



EDITORIAL COMMENT

Assessing response to cardiac resynchronization therapy: Time to settle on some definitive criteria



Avaliação da resposta à terapêutica de ressincronização cardíaca. É necessário estabelecer critérios definitivos

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Cardiac resynchronization therapy (CRT) is a 20-year-old technology. Since its introduction, there has been considerable debate about the non-response rate, especially in view of the initial cost of the system and the need for a surgical procedure to implant it. In fact, the non-response rate, generally around 30%, is not so different from that of other therapies for heart failure (HF).

There is much confusion about response to CRT. Firstly, it is highly dependent on the criteria used to define response; studies have shown that response rates range from 32% to 91% depending on the criteria used.¹ Rates tend to be higher when subjective clinical measures are used, but much lower on outcome measures. Secondly, there is disagreement between different methods of assessing response. The lack of correlation between different ways of defining success, and their association with prognosis in terms of decreased mortality and morbidity, was first addressed by Yu et al.,² who demonstrated that increase in left ventricular ejection fraction (LVEF) was associated with longer survival but not with improvement in symptoms.

Subsequently, Cha et al.³ concluded otherwise, demonstrating that clinical improvement influenced outcome but

that reverse remodeling was not needed for this survival benefit.

It is necessary to decide which should be defined as response to CRT: living better or living longer.

The class I indication for CRT in HF was based not on improvement in symptoms or exercise capacity, but on its effect on mortality or morbidity. The ultimate response to CRT should accordingly be a decrease in mortality and morbidity, i.e. fewer HF events. All other clinical, echocardiographic or laboratory improvements are merely surrogate markers of the real response. Any attempt to predict outcome by means of clinical or echocardiographic surrogates is hampered by its subjective nature. Although non-responders usually have worse outcomes than responders, this is not always the case.

Finally, there is an additional issue to consider when using surrogate markers of outcome, which is the timing to assess results and cutoff values.

In addition to the above, HF is a progressive disease, so many factors may influence outcome, not only CRT response.

In this issue of the *Journal*, Rodrigues et al.⁴ chose eleven criteria used in previous CRT trials and assessed the accuracy of each of these criteria alone and in combination for predicting survival free from major adverse cardiac events (MACE). They found that the only three isolated criteria that could predict outcome were a clinical criterion (a decrease of at least one New York Heart Association [NYHA] functional

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class) and two echocardiographic parameters, reflecting an absolute and a relative increase in LVEF. No other criteria were able to predict outcome. However, even these three were not ideal: a reduction of ≥ 1 NYHA functional class showed an unadjusted reduction of 61% in the probability of MACE, and a $>15\%$ increase in LVEF showed an unadjusted reduction of 57%.

One of the disadvantages of clinical criteria is the subjective nature of their measurement, which depends on the patient's or physician's point of view, but this study demonstrates that measurement of peak oxygen consumption (pVO_2) was less accurate than reduction in NYHA class. When no hospitalization for HF within six months was added to reduced NYHA class and increased pVO_2 , the risk reduction was 79%, highlighting the superiority of an objective clinical criterion (absence of hospitalization).

Composite endpoints are often used in clinical trials of CRT. However, they are only reliable when each component is of similar importance, and previous studies have shown that combining parameters, which complicates the reporting of results, does not increase accuracy.⁵

In my opinion, it would have been useful if this paper had assessed adjusted hazard ratios, at least with the more representative variables. The authors did not test interactions between the criteria considered and prognostic parameters such as age, QRS duration, serum creatinine, B-type natriuretic peptide and HF etiology. Boidol et al.⁵ showed that response criteria have different predictive power in different patient subgroups depending on baseline characteristics. Similarly, Rodrigues et al. highlight the lack of agreement between different criteria; in their study only three criteria (5.5%) had Cohen's kappa (κ) values in the range of strong agreement. More worrisome is the lack of correlation between the two most accurate criteria (κ 0.20 between >1 reduction in NYHA class and $>5\%$ absolute increase in LVEF), which calls into question the usefulness of comparing studies using different criteria.

Another important issue is the timing of response assessment. In Rodrigues et al.'s study, the second echocardiogram was performed six months after CRT. It is now known that late reverse remodeling occurs in some patients,⁶ the effect

of which on survival is similar to that of early reverse remodeling. It therefore cannot be ruled out that some of the echocardiographic non-responders in this study may have been late responders.

This paper highlights the fallacy of cataloging patients into categories according to clinical or echocardiographic response criteria. However, at times some way of assessing CRT response is necessary in order to assess the need to optimize device programming, and this paper demonstrates that simple criteria like increased LVEF and decreased NYHA class may be suitable for this purpose.

Nevertheless, it is important to remember that response to CRT should always be based on hard endpoints, namely improved survival and reduction of HF events, rather than on surrogate endpoints.

Conflicts of interest

The author has no conflicts of interest to declare.

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