

## HEART FAILURE UPDATE

# Cardiac Contractility Modulation for Patients with Heart Failure

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A substantial proportion of patients with heart failure remain either not eligible for cardiac resynchronization therapy (CRT) or do not respond to this therapy. CRT is indicated in patients with prolonged QRS duration ( $>120$  ms).<sup>1</sup> However, up to 60% of patients with heart failure have a normal QRS duration and are not appropriate candidates for CRT. In addition, a significant number of patients (25-30%) who meet the current indications to CRT therapy are non-responders.<sup>2</sup> New device-based therapies including cardiac contractility modulation (CCM) have been developed over the last decade.

Cardiac contractility modulation signals are non-excitatory signals which, when applied during the absolute refractory period, enhance the strength of left ventricular (LV) contraction. CCM signals are electrical impulses delivered during the absolute refractory period.<sup>3,4</sup> CCM signals used in clinical practice are delivered 30 ms after detection of the QRS complex onset and consist of two biphasic +7 V pulses spanning a total duration of 20 ms. These signals do not elicit a new action potential or contraction.<sup>3,4</sup>

Preliminary data have shown that CCM improves LV cellular and biochemical remodelling. There is an increase in phosphorylation of phospholamban, a key protein that modulates the activity of sarco-endoplasmic reticulum calcium ATPase type 2a (SERCA2a), which in turn modulates calcium handling by the sarcoplasmic reticulum.<sup>5</sup>

Within several minutes of acute CCM signal application, a mild increase in ventricular contractile strength can be detected as indexed by increases in LV pressure and the rate of rise of LV pressure (LV dP/dtmax). The acute change dP/dtmax is independent of QRS duration.<sup>6</sup> Acute CCM was associated with an increase in dP/dtmax from 630 to 800 mmHg/s (20% increase). Despite an acute increase in contractility, there was no detectable increase in myocardial oxygen consumption.<sup>7</sup> In a previous study, LV ejection fraction increased by  $4.8 \pm 3.6\%$  and LV end-systolic volumes decreased by  $11.5 \pm 10.5\%$  at 3 months after CCM treatment.<sup>8</sup> In the multicenter studies FIX-HF-4 and FIX-HF-5, CCM increased peak oxygen consumption and improved quality of life in patients with heart failure.<sup>9,10</sup> These findings indicate that LV reverse remodelling can be achieved by CCM in the background of optimum medical therapy.

## ABBREVIATIONS

CCM = cardiac contractility modulation  
LV = left ventric-le(-ular)  
SERCA2a = sarco-endoplasmic reticulum  
calcium ATPase type 2a

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