

# Dynamic left ventricular dyssynchrony and severe mitral regurgitation caused by exercise: should we go beyond the guidelines?

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**Abstract:** Guidelines for cardiac resynchronization therapy (CRT) have been established, but there may be a subgroup of patients not identified in these guidelines who may benefit from this therapy. We report a patient with a dynamic left ventricular dyssynchrony and severe mitral regurgitation caused by exercise successfully treated with CRT. Exercise testing should be considered in patients with left ventricular ejection fraction <35% and QRS <130 ms with severe heart failure symptoms that are unexplained by rest echocardiography evaluation in order to rule out ischemia and/or dynamic left ventricular dyssynchrony. In the presence of exercise-induced left ventricular bundle branch block, the implantation of CRT should be contemplated.  
**Keywords:** cardiac resynchronization therapy, mitral regurgitation, left ventricular dyssynchrony, heart failure, exercise

## Plain language summary

Guidelines for cardiac resynchronization therapy (CRT) have been established, but there may be a subgroup of patients not identified in these guidelines who may benefit from this therapy. We report a patient with a dynamic left ventricular dyssynchrony and severe mitral regurgitation caused by exercise successfully treated by CRT.

## Introduction

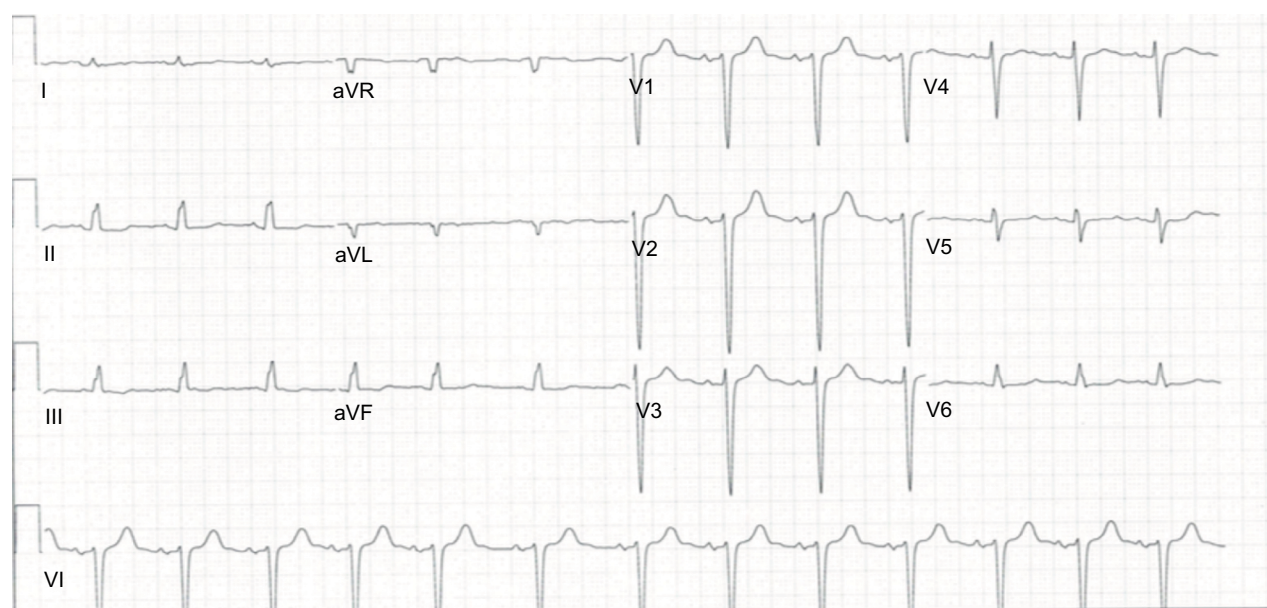
Cardiac resynchronization therapy (CRT) is an established therapy for symptomatic heart failure (HF). In the most recent Canadian Cardiovascular Society (CCS)/Canadian Heart Rhythm Society (CHRS) guidelines, indications for CRT are as follows: patients in sinus rhythm with a left bundle branch block (LBBB)  $\geq 130$  ms, ejection fraction  $\leq 35\%$ , and who remain in New York Heart Association (NYHA) functional class II, III, or ambulatory class IV despite optimal medical therapy. It is also recognized that patients with a QRS duration  $>150$  ms benefit the most from CRT.<sup>1</sup> ACCF/AHA/HRS guidelines were updated in 2012, showing Class IIa indication for CRT in patients with left ventricular ejection fraction (LVEF)  $<35\%$  and LBBB with a QRS duration between 120 and 149 ms with Class II, III, or ambulatory class IV symptoms despite optimal medical therapy.<sup>2</sup> In patients with chronic HF and a QRS duration  $<120$  ms or in the presence of exercise-induced LBBB, CRT is not recommended. Responders to CRT have been identified, but there may be a subgroup of patients who may benefit from this therapy despite not being represented in clinical trials.<sup>4</sup> In this case report, we present a patient with a dynamic LV dyssynchrony and severe mitral regurgitation (MR) caused by exercise who presented with multiple episodes of pulmonary edema. He was

successfully treated by CRT. This case report was written with the agreement of the Institut universitaire de cardiologie et de pneumologie de Québec direction, and the patient provided written informed consent for the case details to be published.

## Case description

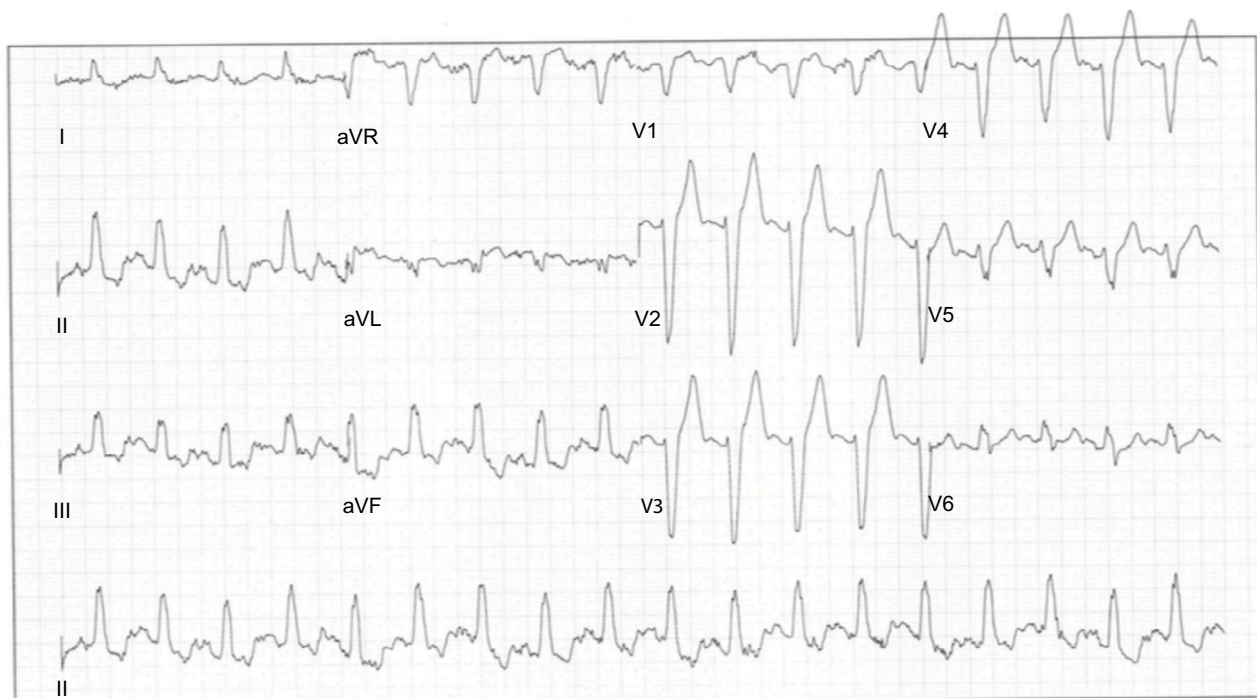
A 69-year old patient was first evaluated at the Institut universitaire de cardiologie et de pneumologie de Québec in 2009 for shortness of breath. Past medical history included peripheral vascular disease, asthma, and dyslipidemia. The initial investigation led to a percutaneous revascularization procedure for significant coronary disease. He presented over the next 2 years with various episodes of angina that required further stenting, and he finally had quadruple coronary artery bypass grafting in 2011. A year later, despite optimal medical therapy, the patient remained in NYHA functional class III and experienced multiple acute pulmonary edema episodes after light exercise that required mechanical ventilation twice. After surgery, the patient was followed at our HF clinic regularly (every 2 months) and medication was up-titrated as tolerated (bisoprolol 10 mg daily, ramipril 10 mg twice daily, furosemide 40 mg twice daily, and spironolactone 25 mg daily). Blood pressure was well controlled, and no cardiac arrhythmia was documented. A thallium stress test demonstrated significant viability in all myocardial segments without residual ischemia. The electrocardiogram showed sinus rhythm with incomplete LBBB (QRS interval of 116

ms, Figure 1). The echocardiography showed a 35% LVEF (LV end diastolic and systolic diameter of 65 mm and 53 mm respectively), a mild functional MR with an effective regurgitant orifice area (EROA) of 10 mm<sup>2</sup>, and right ventricle systolic pressure (RVSP) at 24 mmHg plus central venous pressure. He underwent a bicycle ergometer test to evaluate MR under dynamic conditions. Exercise tolerance was poor, with less than 50 W reached in 5:30 minutes. The echocardiography performed during exercise showed a 35% LVEF and a gradual worsening of MR from mild to severe with an EROA of 38 mm<sup>2</sup> at peak stress. The RVSP reached 55 mmHg plus central venous pressure, and the QRS interval during the exercise widened from 116 ms to 135 ms (Figure 2). Based on multiple acute HF episodes, poor exercise tolerance, presence of dynamic MR and the widening of the QRS >130 ms at peak stress, a CRT was implanted. After CRT implantation, the patient remained free from acute HF episodes and his functional class improved (NYHA II). Medication remained similar, but furosemide was decreased to 40 mg daily. In January 2015, he performed another bicycle ergometer. Exercise tolerance improved significantly at 9:45 minutes (125 W) and he remained asymptomatic. The rest LVEF was 40% (LV end diastolic diameter and LV end systolic diameter of 54 mm and 42 mm, respectively) and reached 45% at peak exercise without ischemia. From rest to maximal exercise, MR went from mild to moderate (EROA 15 mm<sup>2</sup>) and the RVSP increased from 24 mmHg to 45 mmHg.



**Figure 1** ECG (QRS 116 ms) at rest before CRT.

**Abbreviations:** CRT, cardiac resynchronization therapy; ECG, echocardiogram.



**Figure 2** ECG (QRS 135 ms) demonstrating LBBB during stress before CRT.

**Abbreviations:** CRT, cardiac resynchronization therapy; ECG, echocardiogram; LBBB, left bundle branch block.

## Discussion

The annual incidence of LBBB is about 10% in ambulatory patients with LV systolic dysfunction and chronic HF.<sup>1</sup> Based on current guidelines criteria, only a small proportion of patients with HF are indicated for CRT. Moreover, in the RETHINQ trial and in the recent randomized double-blind LESSER-EARTH trial, there was no evidence of CRT benefits in patients with HF and a QRS <120 ms, and morbidity was not favorably modified by CRT.<sup>1</sup> However, despite those studies, our case describes a patient who might benefit from CRT without fulfilling traditional guidelines criteria. The prevalence of exercise-induced LBBB is approximately 0.4%–1.1%. It is usually associated with adverse prognosis, higher mortality, and major cardiovascular events.<sup>3</sup> The etiology of exercise-induced LBBB is unclear, but its development could be related to myocardial ischemia and/or conduction abnormality in response to increasing heart rate. Both ischemia and aberrant conduction can precipitate LV dyssynchrony, leading to reduced cardiac output and high LV filling pressure with or without increase in functional MR manifesting in shortness of breath or eventually in pulmonary edema. Of note, our patient required multiple intubations because of severe pulmonary edema which seemed to be induced by light exercise. The widening of QRS >130 ms with dynamic MR at peak

stress echocardiography pre-CRT and the reduction of MR at peak stress echocardiography post-CRT suggest that both exercise LBBB and dynamic MR may have contributed to the patient's symptomatology.<sup>3</sup> Increased tenting area resulting from LV remodeling has been identified as a determinant of the severity of resting and exercise functional MR. Besides reducing cardiac performance, myocardial dyssynchrony may decrease mitral valve closing forces, thereby exacerbating functional MR during exercise in patients with HF. In a previous manuscript, D'Andrea et al<sup>4</sup> included 60 patients with idiopathic dilated cardiomyopathy and narrow QRS (<120 ms). Cardiac synchronicity measured between the onset of QRS complex and the peak myocardial systolic velocity at peak exercise demonstrated a significant electromechanical delay (dyssynchrony) in 58% of patients. In 78% of patients, exercise induced an increased mitral EROA. Piérard and Lancellotti<sup>5</sup> demonstrated that patients who presented acute pulmonary edema were more likely to present a dynamic MR, therefore suggesting an important pathological role of exercise-induced MR in acute HF episodes. The absence of association between rest and exercise EROA in MR has previously been demonstrated, enlightening the importance of stress evaluation. The dynamic modifications in MR are mostly driven by geometrical distortion in LV configuration

and after load under stress.<sup>4</sup> Moreover, LV contractility is clearly influenced by the presence of widening QRS/increased asynchrony at stress in a subgroup of patients with HF. It is already known that CRT might improve rest MR. Ennezat et al<sup>6</sup> found that CRT reduced MR at rest but also prevented the increase of EROA and regurgitant volume during exercise. They observed that positive impact on dynamic MR might be related with an improvement in contractility, which increases in transmitral force closure. This report concerns a patient with narrow QRS complex who experienced an acute exacerbation of HF after light exercise. Increase of heart rate induced acceleration-dependent LBBB with severe functional MR followed by acute HF necessitating mechanical ventilation twice. Exercise testing evaluation pre- and post-CRT implantation and the favorable long-term clinical evolution without recurrence of pulmonary edema suggest that CRT may have prevented the acute consequences of the exercise-induced LBBB in this patient. Patients with mild HF, narrow QRS complex, and episodes of severe HF following stress may benefit from exercise testing. It seems reasonable to rule out acceleration-dependent LBBB with LV dyssynchrony in these patients before excluding them from CRT.<sup>7</sup>

## Conclusion

Our case report depicted a patient with severe HF symptoms and repetitive life-threatening pulmonary edema episodes. Exercise testing with or without echocardiography should be considered in patients with an LVEF <35% and QRS <130 ms with severe HF symptoms that are unexplained by rest

echocardiography evaluation in order to rule out ischemia and dynamic LV dyssynchrony. In the presence of exercise-induced LBBB, the implantation of CRT should be contemplated.

## Disclosure

The authors report no conflicts of interest in this work.

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