Cardiac resynchronization therapy responders can be better identified by specific signatures in myocardial function

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...it is all about mechanics

We are in the third decade of the cardiac resynchronization therapy (CRT) era and CRT has become a standard treatment option for heart failure patients with reduced ejection fraction and conduction delays. Although CRT cannot cure any underlying myocardial disease causally, it leads to reverse remodelling, relieves symptoms, reduces the need for hospitalization, and prolongs survival of heart failure patients. Unlike many other therapies in modern medicine, its mode of action is intriguingly simple: it is purely mechanical.

In the classic example of a left bundle branch block, the early activated septum contracts first, which ends left ventricular (LV) filling by closing the mitral valve, but which does not lead to a relevant pressure rise in the LV as the contracting myocardial volume is too small. Only the delayed activation of the remaining myocardium, particularly the lateral wall, enables LV ejection. As the septum is already relaxing at this time, most of the ejection work is borne by the late contracting lateral regions which then hypertrophy while the unused septum virtually atrophies. Besides the uneven workload distribution which can be visualized by scintigraphy,1 the mutual stretching of opposing walls leads to the typical back-and-forth motion of the LV apex for which we had coined the term “Apical Rocking (AR)” in the early 2000s.2

As a consequence of this mechanical dyssynchrony which is caused by the delay in electrical activation, the left ventricle remodels. It is not sure, however, if a pure delay in excitation can cause myocardial remodelling on its own. For example, patients with otherwise healthy hearts who receive right ventricular pacing, e.g. for AV block, and henceforth have an LBBB like conduction pattern, do not remodel. This suggests that remodelling requires underlying myocardial pathology in addition to the conduction delay. Such pathology might be ischaemic scar in the case of a post-infarct patient or another, less well-understood problem in case of a patient with dilated cardiomyopathy. It must be noted that underlying pathology does not only provide the substrate for the adverse effects of a conduction delay but may by itself trigger remodelling of the ventricle. This explains the lesser CRT success in ischaemic cardiomyopathy patients and the inverse relation between CRT effect and infarct size.3

How to find Mr/Mrs right?

Cardiac resynchronization therapy antagonizes the delay in regional myocardial contraction by pre-exciting the delayed segments. Conversely, this means that successful CRT would require the presence of a regional contraction delay and that patient selection should focus on the detection of such a delay. Echocardiography appears as the natural method of choice for this task and many echocardiographic parameters to describe mechanical dyssynchrony of the LV had been proposed in the past. Unfortunately, most parameters failed in prospective studies and have consequently never been considered in CRT implantation guidelines.

The failure of most mechanical dyssynchrony parameters can be explained by the aforementioned: they were not sufficiently specific. Detecting mechanical de-coordination alone is not enough. A specific parameter has to detect the mechanical signature of an LV which is amenable to CRT. For this, it needs to identify typical motion or deformation patterns and it has to differentiate those from patterns which are caused by underlying and/or concomitant pathology, e.g. ischaemic scar. If a parameter cannot accomplish this, it cannot add diagnostic value to the patient selection criteria which have led in the past to unsuccessful treatment in almost one-third of the patients. This notion is also indirectly confirmed by the recent editions of the patient selection recommendations for CRT which put more emphasis on an electrical phenomenon which is the closest surrogate of a mechanical contraction pattern amenable to CRT: the LBBB in the ECG. While older guideline versions relied on a broad QRS as non-specific sign of dyssynchrony, highest recommendations are now given for patients with LBBB while device implantation in non-LBBB patients is more discouraged.

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A pathophysiology-driven approach

However, QRS morphology can only be a surrogate for myocardial mechanics and the question remains, if echocardiographic parameters could do even better. Recent computer modelling has demonstrated that mechanical signatures of conduction delays and of regional myocardial dysfunction can be detected and distinguished. It appears therefore likely that well-chosen echocardiographic parameters could improve patient selection further. Evidence is growing that AR might be such a parameter. In the past years, several studies have investigated AR or one of its components, Septal Flash, and showed concordantly a predictive value of this marker which is independent and above of QRS width and the existence of a LBBB like pattern in the ECG. A recent study in LBBB patients with and without ischaemic cardiomyopathy could further demonstrate that AR favourably combines the mechanical influences of temporal differences in contraction and of regional inhomogeneity of myocardial contractility: most AR is visible in pure LBBB while increasing scar size reduces AR independent of the presence of an LBBB.

The study of Ghani and colleagues which is published in the current issue of this journal adds to the evidence that the search for specific mechanical signatures in LV function can improve CRT patient candidate selection. The authors have analysed 295 patients of their registry which underwent echocardiography prior to CRT implantation according to guideline criteria and which were followed over a mean time of 5.2 years. Patients with AR at baseline had a significantly better survival and remained 2.3 times more often free of major adverse events during follow-up while the bundle branch block morphology before implantation had no significant predictive value. The authors have to be congratulated for their valuable contribution to this search for a more specific parameter for CRT patient candidate selection. As the authors correctly state, their data need now to be flanked by larger, multi-centric studies, and studies which particularly focus on narrow QRS cardiomyopathies. It is therefore reassuring that their data are in-line with a recent multi-centric study which has investigated outcome of 1060 CRT patients and which found that patients with AR at baseline had a 2.5 times higher chance of survival during a median follow-up of 46 months.

Both studies strongly support the added value of AR beyond current guideline criteria and should lead us to a more pathophysiology-driven selection of CRT patient candidates based on the specific mechanical signatures of an LV amenable to CRT instead of simply describing its myocardial de-coordination.

References