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iVIEW

EDITOR'S PAGE

Dyssynchrony Measurements to Predict Functional Recovery After CRT: Too Good to Be True?

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The randomized clinical trial is the reference standard of evidence-based medicine, but these are difficult to apply to imaging—indeed, their representation in the guidelines is a rarity (1)—and the ability of patients to participate in these studies introduces an element of selection bias. On the other hand, observational studies fill a critical gap in clinical evidence about cardiovascular imaging. The questions that observational studies address and the answers that they provide are considered by clinicians to be useful because they reflect daily practice. The big problems are that observational studies are performed in a "noisy" environment, where the inherent variability of testing may be magnified, and that they are susceptible to bias (2).

In this issue of *iJACC*, Nijjer et al. (3) report a meta-analysis of studies that have used markers of mechanical dyssynchrony to predict left ventricular (LV) remodeling responses to biventricular pacing. These studies are no strangers to controversy. Markers of clinical response may include symptoms and quality of life (susceptible to placebo effect), exercise capacity (influenced by features unrelated to cardiac resynchronization therapy [CRT] or indeed the heart), or morbidity and mortality. Cleland, in particular, has pointed out that "a good outcome does not mean that the intervention was effective and a seemingly poor outcome could have been worse without intervention" (4). Irrespective of these reservations, a commonly-voiced concern is that a sizable proportion of patients seem to experience no benefit from biventricular pacing, and a literature has grown up around the prediction of change of a variety of echocardiographic variables. The correlation between dyssynchrony and change in ejection fraction (EF) ranges from 0.47 to 0.70, with a correlation of 0.0 to 0.84 for change in end-systolic volume (3). Such meta-analyses are bedeviled by the heterogeneity of synchrony measurements and outcome variables, and indeed, while it is often expected that a linear association should exist between the degree of dyssynchrony and the physiological responses, there is no reason that such an association should be linear.

While this systematic review of the dyssynchrony literature is of value, it is the next step in the paper by Nijjer et al. (3) that is of particular interest. The authors have identified that such analyses involve a comparison of 2 inherently variable measurements, the change of LV volume from 1 visit to the next, and the measurement of LV synchrony, based upon the delay between electrical and mechanical activation in a variety of LV segments. Based upon the spontaneous variability of the response markers and the test-retest variability of dyssynchrony measurements, Nijjer et al. (3) were able to define the optimal achievable correlation between these measures, and then compare this with reports in the literature. The combination of these sources of variability leads to what the authors describe as a contraction factor, which will reduce the observed r^2 below the underlying correlation. Effectively, this factor provides a ceiling to the maximum observable correlation. The contraction factor reported by the investigators is 0.29 for change of EF, 0.24 for change of end-systolic volume, and 0.30 for change of end-diastolic volume. Comparison with the literature demonstrated that externally monitored studies did not exceed the mathematical

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limits of these calculations, but single center studies overestimated the correlation between synchrony and left ventricular remodeling by between 5- and 20-fold. This work is a salient reminder about the limitations of a very common study design in imaging, in which the ability of 1 test to predict the findings of another is evaluated in either a cross-sectional or a longitudinal design.

The lessons of this paper are numerous. First, this work is a reminder to investigators that when 2 biological measurements are being compared, the uncertainty of each of them is magnified and effectively limits the ability of 1 to predict the other. While choosing the most accurate and reliable technique for the measurement of interest (in this case, LV synchrony) is important, this is doubly true for the reference technique that defines physiological changes over time, as this change is dependent upon the error of both the baseline and follow-up studies. Surprisingly, the test-retest variation of parameters (5), measured on 2 occasions without an intervening change of clinical status is rarely described, but may be surprisingly high. For example, the 95% confidence interval for 2-dimensional echocardiographic EF exceeds 10% (6). Means of reducing error include averaging multiple measurements and using a test with less variance. If patients were not precluded from undergoing cardiac magnetic resonance (CMR) following device implantation, the reported contraction factor would be substantially less because the variance of CMR is less than echocardiography (7). Provided image quality is adequate, 3D echocardiography not only correlates better with CMR (8) but its temporal variation seems less as well (9), and should be considered for future prospective studies of CRT. Likewise, new measures of mechanical synchrony that are able to average multiple cardiac cycles may have less variability than single-beat measures (10).

Second, this work is a reminder to the readers about how readily bias can creep into science (11), and one of the reasons why the randomized control trial is looked upon as the reference standard. Steps to avoid bias such as having a separate core laboratory (even independent blinded review of a proportion of the studies), and a documented blinding process are important scientific steps that we must not ignore. Such bias does not necessarily imply scientific misconduct.

Third, this work is a reminder to reviewers and editors regarding publication bias (12). A vast number of papers on the prediction of CRT response have been published, but these are likely a mere fraction of the numbers of studies that have been actually performed or initiated. Failures to predict outcome that are readily identified from talking with other clinicians and investigators rarely turn into meeting presentations, and certainly not into written reports. Publication of negative studies is especially difficult after a number of positive early reports have been published, because the existing publications are held up as a model of success. The metric of a successful journal is citations, so editors may be reluctant to publish negative studies, which are not likely to be cited. Despite mandatory reporting of controlled trials, no such process is available for observational studies. Thus, publication bias is a significant contributor to the problem identified by Nijjer et al. (3).

Skepticism is a valuable attribute for all users of the research enterprise. The original single-center reports may have provided an optimistic picture about the ability to predict a response based on a single, variable parameter. But nonetheless, mechanical synchrony represents an important physiological signal that has been shown to predict outcome in large multicenter studies (13). Negative findings or even positive findings attributed to publication bias should not distract us from the task of identifying more robust tools for both assessment of mechanical synchrony and the recognition of treatment response.

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