CONTEMPORARY REVIEW

Nonspecific intraventricular conduction delay: Definitions, prognosis, and implications for cardiac resynchronization therapy

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Abstract

Cardiac resynchronization therapy (CRT) is an electrical treatment of heart failure with reduced ejection fraction and wide QRS. It aims to correct the electrical dyssynchrony present in 30% to 50% of patients in this population. Dyssynchrony results in widening of the QRS complex on the electrocardiogram (ECG). CRT was initially developed to treat patients who had left bundle branch block (LBBB) and delayed activation of the lateral left ventricular wall. However, a large proportion of heart failure patients present with a widened QRS that is neither an LBBB nor a right bundle branch block (RBBB): nonspecific intraventricular conduction delay (NICD). Less studied than RBBB or LBBB, its pathophysiology is both complex and varied yet still reflects intramyocardial conduction delay. NICD is most often associated with cardiomyopathy (eg, ischemic or hypertensive). Conduction pathways can be either healthy or affected. Results from CRT are contradictory in this patient group, despite a seemingly neutral trend. Unfortunately, prospective studies are lacking. Guidelines recommending implantation of CRT devices in this group are based solely on analyses of subgroups with small sample sizes. A dedicated prospective study is therefore warranted for this question to be answered properly. A detailed study of the ECG and noninvasive study of ventricular electrical activation may enable clinicians to better identify patients with NICD who will respond to CRT.

KEYWORDS Cardiac resynchronization therapy; Nonspecific intraventricular conduction delay; Prognosis; QRS morphology

ABBREVIATIONS **AHA/ACCF/HRS** = American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society; **CI** = confidence interval; **CRT** = cardiac resynchronization therapy; **ECG** = electrocardiogram/electrocardiographic; **HFREF** = heart failure with reduced ejection fraction; **LBBB** = left bundle branch block; **LV** = left ventricle; **NICD** = nonspecific intraventricular conduction delay; **RBBB** = right bundle branch block; **RR** = relative risk; **RV** = right ventricle/ventricular; **VEU** = ventricular electrical uncoupling

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Introduction

Many randomized controlled trials[1–6] have found cardiac resynchronization therapy (CRT) to be beneficial in patients with heart failure with reduced left ventricular (LV) ejection fraction (HFREF) and prolonged QRS duration. The concept of biventricular resynchronization was developed in accordance with the understanding of the deleterious biological, hemodynamic, and clinical effects of the abnormal activation sequence observed in patients with a left bundle branch block (LBBB)[7–9] and the beneficial effect of CRT in this population.[1,10] QRS width has traditionally been the main inclusion criterion in large randomized studies.[3,4,11,12] More recently, subgroup analyses have suggested a greater efficacy of CRT in patients with LBBB than in patients with right bundle branch block (RBBB) or nonspecific intraventricular conduction delay (NICD), which underscores the importance of the pattern of activation over and above that of QRS width.[13,14] There is abundant evidence from data from both animal models[15] and clinical observations to enable us to validate the effectiveness of CRT in LBBB.[13,14,16] Biventricular resynchronization corrects the deleterious electrophysiological, genetic, molecular, cellular, and tissue remodeling generated by the activation sequence and the

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various levels of dyssynchrony that characterize LBBB. In contrast, current literature is much sparser with regard to nonspecific block. Its definition,[17] "wide QRS without the appearance of left or right bundle block," corresponds to a definition by default. NICD is observed in a variety of pathologies, and the results obtained after CRT include only small numbers of patients, with no dedicated randomized studies. Moreover, the observed results can be conflicting.[13,14,16] The latest international guidelines restrict CRT device implantation in these patients, and the question arises as to whether to continue to implant CRT devices in heart failure patients with NICD.

In the present review, we propose to revisit and discuss the various elements described in the literature in terms of definition, prevalence, pathophysiology, and prognostic character of NICD. We will also discuss the results described after CRT in this subgroup of patients and attempt to identify future perspectives with a reflection on optimizing the selection of candidate patients and the need for dedicated studies.

Definition

Different designations can be found in the literature, including unspecified intraventricular conduction disturbance, nonspecific intraventricular conduction disturbance/delay (NICD), and intraventricular conduction disturbance, to define the same entity: the existence of a widened QRS without the features of RBBB or LBBB. It thus boils down to a definition by default, with certain variations depending on the study. The American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (AHA/ACCF/HRS) recommendations,[17] published in 2009 and used in the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT),[13] specified that nonspecific or unspecified intraventricular conduction disturbance is defined by "a QRS duration greater than 110 ms in adults, greater than 90 ms in children 8 to 16 years of age, and greater than 80 ms in children less than 8 years of age without meeting the criteria for RBBB or LBBB. The definition may also be applied to a pattern with RBBB criteria in the precordial leads and LBBB criteria in the limb leads, and vice versa." In the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT),[14] NICD was defined according to the criteria approved by the World Health Organization.[18] The definitions of LBBB (QRS duration $\geq$130 ms; QS or rS in lead V_1; broad R waves in leads I, aVL, V_5, or V_6; and absent q waves in leads I, V_5, and V_6) and RBBB (QRS duration $\geq$130 ms; rsr′, rsR′, rSR′, or qR in leads V_1 or V_2; and occasionally, a wide and notched R wave and wide S waves in leads I, V_5, and V_6) are very precise and seek to define the components of a characteristic activation sequence on the electrocardiogram (ECG). The definition of NICD, on the other hand, is much less detailed and once again a diagnosis of exclusion: "wide QRS ($\geq$130 ms) but without typical features of LBBB or RBBB."

Finally, masquerading bundle branch blocks (RBBB pattern in the precordial leads and left anterior fascicular block pattern in the limb leads) may be a specific entity and sometimes may be mistaken for LBBB (the S wave can be absent or very small in lead I, resulting from a not only purely left anterior fascicular block associated with LV hypertrophy or focal block caused by scar or fibrosis).

Prevalence

Depending on the studies/registries, QRS duration prolongation >120 ms has been described in 14% to 47% of patients with heart failure. Among these patients with a wide QRS, the proportion of patients with NICD (6.1%–30.3% in dilated cardiomyopathy) is relatively small and less than that with LBBB (25%–36% with LBBB).[19–21] Sandhu et al[22] noted that patients with NICD represented 3.8% of the overall HFREF population and 15.3% of HFREF patients with QRS duration >120 ms. In the Spanish Network for the Study of Heart Failure (REDINSCOR), which included 2254 patients with LV ejection fraction $\leq$40%, 5.8% patients presented with an NICD pattern.[23] The proportion of patients with NICD included in major CRT clinical trials is presented in Figure 1.[13,14,16,24]

Pathophysiology

There are various causes of a widened QRS complex without the typical feature of a bundle branch block. The different subgroups of NICD corresponding to the AHA/ACCF/HRS definition[17] include relatively diverse pathophysiological processes that have been described in the literature. In the following paragraphs, we describe the pathophysiology of this conduction disorder and use noninvasive electrical mapping to highlight the diversity of biventricular activation in this patient group.

Atypical LBBB

In the NICD subgroup, one must include the appearance of atypical bundle branch block observed in post–myocardial infarction patients that corresponds to the probable existence of a true LBBB, in which the superposition of the electrical abnormality in relation to the necrotic area alters the typical ECG appearance (Figure 2). The ECG reveals the presence of wide, deep Q waves in multiple leads after a massive myocardial infarction or that affect multiple areas (eg, in a patient with a preexisting LBBB, a QS complex may be present in the anterior leads and a QR wave in lateral leads after an anterior or lateral myocardial infarction). A part of the fragmented bundle branch block described by Das et al[25] has been shown to be related to scar in patients with known or suspected coronary artery disease. The activation sequence in these patients should be very close to that observed in patients with a typical LBBB.

Intraventricular parietal block

In contrast, in the NICD subgroup, we also find patients with a wide QRS complex despite an unaltered or slightly altered