of the Post-Myocardial Infarction Pacing Remodelling Prevention Therapy (PRomPT) trial decided to evaluate this concept in a new clinical trial with substantial changes compared with the previous one. The required concentration of creatine kinase was higher, implantation of the device was earlier, the follow-up time was longer (18 vs. 12 months), and the number of patients was higher (250 vs. 80). Interestingly, two pacing configurations were tested—biventricular and LV alone pacing, the latter to avoid the potential deleterious effects of right ventricular pacing. In line with earlier trials, the results of the PRomPT trial demonstrate that the delivery of biventricular or LV peri-infarct pacing does not affect LV remodelling. No difference was observed for the various clinical endpoints.

Do we have to conclude, on the basis of this study, that the concept of peri-infarct pacing is not efficient to prevent LV remodelling? Before answering this question we have to emphasize some limitations of the PRomPT study. As highlighted by the authors, recruitment was lower than expected, leading to a reduction in the power of the study (from 90% to 80%) and an alteration of alpha (from 0.05 to 0.1). Ultimately, only 120 patients were included, thereby limiting definitive conclusions, with regards not only to efficacy, but also to safety. Importantly, the total complication rate in the entire population was 19%, with an 8% rate of lead dislodgement, which is common with this technique but has to be kept in mind in assessing the net clinical benefit, if any, for the patient. Since the implantation of an LV lead in the coronary sinus is highly dependent on the anatomy, but also the pacing threshold (especially in scar tissue and areas close to the scar), it is not surprising that only 60% of the LV leads were implanted in the anticipated optimal pacing site. While a comparison of the effect of optimal and suboptimal location did not show any difference, the relatively small sample size limits the power of this subanalysis.

In all of these human studies evaluating the concept of peri-infarct pacing to prevent LV remodelling, the QRS duration was normal. In the PRomPT study, pacing was associated with an unsurprising increase in QRS duration of 20 ms. We have to keep in mind that the Echocardiography Guided Cardiac Resynchronization Therapy (EcoCRT) trial, which assessed the efficacy of CRT in patients with narrow QRS, was terminated for futility and an increase in mortality in the CRT group. In the EchoCRT trial, biventricular pacing did not affect reverse remodelling in patients with narrow QRS. It is also worth remembering that in the experiment study by Saba et al., the myocardial infarction induced by coronary occlusion was associated with a significant prolongation of QRS duration, and biventricular pacing significantly reduced the QRS width.

In summary, the PRomPT trial was initially designed to test whether peri-infarct pacing would attenuate post-myocardial infarction adverse remodelling, thereby hopefully setting the stage for a definitive outcome trial. In view of the neutral results of the PRomPT trial, as well as those of the earlier randomized, smaller MENDMI trial, however, such an adequately powered outcome trial of peri-infarct pacing is now unlikely to be conducted. This leaves us with the unmet clinical need to develop novel interventions to attenuate adverse LV remodelling to reduce the morbidity and mortality of patients with a large STEMI, particularly in the early post-infarction period.

Conflicts of interest: none declared.

References