# Comparison of Usefulness of Cardiac Resynchronization Therapy in Patients With Type 1 Myotonic Dystrophy With Versus Without Left Bundle Branch Block

Anish Nikhanj, BSc[a,b], Soori Sivakumaran, MD[a,b], Haran Yogasundaram, MD[a,b], Harald Becher, MD[a,b], Shane Kimber, MD[a,b], Zaeem A. Siddiqi, MD, PhD[c], and Gavin Y. Oudit, MD, PhD[a,b,*]

**Patients with type 1 myotonic dystrophy show reduced left ventricular systolic function in the presence of left bundle branch block due to electromechanical dys-synchrony. Our prospective study tracked a cohort of 64 type 1 myotonic dystrophy patients that demonstrated a high burden of atrial and ventricular arrhythmias and conduction delays. Of these patients, 12 (19%) patients had left bundle branch block, which was associated with reduced left ventricular systolic function. Eight of these patients received cardiac resynchronization therapy devices resulting in reduction of median QRS complex duration from 173 to 166 ms ($p = 0.04$), and improvement in median left ventricular ejection fraction from 37% to 46% ($p = 0.007$). In conclusion, cardiac resynchronization therapy device therapy is both feasible and effective in treating advanced cardiac disease in this vulnerable group of patients by improving left ventricular function.**  **(Am J Cardiol 2019;124:1770−1774)**

In patients without type 1 myotonic dystrophy (MD1), conduction disease including left bundle branch block (LBBB) leading to electromechanical dys-synchrony, has prognostic implications due to its association with systolic dysfunction and adverse outcomes.[1,2] Use of pacemakers and implantable cardiac defibrillators (ICDs) in MD1 patients is driven by the high burden from conduction disease and ventricular arrthymias.[3−10] Cardiac resynchronization therapy (CRT) is standard therapy for patients with LBBB and reduced left ventricular ejection fraction (LVEF) ≤35%, and a prolonged QRS complex duration, who remain in New York Heart Association functional classes II and III, despite optimal medical therapy.[11−13] Specialized and unique patient cohorts not included in clinical trials may also benefit from CRT. We performed a prospective cohort study of patients with MD1 to assess the presence of LBBB and systolic dysfunction, and the response to CRT.

## Methods

Patients were seen at the Neuromuscular Multidisciplinary (NMMD) Clinic located at the Kaye Edmonton Clinic in Alberta, Canada, where they received specialized care from a team of cardiologists, neurologist, respirologists, and physiatrists in conjunction with allied health care professionals. A cohort of 64 patients diagnosed with genetically confirmed MD1 were recruited and followed for approximately 4 years, from May 20, 2015 to April 1, 2019. Patients provided informed, written consent before their enrolment into our prospective cohort study. Our study maintains ethical approval and abides by the guidelines of the Health Research Ethics Board at the University of Alberta.

LBBB was defined as QRS duration >120 ms in addition to conventional criteria, defined as mid QRS notching or slurring in 2 of the following leads (I, aVL, V1, V2, V5, and V6), QS or rS in V1, and a monophasic R with no q waves in I and V6. MD1 patients were separated into 2 cohorts based on the presence of LBBB (12 patients), or the absence of LBBB (52 patients). Demographic data, clinical profile, biochemical testing, electrocardiogram (ECG), Holter monitoring, and transthoracic echocardiogram were prospectively collected to create detailed patient profiles. Eight patients with LBBB who received CRT devices over the course of the study were evaluated by serial 12-lead ECGs and echocardiograms obtained during the subsequent follow-up visit to evaluate the effectiveness of the device intervention in this patient cohort.

Continuous data are presented as median values with interquartile ranges and categorical data are presented as quantity with a percentage. All continuous variables analyzed were compared using a Mann-Whitney U test, and all categorical data were compared using Pearson's chi-square tests. A $p < 0.05$ was considered significant through all statistical analysis. Statistical analyses were conducted using SPSS Statistics Version 25 (IBM, NY).

## Results

The LBBB cohort represented 19% of our MD1 patients (Table 1; Figure 1). Clinical features were comparable between the non-LBBB and LBBB cohorts with the latter group being slightly older (Table 1). Respiratory abnormalities, such as sleep-disordered breathing, were common in

[a]Division of Cardiology, Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada; [b]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada; and [c]Division of Neurology, Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada. Manuscript received June 15, 2019; revised manuscript received and accepted August 26, 2019.

Funding: University Hospital Foundation, University of Alberta (Edmonton, Canada) Hospital (Grant number: 41769).

See page 1773 for disclosure information.

*Corresponding author: Tel: 780-407-8569; fax: 780-407-6452.

*E-mail address:* gavin.oudit@ualberta.ca (G.Y. Oudit).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.08.039

Table 1
Clinical characteristics our cohort with type 1 myotonic dystrophy (MD1)

| Variable | MD1 Without Left Bundle Branch Block (n = 52) | MD1 With Left Bundle Branch Block (n = 12) | p value |
|---|---|---|---|
| Men/women | 26 (50%)/26 (50%) | 7 (58%)/5 (42%) | 0.60 |
| Median age (years) | 42 (33-50) | 47 (43-59) | 0.049 |
| Dyslipidemia* | 7 (14%) | 0 | |
| Diabetes | 5 (9.6%) | 1 (8.3%) | 0.89 |
| Respiratory disease | 13 (25%) | 2 (17%) | 0.54 |
| Sleep disordered breathing | 12 (23%) | 6 (50%) | 0.06 |
| Hypertension† | 3 (5.8%) | 1 (8.3%) | 0.74 |
| Mobility aids | 8 (15%) | 4 (33%) | 0.38 |
| Non-invasive ventilation | 7 (14%) | 3 (25%) | 0.32 |
| Heart rate (bpm) | 71 (64-84) | 70 (60-75) | 0.37 |
| Systolic blood pressure (mmHg) | 114 (110-123) | 108 (101-123) | 0.23 |
| Diastolic blood pressure (mmHg) | 75 (70-80) | 70 (61-73) | 0.009 |

* Dyslipidemia defined as low-density lipoprotein cholesterol ≥ 3.5 mmol/L or non−high-density lipoprotein cholesterol ≥4.3 mmol/L.

† Hypertension defined as systolic blood pressure >130 mm Hg or diastolic blood pressure > 89 mm Hg.

Table 2
Cardiac assessment of our cohort with type 1 myotonic dystrophy (MD1)

| Modality | MD1 Without Left Bundle Branch Block (n = 52) | DM1 With Left Bundle Branch Block (n = 12) | p value |
|---|---|---|---|
| *12-Lead ECG* | | | |
| Heart rate (bpm) | 69 (63-81) | 64 (63-71) | 0.40 |
| PR interval (ms) | 192 (176-210) | 217.5 (203-235) | 0.03 |
| QRS duration (ms) | 104 (92-108) | 156 (141-171) | <0.001 |
| QTc interval (ms) | 410 (391-431) | 440 (422-488) | 0.004 |
| First-degree atrioventricular block | 10 (19%) | 5 (42%) | 0.10 |
| Left Anterior fascicular block | 8 (15%) | 12 (100%) | |
| *Echocardiogram* | | | |
| Left ventricular internal dimension at end-diastole (cm) | 4.2 (3.9-4.5) | 5.0 (4.7-5.6) | 0.001 |
| Left ventricular internal dimension at end-systole (cm) | 2.8 (2.6-2.9) | 3.4 (2.9-4.5) | 0.003 |
| Left ventricular posterior wall thickness at end-diastole (cm) | 0.9 (0.7-1.0) | 0.9 (0.7-1) | 0.51 |
| Left ventricular ejection fraction (%) | 60 (58-61) | 40 (35-45) | <0.001 |
| Left ventricular mass index (g/m$^2$) | 63 (55-73) | 88 (67-118) | 0.017 |
| Tricuspid annular plane systolic excursion (mm) | 2.1 (1.8-2.4) | 2.2 (1.9-2.4) | 0.87 |
| Right ventricular systolic pressure (mmHg) | 24 (18-27) | 20 (17-23) | 0.40 |
| Right ventricle size | Normal | 3 Hypertrophic | |
| Right ventricular systolic function | 1 Reduced | 2 Reduced | |

this group of patients (Table 1). In the non-LBBB cohort, 12-lead ECG assessment showed normal QRS duration and minor prolongation of the PR interval (Table 2). First-degree atrioventricular block and left anterior fascicular block were common diagnoses (Table 2). Echocardiography showed normal LV dimensions and normal systolic function; right ventricular size and function were unremarkable (Table 2). Atrial fibrillation or flutter was detected in 14% of patients and by this study's conclusion, 2 patients had received permanent pacemakers for secondary prophylaxis. Additionally, 2 patients had a dual chamber ICD inserted due to symptomatic ventricular tachycardia (VT) and cardiac arrest.

In contrast, 12-lead ECGs of patients in the LBBB cohort showed prolonged PR intervals with a high incidence of first-degree atrioventricular block in association with widened QRS duration (Table 2). Echocardiogram data of the LBBB cohort showed signs of eccentric hypertrophy with LV dilation with modest involvement of the right ventricular (Table 2). LV systolic function was markedly reduced (Table 2). Cardiac magnetic resonance imaging was performed in 4 patients confirming LV systolic dysfunction with only 1 patient showing myocardial fibrosis as identified by late gadolinium enhancement. Atrial fibrillation or flutter was detected in 3 patients, and VT in 4 patients (4 of 12, 33%) with reduced systolic function (median LVEF = 46% [interquartile range 43% to 46%]). At the initiation of this study, 1 patient previously had a dual chamber implantable cardiac defibrillator implanted due to a history of recurrent VT, and 3 patients had pacemakers as secondary prophylaxis for bradyarrhythmias.

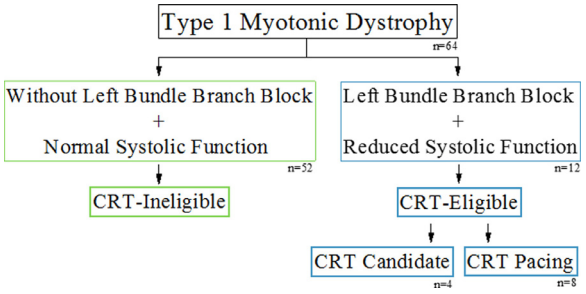


Figure 1. Appropriate use of cardiac resynchronization therapy in patients with type 1 myotonic dystrophy.

Five male and 3 female LBBB patients received a CRT device (Figure 1). Device implantation was successful in all 8 patients without complications, and all patients were discharged on the same day of the surgery. Two patients with existing pacemaker devices, and 2 patients with existing ICDs were upgraded to CRT-defibrillator (CRT-D) devices; 4 patients received de novo CRT-pacemaker devices. Within a 6-month time frame, follow-up 12-lead ECGs showed biventricular-paced rhythms in all 8 patients, with a significant reduction in median QRS complex duration from 173 to 166 ms (p = 0.04; Figures 2 and 3A). Follow-up echocardiogram data obtained within 6 months of device implantation showed a median LVEF increase from 37% to 46% (p = 0.007; Figure 3B). The implantation of a CRT device in these patients allowed for the initiation of beta-blocker therapy, which was supported by angiotensin converting enzyme

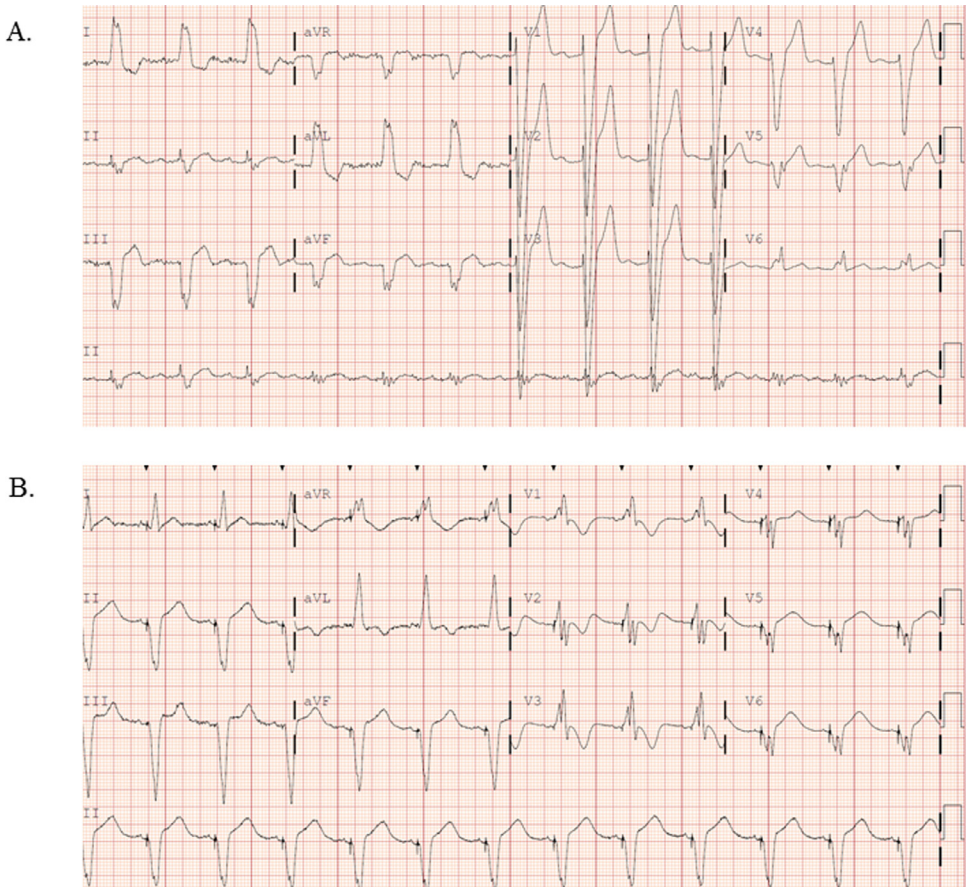


Figure 2. A representative case showing the initial 12-lead ECG of a 46-year-old male patient with type 1 myotonic dystrophy with first-degree atrioventricular block and a LBBB with a QRS duration of 194 ms (HR = 78 beats/min, PR = 234 ms) (*A*) and a follow-up 12-lead ECG after CRT device implantation showing a biventricular paced rhythm with a QRS duration of 166 ms (HR = 76 beats/min, PR = 175 ms) following CRT device implantation (*B*). CRT = cardiac resynchronization therapy, ECG = electrocardiogram, LBBB = left bundle branch block, QRS duration = duration of ventricular depolarization.

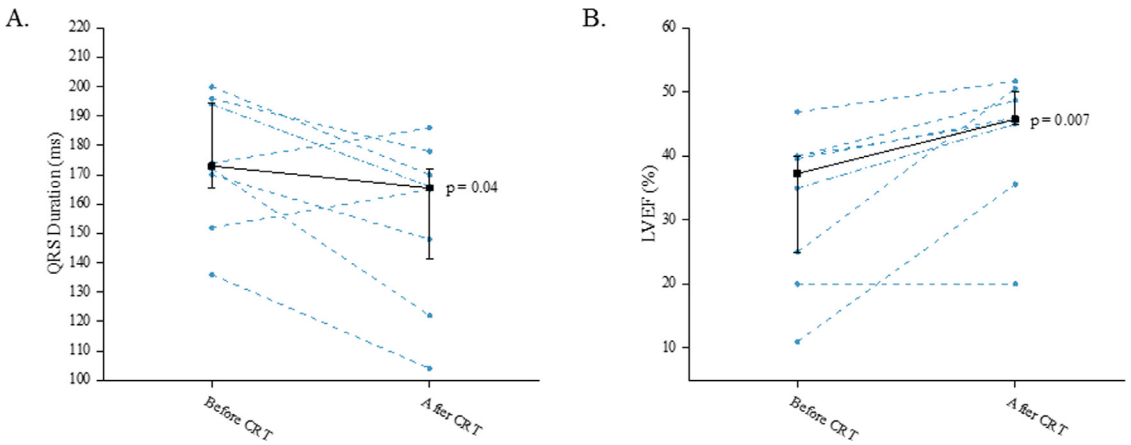


Figure 3. Effect of cardiac resynchronization therapy on QRS duration (*A*) and left ventricular ejection fraction (*B*) in patients with LBBB. CRT = cardiac resynchronization therapy, LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, QRS duration = duration of ventricular depolarization.

inhibitor/angiotensin receptor blocker and mineralocorticoid receptor antagonist therapies (Figure 4A) and uptitration of the doses of these medications (Figure 4B), which likely contributed to improved LV function. In contrast, the 4 patients with LBBB who have not received a CRT device showed a mild decline in LV systolic function (median decrease in LVEF = 4%) over the course of this study.

## Discussion

Our study demonstrates the effectiveness of CRT device therapy in a vulnerable group of patients that demonstrates a high burden of cardiac arrhythmias and conduction abnormalities. LBBB is of particular concern as it leads to early signs of pathological remodeling of the heart due to

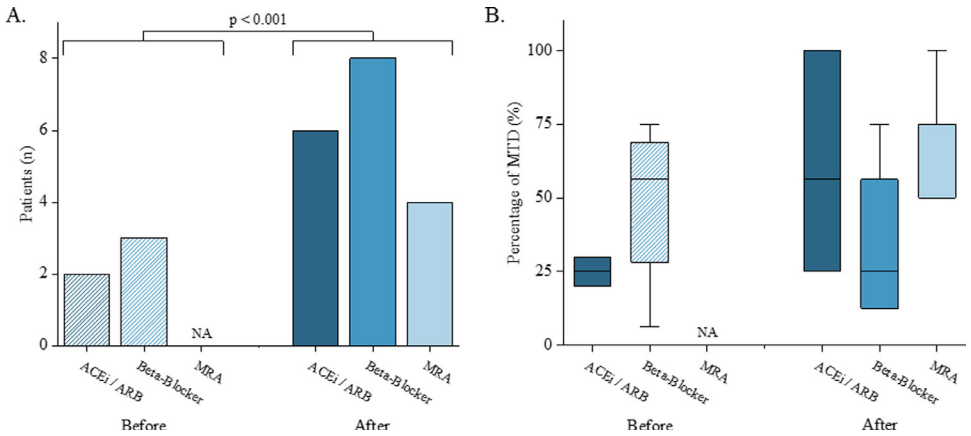


Figure 4. Pharmacological therapy use before and after cardiac resynchronization therapy device intervention (*A*) and uptitration in conjunction with device therapy (*B*). ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist, MTD = maximum tolerated dose, NA = not applicable.

electromechanical dys-synchrony.[1,2,14] Patients with LBBB showed eccentric remodeling with increased LV chamber dimensions and mass associated with moderate LV systolic dysfunction. In contrast, MD1 patients without LBBB did not show any indications of pathological remodeling and LV systolic function was normal. In addition to LBBB, there was a high prevalence of left anterior fascicular block in our cohort of patients suggesting early progression of conduction disease and pathology in patients with MD1 and highlights the important for regular monitoring and follow-up care. These findings suggest that the established relation between systolic dysfunction and LBBB in traditional non-MD1 patients can be applied to MD1 patients.[2,12,15,16]

Studies in the traditional non-MD1 heart failure patients with reduced LVEF (LVEF ≤35%) have presented findings on the pathological effects of electromechanical dys-synchrony and the use of CRT devices to improve clinical outcomes.[1,6,15,17] We have demonstrated that these are applicable to the MD1 patient population. Although some of our patients in the LBBB cohort did not have an LVEF ≤35%, CRT devices were implanted on a clinical basis, in anticipation of patients developing complete heart block, given the progressive nature of their conduction system disease.[6,13] In contrast to our 8 patients who have received a CRT device, the 4 LBBB patients who have not received a CRT device showed a progressive decrease in LV systolic function, further demonstrating the critical need for CRT intervention in these patients. We believed that the high degree of responsiveness to CRT intervention, as indicated by a marked increase in LVEF, is related to the prolonged QRS duration of our LBBB patient cohort. Optimizing cardiac medications, such as $\beta$ blockers, in MD1 patients is particularly challenging due to the high risk of bradyarrhythmias in MD1 patients.[18] CRT device therapy allows the initiation and uptitration of beta-blocker therapy. Uptitration of the doses of angiotensin converting enzyme inhibitor/angiotensin receptor blocker was facilitated by improved blood pressure likely driven by larger stroke volume in the setting of increased ejection fraction. Additionally, we considered the high risk of ventricular tachyarrhythmias in our MD1 patient cohort, and the associated risk of SCD due to VT.[5,7,8] The use of CRT devices with an ICD (CRT-D) is an effective device therapy in these patients. Four of our patients with LBBB and recurrent VT were upgraded from their standard pacemakers or ICDs to CRT-D devices.

The presence of respiratory disease and inspiratory muscle weakness in patients with MD1 provides an additional challenge for device implantation. Respiratory therapy was involved in monitoring and providing noninvasive ventilation during the procedure. Device implantation was appropriate and safe in all patients. We have demonstrated that LBBB is a marker of advanced cardiac disease in patients with MD1, as is accepted for traditional non-MD1 patients. We have also demonstrated that CRT device use is both feasible and effective in this patient population. Our screening of conduction disease in this vulnerable group of patients now incorporates a routine 12-lead ECG as part of the clinical assessment in the NMMD clinic. We believe CRT device use to be an asset when treating this nontraditional group of patients. Although our sample size is modest, we continue to recruit patients with muscular dystrophy to the NMMD clinic, thereby expanding the size of our patient cohort.

## Disclosures

The authors have no disclosures to make.

## Acknowledgment

The authors would like to acknowledge the patients, their families, and caregivers for their willing participation in this study.

1. Kirk JA, Kass DA. Cellular and molecular aspects of dyssynchrony and resynchronization. *Heart Fail Clin* 2017;13:29–41.
2. Auffret V, Martins RP, Daubert C, Leclercq C, Le Breton H, Mabo P, Donal E. Idiopathic/iatrogenic left bundle branch block-induced reversible left ventricle dysfunction: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;72:3177–3188.
3. Bhakta D, Shen C, Kron J, Epstein AE, Pascuzzi RM, Groh WJ. Pacemaker and implantable cardioverter-defibrillator use in a US myotonic dystrophy type 1 population. *J Cardiovasc Electrophysiol* 2011;22:1369–1375.

4. Nguyen HH, Wolfe JT 3rd, Holmes DR Jr., Edwards WD. Pathology of the cardiac conduction system in myotonic dystrophy: a study of 12 cases. *J Am Coll Cardiol* 1988;11:662–671.
5. Wahbi K, Babuty D, Probst V, Wissocque L, Labombarda F, Porcher R, Becane HM, Lazarus A, Behin A, Laforet P, Stojkovic T, Clementy N, Dussauge AP, Gourraud JB, Pereon Y, Lacour A, Chapon F, Milliez P, Klug D, Eymard B, Duboc D. Incidence and predictors of sudden death, major conduction defects and sustained ventricular tachyarrhythmias in 1388 patients with myotonic dystrophy type 1. *Eur Heart J* 2017;38:751–758.
6. Wahbi K, Meune C, Porcher R, Becane HM, Lazarus A, Laforet P, Stojkovic T, Behin A, Radvanyi-Hoffmann H, Eymard B, Duboc D. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. *J Am Med Assoc* 2012;307:1292–1301.
7. Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E, Pourmand R, Otten RF, Bhakta D, Nair GV, Marashdeh MM, Zipes DP, Pascuzzi RM. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. *N Engl J Med* 2008;358:2688–2697.
8. Nikhanj A, Sivakumaran S, Miskew-Nichols B, Siddiqi ZA, Oudit GY. Ventricular tachycardia in patients with type 1 myotonic dystrophy: a case series. *Eur Hear J Case Rep* 2019;3:1–5.
9. Arbustini E, Di Toro A, Giuliani L, Favalli V, Narula N, Grasso M. Cardiac phenotypes in hereditary muscle disorders. *J Am Coll Cardiol* 2018;72:2485–2506.
10. Tanawuttiwat T, Wagner KR, Tomaselli G, Nazarian S. Left ventricular dysfunction and conduction disturbances in patients with myotonic muscular dystrophy type i and ii. *JAMA Cardiol* 2017;2:225–228.
11. Normand C, Linde C, Singh J, Dickstein K. Indications for Cardiac resynchronization therapy: a comparison of the major international guidelines. *JACC Heart Fail* 2018;6:308–316.
12. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS. Rouleau JL and resynchronization-defibrillation for ambulatory heart failure trial I. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;363:2385–2395.
13. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. American College of Cardiology F. American Heart Association Task Force on Practice G. Heart Rhythm S. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2013;127:e283–e352.
14. McNally EM, Sparano D. Mechanisms and management of the heart in myotonic dystrophy. *Heart* 2011;97:1094–1100.
15. Appert L, Menet A, Altes A, Ennezat PV, Bardet-Bouchery H, Binda C, Guyomar Y, Delelis F, Castel AL, Le Goffic C, Guerbaai RA, Graux P, Tribouilloy C, Marechaux S. Clinical significance of electromechanical dyssynchrony and QRS narrowing in patients with heart failure receiving cardiac resynchronization therapy. *Can J Cardiol* 2019;35:27–34.
16. Groh WJ, Bhakta D. Arrhythmia management in myotonic dystrophy type 1. *J Am Med Assoc* 2012;308:337–338.
17. Lazarus A, Varin J, Babuty D, Anselme F, Coste J, Duboc D. Long-term follow-up of arrhythmias in patients with myotonic dystrophy treated by pacing: a multicenter diagnostic pacemaker study. *J Am Coll Cardiol* 2002;40:1645–1652.
18. Gagnon C, Chouinard MC, Laberge L, Veillette S, Begin P, Breton R, Jean S, Brisson D, Gaudet D, Mathieu J, Panel DMIE. Health supervision and anticipatory guidance in adult myotonic dystrophy type 1. *Neuromuscul Disord* 2010;20:847–851.