Perspective and future direction of intraventricular mechanical dyssynchrony assessment

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This editorial refers to the article published by Peix et al.¹ titled '*Value of intraventricular dyssynchrony assessment by gated-SPECT myocardial perfusion imaging in the management of heart failure patients undergoing cardiac resynchronization therapy (VISION-CRT)*' on the Journal of Nuclear Cardiology.

This study shows the importance of the current problem in cardiac resynchronization therapy (CRT). In this study, we observe multiple variables that can affect the CRT response in clinical practice²: patients with or without previous myocardial infarction, patients in ischemic cardiomyopathy phase, patients with or without myocardial ischemia, patients with or without coronary revascularization before gated SPECT study, patients with complete or incomplete revascularization, patients with or without myocardial viability criteria, patients with different large infarct size, patients with or without medical treatment optimizations during the follow-up, the cut-off value to define significant dyssynchrony, responder and non-responder patients, on-target group patients and off-target group patients, acquisition of images with different frames (8 or 16

frames), and different algorithms to guide left ventricular (LV) lead position placement, and the selected variables for the multivariate analysis.

The importance of perspective and the future direction of intraventricular dyssynchrony assessment lies in the multiple variables that must be taken into account, and the fact that the heart failure (HF) represents a rapidly growing epidemic.³ Approximately 5.8 million patients in the United States currently suffer from HF, and over 670,000 of them are newly diagnosed with HF each year.³ Currently, the prediction is that in the United States by 2035, > 9 million will have HF⁴; the 5-year mortality after a diagnosis of HF is approximately 50%. Also, in United Kingdom, Conrad et al.⁵ observed that from 2002 to 2014, HF incidence decreased, similarly for men and women. However, the estimated absolute number of individuals with newly diagnosed HF in the UK increased by 12% (from 170727 in 2002 to 190798 in 2014), largely due to an increase in population size and age. The estimated absolute number of prevalent HF cases in the UK increased even more, by 23% (from 750127 to 920616).

The most important issue to be resolved in the future is, how to improve the criteria for cardiac resynchronization therapy (CRT)? Recently, Lyons et al.⁶ identified 25,102 hospitalizations for HF that included patients with a LV ejection fraction (LVEF) $\leq 35\%$ from 283 hospitals. Observed, that 49.1% ($n = 12,336$) of patients with HF, an LVEF $\leq 35\%$, and no documented contraindication were eligible for CRT on the basis of historical guidelines (LVEF $\leq 35\%$, QRS duration ≥ 120 ms, and NYHA functional class III or IV),⁷ and 33.1% ($n = 8299$) of patients were eligible for CRT on the basis of current guidelines (LVEF $\leq 35\%$, left bundle branch block [LBBB] with a QRS duration

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≥ 120 ms or non-LBBB (right bundle branch block or interventricular conduction delay) with a QRS duration ≥ 150 ms and NYHA functional class II, III, or IV).⁸ Concluded that, in this population of patients with HF, an LVEF $\leq 35\%$, and no documented contraindication for CRT, the current ACCF/AHA HF guidelines reduce the proportion of patients eligible for CRT by approximately 15%.⁶

Currently, all the information provided in relation to CRT¹⁻³⁷ and the experience in the clinical practice site of patients with HF, suggests that probably the criteria for CRT should be considered again. If a patient with HF and severely depressed LVEF does not respond to pharmacological treatment, CRT should be considered (Figure 1-1st); before the appearance of a branch block or an increase in the duration of the QRS complex.^{9,10} Why? because there may be ventricular mechanical dyssynchrony without branch block with normal QRS⁹ (Figure 2); and although electrical and mechanical dyssynchrony often coincide, electrical and mechanical dyssynchrony are commonly not present at the same time in a given patient.¹⁰ LBBB is not always accompanied by mechanical dyssynchrony.¹¹ Moreover, the percentage of non-responder patients remains high and heterogeneous (20%-40%).^{10,12}

Another aspect little studied is the relationship between the contractile reserve (Figure 1-2nd) prior to the CRT and responder and non-responder patients.^{13,14} The correct thing would be to study the contractile reserve prior to CRT.¹⁶ Kloosterman et al.¹⁷ observed that, a cardiac muscle without or poor contractile response will not have an effective response to CRT (the positive association between contractile reserve and CRT response remained with an odds ratio of 2.42 (95% CI 1.17-5.05, $P = 0.018$).¹⁷ Also, the U-shaped contraction pattern is associated with improved CRT response.¹⁴ In addition, myocardial fibrosis is associated with a worse response to CRT, particularly if it is sizable, transmural, or located in posterolateral left ventricular segments where the LV lead is usually positioned.³⁷

The degree of mechanical dyssynchrony (Figure 1-3rd) is important to select patients for CRT.¹⁸⁻²⁰ We can define the degree according to the number of altered phase parameters (one, two, three, or four: SD $> 18.4^\circ$, B $> 51^\circ$, S $\leq 3.2^\circ$, and K $\leq 9.3^\circ$)²⁰ or according to bandwidth degree. Ninety-two percent of patients with criteria for cardiac resynchronization therapy have 3 or 4 abnormal parameters in the phase analysis.²⁰

If we think about ventricular mechanical resynchronization, we cannot forget the right ventricle (RV) (Figure 1-4th). We cannot separate LV function and RV function, since there is an interdependent relationship; dilatation of the RV shifts the interventricular septum

Figure 1. Possible and different steps to consider in the future for the indication of CRT in patients with heart failure. *cRVSVU*, correct right ventricular standard uptake value; *FC*, functional class; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *PAP*, pulmonary artery pressure; *RVSP*, right ventricular systolic pressure; *RVEF*, right ventricular ejection fraction; *RVFAC*, right ventricular fractional area change. RVFAC is an echocardiographic parameter, but in Nuclear Cardiology Unit, gated pool SPECT is a good technique for the evaluation of right ventricular volume and function.³⁴ In the seventh step of this possible algorithm, the presence of LBBB would help to select the best technique for CRT. It should be noted that each step in addition to being related to ventricular dyssynchrony is related to cardiac mortality.

toward the left, changing LV geometry.²¹ RV dysfunction is an important predictor of survival and exercise capacity in cardiopulmonary disease, and RV failure is a progressive disorder that starts with an initial myocardial injury or stress.²¹ In some patients with chronic HF (Figure 3), the disease process not only impairs cardiac contractility but also causes a delay in the onset of RV or LV systole by affecting the conduction pathways.⁸ Despite this information, RV function is not taken into account in the latest ventricular resynchronization guidelines. For example, in CRT patients with non-ischemic dilated cardiomyopathy and impaired baseline RV function, at mid-term follow-up (3 months), an improvement in RVEF and RV dyssynchrony is noted.²² Besides that, van Everdingen et al.²³ observed that the mechanical dyssynchrony parameters do not reflect the negative impact of reduced RV contractility on CRT response, and commonly used mechanical dyssynchrony parameters are not associated with CRT response when RV dysfunction (RV fractional area change $< 35\%$) is present. Thus the prediction of CRT response should therefore include parameters of mechanical dyssynchrony and RV function.²³ Also, RV dysfunction is associated with an increase in RV FDG uptake (Figure 1-5th), the magnitude of which may be correlated with severity.²⁴ Increased RV FDG uptake is associated with RV dysfunction (Figure 3) and may be a prognostic predictor of all-cause mortality or heart transplantation in patients with dilated cardiomyopathy.²⁵ There is a significant correlation between RVEF and RV FDG uptake; in patients with a *cRVSVU* (correct RV standard uptake value) > 7.01 , heart transplantation is more frequent. Furthermore, there is a good correlation between RV dysfunction, RV FDG uptake, and severe pulmonary hypertension (mean pulmonary artery pressure ≥ 40

Figure 2. The above case corresponds to a patient with heart failure, with wide QRS and ventricular dyssynchrony (Histogram Bandwidth HB:126, Standard Deviation SD: 39.9), and the case below corresponds to a patient with heart failure, with normal QRS, and ventricular dyssynchrony (HB: 67, SD: 21.4). EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume.

Figure 3. At the top (equilibrium radionuclide ventriculography images) of the figure, marked dyssynchrony between the right (RV) and left ventricle (LV) is observed. At the bottom of the figure, RV dilation and dysfunction are associated with an increase in RV PET ¹⁸F-FDG uptake. EF, ejection fraction.

mmHg, or an RV systolic pressure ≥ 50 mmHg); and severe pulmonary hypertension has a poor prognosis.^{24,25} Thus, RV performance in patients of pulmonary

hypertension requires optimal assessment; and RV dyssynchrony measured by phase analysis of FDG-PET is significantly related to RV dysfunction.²⁶

Figure 4. In this case, a relationship between regional sympathetic denervation with H/M (heart/mediastinum) ratio 1.39, mismatch innervation/perfusion, and left ventricular dyssynchrony is observed (Histogram Bandwidth HB 191, Standard Deviation SD 53.5). MIBG, ^{123}I -metaiodobenzylguanidine.

The evaluation of LV sympathetic innervation on ^{123}I -metaiodobenzylguanidine (^{123}I -MIBG) imaging (Figure 1-6th) is another useful tool to assess CRT.^{27–29} Gimelli et al.²⁸ observed that patients with LV dyssynchrony show an extensive burden “innervation/perfusion” mismatch that is concentrated at the level of the dyssynchronous LV walls, suggesting a relationship between regional sympathetic denervation and abnormal LV mechanics (Figure 4). The optimal heart/mediastinum uptake ratio cut-off point is between 1.36 (sensitivity, 75%; specificity, 71%) and < 1.6 to CRT response.^{30,31}

The presence of branch block (Figure 1-7th) is probably more important to define the type of CRT, rather than the indication for CRT.^{32,33} Recently, Arnold et al.³² analyzed patients with HF and LBBB referred for conventional biventricular CRT, and concluded that His resynchronization delivers better ventricular resynchronization, and greater improvement in hemodynamic parameters, than biventricular pacing.

In conclusion, the perspective and future direction of intraventricular mechanical dyssynchrony assessment should consider all these aspects in HF patients (Figure 2), and not focus solely on the LBBB and QRS duration to select the best candidates for an effective CRT because electrical and mechanical dyssynchrony are not interchangeable.³⁵ Prior to CRT, it is important to consider jointly, the assessment of right and left ventricular systolic function, the myocardial scar areas, the degree of mechanical dyssynchrony, the cardiac sympathetic activity, and the pulmonary artery pressure; and probably use the LBBB to choose the best resynchronization technique for each individual patient; in order to reduce the high rate of non-responder patients. In addition, the presence of mechanical dyssynchrony

predicted long-term outcome better than guideline Classes I, IIa, IIb.³⁶

Disclosures

The authors report no potential conflict of interest relevant to this editorial.

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