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EDITORIAL

Can cardiac resynchronization therapy cause harm?

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This editorial refers to 'Effect of cardiac resynchronization therapy in patients without left intraventricular dyssynchrony'†, by D. Auger *et al.*, on page 913

Most beneficial and effective therapies also have the potential to cause harm. Cardiac resynchronization therapy (CRT) is now proven by large-scale clinical trials to be highly beneficial for chronic heart failure patients, with reduction in mortality and re-hospitalization, and improved quality of life.[1,2] However, it does have potential adverse effects such as those associated with any pacemaker procedure (infection, lead dislodgement, perforation, etc.) but, in addition, it is also clear that not all patients improve, with ~11–46% apparently failing to benefit from CRT (the rates are lower if clinical parameters are used and higher with echocardiographic measurements).[3] Also, there has been suspicion that in some patients CRT may make the condition worse. In the recent PROSPECT (Predictors of Response to CRT) trial, the clinical composite response was unchanged in 50% but actually worsened in 16%; and 35% had a reduction in left ventricular (LV) end-systolic volume of 15% while 9% had LV volumes actually increased by >15%.[4] The updated ESC guidelines recommend that CRT should be considered in patients with New York Heart Association functional class II–IV symptoms, LV ejection fraction ≤35%, and electrocardiographic (ECG) QRS widening of at least 120 ms.[5] Although it seems reasonable to assume that QRS widening on the ECG represents delays in regional ventricular mechanical activation, a large volume of data has demonstrated that there is a subset of patients with widened QRS complexes who have no significant mechanical dyssynchrony.[6] If reversal of mechanical dyssynchrony is the mechanism of benefit with CRT, then this finding has important implications.

Two recent studies have examined the relationship of baseline echocardiographic dyssynchrony to long-term survival after CRT. Gorscan *et al.* in a single-centre study found that the presence of dyssynchrony before CRT as evident by tissue Doppler imaging or speckle tracking echocardiography was associated with fewer deaths, transplants, or the need for an LV assist device.[7] A second study, the STAR study (speckle tracking and resynchronization), enrolled 132 heart failure patients from three centres for CRT to assess the relationship of dyssynchrony measured by speckle tracking and clinical outcome.[8] The presence of baseline dyssynchrony, defined as peak strain delay ≥130 ms, was associated with a better ejection fraction response as well as reduced mortality and need for cardiac transplant or LV assist device over 3.5 years. Unfavourable clinical events occurred in 53% of patients who lacked both radial and transverse plane dyssynchrony, whereas if baseline dyssynchrony was present only 12% had negative events ($P < 0.01$). These two long-term outcome studies support the notion that baseline dyssynchrony measured by tissue Doppler imaging, routine pulsed Doppler, or speckle tracking methods is associated with a more favourable outcome following CRT. In addition, a subanalysis of the PROSPECT trial, including 286 patients treated with CRT, demonstrated that larger baseline LV dyssynchrony as assessed with tissue Doppler imaging was strongly associated with larger reduction in end-systolic volume at 6 months follow-up ($P = 0.0022$).[9] Conversely, several studies (using echocardiography principally) have demonstrated that the lack of baseline mechanical dyssynchrony is associated with a less favourable outcome after CRT.[10] Recently, the lack of dyssynchrony before CRT has been shown to be associated with a significantly lower long-term probability of freedom from heart transplantation, LV assist device placement, or death.[7] Also, patients who failed to improve their tissue Doppler measures of dyssynchrony after CRT have a lower chance of LV reverse remodelling improvement.[11,12] A recent substudy from the MADIT-CRT trial found that worsening of LV mechanical dyssynchrony was more frequently observed among the patients in the implantable cardioverter defibrillator (ICD) only arm compared with patients who received a CRT-D (35% vs. 18%).[13] Moreover, the primary outcome of death or a heart failure event was more frequent in the ICD-only group compared with the CRT-D group (15.9% vs. 6.9%, respectively). Intriguingly, worsening of LV dyssynchrony and contractile function was associated with increased risk of a primary outcome (hazard ratio 3.36, 95%

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confidence interval 1.7–6.64, $P < 0.0001$). Thus, all these studies support the concept that there is a relationship between the presence of mechanical dyssynchrony and response to CRT, and that reversal of dyssynchrony in the main mechanism of benefit of CRT.

However, the important question of whether CRT can worsen LV function in patients who do not have mechanical dyssynchrony pre-operatively, despite the presence of left bundle branch block (LBBB), remains unaddressed. It is now established that right ventricular apical (RVA) pacing can induce LV dyssynchrony where none existed before and was associated with deterioration of LV systolic function.[14] Recently the Pacing to Avoid Cardiac Enlargement (PACE) study has confirmed the superiority of biventricular pacing to RVA pacing in preventing the deterioration of ejection fraction and LV remodelling at up to 24 months, in patients with bradycardia and preserved systolic function.[15,16] In a further report from the PACE study it was found that over the medium term, LV remodelling and deterioration of ejection fraction occurred in those who developed early LV systolic dyssynchrony after RVA pacing.[17]

In view of these findings, the study of Auger *et al.*[18] is particularly relevant and interesting. This was a retrospective analysis of 290 heart failure patients without significant baseline LV dyssynchrony (<60 ms as assessed with tissue Doppler imaging) treated with CRT. In the group of patients without significant LV dyssynchrony at baseline, median LV dyssynchrony increased from 22 ms (interquartile range 16–34 ms) at baseline to 40 ms (24–56 ms) 48 h after CRT. The cumulative mortality rates after 1, 2, and 3 years follow-up in the subgroup with LV dyssynchrony ≥40 ms after CRT implantation for 48 h were significantly higher compared with patients with LV dyssynchrony <40 ms (10, 17, and 23% vs. 3, 8, and 10%, respectively; log-rank $P < 0.001$). Induction of LV dyssynchrony after CRT in those without it beforehand was an independent predictor of mortality (hazard ratio 1.247; $P = 0.009$). Thus, the group of patients with induced LV dyssynchrony after CRT had a lower response rate and worse long-term outcome as compared with patients without induced LV dyssynchrony. In contrast, a control group formed by heart failure patients with overt LV mechanical dyssynchrony at baseline showed a significant decrease in LV mechanical dyssynchrony and improved long-term outcome. As the authors conclude 'LV mechanical dyssynchrony assessment at baseline in heart failure patients undergoing CRT implantation could be crucial in order to anticipate the results of the therapy'. Their results also raise the question of whether CRT should be switched off in those patients who have worsening dyssynchrony after implantation, especially if they had no evidence of mechanical dyssynchrony before implantation despite the presence of wide QRS complexes. There are selected ECG subgroups who are observed to have a lower response rate based on current criteria of patient selection, which include QRS duration 120–150 ms and conduction pattern of right bundle branch block (RBBB) or intraventricular conduction delay.[19] These patients are believed to have less severe pre-existing systolic dyssynchrony, and, based on the observation of the current study, more studies are needed to address if CRT may be ineffective or even potentially harmful.[20] Of course this was a retrospective study and not randomized, so merely hypothesis generating, but the results are persuasive. In future, in larger clinical trials more attention should be given to those who do not benefit from CRT—it may not be just progression of the underlying disease but the treatment may be actually worsening an already bad condition. These results also remind us that although large-scale randomized trials are the only way to assess effectiveness and harm in large populations, there will be individuals within that population who will derive no advantage and only experience the adverse and unwanted side effects. In part this is due to the wide and often imprecise criteria for entry into clinical trials which reflect our current inability to identify those who will benefit the most and avoid others being exposed to potential harm for no benefit whatsoever.

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CARDIOVASCULAR FLASHLIGHT

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Intracardiac emboli as first presentation of cardiac AL amyloidosis

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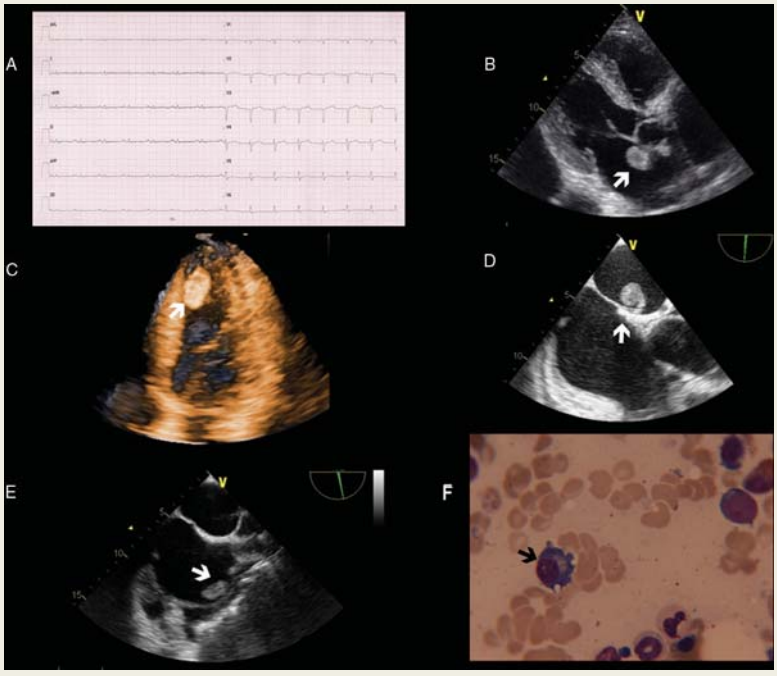

A 74-year-old patient presented at the Emergency Room with exercise-induced shortness of breath. Clinical examination revealed arterial hypertension (167/110 mmHg), decreased breathing sounds, and bilateral oedema. Electrocardiogram showed low voltage (*Panel A*) and aspecific repolarization changes. Chest X-ray confirmed bilateral pleural effusion. D-dimers (7644 ng/mL) and NTproBNP (9650 pg/mL) were elevated. Transthoracic echocardiography demonstrated a concentric hypertrophic left ventricle with myocardial sparkling, poor systolic function (ejection fraction 28%), dilated left atrium, and restrictive filling pattern. A large thrombus was seen in the left atrium (*Panel B*) and left ventricle (*Panel C*). Transoesophageal echocardiography demonstrated a left atrial thrombus passing through a patent foramen ovale (*Panel D*) and thrombotic material in the right atrium (*Panel E*) originating from the inferior caval vein. Deep venous thrombosis was confirmed in the superficial femoral vein. Angio-CT did not show pulmonary embolism. The patient was immobilized and treated with low-molecular-weight heparin. Four days later, left-sided thrombi had disappeared. Cereberal MRI demonstrated recent parieto-occipital infarction without neurological symptoms. Laboratory diagnosis of cardiac AL amyloidosis was suggested by elevated serum-free light chains: λ, 181 mg/L (ref: 5.7–26.3); κ, 20.3 mg/L (ref: 3.3–19.4); ratio: 0.11 (ref: 0.26–1.65), suspicion of clonal lambda fraction on serum immunofixation, monoclonal free lambda chains on urine immunofixation and urine lambda secretion: 16.4 mg/dL (ref: 0–1). Bone marrow showed a small clone of abnormal plasmacells (3%) (*Panel F*). Flow cytometry could confirm the abnormal clone (lambda) plasma cells. Characteristics of multiple myeloma such as hypercalcemia, bone pain, or lytic bone lesions were not present. Subsequently, coronary angiography was performed and myocardial right ventricular biopsy performed. There was non-obstructive coronary artery disease. Histological diagnosis of primary (AL) amyloidosis was confirmed on the congo red stain. Treatment was initiated with oral anticoagulants, thalidomide, and dexamethasone; serum-free lambda levels diminished subsequently.