Exploring the Electrophysiologic and Hemodynamic Effects of Cardiac Resynchronization Therapy

From Bench to Bedside and Vice Versa

Rick Schreurs, MD, Rob F. Wiegerinck, PhD,
Frits W. Prinzen, PhD*

KEYWORDS

• Left bundle branch block • Cardiac resynchronization therapy • Animal research
• Electrophysiology • Hemodynamics

KEY POINTS

- CRT reduces the dyssynchronous activation pattern caused by LBBB and improves the hemodynamic state. This results in reduced mortality and improved quality of life.
- For the best CRT response the LV lead should be positioned in a late activated area while avoiding sites with transmural myocardial infarction.
- The addition of more pacing sites further improves the hemodynamic state, but only if the first LV pacing site yielded a low hemodynamic response.
- An endocardial LV pacing site is superior to an epicardial LV pacing site with respect to CRT response.
- AV and VV optimization further increase the response to CRT by fusing intrinsic and paced electrical activation fronts.

INTRODUCTION

Patients with heart failure (HF) combined with left bundle branch block (LBBB) have broad QRS complexes and an impaired cardiac function. In these patients it is unclear whether HF leads to LBBB or vice versa. Animal models, however, have shown that induction of LBBB reduces cardiac contractility.[1] Similarly, inadvertent induction of LBBB during transcatheter aortic valve replacement worsens outcome.[2] In LBBB cardiac function is impaired because the left (LV) and right ventricle (RV) and various regions within the LV are not activated simultaneously, leading to dyssynchronous

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Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands
* Corresponding author. Department of Physiology, Maastricht University, PO Box 616, Maastricht 6200 MD, The Netherlands.
E-mail address: frits.prinzen@maastrichtuniversity.nl

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contraction and reduced cardiac pump function.[3] Animal studies have shown that isolated LBBB causes reduction in ejection time, slower rates of rise and fall of the LV pressure, and prolonged duration of isovolumic contraction and relaxation.[4]

Cardiac resynchronization therapy (CRT) aims to restore synchronous contraction of the heart by either LV free wall or biventricular (BiV) pacing. The first studies started during the late 1990s to evaluate the effect of CRT.[5–7] According to the current guidelines a CRT device is indicated for patients with HF and prolonged QRS duration, preferably with LBBB morphology on the electrocardiogram (ECG).[8] CRT reduces mortality and improves quality of life,[9] but additional research is needed to optimize this therapy. To this purpose investigations have also been performed in animal models of dyssynchrony.

Animals have long been used to study hemodynamics and electrophysiology in HF. As reviewed by Strik and colleagues[10] the canine seems to be the best species to study ventricular conduction abnormalities that occur during pacing and LBBB, because the anatomic structures of the bundle branches are comparable with those in human. Percutaneous radiofrequency ablation of the LBBB results in a model perfectly suited to study the effects of CRT.[1,4,11,12] This model enables the investigation of the role of LBBB and CRT in the absence of HF, but if needed, also in combination with HF (created by chronic tachypacing) or myocardial infarction.[10]

This article reviews the electrophysiologic and hemodynamic effects of CRT in animal models and patients with LBBB.

ELECTROMECHANICS OF DYSSYNCHRONY

In LBBB the normal activation pattern is disturbed because the LV is no longer activated via the left bundle branch and Purkinje fibers. Instead, the electrical activation spreads from the normally activated RV through the septum toward the LV. Because activation moving from myocyte to myocyte is much slower, the LV free wall, which is the site most remote from the RV, is activated latest. Several clinical[13,14] and preclinical[15] invasive electrocardiac mapping studies have shown that the activation in LBBB hearts follows a specific pattern. LV depolarization moves from the septum in a circumferential and longitudinal direction. However, because conduction often appears slow at the RV-LV junctions an important contribution of activation comes from the wavefront passing over the apex toward the LV lateral wall (referred to as U-shaped activation pattern). Another characteristic feature is the slow transseptal conduction in LBBB, possibly caused by the vertical orientation of the laminar sheets of myocytes in the septum.[16,17] Epicardial activation maps generated with noninvasive electrocardiographic imaging show comparable electrical patterns, as illustrated by the *white arrow* in the upper left of **Fig. 1**.[18] The prolonged activation of the LV results in an increased total activation time (TAT) of both ventricles, which is characterized by a widened QRS complex on the surface ECG.[13] These findings are similar in dogs.[10]

Fig. 2 (*left*) describes how the dyssynchronous electrical activation of the LV causes the early activated septum to contract against a reduced load, which leads to prestretch of the LV lateral wall (ie, more positive strain; *middle*, *solid line*).[13] This prestretch increases contractile force of the LV free wall, which on its turn paradoxically stretches the septum later in systole (positive strain of the septum, *dashed line*). Both types of systolic stretching can be considered wasted work, which is the ratio of negative and positive work (*red* and *black lines*, respectively; *bottom*).[3,19]

In canine hearts, the maximum rates of rise and fall of the LV pressure (dP/dt_{max} and dP/dt_{min}) decrease immediately on creating LBBB and this decrease is still present after 8 weeks. Echocardiographic follow-up shows an increase of end-diastolic volume (EDV) and end-systolic volume (ESV) and decrease of ejection fraction (EF) with longer lasting LBBB.[3] These findings replicate the low EF, increased LV wall stress and ESV, and impaired myocardial relaxation as seen in patients with LBBB.[20]

ELECTROPHYSIOLOGIC EFFECTS OF CARDIAC RESYNCHRONIZATION THERAPY

The basic idea behind CRT is to resynchronize the late and more slowly activated LV by individually pacing both ventricles. **Fig. 1** shows that RV pacing alone results in an activation pattern that resembles the intrinsic activation pattern of LBBB and leads to a QRS duration of 250 milliseconds (ms) in this example. At a short atrioventricular (AV) delay LV pacing increases QRS duration, but with a completely reversed activation pattern compared with LBBB and RV pacing. With BiV pacing the left and right activation wavefronts fuse in the LV, which accelerates its activation, and consequently result in a shorter QRS duration of 150 ms.

In dogs simultaneous RV and LV pacing shortens TAT and QRS duration compared with the LBBB situation and immediately improves hemodynamics.[10] However, note that BiV pacing does not necessarily reduce QRS duration[6,7] or