# Electrical dyssynchrony induced by biventricular pacing: Implications for patient selection and therapy improvement

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**BACKGROUND** Biventricular pacing (BVP) may not achieve complete electrical resynchronization.

**OBJECTIVE** The purpose of this study was to assess whether the resynchronizing effect of BVP varies among patients depending on the underlying electrical substrate.

**METHODS** High-resolution electrocardiographic mapping with invasive measurement of the maximal rate of systolic left ventricular (LV) pressure rise ($LVdP/dt_{max}$) was performed during baseline activation and during BVP in 61 patients with heart failure with various conduction delays: 13 with narrow QRS duration (<120 ms), 22 with nonspecific intraventricular conduction disturbance, and 26 with left bundle branch block. Electrical dyssynchrony, both during baseline activation and BVP, was quantified by total and LV activation times (TAT and LVTAT) and by ventricular electrical uncoupling (VEU = mean LVTAT − mean right ventricular activation time). Response to BVP was defined as a ≥10% increase in $LVdP/dt_{max}$.

**RESULTS** The electrical activation pattern during BVP was similar for all patient groups and, hence, not dependent on baseline conduction disturbance. During BVP, TAT, LVTAT, and VEU were similar for all groups and were either not correlated or weakly correlated with the change in $LVdP/dt_{max}$. In contrast, changes in electrical dyssynchrony correlated significantly with the change in $LVdP/dt_{max}$: $r$=0.71, 0.69, and 0.69 for ΔTAT, ΔLVTAT, and ΔVEU, respectively (all $P < .001$). Responders showed higher baseline dyssynchrony levels and BVP-induced dyssynchrony reduction than did nonresponders (all $P < .001$); in nonresponders, BVP worsened activation times than did baseline activation.

**CONCLUSION** BVP does not eliminate electrical dyssynchrony, but rather brings it to a common level independent of the patient's underlying electrical substrate. Therefore, BVP is of benefit to patients with dyssynchrony but not to patients with insufficient electrical dyssynchrony in whom it induces an iatrogenic electropathy.

**KEYWORDS** Cardiac resynchronization therapy; Electrocardiographic mapping; Hemodynamic; Heart failure; Pacing; Left bundle branch block; Nonspecific intraventricular conduction disturbance

**ABBREVIATIONS** **AV** = atrioventricular; **AVD** = atrioventricular delay; **BVP** = biventricular pacing; **CRT** = cardiac resynchronization therapy; **LBBB** = left bundle branch block; **LV** = left ventricle/ventricular; **$LVdP/dt_{max}$** = maximal rate of systolic left ventricular pressure rise; **LVTAT** = left ventricular total activation time; **NICD** = nonspecific intraventricular conduction disturbance; **RV** = right ventricle/ventricular; **SR** = sinus rhythm; **TAT** = total activation time; **VEU** = ventricular electrical uncoupling

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## Introduction

Biventricular pacing (BVP) is known to induce hemodynamic and clinical improvements as well as left ventricular (LV) reverse remodeling in patients with heart failure with depressed LV ejection fraction and conduction disorders.[1,2] Cardiac resynchronization therapy (CRT) is generally assumed to act by restoring synchrony of ventricular activation, and baseline QRS duration has historically been considered as the hallmark of electrical dyssynchrony.[3,4]

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However, patient selection based on QRS duration is associated with a substantial rate of nonresponse. The concept of resynchronization is challenged by the observation that in patients with similar QRS duration, those with left bundle branch block (LBBB) respond significantly better than those with nonspecific intraventricular conduction disturbance (NICD).[5,6] This difference may be explained by a differential effect of BVP depending on the underlying baseline electrical substrate. This hypothesis is buttressed by the recent reports showing that in patients with non-LBBB, BVP can be inefficient or even harmful.[7–10] An improved mechanistic understanding of the limitations and beneficial effects of current methods for delivering BVP therapy is therefore required (1) to identify targets for improving this therapy and (2) to avoid worsening of patients' prognosis.

In the present study, we specifically address the electrical consequences of BVP in relation to the patients' underlying electrical substrates and set out to determine whether this influences the magnitude of the hemodynamic response to this therapy. To this purpose, we performed electrocardiographic mapping of both ventricles together with invasive hemodynamic measurements before and after BVP in a population of patients with heart failure covering a wide spectrum of conduction disorders, that is, narrow QRS duration, NICD, and LBBB.

## Methods

The conduct of the study conformed to the principles outlined in the Declaration of Helsinki on research in human subjects. All patients granted their written approval to participate in the study, which was approved by the institutional ethics committee.

### Patient population

The study population consisted of a cohort of 61 patients scheduled for CRT device implantation. To obtain a large range of electrical ventricular dyssynchrony, we included, between September 2009 and June 2013, patients with narrow QRS duration ($<120$ ms; 13 patients [21%]), NICD (22 patients [36%]), or LBBB (26 patients [43%]) on the 12-lead surface electrocardiogram. Intraventricular conduction disturbances were defined according to the most recent AHA/ACCF/HRS criteria.[11] All patients fulfilled the following criteria: New York Heart Association functional class II, III, or IV despite optimal medical therapy, ejection fraction $\leq 35\%$, and sinus rhythm (SR) during the experiments. Second- or third-degree atrioventricular (AV) block, severe aortic valve stenosis, or LV intracavitary thrombus were criteria for exclusion. In the narrow QRS duration group, 6 patients had a bradycardia indication for pacing (3 with paroxysmal AV block and 3 with brady-tachy syndrome with slow ventricular conduction) while 7 patients had previous persistent AF with uncontrolled heart rate and were candidate to AV node ablation.

The 61 patients were implanted with a CRT with defibrillator by using a percutaneous transvenous approach. The right ventricular (RV) lead was implanted preferentially at the RV apex. The position of the LV lead depended on coronary venous anatomy, lead stability, and pacing threshold (sites with phrenic nerve capture were avoided). Within 72 hours of implantation, every patient underwent a hemodynamic and an electrocardiographic mapping assessment.

### Acute hemodynamic studies

The hemodynamic study was performed at the time of implantation under general anesthesia with controlled ventilation. Continuous invasive LV pressure measurement was performed using a micromanometer (Radi Medical Systems, St Jude Medical, St. Paul, MN) placed in the LV cavity using retrograde transaortic catheterization. The LV pressure signal was used to measure the maximal rate of systolic LV pressure rise ($LVdP/dt_{max}$) during baseline sinus rhythm and during atrial sensed biventricular stimulation (VDD mode). The AV delay (AVD) was set to 80 ms. In cases of sinus bradycardia (rate $<45$ beats/min) or frequent extrasystoles, LV pressure during baseline activation and BVP were alternatively measured in the AAI and DDD mode, respectively (same atrial pacing rate). In these cases, the AVD was set to 100 ms (a compromise between the need for AVD extension in the atrial paced condition and the need for AVD reduction at higher pacing rates). The VV delay was programmed to 0 ms. Pressure data were recorded after a 30-second period of hemodynamic stabilization. $LVdP/dt_{max}$ was calculated as the average over a 10-second recording (ie, over more than 2 respiratory cycles) that was free from ventricular or supraventricular extrasystoles. Hemodynamic response was expressed as a relative change in $LVdP/dt_{max}$ (%) compared with the baseline recording immediately before or after the test pacing intervention (generally within 2 minutes).[12] Patients demonstrating a $\geq 10\%$ increase in $LVdP/dt_{max}$ were defined as hemodynamic responders to CRT.[3,13]

### Noninvasive mapping of electrical activation

Ventricular activation maps were acquired during baseline activation and BVP (with the same pacing settings as during the hemodynamic assessment) using a noninvasive high-resolution electrocardiographic mapping system (ECVUE, CardioInsight Technologies Inc, Cleveland, OH). As previously described in detail, body surface potentials were recorded from 252 sites around the entire surface of the torso.[14,15] A thoracic computed tomographic scan was acquired with the electrodes attached to the patient. The body surface potentials and computed tomographic images were then combined and processed to reconstruct 1500 epicardial unipolar electrograms. Local ventricular activation times were calculated from the onset of the QRS complex (baseline) or the pacing spike (BVP) to the maximal negative slope of each unipolar electrogram. An epicardial breakthrough site was defined as the earliest location identified on the isochrone map. A line of slow conduction was recorded if the activation times of adjacent points on either side of this