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Electrocardiographic markers of cardiac resynchronization therapy response: delayed time to intrinsicoid deflection onset in lateral leads

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ABSTRACT Cardiac resynchronization therapy (CRT) has emerged as an important intervention for patients with heart failure (HF) with reduced ejection fraction and delayed ventricular activation. In these patients, CRT has demonstrated to improve quality of life, promote reverse left ventricular (LV) remodeling, reduce HF hospitalizations, and extend survival. However, despite advancements in our understanding of CRT, a significant number of patients do not respond to this therapy. Several invasive and non-invasive parameters have been assessed to predict response to CRT, but the electrocardiogram (ECG) has remained as the prevailing screening method albeit with limitations. Ideally, an accurate, simple, and reproducible ECG marker or set of markers would dramatically overcome the current limitations. We describe the clinical utility of an old ECG parameter that can estimate ventricular activation delay: the onset to intrinsicoid deflection (ID). Based on the concept of direct measurement of ventricular activation time (intrinsic deflection onset), time to ID onset measures on the surface ECG the time that the electrical activation time takes to reach the area subtended by the corresponding surface ECG lead. Based on this principle, the time to ID on the lateral leads can estimate the delay activation to the lateral LV wall and can be used as a predictor for CRT response, particularly in patients with non-specific intraventricular conduction delay or in patients with left bundle branch block and QRS < 150 ms. The aim of this review is to present the current evidence and potential use of this ECG parameter to estimate LV activation and predict CRT response.

The number of patients with clinical heart failure (HF) continues to climb and remains the primary discharge diagnosis of older adults, economically burdensome, and characterized by high morbidity and mortality. Worldwide, it is estimated that 64 million suffer from HF; in the US, approximately 6.5 million patients are afflicted.[1,2] Furthermore, the incidence of HF patients in the US has increased from 870,000 cases in 2005-2011 to 1 000,000 in 2014, likely reflecting the growth in the aging population, and it has been associated with over 80,000 annual deaths.[1,3,4] Patients with HF and reduced ejection fraction (HFrEF), account for approximately 50%, whose clinical course is often characterized by progressive symptoms, frequent HF exacerbations, emergency room visits, and recurrent hospitalizations.[4,5] In the US, the estimated total cost of care of HF in 2020 was $43.6 billion,[6] the annual total medical cost for HF care was $24,383 per patient, and the HF hospitalization costs are higher for patients with HFrEF resulting in $12,945 per stay.[7] These statistics make HF the costliest medical condition in the US.

Cardiac resynchronization therapy (CRT) has emerged as an effective therapeutic option for patients with HFrEF. The impaired systolic performance of the heart in HFrEF is coupled with electrical dyssynchrony, which is manifested as a left bundle branch block (LBBB) on the electrocardiogram (ECG). This electro-mechanical dyssynchrony can be corrected with the use of CRT. In multiple, randomized clinical trials, CRT has demonstrated marked benefits, including improvement in HF symptoms, HF related quality of life, functional capacity, reduction in hospitalizations, reduction in mitral regurgitation, adaptations to promote left ventricular reverse remodeling, reduction in ventricular arrhythmias, and reduced mortality.[8–15] Un-

fortunately, CRT has demonstrated to offer these multiple benefits to a limited number of patients with evidence of left ventricular (LV) dyssynchrony, but even among this selected group of patients, only two thirds will respond to this advanced therapy.[16–21] Despite advances in cardiac imaging and the potential promise of imaging to guide patient selection for CRT response, the ECG has remained the main screening tool to identify patients that may benefit from resynchronization therapy. Current guidelines support a class I recommendation for CRT in patients with HFrEF (EF ≤ 35%), functional class ≥ II, and left bundle branch block (LBBB) with wide QRS duration, preferably longer than 150 milliseconds.[19,22–26] Therefore, there is a critical need to develop better screening tools or parameters to select patient with HFrEF who could potentially benefit from this therapy. The current review aims to detail and address specific parameters of delayed LV activation that may be useful to screen in potential CRT patient candidates.

INTRINSIC DEFLECTION AND INTRINSICOID DEFLECTION ONSET: AN OLD ECG PARAMETER OF DELAYED LV ACTIVATION

In 1914, Thomas Lewis coined the term intrinsic deflection[27] as a parameter to determine the timing of cardiac activation at determined anatomical sites. Based on an animal model, Lewis measured the electrical activation time recorded when a unipolar electrode was placed in direct contact to the ventricular epicardium[27]. As the electrical activation wavefront approached the site of unipolar recording, the electrode registers a positive deflection that changes in polarity as the electrical impulse arrives immediately beneath the electrode and then moves away. The generated unipolar electrogram includes electrical activity at the area where the electrode is placed, which was called intrinsic, but due to the larger "antenna" of the unipolar recording, it also includes electrical activity distant from the site of recording, which was called extrinsic. The time of the intrinsic deflection was defined as the time from the onset of electrical activation to the time when the positive deflection turns abruptly into a negative deflection, and this was considered to coincide with the time when the electrical wavefront arrived at the site of the recording electrode (Figure 1). This concept was later modified and popularized by other authors.[28–30] Nevertheless, where exactly in the registered electrogram the activation wavefront passes beneath the recording electrode was a moot point back then and even some experts denied its existence and utility. In clinical electrocardiography, the recording

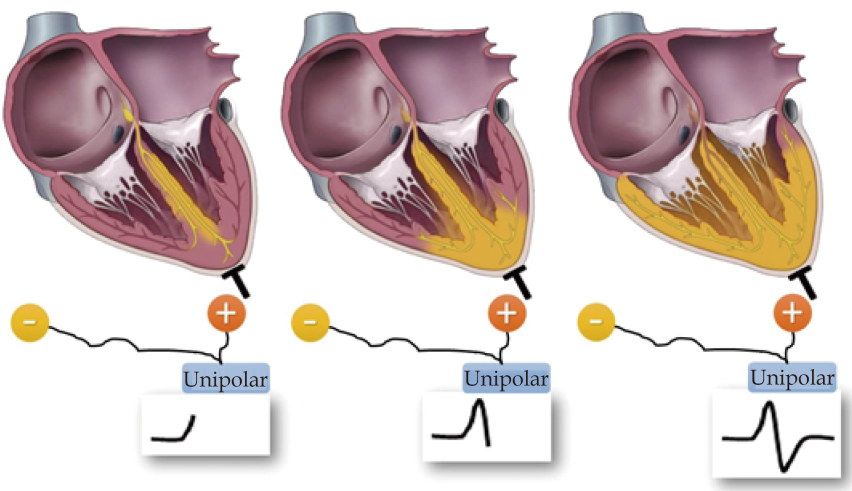

Figure 1 The intrinsic deflection. A unipolar electrode placed directly in contact with the epicardium registers the activation wavefront of the ventricle (yellow color on the heart illustration). As the activation wavefront approaches the electrode, the electrogram registers a positive deflection (left panel). As the wavefront passes underneath the unipolar electrode the electrogram registers a sudden change (middle panel). As the wavefront moves away from the unipolar electrode the electrogram registers a negative deflection and reaches the baseline (right panel). The point in the unipolar electrogram that coincides with the time when the wavefront passes underneath the unipolar electrogram is the onset of the intrinsic deflection.

electrodes are not directly in contact with the epicardium, therefore the concept of 'invasive' intrinsic deflection was not applicable, rather the term "intrinsicoid" deflection (ID) was coined by MacLeod in 1930.[31] The ECG registration was observed to have a transition from a positive deflection as less abrupt when an electrode is placed on the body surface than directly in contact to the epicardium. In 1977, Talbot[32] described the intrinsicoid deflection as the time from the onset of the QRS to the time at or after the peak of the R wave, when the maximum deflection toward the baseline occurs (Figure 2). Currently, the onset of ID is a useful ECG marker for the diagnosis and prognosis of both structural and electrical cardiac abnormalities (i.e., LBBB), though some authors have not preserved the nomenclature.[33] Measurement of ID can lend to variability due to the diversity of electrocardiographic patterns (Figure 3), for instance in severe cardiomyopathy and myocardial disease (multiple notches, QRS fractionation, more than one long/steep deflection, etc).[34]

WHAT OTHER PARAMETERS EVALUATE DELAYED LEFT VENTRICULAR LATERAL WALL ACTIVATION?

The main goal of CRT in patients with HFrEF and LV dyssynchrony is to reduce the LV conduction delay, in most instances, to the lateral wall. Therefore, any parameter that can estimate this LV lateral wall delay should bode response to CRT if the LV lead is placed in the area of delayed activation. Since CRT corrects primarily electrical dyssynchrony, the ECG or the direct measurement of the local electrical activation time to the lateral wall should be useful parameters to determine delayed LV activation. Several authors have thus worked on these noninvasive or invasive parameters.

In a prospective study of 200 patients with HFrEF and complete LBBB, Sweeney, *et al.*[35] used the ECG to estimate the baseline LV conduction delay and the LV activation sequence before and after CRT as predictors for reverse remodeling response to CRT. One of the predictive parameters was the LV activation time which, similar to the onset ID, estimates the delay to the lateral LV wall. The longest left ventricular activation time was calculated by first estimating the right ventricular activation time and subsequently subtracted this value from the global QRS duration. Even though they do not mention the ID onset, they used the first peak in any lead as the point when right ventricular activation was completed and used the shortest value in any lead so that after subtracting it from the QRS duration, the longest LV activation time could be deduced. Additionally, using QRS hieroglyphs, several patterns of ventricular activation were characterized.[36] The most relevant finding was that a longer baseline LV activation time was associated with higher probability of reverse remodeling. After CRT, evidence of ventricular fusion (greater changes in R-wave amplitudes in V1-V2) and the change of axis quad-

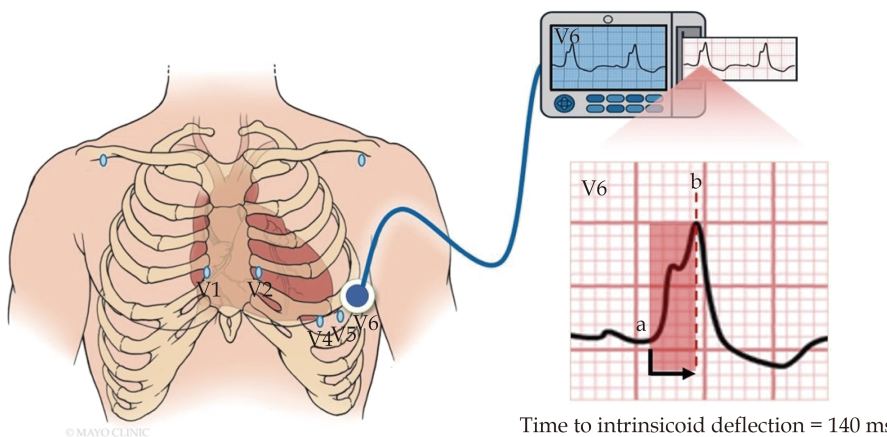

Figure 2 The intrinsicoid deflection. Based on the concept of the intrinsic deflection, the time to intrinsicoid deflection onset (shaded area) is the time point after the onset of ventricular activation (onset of the QRS complex represented by point 'a') at which the electrical activation wavefront reaches the nearest site to the recording surface electrocardiographic lead; 'b' represents R wave peak, when the maximum deflection toward the baseline occurs.

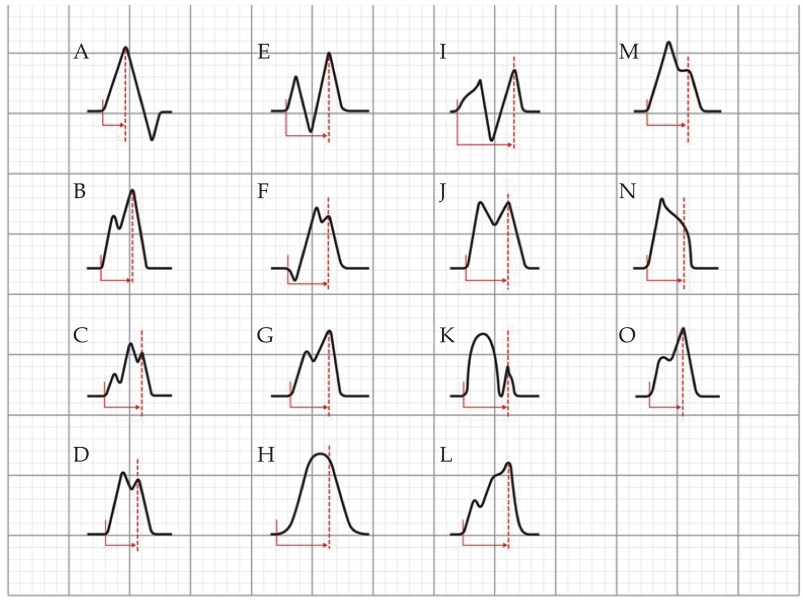

Figure 3 Possible QRS morphologies in patients with wide QRS and the determination of the time to ID onset. These examples show baseline intrinsic ventricular conduction. It was not possible to accurately define consistent patterns to determine the time to ID onset in bi-ventricular pacing due to significantly variation in QRS morphologies. ID: intrinsicoid deflection.

rant (left to right deviation) were also associated with increased probability of reverse remodeling. This study confirmed that estimation of delayed LV activation is possible from analysis of the 12-lead ECG, which is exactly what ID aims to do.

In another study, Singh, *et al.*[37] assessed invasively LV delay activation at the time of LV lead implantation. The time from the onset of QRS on the surface ECG to the first signal recorded on the LV lead when this lead was placed in a branch of the coronary sinus. The LV lead electrical delay is expressed as a percentage of the total baseline QRS duration. This parameter was associated with an acute hemodynamic response to CRT (increase in contractility ≥ 25%) and with long-term clinical outcomes as lower risk of hospitalization, transplantation, and mortality. Subjects with LV delay greater than 50% of the baseline QRS duration had longer survival post CRT regardless of whether the cardiomyopathy was ischemic or not. The favorable acute hemodynamic response was observed only in non-ischemic cardiomyopathy patients while the best outcomes were observed in patients in whom the lead was placed at the site with the longest LV delay, most commonly if the lead was placed in the lateral or posterolateral LV wall. The results of this study add to the evidence of placing a lead at the site of latest LV activation time. However, a parameter identified only at the time of implantation has limitations and may not be useful for patient selection. In addition, there may be scenarios where no adequate target vessel exists or that the latest activation time is not localized to the lateral LV wall. Thus, this method is not suited for preprocedural screening of patients that would most likely respond the CRT. In contrast, measurement of the ID in lateral leads can be used as a screening tool and may avoid attempting implantation in patients who are less likely to respond to CRT because there is no LV delayed activation.

A similar invasive parameter of delayed LV activation was developed by Gold et al based on a substudy of the SMART-AV trial.[38] The QLV interval was measured from the onset of QRS (first deflection recorded on the surface ECG) and the activation at LV lead site (positive or negative peak recorded from the LV lead local electrogram). After dividing QLV in quartiles, the longest QLV (QLV > 120 ms) compared to shortest QLV (< 70 ms) was associated with better hemodynamic response to CRT and this translated into favorable reverse remodeling and better quality of life at 6 months. Analogous to Singh et al, this study suggests that the QLV interval is useful to find an optimal LV pacing site and improve response to CRT. However, it requires an invasive measurement at the time of implantation.

LEFT VENTRICULAR ACTIVATION IN PATIENTS WITH HEART FAILURE AND LEFT BUNDLE BRUNCH BLOCK

Currently, a wide QRS and the presence of a complete LBBB are the main ECG parameters to select patients most likely to respond to CRT.[39,40] The activation sequence during LBBB has been the subject of investigation. Auricchio et al used a 3-dimensional contact and non-contact electroanatomical mapping systems to track the ventricular activation wavefront in patients with LBBB and dilated cardiomyopathy.[41] When unipolar non-contact mapping was used, the activation sequence and analysis of electrograms found a U-shaped activation turning around a line of block traversing from base to apex and variable location (anterior, inferior, or lateral). In contrast, bipolar contact mapping revealed uninterrupted propagation sequence with no definite line of block. These findings reflect a complex and heterogenous LV activation in dilated cardiomyopathy and LBBB. Mapping during asynchronous pacing revealed that the line of block could be shifted to different locations and the local electrograms at the line of block were also dependent on the activation sequence, which supports a functional line of block rather than a fixed anatomical barrier. The fact that the unipolar mapping detected this line of block is consistent with an inhomogeneous propagation of intramural activation, while the endocardial activation seems to be relatively well preserved. Additionally, subjects who had a normal or slightly prolonged trans-septal activation had a more distant lateral line of block and shorter QRS duration, while subjects with delayed trans-septal activation had a shorter distance to the line of block. The implications of these findings for CRT response include the heterogeneity of the LV activation sequence in LBBB and that patients with shorter QRS duration have shorter delay to the lateral wall and a more tailored approach to CRT may consider a more basal site. Furthermore, it can be inferred that QRS duration and LBBB morphology are not sufficient parameters to determine CRT response. An ECG parameter like the delayed onset of ID to lateral leads may overcome the limitations of QRS duration, since it may reflect more precisely the lateral wall LV delay.

TIME TO ID ONSET AS A PARAMETER TO DETERMINE DELAYED LV ACTIVATION AND SELECT PATIENTS FOR CRT

In a retrospective study from the Mayo Clinic, Del-Carpio, *et al*.[34] analyzed patients with HF (LVEF < 35%) and prolonged QRS who received a successful CRT implantation per standard clinical indications. The investigators evaluated the time to ID in lateral leads and evaluated its predictive value of CRT reverse remodeling response at 6 months (LV end-diastolic and end-systolic volume and LVEF), cardiopulmonary exercise test, and 6-minute walk distance. They used the aforementioned definition of time to ID onset (the time from the earliest onset of the QRS complex in any lead to the point where the maximum deflection is traced toward the baseline, at or after the peak of the R wave). The primary endpoint was reverse remodeling response (defined as ≥ 15% reduction in LVESV from baseline to 6 months). The investigators found through univariate and multivariate analysis that delayed LV activation expressed by a prolonged time to ID in lateral leads (> 110 ms in I and > 130 ms in aVL), ID in lead I/QRS duration ratio > 0.69, and ID difference in lead I and lead V1 > 90 ms, was associated with RR response 6 months post-CRT. Furthermore, these parameters were better ECG predictors of RR than QRS duration or changes of QRS duration post-CRT predominantly in patients with LBBB and nonspecific intraventricular conduction delay. Thus, using this simple ECG parameter, delayed LV activation could be identified non-invasively and was associated with the likelihood of reverse remodeling response in patients undergoing CRT (Figure 4).

The time to ID has been applied by other authors to evaluate CRT response. Vereckei, *et al*.[42] demonstrated that the ID can be used to estimate intraventricular (LV) and interventricular dyssynchrony. The novel parameters consisted of calculating the difference between ID in lead aVL and aVF and dividing by the QRS duration (for intraventricular dyssynchrony) and the difference between ID in lead V6 and V1 divided by QRS duration (for intraventricular dyssynchrony); either or both above 25% were indicative of dyssynchrony. These criteria proved to be useful to predict CRT reverse remodel-

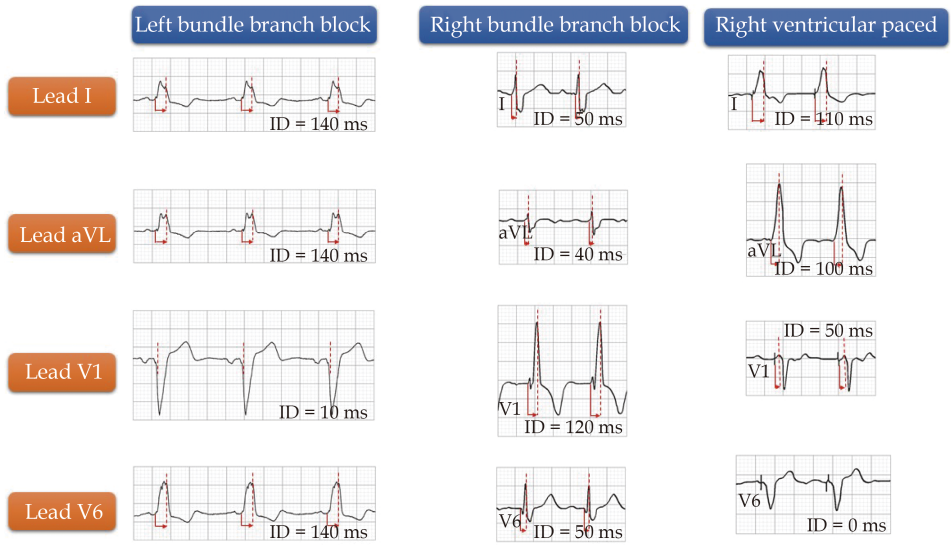

Figure 4 The time to ID onset (red arrows) in different ventricular conduction abnormalities: left and right bundle branch blocks and asynchronous right ventricular pacing. ID: intrinsicoid deflection.

ing response at six months, particularly in patients with non-specific intraventricular conduction delay or in patients with LBBB and QRS durations shorter than 150 ms.

CLINICAL CASE: TIME TO ID ONSET IN LATERAL LEADS. NON-ISCHEMIC CARDIOMYOPATHY

A 54-year-old woman with a history of non-ischemic cardiomyopathy hypertension, and sleep apnea was referred for an ischemic evaluation after her LVEF was estimated at 20%. Her medical therapy was optimized and included carvedilol, sacubitril/valsartan, furosemide, and spironolactone. Her baseline functional class was consistent with a New York Heart Association functional class III. Her baseline ECG showed sinus rhythm and complete LBBB (Figure 5). Despite an optimized medical regimen, her functional capacity and cardiac function did not improve. Her ejection fraction remained at 20%−25% with severe LV enlargement. The time to ID onset in leads I, aVL, and V6 were 130, 120, and 130 ms, respectively. The time to ID onset in lead V1 was 10 ms. She underwent placement of triple lead, single coil internal cardioverter defibrillator and cardiac resynchronization therapy. At implant she had moderate size middle cardiac, posterior, and lateral branches, as potential options for lead placement. A quadripolar lead was placed in the lateral branch, as shown in the figure (Figure 6). The post-procedure ECG during bi-ventricular pacing (LV lead pacing preceding RV by 20 ms) shows a shortened QRS duration and a remarkable reduction in the time to ID in lateral leads (ID lead I 80, ID in lead aVL 80, and ID in lead V6 of 70 ms) (Figure 7).

At a follow up 6-month visit, the patient had an improved clinical status with a functional class I-II, her LV ejection fraction improved to 40%, and the size of the LV was only mild. She continued the same medical regimen.

DISCUSSION

The search for a reliable, safe, and accurate parameter or set of parameters to predict CRT response remains elusive. So far, the ECG remains a critical tool to select patients undergoing CRT and QRS width remains the biomarker of choice for selection of CRT candidates in practice guidelines. The challenge is to find parameters that are not only reliable, but that are simple, consistent, and reproducible. To this end, an old and almost forgotten parameter as the time to ID may be one of those parameters to take into consideration. The evidence of ID as predictive of CRT response is only emerging, but it has a strong physiologic basis and addresses the fundamental basis that CRT aims to correct electrical LV dyssynchrony and delayed activation. Many other ECG parameters studied so far can be complex and

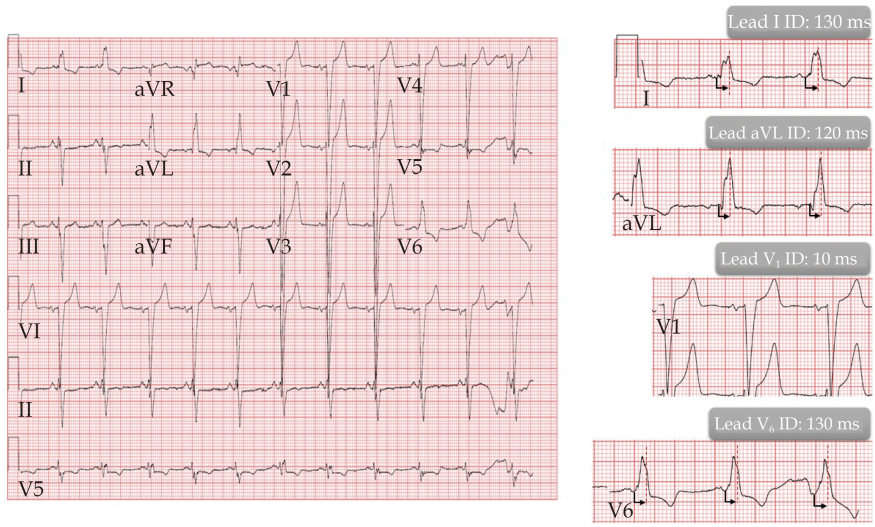

Figure 5 Baseline 12-lead ECG in a patient with non-ischemic cardiomyopathy, severely depressed LV function, and complete LBBB. The right panels show the measurements of the time to ID onset in lateral leads (I, aVL, V6) and V1. ID: intrinsicoid deflection; LBBB: left bundle branch block; LV: left ventricle.

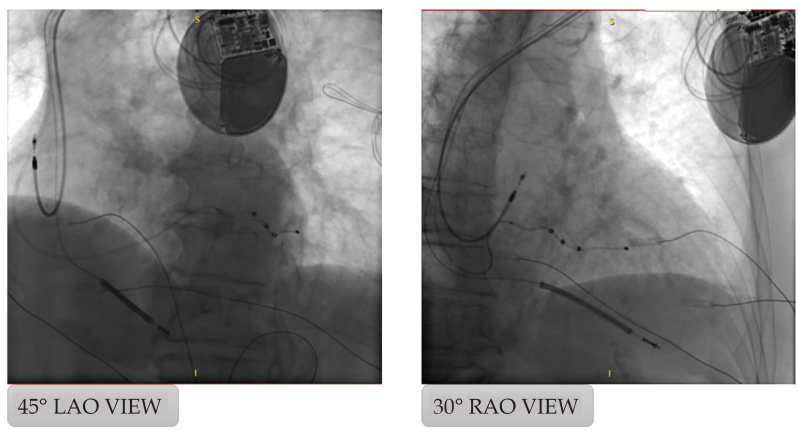

Figure 6 Fluoroscopic images after implantation of a triple lead (atrial and bi-ventricular leads) internal cardioverter defibrillator and CRT system. The LV lead is a quadripolar lead positioned in the lateral LV wall. Notice the wide separation of the right ventricular and LV leads in the LAO view. CRT: cardiac resynchronization therapy; LAO: left anterior oblique; LV: left ventricle; RAO: right anterior oblique views.

others used invasive approaches which may not lend to easy and pre-procedural screening. The present prevailing parameter of QRS duration[43–45] has shown limitations because it reflects global ventricular activation and not specifically delayed LV activation. Delayed time to ID is a non-invasive ECG parameter that can be used to select candidates for CRT and has been described to identify patients at risk of future HF events before ventricular conduction alterations occur,[44] presence of myocardial scarring in HF subjects,[46] and it is associated with sudden cardiac arrest risk.[47] The additive predictive value of ID to current clinical parameters, such as LVEF, functional classification, and QRS width to predict CRT responsiveness requires additional study.

CONCLUSION

HF is a global health burden affecting millions of people worldwide. In addition to guideline directed medical therapy, CRT therapies have provided significant benefits with respect to reduced morbidity and mortality among HF patients that respond to its effects. Despite initial enthusiasm regarding predictive biomarkers for selecting CRT candidates, these studies have not provided incremental value as a prognostic aid in predicting CRT response. Al-

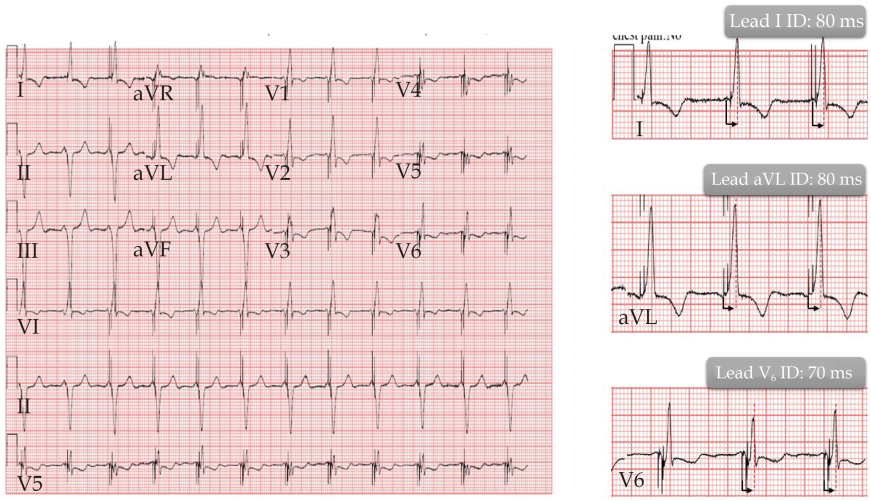

Figure 7 Post-procedure 12-lead ECG showing sinus rhythm and bi-ventricular pacing. Notice the shortened QRS duration and the shortening of the time to ID onset in lateral leads compared to the pre-procedure baseline tracing. ID: intrinsicoid deflection.

though the 12-lead ECG has prevailed as the standard criterion tool, the value of other parameters to aid in predicting CRT response is still not known. The present article provides the electromechanical basis for time to ID to the lateral leads as an adjunct criterion to assist with selection of potential responders to CRT. Further studies in larger patient cohorts, including its inclusion in prospective clinical trials, are needed to fully gauge its role in predicting response to CRT.

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