

Abnormal conduction-induced cardiomyopathy: a poorly explored entity

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KEYWORDS

Cardiomyopathies;
Cardiac conduction disorders;
Dyssynchronopathy;
Genetics

A dyssynchronous biventricular activation, which can be determined by left bundle branch block, chronic right ventricular pacing, frequent premature ventricular complexes, or pre-excitation, can cause a global abnormal contractility, thus leading to systolic dysfunction and left ventricular remodelling in a unique nosological entities: abnormal conduction-induced cardiomyopathies. In this clinical scenario, the mainstay therapy is eliminating or improving LV dyssynchrony, removing the trigger. This usually ensures the improvement and even recovery of cardiac geometry and left ventricular function, especially in the absence of genetic background. A multidisciplinary approach, integrating advanced multimodal imaging, is essential for the systematic aetiological definition and the subsequent evaluation and aetiology-guided therapies of patients and their families. This review aims to describe mechanisms, prevalence, risk factors, and diagnostic and therapeutic approach to the various abnormal conduction-induced cardiomyopathies, starting from reasonable certainties and then analysing the grey areas requiring further studies.

Introduction

Cardiomyopathies are defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease (CAD), hypertension, valvular disease, and congenital heart disease (CHD) sufficient to cause the observed myocardial abnormality.¹

Aetiology has been traditionally classified in genetic/familial and acquired/sporadic (i.e. inflammatory, toxic, and multisystem diseases), but several forms of cardiomyopathy previously considered secondary only to external factors were recently proved to have genetic contributors (i.e. the 'second hit theory').¹ The phenotypic expression can be so considered as the

complex result of a possible genetic background associated with environmental factors.

Starting from the phenotype at presentation, an accurate aetiological definition in a comprehensive and systematic approach is required, as it has proved effective in driving therapeutic choices and significantly influencing the prognosis.²

The acquired environmental causes may include the use of potentially cardiotoxic drugs (i.e. some classes of chemotherapy agents as the anthracyclines), the exposure to ionizing radiation, alcohol abuse, nutritional deficiencies, endocrine disorders, infections, and inflammatory and autoimmune diseases.²

Sustained supraventricular tachyarrhythmias can induce systolic dysfunction (the so-called 'tachycardia-induced or tachy-induced' mechanism) (Figure 1), too. Moreover a dyssynchronous ventricular activation, due to left bundle

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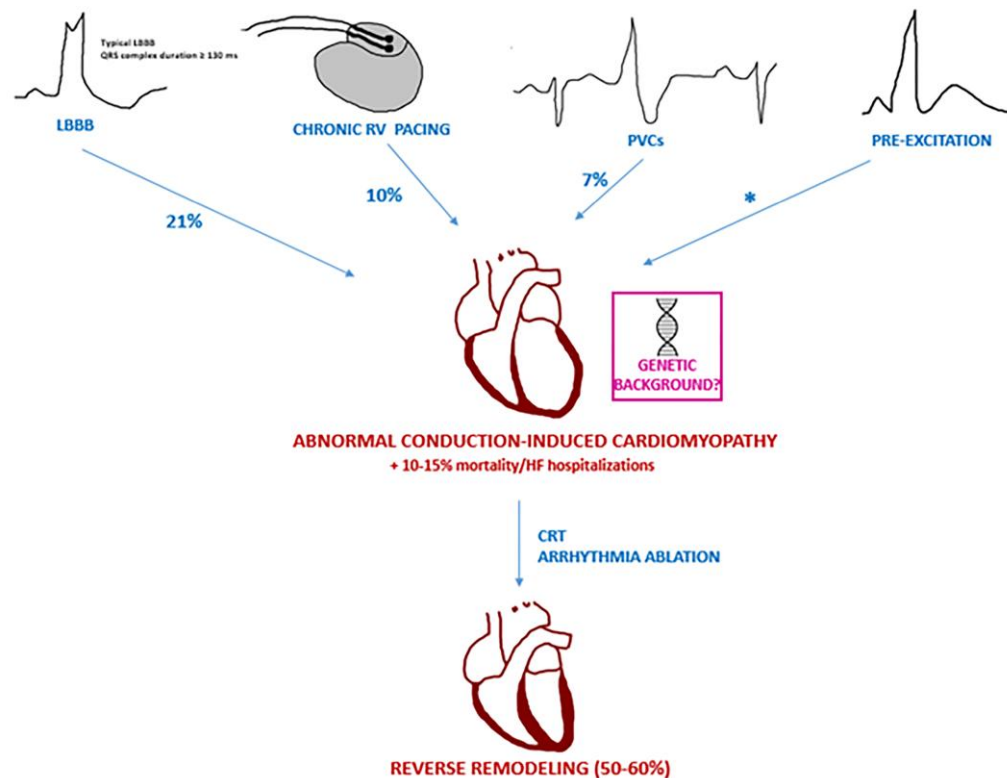


Figure 1 Abnormal conduction-induced cardiomyopathy: aetiological heterogeneity and natural history. LBBB, left bundle branch block; CRT, cardiac resynchronization therapy; HF, heart failure; PVCs, premature ventricular complexes; RV, right ventricle.

branch block (LBBB), chronic right ventricular pacing, frequent premature ventricular complexes (PVCs), or pre-excitation, can result in an abnormal global cardiac contractility.³

Left bundle branch block-induced cardiomyopathy

The prevalence of 'isolated' LBBB (i.e. without any other heart diseases) in the general population has been estimated to be between 0.2% and 1.1%.⁴ In patients with dilated cardiomyopathy (DCM), its prevalence increases up to 31% while, on the other hand, left ventricular (LV) dilation and systolic dysfunction can be detected in 21% of patients with left intraventricular conduction disorders.^{3,5}

The presence of LBBB is a predictor of unfavourable clinical outcomes in terms of both development of cardiac systolic and diastolic dysfunction (three-fold increase than in subjects with normal intraventricular conduction) and mortality and hospitalizations for heart failure (HF), particularly in the elderly.⁴

Left bundle branch block cardiomyopathy (LBBB-CM) is defined as a CM caused by persistent/chronic LBBB but the abovementioned epidemiological data suggest a complex relationship between the two conditions, in which it is not easy to differentiate between the observed 'cause' and 'effect'.

When facing a patient with LBBB and LV dysfunction, a co-ordinated and multiparametric approach is

needed. It has to include an accurate combination of personal and family history and clinical examination, a 'cardiomyopathy-oriented' analysis of the electrocardiographic abnormalities (not exclusively focused on the duration and morphology of QRS complex), and the use of multimodality imaging, including myocardial deformation imaging (speckle tracking or tissue Doppler) with global longitudinal strain and mapping sequences for cardiac magnetic resonance (CMR), as they have proved to be sensitive markers to detect morpho-functional anomalies even in the subclinical phase.¹

A deep characterization of the patient phenotype can also guide the therapeutic management. Indeed, the use of cardiac resynchronization therapy (CRT) or left bundle branch pacing has been demonstrated to determine a significant or even complete reverse remodelling, also in advanced stages of left ventricular dysfunction and dilation (*Table 1*),³⁻⁸ above all in female and patients with 'true' or 'typical' LBBB (QS morphology or rS in V1-V2 leads, a QRS complex duration ≥ 140 ms in or ≥ 130 ms in female, the notching in at least two leads between DI, aVL, V1, V2, V5, and V6).

Current guidelines recommend CRT implantation when the conduction disorder becomes phenotypically and clinically evident (i.e. with a LV ejection fraction lower than or equal to 35% in symptomatic HF patients despite optimized medical therapy for at least 3 months, in sinus rhythm and with a QRS complex duration ≥ 130 ms—class of recommendation I, level of evidence A if QRS complex duration ≥ 150 ms or class of recommendation IIa, level

Table 1 Proposal for differential diagnosis between dilated cardiomyopathy and dyssynchronopathy

	Dilated cardiomyopathy	Dyssynchronopathy
Positive family history	+	±
Pathogenic/likely pathogenic monogenic variants	30-50% of patients	Undetermined
Genetic-background-environmental interaction	+ (largely unknown)	Unknown mechanisms
Presence of left bundle branch block since presentation	±	+
Left ventricular dilatation > 2 SDs	Frequent	Possible
Relative wall thicknesses	At lower/reduced limits	Frequently normal
Wall thicknesses	Frequently normal/at lower limits	Frequently normal/possible lateral wall hypertrophy
Left ventricular systolic dysfunction	+	+
Contraction dyssynchrony	±	+ (septal flash and apical rocking)
Diastolic dysfunction	± (often second or third degree)	± (less marked, often first degree)
Left atrial dilatation	± (often severe)	± (often not present/slight dilation)
Persistence of right ventricular systolic dysfunction after optimized medical therapy	±	±
Presence of late gadolinium enhancement	±	±
Prognosis	Extremely variable	Estimated best after resynchronization
Response to resynchronization	Variable	Excellent if 'typical' left bundle branch block and QRS complex duration of at least 130 ms (often reverse remodelling)

Modified from Sanna GD, Merlo M, Moccia E, *et al.* Left bundle branch block-induced cardiomyopathy: a diagnostic proposal for a poorly explored pathological entity. *Int J Cardiol.* 2020;299:199-205.³

of evidence B if QRS complex duration is between 130 and 149 ms).⁹

In asymptomatic subjects with 'isolated' LBBB and normal biventricular systolic function at a first evaluation, a routine follow-up is still recommended, as the population-based studies of patients with LBBB demonstrated that CM and HF can develop several years after diagnosis of LBBB. Moreover, LBBB can be the first expression of an underlying structural heart disease.⁵

Table 2 shows that the factors proved to be associated with worsening of LV systolic function in patients with LBBB.¹⁰

Chronic right ventricular pacing-induced cardiomyopathy

The use of pacemakers (PM) is rapidly growing alongside the aging trend of the general population.

Chronic 'conventional' (i.e. apical right ventricular) pacing can be the cause of a global cardiac systolic dysfunction, due to a dyssynchronous contraction both at interventricular level (the right ventricle contracts before the left) and intraventricular level (the interventricular septum contracts before the free wall of the right ventricle).^{5,11,12}

Right ventricular pacing CM (RVP-CM) is defined as a LV systolic dysfunction only caused by frequent RVP, without other determining factors. A decline of 10% or absolute value < 50% in LVEF is the most sensible and

used definition, also because it allows for an early diagnosis and treatment.⁵

However, since no univocal definition has been postulated, the incidence reported in different studies can vary from 6-25%, affecting ~10% of PM carriers.¹¹

Risk factors associated to RVP-CM onset are shown in **Table 2**.¹¹ For example, a percentage of RVP ≥ 20% has been shown to be strongly associated with the development of LV systolic dysfunction, with a direct proportionality between pacing percentage and risk of CM. On the other hand, a 'safe' threshold has not been identified.¹²

As reported by retrospective studies, the development of RVP-CM would determine a 10-15% increase in the composite endpoint of HF mortality and hospitalizations compared to PM carriers with preserved biventricular systolic function.⁵

Guideline-directed HF medical therapy should be initiated promptly and optimized even though its clinical benefit may be limited.⁵ RVP-CM is fully or partially reversible if RVP can be avoided or eliminated. This can be achieved by enabling algorithms to minimize RVP or by upgrading to biventricular pacing (i.e. CRT) that has proved to be effective in terms of reverse remodelling and clinical outcomes (above all HF hospitalizations) and is therefore recommended in patients with HF with reduced ejection fraction (HFrEF) and advanced atrioventricular conduction disorders or atrial fibrillation if ventricular pacing is needed, regardless of the New York Heart Association class and the QRS complex duration.^{5,9,11,12}

Table 2 Risk factors associated with worsening of systolic function in patients with left bundle branch block, dilated cardiomyopathy and ejection fraction $\geq 35\%$, and development of pacemaker-induced cardiomyopathy

Factors associated with worsening of systolic function in patients with left bundle branch block, dilated cardiomyopathy and ejection fraction $\geq 35\%$	Hazard ratio and univariate and multivariate Cox regression analyses
Persistence of moderate to severe mitral regurgitation	HR 2720; 95% CI 1.131-6.541; $P = 0.025$ (univariate) HR 3.004; 95% CI 1.130-7.989; $P = 0.027$ (multivariate)
Left atrial remodelling (left atrial end-systolic area index) ^a	HR 1260; 95% CI 1.078-1.473; $P = 0.004$ (univariate) HR 1233; 95% CI 1.038-1.464; $P = 0.017$ (multivariate)
Left ventricular remodelling (left ventricular end-diastolic volume index) ^a	HR 1022; 95% CI 1.005-1.039; $P = 0.010$ (univariate) HR 1027; 95% CI 1.008-1.067; $P = 0.017$ (multivariate)
Risk factors associated with development of right ventricular pacing-induced cardiomyopathy	
Male sex	
History of myocardial infarction	
Chronic renal failure	
Atrial fibrillation	
Pre-implantation left ventricular systolic function	
Native QRS duration	
Right ventricular pacing percentage	
Paced QRS duration	

Courtesy from Gentile P, Paldino A, Cannatà A, *et al.* Left bundle branch block in dilated cardiomyopathy with intermediate left ventricular dysfunction: clinical phenotyping and outcome correlates. *Int J Cardiol.* 2019 Mar 1;278:180-185 and by Somma V, Ha FJ, Palmer S, Mohamed U, Agarwal S. Pacing-induced cardiomyopathy: a systematic review and meta-analysis of definition, prevalence, risk factors, and management. *Heart Rhythm.* 2023;20(2):282-290.^{10,11}

CI, confidence interval; HR, hazard ratio; ms, milliseconds; OR, odds ratio; P , P -value.

^aThe HR estimate refers to each unit increase or decrease for continuous variables.

Premature ventricular complexes induced cardiomyopathy

LV remodelling mediated by frequent (i.e. >1000 PVCs/24 h) PVCs can be considered as another model of dyssynchrony-induced CM. It is estimated that $\sim 7\%$ of patients with frequent and long-lasting isolated PVCs present LV dysfunction, with the risk substantially increasing when PVCs represent more than 10% of the total QRS complexes (i.e. an absolute number of ectopic beats $\geq 10\,000$ in 24 h).¹³ But there also other risk factors associated with adverse cardiac remodelling: LBBB morphology, ectopic QRS complex duration ≥ 150 ms, and an epicardial origin.¹³

If on the one hand PVCs can induce LV dysfunction (through mechanical dyssynchrony), on the other, they can be the epiphenomenon of an underlying structural heart disease.¹⁴

To make a differential diagnosis between the two entities is mandatory because in the first case, the anti-arrhythmic therapy, whether pharmacological or ablation-mediated, can lead to improved LVEF, also reducing morbidity and mortality.⁵ Indeed, the latest guidelines of the European Society of Cardiology on the management of ventricular arrhythmias recommend an ablative approach (class I) if the LV dysfunction is induced by predominantly monomorphic ectopic beats.¹⁵

A systematic diagnostic work-up has to include careful personal and family history and complete physical examination, electrocardiogram, laboratory testing in order to exclude metabolic disorders, transthoracic echocardiography, ambulatory electrocardiographic monitoring to find out PVCs rate, and the presence of

repetitive beats but also exercise testing to verify increase/reduction in PVCs number during effort and during recovery. Moreover, if there is a suspicion of an underlying pathological substrate, CMR has to be taken into account, given that clinical studies have shown that late gadolinium enhancement is a predictor of adverse outcome in patients with PVCs, regardless of ejection fraction.¹⁴

Pre-excitation-induced cardiomyopathy

Large-scale epidemiological studies report a prevalence of ventricular pre-excitation (i.e. the electrocardiographic finding of the presence of accessory conduction pathways between atria and ventricles) between 0.01% and 0.3%. These pathways may not express themselves clinically longlife while, when the electrocardiographic finding is accompanied by symptoms, that is Wolff-Parkinson-White (WPW) syndrome.

The most common clinical expressions are arrhythmic and include paroxysmal supraventricular tachycardias, atrial fibrillation, and atrial flutter, which can cause tachy-induced LV dysfunction, usually recovering upon the resolution of the arrhythmia. However, since the 1970s, cases of LV dysfunction have been reported in patients with pre-excitation, even in the absence of atrial tachyarrhythmias. This could be explained by the abnormal impulse propagation through the accessory pathway determining a dyssynchronous cardiac activation: part of the myocardial tissue is activated prematurely through the accessory pathway, while the remaining is activated later, through the normal

conduction pathways. Abnormal ventricular systolic function in patients with pre-excitation had already been described in pioneering echocardiographic studies that also clarified how the contraction pattern depended on the location of the accessory pathway. Right accessory pathways were associated with an abnormal activation of the interventricular septum, likewise in LBBB, with normalization of contraction dynamics with the loss of pre-excitation, as initially observed in intermittent WPW. Otherwise, the left accessory pathways did not appear to be associated with significant dyssynchrony, probably because the part of pre-excited myocardium is smaller.¹⁶

The real prevalence of this condition is not known as the evidence is scarce, deriving mostly from case series or small observational studies. The largest to date enrolled 310 patients with pre-excitation from the Danish national registry. They were followed for a median follow-up of 7.4 years, reporting a significantly greater risk of HF if compared to the general population [hazard ratio (HR), 2.11; 95% confidence interval (CI), 1.27–3.50].¹⁷ The subgroup analysis highlighted a significant difference due to the location of the accessory pathway, confirming a greater risk in case of right antero-septal accessory pathway.¹⁷

The prognosis of patients with pre-excitation-induced CM is excellent, thanks to the reverse remodelling described after eliminating pre-excitation. Tomaske *et al.*¹⁸ analysing a cohort of 34 patients with right septal and paraseptal accessory pathways reported a 56% prevalence of LV dysfunction with a complete recovery (i.e. reduction in QRS duration and reverse remodelling) after radiofrequency ablation of the accessory pathway.

What role for genetic background?

Only a minority among all the patients affected by LBBB, PVCs, pre-excitation, and PM carriers will develop cardiomyopathy. On the other hand, the appropriate treatment of dyssynchrony (via CRT or PVCs/accessory pathway therapy) provides a complete recovery of LV size and function in a substantial number of patients (defined as super-responders) but not in all of them.

Therefore, it seems that abnormal conduction, despite representing an undeniable trigger, cannot always be considered a sufficient cause for the development of LV dysfunction. At the best of our knowledge, the reason remains unknown.

A complex interaction between genetic and environmental factors can be assumed, in a relationship that needs to be further investigated. Abnormal contractility and the subsequent dyssynchrony could be a second hit, as recognized for viral infections or alcohol, acting on genetic background and so determining CM. Furthermore, the genetic substrate could explain the reported interindividual variability in the incidence of complete reverse remodelling after elimination or the trigger.

Starting from these hypotheses, Te Rijdt *et al.*¹⁹ performed genetic testing in 16 patients with dyssynchronopathy due to LBBB that were super-responders to CRT. Even if 25% of them had a family

history of DCM, only one patient was carrier of a pathogenic variant (in the TNNT2 gene, encoding troponin T) while nine were carriers of variants of uncertain significance.

On the other hand, in a preliminary analysis by our group on a cohort of 73 patients with LBBB dyssynchronopathy, 30% were found to be carrier of pathogenic/likely pathogenic variants. Patients with a negative genotype showed a better response to resynchronization therapy.²⁰ This evidence, despite interesting, does not currently allow solid conclusions to be drawn because of small numbers.

Larger and specifically designed studies are needed to investigate the real prevalence of monogenic mutations in dyssynchronopathy, the differences in the genetic background between CRT non-responders and super-responders, but also the weight of the so-called polygenic inheritance, determined by common polymorphisms that, combined together and by interacting with environmental factors, could contribute to the risk of developing complex, beyond the classic Mendelian paradigm.

Conclusions

Abnormalities in the intraventricular propagation of the cardiac impulse, whether attributable to LBBB, apical RVP, frequent PVCs, or ventricular pre-excitation, can be the cause of LV dysfunction and remodelling, in a peculiar model of cardiomyopathy (i.e. dyssynchronopathy) often reversible eliminating the underlying cause. Therefore, a correct differential diagnosis is necessary, as it allows appropriate prognostic stratification and therapeutic management, thus reducing morbidity and mortality.

There remain some critical issues to be resolved such as the specific weight of the genetic background and the definition of criteria that can distinguish between super-responders and no-responders to therapies. Further targeted and dedicated studies with large case series and adequate follow-up are needed to answer these questions.

Funding

No funding provided.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

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