The CRT Monopoly Game – Return to “Go” Without Dyssynchrony Bonus? –

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Cardiac resynchronization therapy (CRT) has become an important adjunct to the treatment of patients with heart failure and wide QRS-complex. Unfortunately, a considerable number of patients (30–50%), selected according to current guidelines, do not appear to respond significantly to CRT. A considerably higher response rate would be desirable for a treatment that is relatively expensive and requires life-long implantation of device and leads.

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To this purpose, several single-center studies have investigated the possibility of improving patient selection using echocardiographic parameters of mechanical dyssynchrony on top of QRS duration. These studies provided a host of novel echocardiographic indices, such as septal-to-posterior wall motion delay (SPWMD), time to peak velocity difference between septal and lateral wall (Ts-SL), standard deviation of velocity in 12 wall segments (Ts-SD) and interventricular mechanical delay (IVMD). The Predictors of Response to CRT (PROSPECT) trial, a multicenter prospective cohort study, investigated the ability of predefined baseline echocardiographic parameters to predict clinical and echocardiographic response to CRT.¹ PROSPECT showed that, although various markers of dyssynchrony contributed significantly to the prediction of clinical outcome and reverse remodeling at 6-month follow-up, sensitivity and specificity were modest with an area under the receiver-operator characteristics curve (AUC) ≤ 0.62 . The authors concluded that no single echocardiographic measure of dyssynchrony can be recommended as a tool for patient selection for CRT. These negative results caused extensive formal and informal reactions, the nature of which depends on the background of the commentator: echocardiographers usually claiming technical flaws, electrocardiologists cheering about the incapability of technologies that are foreign to them.

Although the concept of mechanical dyssynchrony assessment by echocardiography seemed plausible, many researchers and physicians felt that they had to return to “Go” without receiving an echocardiographic dyssynchrony bonus.

In this issue of the Journal, the J-CRT study is reported.² This study is in many respects comparable to the PROSPECT study. It is a multicenter, prospective cohort study designed to identify the ability of echocardiographic dyssynchrony param-

eters to predict reverse remodeling induced by CRT. Seven echocardiographic parameters were evaluated in 217 patients in Japan. As in the PROSPECT study, no single echocardiographic criterion had significant power to detect responders. However, in their next step, the investigators found that a combined dyssynchrony measurement of SPWMD and Ts-SL significantly and independently correlated with reverse remodeling and improvement in NYHA class. Therefore, the J-CRT study first of all confirms the results of the PROSPECT study, but in addition, it indicates that combined dyssynchrony indices may have added value.

However, there is yet another interesting observation in this study: the presence of an electrocardiographic left bundle branch block (LBBB) pattern predicts reverse remodeling even better than the combined dyssynchrony index of SPWMD and Ts-SL. Again, return to “Go”: just as in the early years of CRT, the ECG seems the only thing that matters.

With respect to these results one may wonder: “Is the ECG so good or is echocardiography so bad?” To answer the first question: the ECG is a simple measurement, but represents some aspects and information of different electrical events in the heart. Recently, MADIT-CRT³ and RAFT⁴ showed the superiority of the LBBB pattern over total QRS duration in predicting the CRT response. In addition, Sweeney et al showed in a retrospective study that analysis of the ECG beyond measuring QRS duration provides quite a reasonable prediction of CRT response.⁵ Therefore, the predictive value of the ECG can be improved when assessing not only QRS duration, but also the ECG-pattern.

Is echocardiography so bad? Not at all! However, it should be remembered that various techniques have limitations. This is especially true for tissue-Doppler imaging: it measures velocity along the ultrasound beam, but not tissue deformation in the fiber direction. This can create considerable errors.⁶

Moreover, common definitions in echocardiography may be flawed for determining mechanical dyssynchrony in LBBB hearts. In LBBB, the septum shows a very early start of contraction, evidenced by leftward septal motion and strain and strain rate (Figure). However, this phase is only brief and may occur in the isovolumic phase, because subsequently the severely contracting lateral wall, once activated, overrides the septum and pushes it in a rightward direction, stretching the septal muscle. If the early septal motion occurs before aortic valve opening, this velocity peak is not taken into

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Figure. Echocardiographic measurements in a canine heart with LBBB. (**Upper**) Grey level and color M-mode echocardiograms. (**Lower**) Strain and strain rate (obtained by speckle-tracking analysis) in septum (blue) and LV lateral wall (red). The small arrows indicate the double peaks in septal strain and strain rate that may make determination of time to peak shortening subject to confusion. SPWMD and septal flash are also indicated. LBBB, left bundle branch block; LV, left ventricular; SPWMD, septal-to-posterior wall motion delay.

account when measuring systolic dyssynchrony. **Figure** is an example of when septal strain shows 2 peaks, indicating that the choice of the peak highly determines the value of mechanical dyssynchrony. Even worse, the value of dyssynchrony is always presented as an absolute value, not distinguishing between whether the septum or lateral wall is shortening or moving first. Dyssynchrony presented in this way can not discriminate between left and right bundle branch block or other conduction abnormalities. (The authors of the J-CRT are to be applauded for clearly outlining the tested dyssynchrony criteria in Table 1.) The aforementioned problems may also explain the observation in the J-CRT study that in only 49% of the patients was mechanical dyssynchrony identified by both SPWMD and Ts (lateral-septal).

However, these factors may not be the only ones to blame

for the poor performance of dyssynchrony indices. Several studies have shown that even with the gold standard MRI tagging technique for measuring myocardial strains, time-to-peak measurements do not predict CRT response very well. In contrast, better predictions are acquired using analysis of the amount of stretch during the systolic phase. Indices developed are, for example, the circumferential uniformity ratio estimate (CURE)⁷ and the internal stretch fraction (ISF).⁸ More recently De Boeck et al showed that the septal strain pattern alone (without taking into account the strain in other wall segments) is sufficient to predict CRT response.⁹ The presence of the so-called septal rebound stretch (**Figure**) was able to predict response with an AUC of 0.90. These findings suggest that indices of discoordination (motion patterns) are to be preferred over those for dyssynchrony (timing parameters). Of note, the study by De Boeck et al was performed using speckle tracking, a novel echocardiographic technique. It has to be kept in mind that the speckle-tracking technique is relatively new, requires dedicated scanning and that equipment from different vendors provides different results. Still, while an increasing number of single-center studies provide promising evidence that speckle tracking may become the way to go, there is no cause for jubilation before randomized multicenter studies have shown the benefit of this technique. For the time being, we have to keep in mind that returning to “Go” without a bonus, is better than “going to jail” (in terms of the Monopoly game, that is).

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