

Should Echocardiographic Parameters Guide the Indications for Cardiac Resynchronization Therapy?

Agonist

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Chronic congestive heart failure (CHF) is the final common pathway of most heart diseases, affecting 0.5% to 2% of the western populations; it is the main cause of admissions in patients older than 65 years. (1, 2)

Atrioventricular (AV) conduction delays and QRS complex duration are prognostic markers in patients with chronic CHF. More than 30% of chronic CHF patients in functional class III-IV present intraventricular conduction delays generally related to left bundle branch block. (3-6)

A QRS duration ≥ 120 msec is worldwide accepted for the diagnosis of intraventricular dyssynchrony. In this sense, the principal papers performed to assess the efficacy of cardiac resynchronization therapy (CRT) (MIRACLE, CONTAK CD, MUSTIC SR) used the QRS complex duration as an indirect criterion for dyssynchrony, leaving echocardiography as a method for evaluating left ventricle diastolic diameter. (7-9) In the CARE HF study, patients with a QRS complex duration between 120 and 149 msec were eligible for CRT only in presence of two of the following three criteria:

- An aortic preejection delay of more than 140 msec.
- An interventricular mechanical delay of more than 40 msec.
- A delayed activation of the posterolateral left ventricular wall. (10)

Cardiac resynchronization therapy started in 1983, but it took the method 10 years to develop (11, 12). According to the guidelines for the treatment of chronic CHF, CRT should be indicated to patients in NYHA functional class III-IV, with a left ventricle ejection fraction $\leq 35\%$, who are unresponsive to full medical therapy and with a QRS complex duration ≥ 120 msec. This is a class I indication, level of evidence A. (2)

Galizio et al. combined the criteria expressed in most clinical trials and demonstrated that only 7.5% of patients with chronic CHF were candidates for CRT. (13) In that sense, a cooperative study performed in hospitals of Andalucia found that only 5.6% of those patients were eligible for CRT. (14)

Despite such strict selection, the different published trials have reported an incidence of “non re-

sponders” from 25% to 38%, and in some cases the proportion of patients with no improvement after the therapy reaches a value of 50%.

Then, the question is: does a QRS duration ≥ 120 msec mean intraventricular dyssynchrony?

Yu et al. found that 27% of patients with a QRS duration ≥ 120 msec had **no** signs of intraventricular dyssynchrony. (15) In our experience, there are patients who, in spite of fulfilling all the criteria for CRT, do not present signs of intraventricular dyssynchrony, thus we conclude that dyssynchrony is a mechanical characteristic of ventricular contraction that does not depend strictly on the duration of the QRS complex. Obviously, the inverse situation is also possible, that is to say a QRS duration < 120 msec with evidence of intraventricular dyssynchrony. (15)

After concluding that a QRS duration ≥ 120 msec is not exactly the same as intraventricular dyssynchrony, the following question is unavoidable: Which is the role of echocardiography in the assessment of candidates for CRT?

Before answering this question, it should be mentioned that there are three levels of dyssynchrony seen at the echocardiogram: (16)

- Atrioventricular (AV) dyssynchrony.
- Interventricular dyssynchrony (InterV).
- Intraventricular dyssynchrony (IntraV).

Assessment of AV synchrony is useful to evaluate the characteristics of ventricular filling, ventricular filling time, and the importance of the atrial contribution to ventricular filling. An optimal AV sequence implies a more efficient left atrial emptying and, subsequently, a better LV filling. Doppler echocardiography is the most practical, efficient and reproducible method for the assessment of this sequence.

The second level of dyssynchrony, InterV, is estimated by pulsed Doppler echocardiography comparing aortic and pulmonary preejection delays (time interval between the first deflection of the QRS complex and the beginning of the aortic and pulmonary flows) in their respective outlet tracts.

Finally, the third level of dyssynchrony, IntraV, is apparently the most important. The objective of CRT is the improvement of IntraV dyssynchrony. Intraventricular dyssynchrony is defined as the maximum de-

lay (greater than 65 msec) between two symmetrical segments of the ventricular walls. (17) This measurement is also estimated by Doppler echocardiography.

The detection of these three levels of dyssynchrony is useful not only for the diagnosis of mechanical anomalies related to conduction delays but also to identify the potential responders to CRT.

The PROSPECT study was designed to find those signs that might identify these patients. (18, 19) The presence of sub-optimal results might be explained by the inclusion of 54.5% patients with coronary heart disease, as this condition decreases the proportion of responders. (20) The high incidence of interobserver variability was another pitfall, demonstrating the need for highly trained operators and technological requirements to perform the studies (some Doppler studies performed with certain brand of equipments were withdrawn from the registries due to the low quality of the images obtained). Nevertheless, the analysis of a single echocardiographic parameter added a success rate of 11% to 13% and 13% to 23% to the predictive value of the responses on the combined cardiovascular score and on LV reverse remodeling, respectively.

In single-center studies performed on smaller populations, intraventricular dyssynchrony yielded a sensitivity and specificity of 92% to identify responders. (17)

Other issues should be considered before indicating CRT. An aortic velocity-time integral < 12 cm implies that the cardiac output is so low that it is unlikely CRT will produce favorable outcomes. (21) Another factors that contribute to the proportion of non responders reported in the different papers are: the anatomy of the coronary veins, the "quality" of the tissue to be stimulated, the percentage of daily hours the patient is paced, a resynchronization device programmed at rest in a patient who is likely to perform some type of activity, and the need of highly-trained operators.

Finally, it seems strange that Doppler echocardiography is not considered the most effective method to detect candidates for CRT, instead of performing it only to guide the optimization of the device, although the same parameters are measured in both stages.

In conclusion, the patient should be assessed as a whole, and management of chronic CHF should be carried out by a multidisciplinary team composed by specialists in pacemakers working together with cardiologists specialized in echocardiography - in charge of obtaining objective and direct data of dyssynchrony - and clinical cardiologists responsible for prescribing an adequate drug therapy.

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Antagonist

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In my opinion, cardiac resynchronization therapy (CRT) is one of the most significant advances for the treatment of patients with congestive heart failure in the last five years. This statement is based on the reduction in total mortality and sudden death since its implementation and on fewer hospitalizations and symptoms, with the subsequent improvement in the quality of life. These benefits on hard endpoints (mortality) and soft endpoints (hospitalizations, decrease in heart volumes and improvement in mitral regurgitation) are relevant as they have been proved in patients already under full medical treatment. CRT is indicated in patients with chronic advanced CHF, severe left ventricle dysfunction (ejection fraction < 35%), currently under full medical therapy and with left bundle branch block with a QRS complex duration > 120 msec. (1-4)

In spite of the aforementioned benefits, about 20-30% of patients submitted to CRT are considered non responders. It has been demonstrated that a proportion of patients with wide QRS complexes have no echocardiographic criteria of mechanical dyssynchrony which might probably be responsible for the absence of response to CRT; conversely, a group of patients with narrow QRS complexes and echocardiographic evidence of dyssynchrony might gain benefit with this therapy. This is the reason to search for echocardiographic parameters which might be useful to indicate CRT. (5)

Undoubtedly, echocardiographic criteria are not perfect, but the subject of this controversy is to discuss if they are better than other parameters. Several studies have been published reporting the usefulness of echocardiographic evidence of dyssynchrony and I am sure the agonist of this controversy must have mentioned them; thus I shall try not to be reiterative. These single-center studies used reverse remodeling as a final endpoint at short-term follow-up after CRT and tried to measure new complex and sophisticated parameters with different techniques. The conclusion of these studies was that patients with

the study criterion were more likely to reduce ventricular volumes.

The CARE-HF trial was the only study that included echocardiographic parameters as an indication for CRT and analyzed mortality rates. The interpretation of the results might be that measuring echocardiographic parameters is favorable for CRT; nevertheless, the right meaning of these outcomes is that patients included had prolonged QRS complexes duration with a median of 160 msec (IQ range 25-75 from 0.152 to 0.180 seconds) and that echocardiographic criteria were only used in the sub-group of patients with "intermediate" QRS complexes (between 120 and 149 msec) that represented only 11% of the 814 patients included. We cannot draw valid conclusions as these 80 patients might have two of the three necessary criteria combined in different ways. In this point we may conclude that wide QRS complex was the criterion for dyssynchrony used in this study that demonstrated a reduction in mortality.

The appearance of new ways of measuring dyssynchrony by echocardiography indicates that cardiologists have a restless nature; it is evident that we have not found yet the satisfactory measurement with the adequate sensitivity and specificity to detect those patients who may gain benefit from CRT.

During the last years different parameters have been measured: a delay between right ventricle and left ventricle contraction (interventricular dyssynchrony) and among different segments of the left ventricle, for example, between the septum and the lateral wall or the septum and the posterolateral wall (intraventricular dyssynchrony). In addition, several diagnostic tools have been tested: M-mode and B-mode echocardiography, Doppler color echocardiography, tissue Doppler imaging, and newest techniques as speckle tracking strain.

As clinical cardiologists we have followed these innovations with great interest though with certain degree of difficulty, as this new terminology is neither easy to translate nor to understand; neverthe-

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less, the outcomes have shown that dyssynchrony is associated with echocardiographic improvement at short term. We have intuitively thought that these measurements are too complex and difficult to standardize as they depend on the experience of the observer and are unlikely to be applied routinely.

The PROSPECT trial has been recently published and has shed some light on this issue. The study included 426 patients submitted to CRT in 53 centers in USA, Europe and Hong Kong that were selected after a training program in measuring protocols. These centers should be capable of delivering high quality images and should be accredited by the central laboratory of the corresponding region. (6)

The objective of the study was to assess the value of different echocardiographic measurements to predict outcomes after CRT.

Clinical and echocardiographic endpoints were evaluated at 6 months. The primary clinical endpoint was a composite score that combined mortality, heart failure hospitalization, NYHA class, and patient global assessment. The echocardiographic endpoint was a reduction of the end-systolic volume $\geq 15\%$, a measurement that had been used in previous studies.

The sensitivity and specificity of twelve echocardiographic parameters of dyssynchrony, based on both conventional and tissue Doppler-based methods to predict an improvement in clinical and echocardiographic endpoints were evaluated. Intraoperator variability and interobserver variability for each echocardiographic parameter were also analyzed.

The clinical endpoint improved in 69% of patients. This result is similar to what has been previously reported (30% of non responders), and in this study, the response in ischemic patients was lower than in nonischemic patients (63.7% versus 75.6%, respectively). Fifty six percent of patients with available measurements had a reduction in end-systolic volume within the prespecified definition of improvement.

The sensitivity and specificity of the twelve echocardiographic parameters to predict improvement of the clinical outcome ranged from 6% to 74% and from 35% to 91%, respectively and for end-systolic volume reduction varied from 9% to 77% and from 31% to 93%, respectively. Based on the receiver-operating characteristics analysis, the best ability to predict end-systolic reduction of $<15\%$ achieved an area under the curve of 0.60.

However, the variability of the determinations was the most discouraging result of the trial. Left ventricular end-systolic volume (LVESV), septalposterior wall motion delay (SPWMD), the standard deviation of time to peak systolic velocity of 12 segments of the left ventricular wall at the basal and medial levels (Ts-SD), left ventricular preejection interval, and maximal time to peak systolic velocity difference of 6 segments at the basal level (Ts-peak) were measured to assess intraoperator and interobserver variability.

All these five parameters have been used in previous studies. An adjusted coefficient of variation was calculated, defined as the ratio of the SD and the mean of absolute readings for each echocardiographic parameter.

Intraobserver reproducibility was similar, with low variability for LVESV and left ventricular preejection interval. Interobserver variability was higher for each parameter than intraobserver variability, with high variability for Ts-peak, Ts-SD, and SPWMD (coefficient of variation, 31.9%, 33.7%, and 72.1%, respectively).

I deeply agree with the conclusions of the authors of this trial in the sense that despite promising preliminary data from prior single-center studies, echocardiographic measures of dyssynchrony aimed at improving patient selection criteria for CRT do not appear to have a clinically relevant impact on improving response rates.

The questions are as follows: Are responders correctly defined? In spite of some discrepancies, I believe that clinical endpoint and reverse remodeling outcomes used by the PROSPECT trial were adequate.

Were the proper parameters measured?

Probably some measurements might be missing and the development of echocardiography might generate new parameters. A recent study performed by the group led by Bax used 2-dimensional speckle tracking strain analysis technique to provide information on radial strain, circumferential strain, and longitudinal strain for the assessment of left ventricular dyssynchrony. Radial strain was able to predict a reduction $> 15\%$ in end-systolic volume with a sensitivity of 83% and a specificity of 80%. This technique seems promising; however, data available comes from a single center with a predictive error of approximately 20%. (7)

Were the cut-points adequate?

The answer should arrive from the conclusions of new studies; nevertheless, both this question and the previous one are overshadowed by the great variability of the measurements.

Should echocardiography give us all the answers?

Dyssynchrony is, by definition, a mechanical disorder, which may be associated with a conduction delay. It is logical to consider echocardiography for quantifying the degree of mechanical asynchrony? Let me remind the reader that many things that may seem logical do not always overcome the requirements; for example, in patients with congestive heart failure ejection fraction is not always the best prognostic marker. Patients with similar ventricular function might have a different prognosis according to their functional capacity, and even patients with normal ejection fraction might have unfavorable outcomes compared to those with left ventricular dysfunction. The reader might reason that ischemia and advanced age or associated comorbidities might be responsible for the

poor evolution in the former and the latter examples, respectively. This is true; however, we were capable of arriving at this conclusion when we understood that the complexity of the problem could not be explained by a single parameter. Perhaps only patients with very wide QRS complexes and more dyssynchrony are likely to improve with CRT; maybe QRS complex duration selects a group of patients that might benefit beyond the correction of dyssynchrony.

Might echocardiography help in cases of narrow or intermediate QRS complexes?

Measurements of echocardiographic parameters do not seem necessary to indicate CRT in patients with wide QRS complexes; however, the potential benefits of echocardiography lie in this subgroup of patients. The results of smaller, single-center studies have been promising, yet multicenter, prospective and randomized trials were lacking. The Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes trial (Rethin Q) has been published recently. The study, performed in 34 centers, selected patients with a standard indication for an implantable cardioverter-defibrillator with an ejection fraction of 35% or less, NYHA class III heart failure, a QRS interval of less than 130 msec, and evidence of mechanical dyssynchrony as measured on tissue Doppler imaging. Patients (n = 172) were randomly assigned to the CRT group or to the control group. The device was successfully implanted in 87 patients. At 6 months, the CRT group and the control group did not differ significantly in the proportion of patients with an increase in peak oxygen consumption of at least 1.0 ml per kilogram of body weight per minute (the primary end point). In the subgroup with a QRS interval of 120 msec or more, the peak oxygen consumption increased in the CRT group (P=0.02), but it was unchanged in a subgroup with a QRS interval of less than 120 msec. These data support the hypothesis that QRS complex duration might have an independent value beyond dyssynchrony. (8)

Does the response to CRT depend only on previous dyssynchrony?

Undoubtedly, the response to CRT depends on other factors, such as left ventricular lead placement or the presence of a scar; these technical circumstances might result in an impossibility to correct the mechanical defect with the subsequent reduction on sensitivity and specificity of the method used to predict the response to CRT.

CONCLUSION

At present, the echocardiographic parameters assessing dyssynchrony do not have enough predictive value to be recommended as selection criteria for CRT; we need a reproducible method that might be used in every medical center with sensitivity and specificity adequate enough to predict the therapeutic response. I also want to emphasize that we must keep on using

echocardiography or other imaging tools in order to identify this method in the future.

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ANSWER FROM THE AGONIST

"At present, the echocardiographic parameters assessing dyssynchrony do not have enough predictive value to be recommended as selection criteria for CRT..."

This is how my antagonist starts his conclusion, based on the fact that "... we need a reproducible method that might be used in every medical center with sensitivity and specificity adequate enough to predict the therapeutic response..."

This statement is half-truth, as Bax demonstrated sensitivity and specificity of 92% in intraventricular dyssynchrony with a delay ³ 65 msec between the peaks of the S waves of the TVI in basal segments of opposite walls. The evolutive difference was remarkable in patients with greater or lower cut-points value of dyssynchrony. Another study has recently been published by Bax, quoted by my antagonist, on radial strain. However, the basal characteristics of patients may explain the difference among dyssynchrony in responders and non responders with TDI. The PROSPECT trial demonstrated that echocardiography added value to the improvement in LV reverse remodeling and to the combined score.

How many interventions are defined by a single parameter that can be used in all the centers, with

adequate sensitivity and specificity to predict a therapeutic response?

We have demonstrated that beyond bibliography findings (1066 papers in Medline with “*cardiac resynchronization therapy*”), the echocardiographic analysis of dyssynchrony in a single center working with an interdisciplinary team resulted in an important reduction in the number of dead/transplant patients when this analysis was added to the traditional criteria mentioned in the guidelines.

CONCLUSIONS

1. In patients with dyssynchrony, the duration of the QRS complex has a predictive value to identify responders to CRT.
2. Other factors related to etiology, anatomy and technical factors should be taken into account before indicating CRT.
3. Doppler echocardiography undoubtedly **improves** the detection of responders.

Dr. Eduardo Guevara

ANSWER FROM THE ANTAGONIST

I agree with the agonist of this controversy with the physiopathological issues of cardiac resynchronization therapy. I shall focus on the aspects that might threaten my arguments.

1. When the agonist says that “the analysis of a single echocardiographic parameter added a success

rate of 11% to 13% and 13% to 23% to the predictive value of the responses on the combined cardiovascular score and on LV reverse remodeling, respectively” he is talking about the sensitivity of the method to detect responders. This argument is absolutely true, though it is not correct if one fails to mention that between 60% to 71% of patients without a positive echocardiographic parameter (without dyssynchrony) showed an improvement in the clinical score, and between 45% to 55% of these patients presented a reduction in end-systolic volume despite the absence of echocardiographic dyssynchrony. In other words, we are talking about false positives and false negatives. In this point, we may conclude that echocardiography produced a modest increase in sensitivity to detect responders at the expense of an almost intolerable loss of specificity.

2. It is true that the suboptimal outcomes of the PROSPECT trial were due to the inclusion of 54.5% of ischemic patients that reduced the proportion of responders; unfortunately this is the scenario where we work, as in all the series of patients with advanced congestive heart failure the proportion of ischemic patients might be similar to the aforementioned, or even greater.
3. Finally, there are no studies that justify that echocardiographic parameters might optimize the hard endpoints, and megatrials such as CARE-HF and COMPANION, showed a remarkable benefit for the device without echocardiographic optimization.

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