

## Conduction Disturbances Leading to Heart Failure – What Clinicians Need to Know

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### Abstract

Recently, pre-excitation syndromes, left bundle branch block (LBBB), and right ventricular pacing have been recognized as causes of cardiomyopathies (CMs). They all have abnormal ventricular activation, that results in what is known as left ventricular (LV) dyssynchrony. These three entities show a common feature of wide QRS and LBBB pattern on the electrocardiogram. The term abnormal conduction-induced CM was, then, proposed. Appropriate diagnosis and treatment of these CMs will possibly improve LV ejection fraction, LV functional capacity and reduce morbidity and mortality. In this article we will briefly review these three clinical conditions, aiming to help clinicians to recognize them, manage and refer patients at risk.

### Introduction

Former definitions and classifications of cardiomyopathies (CM) of the American Heart Association<sup>1</sup> and the European Society of Cardiology<sup>2</sup> included genetic diseases and tachycardia-induced CMs as possible causes of heart failure (HF). Recently, pre-excitation syndromes, left bundle branch block (LBBB), and right ventricular pacing (RVP) have been recognized as additional etiologies of CM. They all have abnormal ventricular activation, that results in what is known as left ventricular (LV) dyssynchrony. Although the identification of dyssynchrony requires cardiac imaging, the three entities mentioned show a common feature of wide QRS and LBBB pattern on the electrocardiogram (ECG).<sup>3</sup> The term abnormal conduction-induced CM was, then, proposed. Appropriate diagnosis and treatment of these CM will possibly improve LV ejection fraction (LVEF) and functional capacity and reduce morbidity and mortality.

### Keywords

Cardiomyopathy; Heart Failure; Left Bundle Branch Block; Left Ventricular Dysfunction; Pre-excitation Syndrome; Right Ventricle Pacing.

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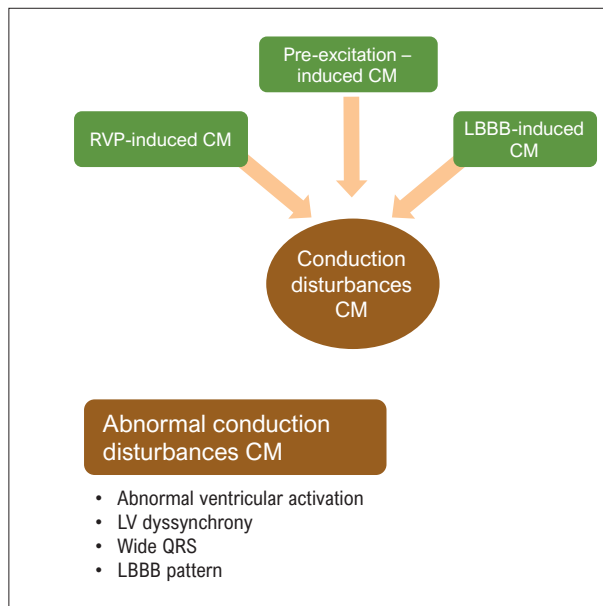
In this article, we will briefly review these three clinical conditions (Figure 1), aiming to help clinicians to recognize them, manage and refer patients at risk.

### RVP-induced CM

Permanent pacemaker (PPM) implantation is the best therapeutic choice for symptomatic bradyarrhythmias. However, apical RVP, or “conventional” artificial cardiac pacing, may induce inter and intraventricular dyssynchrony, increase sympathetic activation, cause abnormalities in myocardial perfusion and endothelial function, worsening cardiac output and leading to HF. This may occur in 10% to 20% of RVP patients.<sup>4</sup> An altered activation pattern similar to LBBB is observed, with electrical activation beginning at the septum and considerably delayed activation of the LV free wall, as the electrical impulse crosses from myocardial cell-to-cell rather than through the fast Purkinje system, prolonging the QRS duration. This results in an inefficient contraction pattern with ventricular dyssynchrony and loss of myocardial work that may lead to LV dilation, systolic dysfunction, and clinical HF.<sup>5</sup> It is likely that the development of CM depends on the degree of LV dyssynchrony, which can vary significantly based on location of RVP lead or atrial pacemaker implantation.<sup>3</sup>

In a Danish Nationwide registry, 27,704 patients, with no history of HF had a PM implanted with an RVP lead between 2000 and 2014 were evaluated retrospectively. For each case, five age- and sex-matched controls were identified ( $n = 138,520$ ). At two years of follow-up, PM with a RVP lead was strongly associated with risk of HF, specifically in the first six months. Patients with history of myocardial infarction and chronic kidney disease had substantially increased risk.<sup>5</sup>

Ahmed et al.<sup>6</sup> demonstrated, in a prospective study, that in patients with normal baseline LVEF, mechanical dyssynchrony observed early after interposition of high-dose RVP was associated with later LVEF decline. They performed transthoracic echocardiograms early (median four months) and late (median 28 months) after implantation of the pacing system, with a significant decline in EF between these studies defined as  $>5\%$ . Speckle-tracking longitudinal strain analysis of the early echocardiogram was performed to quantify dyssynchrony. In addition to standard dyssynchrony indices, a novel index was used. The authors calculated apex-to-base dyssynchrony using the six segments from the apical four-chamber view, named “mechanical propagation delay” (MPD). MPD was the average difference in time to



**Figure 1** – Types and mechanisms of development of abnormal conduction disturbances that lead to cardiomyopathies; RVP: right ventricular pacing. LV: left ventricular; LBBB: left bundle branch block; CM: cardiomyopathy.

peak strain between adjacent segments. MPD of the septum correlated with a significant decline in EF, irrespective of all other dyssynchrony, clinical, or pacing variables.<sup>6</sup>

Safak et al.<sup>7</sup> analyzed the data of 170 patients who were submitted to PPM at the RV apex, in the absence of structural heart disease and a preserved LVEF (> 45%) at the time of PPM. At a median echocardiographic follow-up of 24.5 months there was a non-negligible 6% rate of new-onset RVP-induced CM. The presence of sick sinus syndrome as a primary indication for PPM was inversely and independently related to CM occurrence.<sup>7</sup>

Most acceptable definitions for pacemaker-induced cardiomyopathy (PICM) are LVEF <50%, absolute decline of LVEF by ≥10% and/or new-onset heart failure (HF) symptoms after PPM implantation. HF hospitalization due to systolic or diastolic dysfunction and new-onset atrial fibrillation (AF) should also be considered. Mean time between PPM implantation and the first RVP-related HF event in patients with previously normal LVEF was 2-5 years. Male sex, advanced age, high RVP burden (greater than 20%), coronary artery disease, pre-existing AF, baseline prolonged QRS duration, baseline low LVEF and prolonged paced QRS duration are the risk factors for the development of PICM. Most authors recommend that patients with RVP should undergo a baseline echocardiogram; the test should be repeated annually for patients with reduced LVEF (< 50%) and high rates of RVP (≥ 40%) and every two years for patients with preserved LVEF.<sup>4,8,9</sup>

As mentioned, PICM has been viewed as a form of HF with reduced EF, and most studies reporting the incidence of PICM include impaired LVEF in the diagnostic criteria. However, many patients who experience detrimental effects from RVP may still have a preserved EF and may not meet traditional criteria for PICM. On the other hand, some questions need

to be addressed. Is RVP the cause of new-onset HF or is the need for PPM implantation a presage of an underlying disease that would have resulted in HF independently of the PM? Is the relationship between PPM and HF an association or causation?<sup>25,10</sup>

In the Mode Selection Trial (MOST), the authors analyzed patients with sinus node dysfunction, and randomly compared 707 patients with dual-chamber rate-modulated (DDDR) pacing with 632 with single-chamber ventricular rate-modulated (VVIR) pacing. It was shown that, after a mean follow-up of 33.1 months, the risk of hospitalizations for HF and AF was directly correlated with RVP burden, irrespective of pacing mode (single- or dual-chamber). Ventricular desynchronization caused by right ventricular apical pacing in the DDDR mode may increase the risk of HF and AF, particularly when imposed on the failing left ventricle. Such risks may be reduced by minimal ventricular pacing strategies that preserve the normal ventricular activation sequence as much as possible. Ventricular pacing > 40% was associated with a 2.9 increase in HF hospitalization and a 1.36 increase in the risk of AF. For single-chamber pacing, these numbers were similarly alarming: pacing > 80% was associated with a 2.56 increase in HF hospitalization, and the risk of AF increased 1.21 times with every 25% increase in RVP burden.<sup>11</sup> High RVP burden is commonly seen in patients with the following: 1) DDD pacing mode if the atrioventricular (AV) delay is programmed shorter than intrinsic AV conduction; or 2) VVI pacing mode with intrinsic rate below the programmed lower rate limit. In addition, the PM's features may inadvertently increase RVP (e.g., mode switch for AF with higher lower rate limit, and rate smoothing algorithms).<sup>3,12</sup> A prospective study including patients with complete AV block showed that paced QRS duration <160 ms, 160 to 189 ms, and >190 ms had a three-year HF incidence of 9.4%, 27.8%, and 56.8%, respectively (p < 0.001). Also, a reduction in LVEF was correlated directly with the paced QRS duration (relative risk: 0.423). A paced QRS duration >165 ms was a predictor for long-term risk of HF events.<sup>13</sup>

Not all patients develop PICM during follow-up, and identifying the predisposing

factors would help in mitigating the potential complication. Besides careful patient selection for PPM implantation, the individualized choice of the device and programming are essential initial measures to reduce PICM incidence.<sup>3,5,14,15</sup>

Periodic assessment of patients with RVP is essential. A comprehensive post implantation follow-up program may help in early diagnosis and better management of patients with PICM. Patients should undergo a baseline echocardiogram; the test should be repeated annually for patients with reduced LVEF (< 50%) and high rates of RVP (≥ 40%) and every two years for patients with preserved LVEF.<sup>4,8,9</sup>

#### Left bundle branch block-induced CM

LBBB is often associated with cardiovascular diseases such as high blood pressure, coronary artery disease and HF. Dilated CM registries report rates of LBBB as high as 31%.<sup>16</sup>

Although rare, isolated LBBB (without apparent or suspected heart disease) has been recognized in recent years as

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a causal factor of a distinct pathological entity: LBBB-induced CM. The epidemiological relevance of this hypothesis is due to the fact that although isolated LBBB has a low prevalence in the general population (<1%), in the elderly population it increases, up to 5% in octogenarians.<sup>17,18</sup>

Persistent ventricular dyssynchrony, typical in LBBB, could act as a trigger for the development of CM ("dyssynchronopathy" hypothesis). In patients with LBBB, due to loss of conduction through the left-sided fascicles, electrical activation of the ventricles initiates in the right ventricle and then travels to the left ventricle through the myocardial fibers. In the left ventricle, the earliest activation occurs in the ventricular septum and then travels to the lateral free wall. This altered electrical activation of the left ventricle leads to a delay and heterogeneity of the intraventricular and interventricular depolarization and repolarization. Delayed deformation of the LV lateral wall also causes changes in the movement of papillary muscles and in the kinetics of the mitral valve apparatus with a consequent shortening diastolic filling period. Asynchronous ventricular activation leads to a redistribution of circumferential shortening and myocardial blood flow with decreased perfusion in the septum and increased in LV lateral wall. In the long term, electromechanical and perfusional changes cause LV remodeling and impaired systolic and diastolic filling.<sup>3,19,20</sup>

LBBB-induced CM should be suspected in patients who develop CM, with history of LBBB with duration longer than five years, and LVEF >50% and no cardiovascular disease at the time of CM diagnosis.<sup>3</sup> However, in clinical practice, information about duration of conduction disorder, or on previous systolic function is not available for most patients at the time of diagnosis of LBBB-related heart disease. This creates a chicken or the egg causality dilemma, where it becomes a challenge to define the role of LBBB as a cause or consequence of a cardiomyopathy.<sup>20</sup>

In an attempt to shed light on this difficult diagnostic task, in 2019, Sanna et al.<sup>20</sup> proposed clinical, electrocardiographic and imaging criteria to be red flags of LBBB induced-CM in a patient newly diagnosed with CM and LBBB (Table 1). It is important to highlight that these proposed criteria have not been validated in cohort studies yet.

### Pre-excitation syndrome induced-cardiomyopathy

In ventricular pre-excitation syndrome, AV conduction occurs, partially or totally, through an accessory pathway, which results in earlier activation (pre-excitation) of the ventricles.<sup>21</sup>

It is a relatively common anomaly, estimated to affect 1-3/1,000 live births.<sup>21</sup> The condition may be asymptomatic or manifest as paroxysmal supraventricular tachycardia or, even more rarely, as syncope or sudden death due to the rapid conduction of an atrial tachyarrhythmia through the accessory pathway.<sup>22</sup> Although occasional episodes of paroxysmal supraventricular tachycardia are generally not associated with the development of ventricular dysfunction, this possibility exists in cases of incessant tachycardia. Additionally, abnormal ventricular activation resulting from early anterograde conduction can cause

AV, interventricular, and intraventricular dyssynchrony, as well as CM.<sup>23</sup>

Pre-excitation-induced CM is defined as LV systolic dysfunction exclusively caused by the presence of a manifest accessory pathway that recovers upon ablation. It should not be confused with tachycardia- or AF-induced CM because these two conditions are not uncommon in patients with manifest accessory pathway. So, in order to diagnose pre-excitation induced-CM, we must exclude both AF and supraventricular tachycardia.<sup>3</sup>

A causal association between ventricular septal pre-excitation and ventricular dysfunction, or pre-excitation-induced CM, has been reported as a result of the mechanical dyssynchrony induced by the eccentric propagation of the electrical stimulus to the ventricle via the accessory pathway.<sup>23-26</sup> This abnormality, already described in infants, children and young adults, has been especially apparent in patients with ventricular pre-excitation in the right septal or postero-septal region,<sup>24-26</sup> which causes early electrical activation of the interventricular septum, inducing a mechanical dyssynchrony of the left ventricle.<sup>25</sup> The early detection of the abnormal mechanical motion and morphological degeneration at the basal interventricular septum might lead to early diagnosis of pre-excitation induced-CM. This subgroup is definitively diagnosed when LV function recovers after interventional elimination of antegrade conduction. In these patients, after elimination of the accessory pathway, ventricular dysfunction usually reverses in a time range of one to 17 months.<sup>3,27</sup>

### Treatment

As for any diagnosis of HF, guideline-directed medical therapy should be initiated and optimized as soon as possible.<sup>3</sup> Since PICM is due to electrical and mechanical disturbances induced by RVP, reducing the pacing burden and/or correcting the dyssynchrony by an alternative pacing modality will ameliorate clinical symptoms.<sup>16</sup> Cardiac resynchronization therapy (CRT) using biventricular pacing is the most used approach for the management of PICM. Several studies have confirmed the ability of biventricular pacing to reverse the LV dilatation and dysfunction along with reduction in the severity of mitral regurgitation.<sup>28</sup> In a cohort of 69 PICM patients identified through systematic inclusion and careful screening for alternative causes of CM, CRT upgrade was associated with marked improvement in systolic function, with mean LVEF increasing from 29.3% to 45.2% and more than 70% achieved LVEF >35%. The benefits of CRT upgrade appear to be rapid, and most of LVEF improvement occurs within three months and more gradually over the remainder of the first year.<sup>13,29,30</sup>

RVP-induced CM is reversible or partially reversible if RVP can be avoided or eliminated. Proper programming of AV intervals to allow intrinsic conduction can be achieved with a simple interval prolongation or by using device algorithms intended for this purpose. As for VVIR pacing, programming the device at a lower heart rate than intrinsic, when possible, is the only way to try to reduce PICM.<sup>3,31</sup>

**Table 1 – Proposed red flags for left bundle branch block-induced cardiomyopathy**

Criteria	Red flag feature
ECG	<ul style="list-style-type: none"> <li>Typical LBBB: wide QRS (&gt;140 ms) with notching in lateral leads and QS or rS in V2-V3</li> <li>No pseudonecrosis</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>No family history of DCM</li> <li>Exclusion of cardiovascular causes of CM such as coronary artery disease, genetic CMs, inflammatory CM, toxic causes (e.g. alcohol, anthracyclines), tachycardiomyopathy</li> </ul>
Echocardiography	<ul style="list-style-type: none"> <li>Usually non severe left ventricular dilatation</li> <li>Normal wall thickness</li> <li>Visually marked dyssynchrony</li> <li>Non-severe diastolic dysfunction</li> <li>Mild functional mitral regurgitation</li> <li>Mild left atrial dilatation</li> <li>Usually normal right ventricular function</li> </ul>
CMR	<ul style="list-style-type: none"> <li>No or non-significant scar or fibrosis – usually no LGE, T1 and T2 mapping within normal limits</li> </ul>

ECG: electrocardiogram; LBBB: left bundle branch block; DCM: dilated cardiomyopathy; CM: cardiomyopathy; CMR: cardiac nuclear magnetic resonance; LGE: late gadolinium enhancement; ms: milliseconds.

CRT with either biventricular pacing or conduction system pacing, including His-bundle pacing and left bundle branch area pacing (LBBAP) is the indicated procedure to improve LV function in RVP-induced CM and LBBB-induced CM.<sup>3,10,30</sup> Although biventricular pacing has long been considered the standard treatment for abnormal conduction-induced cardiomyopathy, recent data suggest that conduction system pacing is associated with greater normalization of LVEF (27.6% vs 14.4%;  $p = 0.005$ ) and better outcomes (death or HF admissions 28% vs 38%;  $p = 0.01$ ) compared with biventricular pacing.<sup>32-35</sup>

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## Conclusions

All cardiologists and clinicians taking care of patients with these conduction disturbances must be aware of the potential progression to cardiac dysfunction, CM and HF. Since the time to develop HF varies in patients with high rates of RVP, LBBB and pre-excitation, they should undergo clinical evaluation, measurement of biomarkers and serial echocardiograms. Patients at high-risk of developing abnormal conduction-induced CM should be identified and treated to prevent HF. Early detection is important because both CRT and conduction system pacing can reverse LV dysfunction and reduce morbidity and mortality.

## Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Figueiredo EL, Nunes F, Neunshwander FC, Maia KAP, Carmo AAL.

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This article does not contain any studies with human participants or animals performed by any of the authors.



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