A normal ECG does not exclude infra-Hisian conduction disease in patients with myotonic dystrophy type 1

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Abstract

Introduction: Patients with type 1 myotonic dystrophy (DM1) have an increased risk of sudden cardiac death. The presence of His-Purkinje system disease/prolonged HV interval (≥70ms) is associated with a higher risk of potentially life-threatening bradyarrhythmic events. We aimed to identify ECG predictors of a prolonged HV interval in the DM1 population.

Methods: EPS was performed in all DM1 patients referred to two tertiary centers for routine cardiac assessment. In a subgroup of patients, EPS was repeated at varying intervals.

Results: A total of 154 patients (age 43.7±13.3; 58.1% male) underwent 202 diagnostic EPS. HV≥70ms was found on 58 EPS (28.7%); 9 of 59 patients (15.2%) with PR<200ms and QRS<110ms on baseline ECG had a HV≥70ms on EPS. Among those with either PR≥200ms and/or QRS≥100ms, only 33.9% had a HV≥70ms on EPS. There were 38 patients who underwent repeat EPS, in which 28.8% demonstrated a prolongation of the HV interval overall compared with baseline. QRS duration demonstrated the most powerful discriminative capacity for HV≥70ms (AUC=0.76, 95%CI 0.68-0.84, P<0.001). On multivariate analysis, QRS≥112ms had the highest predictive value for HV≥70ms (OR=7.94, 95%CI 3.85-16.37).

Conclusion: ECG parameters have a poor predictive value for infra-Hisian conduction block in DM1 patients. QRS and PR intervals are normal in up to 15.2% of DM1 patients with prolonged HV, and 66.1% of those with PR≥200ms and/or QRS≥100ms do not have advanced His-Purkinje conduction system disease on EPS. Electrophysiology testing should be a mandatory part of screening for all patients to guide prophylactic pacemaker implantation.

Key words: Myotonic dystrophy; sudden death; permanent pacemaker; electrophysiological study; electrocardiogram.

Condensed abstract

Patients with type 1 myotonic dystrophy (DM1) are at risk of life-threatening bradyarrhythmic events. We aimed to identify ECG predictors of His-Purkinje system disease/prolonged HV interval (≥70ms) in 154 DM1 patients undergoing 202 diagnostic electrophysiology studies (EPS). Our results show that ECG parameters have a poor predictive value, as QRS and PR intervals are normal in 15.2% of DM1 patients with prolonged HV and 66.1% of those with PR≥200ms and/or QRS≥100ms do not have advanced His-Purkinje conduction system disease on EPS. Electrophysiology testing should be a mandatory part of screening for all patients to guide prophylactic pacemaker implantation.

Abbreviations

DM1: myotonic dystrophy type 1

ECG: electrocardiogram

EPS: electrophysiological study

PPM: permanent pacemaker

ACC: American College of Cardiology

AHA: American Heart Association

HRS: Heart Rhythm Society

AVN: atrioventricular node

ERP: effective refractive period

WCL: Wenckebach cycle length

ROC: receiver operating characteristic

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder, with variable clinical penetrance, which affects between 1 in 3000 and 1 in 8000 individuals. It can present at any age and is among the most common forms of adult-onset muscular dystrophy. DM1 is caused by an expansion of cytosine-thymine-guanine (CTG) trinucleotide repeat sequences in the dystrophia myotonica protein kinase gene (DMPK), which is located on Chromosome 19. The repeat expansion is transcribed into RNA, which remains untranslated and forms aggregates exerting a toxic effect by several mechanisms, such as sequestering RNA-binding proteins and causing abnormal splicing of downstream effector genes [2]. DM1 represents a heterogeneous and multisystem condition, characterized by muscular weakness and myotonia, as well as cardiac, endocrine, cerebral, gastrointestinal, and respiratory manifestations [1].

Life expectancy is lower and risk of sudden death higher than in the general population, with a cumulative incidence of sudden death between 2.1 and 6.6% at 10 years [3-5]. Sudden death is likely to result from asystole caused by atrioventricular block, or from ventricular tachyarrhythmias [5]. Myocardial fibrosis and degeneration of the cardiac conduction system are common in DM1 patients [5], initially manifest as asymptomatic abnormalities on electrocardiogram (ECG) such as prolonged PR interval and intraventricular conduction delay. The presence of 2nd, 3rd degree atrioventricular block PR≥240 ms, and/or QRS≥120ms have been shown to independently predict the risk of sudden death [5]. However, up to 50% of DM1 individuals with normal surface ECG might still have infra-Hisian conduction delay at electrophysiological study (EPS) [6].

The best strategy to follow these patients is yet to be determined. The 2018 ACC/AHA/HRS guidelines on bradycardia and cardiac conduction delay [7] suggest that serial ECGs can be performed to assess for development of conduction abnormalities. However, the efficacy of such a strategy remains unclear.

Prolonged His-Purkinje system conduction (HV interval ≥70ms) is recognised as an early sign of developing complete atrioventricular block [7, 8]. Previous non-randomised studies have demonstrated a survival benefit of pacemaker (PPM) implantation in DM1 patients with an abnormally prolonged HV interval [9], while others have suggested a more conservative approach [10-11]. EPS has been proposed as a possible tool to risk stratify DM1 patients and yet its exact role and indications remain unclear [12]. Whether EPS might allow identification of individuals at high risk in spite of a normal surface ECG is also largely unknown but is potentially of enormous value to this population. In many centers worldwide, the ECG alone is used to risk stratify and monitor patients with DM1 but we hypothesize that this strategy may potentially miss some individuals with underlying His-Purkinje disease and yet normal or near normal surface ECGs. The aim of the present study is to determine ECG predictors of prolonged HV interval in patients with DM1.

Methods

We enrolled consecutive adult patients with genetically confirmed diagnosis of DM1 referred for routine cardiac assessment to two tertiary centers between 2003 and December 2017. Each patient underwent cardiac examination including a 12-lead ECG, transthoracic echocardiogram and diagnostic EPS. The ECG considered for the purpose of this analysis was performed on the same day of the EPS. Echocardiographic parameters routinely collected included left ventricular size, wall thickness, systolic and diastolic function, right ventricular systolic function, presence of valvular abnormalities, and atrial size. The echocardiogram and ECG were repeated routinely at each subsequent follow-up, and EPS was repeated at varying intervals based on physician's preference (minimum 12 months) to look for progression of conduction disease depending on the history, ECG changes and previous EPS results. Detailed clinical history was ascertained from medical electronic records, and patients were systematically interviewed about existing symptoms, including syncope, presyncope and palpitations. This was a cross-sectional study, and we aimed to determine ECG predictors of prolonged HV interval at the time of each EPS. Institutional review boards' approval (registration ID 11114) and patients' written informed consent were obtained.

The EPS was performed through femoral venous access with two diagnostic quadripolar catheters. Baseline PR and QT interval, QRS duration, AH and HV intervals, anterograde atrioventricular node effective refractive period (AVN ERP) and anterograde AVN Wenckebach cycle length (WBL) were measured. The HV interval was measured over a mean of 5 separate measurements recorded at different time points.

A normal ECG was defined by the presence of a PR interval ≥120ms and <200ms, and a QRS duration <110ms according to the AHA/ACC/HRS recommendations [13]. We also performed additional analysis using different QRS duration limits, including a 100ms cut-off which is commonly adopted in the clinical practice [14-15]. Besides using standard ECG parameters, we also stratified patients using the ECG criteria proposed by Groh et al. [5] (i.e. any rhythm other than sinus, 2nd or 3rd degree atrioventricular block, PR≥240 ms, and/or QRS≥120 ms) and Mörner et al [16] (i.e. PR + QRS≥320 ms). We calculated a score based on the number of Groh's criteria identified in each patient (none, one, two, or more).

Statistical analysis

Student's t-test or Mann-Whitney test was employed for comparison of continuous variables. The chi-square test was utilized to compare nominal variables expressed as proportions. Multivariate binary logistic regression (forward likelihood ratio method; probability for stepwise 0.05) was performed for identifying independent predictors of prolonged HV interval. Best cut-off points for quantitative ECG variables were assessed using ROC curves and defined as the best combination of specificity and sensitivity (Youden index). All P-values were considered significant when <0.05. SPSS 19.00 was used for descriptive and inferential statistics. MedCalc version 9.2.0.1 was used for comparison of ROC curves.

Results

Population

We included 154 patients (age 43.7±13.3; 58.1% male). Mean left ventricular ejection fraction was 62±8%. Mean PR interval and QRS duration was 204±44ms and 108±21ms, respectively. History of syncope or palpitation was reported by 6.5% (10) and 17.5% (27) of the patients, respectively. A total of 64% (99) had some degree of respiratory dysfunction, and 24% (37) required non-invasive ventilation support. No patients had a PPM or implantable cardioverter-defibrillator (ICD) at the time of the first assessment. Baseline characteristics of the population are summarised in Table 1 and Table 2.

EPS

A total of 202 EPS were performed (1.3±0.6 per patient). At the time of the EPS, the ECG was normal in 29.2%; 68.8% had either PR>200ms or QRS>110ms; and 21.3% had both PR>200ms and QRS>110ms.

Baseline rhythm was sinus in 195 cases (96.5%), and atrial fibrillation/atrial flutter in the remaining 7 (3.5%). Mean AH and HV interval were 115±31ms and 63±14ms, respectively, and HV≥70ms was found in 58 EPS (28.7%). Mean AVN WBL and AVN ERP were 485±170ms and 375±134ms, respectively. A prolonged HV interval (i.e., ≥70ms) on EPS was seen in 9 out of 59 patients (15.2%) with a normal baseline ECG (PR<200ms and QRS<110ms), 2 out of 35 (5.7%) with PR<200ms and QRS<100ms and 11 out of 70 (15.7%) with PR<200ms and QRS<120ms. Among those with either PR≥200ms and/or QRS≥100ms, only 33.9% had HV≥70ms on EPS. Examples of HV≥70ms with normal ECG and vice versa are shown in Figure 1 and 2.

Thirty-eight patients underwent multiple EPS. Among those 38 patients who had at least a second EPS, after a mean period of 986±646 days (median 885 days), progressive His-Purkinje system disease was identified in 12 patients (31.6%). There were 8 (21%) with HV prolongation of less than 10ms, 3 (7.9%) between 10 and 20ms, and one patient (2.6%) had HV prolongation of 29ms. All but one patient (8.3%) with a longer HV interval at the second EPS also had either prolongation of the PR interval and/or QRS on ECG. Among the 9 patients undergoing a third EPS after a mean period of 540±152 days (median 536 days), further prolongation of the HV interval was demonstrated in 5 (55.5%). Of these, 4 (44.5%) had HV prolongation of <10ms and one (11.1%) with HV prolongation of 10-20ms. Of the 5 patients with a prolonged HV interval on the third EPS, 4 (80%) had stable PR and QRS duration compared to previous ECG. No HV prolongation was documented in the only patient undergoing a fourth EPS.

ECG predictors of prolonged HV interval

The prevalence of a prolonged HV interval with different ECG findings is illustrated in Figure 3. The highest rate of HV≥70ms was found for the concomitant presence of 2 Groh's criteria (89%), followed by PR≥230ms + QRS≥112ms (67%), and QRS≥120ms (58%). When considering single ECG criteria (PR interval or QRS duration), the rate of prolonged HV varied from 13% (QRS<100ms) to 58% (QRS≥120ms).

On the ROC curve, among the different ECG criteria analysed, QRS duration demonstrated the most powerful discriminative capacity for HV≥70ms (AUC=0.76, 95%CI 0.68-0.84, P<0.001; Youden index: QRS≥112ms, sensitivity 64.9% and specificity 80.6%). PR interval displayed a much lower discriminative capacity (AUC=0.54, 95%CI 0.45-0.63, P=0.39; Youden index:

PR≥230ms, sensitivity 26.8% and specificity 87.4%). A PR≥230ms and/or QRS≥112ms demonstrated a better discriminative capacity for prolonged HV interval (AUC=0.73, 95%CI 0.65-0.81, P<0.001; sensitivity 71.4% and specificity 68.8%) compared to the Groh's criteria (AUC=0.66, 95%CI 0.58-0.75; sensitivity 57.9% and specificity 70.1%) and PR+QRS≥320ms (AUC=0.63, 95%CI 0.54-0.71; sensitivity 35.9% and specificity 76.5%), but similar to the use of QRS alone. These results are shown in Figure 4. Comparison of the ROC curves is presented in Supplemental Table 1.

Clinical and ECG predictors of prolonged HV: univariate and multivariate analysis

On univariate analysis, male sex, use of non-invasive ventilation support, QRS duration, PR≥230ms and QRS>112ms were predictors of HV≥70ms. After adjustment, on multivariate analysis only PR≥230ms and QRS>112ms remained independent predictors of HV≥70ms (OR=2.47, 95%CI 1.01-6.06, and OR=7.94, 95%CI 3.85-16.37; respectively). These results are shown in Table 3.

Discussion

The main finding of the present study is that ECG criteria have limited utility for identifying all DM1 individuals with advanced His-Purkinje conduction system disease (i.e., HV interval ≥70ms on EPS). The presence of ECG abnormalities such as PR≥200ms and/or QRS≥100ms have a very low specificity for identifying conduction system disease in the present population and, importantly, results from this study show that a normal ECG does not exclude severe conduction system disease. Our data question the use of ECG alone as a means by which to assess for conduction system disease as we found that 15.2% of patients with HV prolongation on EPS had a normal baseline ECG. Prolonged HV intervals can be masked on surface ECG if AVN conduction is good with a short AH interval, preserving a normal atrioventricular time overall. More complex ECG criteria, such as those proposed by Groh et al [5] and Mörner et al [16] performed worse in identifying subjects with prolonged HV interval compared to QRS duration, which represents the single most useful criterion. A QRS≥112ms displayed the best discriminative performance, with a positive predictive value of 56.9% and negative predictive value of 85.2%. Based on our findings, we advocate the routine use of EPS and HV measurement in the assessment of this population.

The value of EPS in the risk stratification of DM1 patients has been previously suggested by Lazarus et al in a prospective analysis in which 49 DM1 individuals with HV≥70ms received a prophylactic PPM [17]. During a follow-up of 53±27 months, 46.7% of patients developed high-grade atrioventricular block. Notably, most of the patients enrolled by Lazarus et al showed ECG abnormalities suggestive of conduction disease at the time of enrolment, while only 4.1% of the patients had a completely normal ECG [18], compared to 29.2% in our cohort. In a more recent observational study by Laurent et al [6], 100 DM1 patients underwent a routine EPS and only those with HV≥70ms had a subsequent PPM implantation; during a follow-up of 74±39 months, 38.8% of the subjects receiving a PPM developed 3rd degree atrioventricular block. Of note, Laurent et al reported that 32.6% (16/49) of the participants with HV≥70ms had a normal baseline ECG, however no specific analysis was performed to investigate possible ECG predictors of advanced His-Purkinje conduction system disease. To the best of our knowledge, we present the first study performing a systematic investigation of ECG predictors of HV≥70ms in an unselected DM1 population, with multiple measurements of the HV interval to minimise bias, and with multiple assessments of the infra-Hisian conduction at repeated EPS.

Although there are no randomised trials evaluating whether pacing reduces mortality and sudden cardiac death in DMI individuals (or indeed any indication for pacing in bradycardia), Wahbi et al. demonstrated a 75% survival benefit in DM1 patients with prolonged HV interval receiving a prophylactic PPM implant in a large retrospective study, compared to those without PPM. Notably, only patients with PR>200ms and/or QRS>100ms underwent a diagnostic EPS in that series [9].

The strategy of PPM implantation in asymptomatic DM1 patients with HV≥70ms, as well as in those with documented 2nd or 3rd-degree atrioventricular block, is currently recommended by the recent guidelines from the American College of Cardiology/American Heart Association/Heart Rhythm Society (class I, level of evidence B) [7]. In addition, a PPM may be considered in DM1 patients with PR≥240ms, QRS≥120ms, or fascicular block (class IIb, level of evidence C) [7, 12].

Exact indications for EPS in DM1 remain controversial [12], however. In a large multicenter prospective register of DM1 patients, the indication for PPM implant came from abnormal EPS in only 6.5% of the cases [18]. Those data highlight that risk stratification in many centers is still primary based on the ECG and therefore the findings from the present study raise concerns about maintaining this practice. In the present cohort, even the best performing ECG criterion (QRS≥112ms) demonstrated only a 64.9% sensitivity, with positive predictive value of only 56.9%.

Current consensus-based recommendation for adults with DM1 suggest that the presence of ECG abnormalities such as PR≥200ms or QRS≥100ms are indicative of cardiac involvement [1]. However, the present cohort had advanced His-Purkinje conduction system disease on EPS in only 33.9% when the PR≥200ms and/or QRS≥100ms; it is concerning that many centers worldwide would have implanted a PPM for these patients, based purely on these ECG abnormalities. The incidence of acute and long-term complications associated with implantation of a PPM is significant [19-20], and should therefore be reserved for selected patients who are likely to benefit. Furthermore, implantation of PPMs in patients with myotonic dystrophy might be more challenging because of associated respiratory muscle involvement, limiting the provision of sedation/anaesthesia [21]. Nonetheless, although the present study highlights the limited ability of ECG in identifying the presence of His-Purkinje conduction system disease, further research is necessary to clarify whether patients with normal HV interval on EPS and yet abnormal ECG are at low risk of life-threatening bradyarrhythmic events.

The diagnosis of any atrial tachyarrhythmia was associated with a higher risk of sudden death according to Groh et al [5]. Possible explanations might include the presence of atrial fibrosis, which could be indicative of conduction involvement, of alternatively a more advanced degree of pulmonary dysfunction with subsequent higher risk of neuromuscular respiratory failure [5]. Indeed, atrial fibrillation or atrial flutter are considered signs of cardiac involvement in DM1 patients according to the aforementioned consensus recommendations [1]. Based on these elements, some centers advocate PPM implantation in DM1 patients with documented atrial tachyarrhythmias but this is not a universally accepted practice. It might also be argued that a PPM should be implanted in all the DM1 patients with PR prolongation because the latter might be expression of atrial fibrosis and has been associated with an increased risk of atrial fibrillation [22]. However, our findings clearly show that the presence of a prolonged PR poorly correlates with a HV≥70ms. Although PR interval prolongation and the implication of atrioventricular node disease (in contrast to His-Purkinje system disease) is not to be discounted, there are no data we are aware of that support device implantation in the presence of PR prolongation but normal HV interval. This is an area which requires further study. Although atrial fibrosis promotes atrial fibrillation, whether this same process also contributes to advanced His-Purkinje conduction system disease in DM1 population is yet to be determined, and implanting a PPM based on such assumptions remains contentious.

Results from the present study suggest a strategy of routinely performing diagnostic EPS in the myotonic population, followed by PPM implant in those with HV≥70ms, and repeating the

EPS at a regular interval of time or when specific features develop (e.g. significant ECG changes, or clinical events such as syncope or presyncope) is a potentially safer option for prevention of sudden cardiac death, compared to a risk stratification based on ECG criteria alone. Randomised trials should clarify whether this strategy might lead to a survival benefit in this group.

Based on the results of the present study, we believe that an EPS should be performed in all adults with DM1 at time of diagnosis; however, further study is required to establish optimal timing for repeat EPS in this population. The same recommendation cannot be made for the pediatric population presenting with DM1, in which the role of EPS has not been rigorously studied. A very important observation of the present is that a subset of patients were found to have HV prolongation at repeat EPS, compared to baseline, in the absence of any corresponding ECG changes. This suggests that the strategy of performing an EPS at baseline and repeating it only in the presence of worsening ECG abnormalities will potentially miss a significant number of patients at risk. By implications, these results raise some concerns of the recommendation from the ACC/AHA/HRS guidelines [7] of relying on performing serial ECGs during follow-up to assess for development of conduction abnormalities. Further studies with larger sample size are required to confirm our findings. Unlike standard ECG recording, EPS is an invasive procedure requiring specialised equipment and trained medical staff, with associated cost, and we recognise that this limits widespread use and patients would need to be screened in specialist electrophysiological centres.

Other potential options might include administering intravenous drugs such ajmaline or procainamide (a pharmacological challenge) to assess for drug-induced prolongation of the HV interval, or using alternative methods of measurement, be they invasive (implantable loop-recorders, transesophageal measurement) or non-invasive monitoring (signal average ECG, magnetocardiography) [23]. However, there are currently no data to support these strategies.

Limitations

Several limitations should be acknowledged. Firstly, this was a non-randomised study with a retrospective design. Secondly, we could not provide prospective survival data to demonstrate a prognostic benefit of routinely performing EPS for guiding PPM insertion, and no assessment of the clinical outcomes or long-term pacing need post implant was available. However, this was not the aim of the present study as we want to determine ECG predictors of prolonged HV interval at the time of EPS. Previous studies have demonstrated the survival benefit of PPM implantation in subjects with HV≥70ms [9], and indeed this strategy is recommended by current guidelines [7]. Thirdly, EPS were repeated in only a sub-group of patients at discretion of the physician and with no pre-defined criteria.

Conclusion

ECG parameters have a poor predictive value for infra-Hisian conduction block in DM1 patients. Normal PR and QRS intervals do not exclude significant infra-Hisian conduction disease in up to 15.2% of DM1 patients. Conversely, the vast majority of those patients with minor ECG abnormalities such as PR≥200ms and/or QRS≥100ms do not have advanced His-Purkinje conduction system disease at EPS. Prophylactic PPM insertion based only on ECG criteria carries the risk of unnecessary PPM implantation or missing some patients with normal ECGs who would still benefit. The results of this study support electrophysiological testing as a mandatory part of screening and follow-up for all patients with DM1 to guide prophylactic PPM implantation.

Perspectives

Competency in Medical Knowledge: ECG has a poor predictive value for infra-Hisian conduction block in DM1 patients. EPS should be a mandatory part of screening for all patients with DM1 to guide prophylactic pacemaker implantation.

Translational outlook: Further studies are needed to determine whether patients with normal HV interval on EPS and yet abnormal ECG are at low risk of life-threatening bradyarrhythmic events. Additional investigations should also clarify the best strategy to follow-up patients with DM1, particularly the appropriate timing for repeating an EPS.

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References

[1] Ashizawa T, Gagnon C, Groh WJ, et al. Consensus-based care recommendations for adults with myotonic dystrophy type 1. *Neurol Clin Pract*. 2018;8:507-520.

[2] Elliott P. Myotonic dystrophy: time for evidence-based therapy. *Eur Heart J*. 2014;35:2135-2137.

[3] Wahbi K, Babuty D, Probst V, et al. 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.

[4] Mathieu J, Allard P, Potvin L, Prévost C, Bégin P. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. *Neurology*. 1999;52:1658-1662.

[5] 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.

[6] Laurent V, Pellieux S, Corcia P, at al. Mortality in Myotonic Dystrophy Patients in the Area of Prophylactic Pacing Devices. *Int J Cardiol*. 2011;150:54-58.

[7] Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay. *Circulation*. 2019;140:e382-e482.

[8] Katritsis DG, Josephson ME. Electrophysiological Testing for the Investigation of Bradycardias. *Arrhythm Electrophysiol Rev*. 2017;6(1):24-28.

[9] Wahbi K, Meune C, Porcher R, et al. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. *JAMA.* 2012;307:1292-1301.

[10] Groh WJ. Rhythm management in myotonic dystrophy: Progress has been made, but unsettled issues remain. *Hear Rhythm*. 2018;15:969-970.

[11] Ha AH, Tarnopolsky MA, Bergstra TG, Nair GM, Al-Qubbany A, Healey JS. Predictors of atrio-ventricular conduction disease, long-term outcomes in patients with myotonic dystrophy types I and II. *Pacing Clin Electrophysiol*. 2012;35:1262-1269.

[12] McNally EM, Mann DL, Pinto Y, et al. Clinical Care Recommendations for Cardiologists Treating Adults With Myotonic Dystrophy. *J Am Heart Assoc*. 2020 Feb 18;9(4):e014006.

[13] Surawicz B, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009; 17;53:976-981.

[14] Goldberger AL, Goldberger ZD, Shvilkin A. ECG Basics: Waves, Intervals, and Segments. In Goldberger's clinical electrocardiography: a simplified approach—8th ed. Philadelphia, PA: Elsevier, 2013:10.

[15] Palhares DMF, Marcolino MS, Santos TMM, da Silva JLP, Gomes PR, Ribeiro LB, Macfarlane PW, Ribeiro ALP. Normal limits of the electrocardiogram derived from a large database of Brazilian primary care patients. BMC Cardiovasc Disord. 2017 Jun 13;17(1):152. doi: 10.1186/s12872-017-0572-8. PMID: 28610624; PMCID: PMC5470250.

[16] Mörner S, Lindqvist P, Mellberg C, et alH. Profound cardiac conduction delay predicts mortality in myotonic dystrophy type 1. *J Intern Med*. 2010;268:59-65.

[17] Lazarus A, Varin J, Babuty D, Anselme Frédéric, 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] 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.

[19] Udo EO, Zuithoff NP, van Hemel NM, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart Rhythm*. 2012;9:728-735.

[20] Creta A, Finlay M, Hunter RJ, et al. Non-vitamin K oral anticoagulants at the time of cardiac rhythm device surgery: A systematic review and meta-analysis. *Thrombosis Research.* 2020;doi.org/10.1016/j.thromres.2020.02.007

[21] Gorelik L, Flores A. Anesthetic Management for Multiple Family Members with Myotonic Dystrophy for Interventional Cardiac Procedures-A Case Series. *Front Med* (Lausanne). 2018; 8;4:243.

[22] Nielsen JB, Pietersen A, Graff C, Lind B, Struijk JJ, Olesen MS, Haunsø S, Gerds TA, Ellinor PT, Køber L, Svendsen JH, Holst AG. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. *Heart Rhythm*. 2013;10:1249-1256.

[23] Senthilnathan S, Selvaraj RJ, Patel R, et al. Noninvasive Determination of HV Interval Using Magnetocardiography. *Pacing Clin Electrophysiol*. 2017;40:568-577.

Legend to Tables and Figures

Table 1. Baseline characteristics

Table 2. ECG and electrophysiological characteristics

Table 3. Univariable and multivariable analysis predictors of HV≥70ms

Figure 1. Normal 12-lead ECG (A; speed 25mm/s) in a subject with prolonged HV interval on EPS (B; speed 100mm/s)

Figure 2. 12-lead ECG (A; speed 25mm/s) showing PR=280ms and QRS=150ms in a subject with normal HV interval on EPS (B; speed 100mm/s)

Figure 3. Incidence of HV≥70ms according to each ECG parameter

Figure 4. ROC curve- discriminative capacity of different ECG criteria for HV≥70ms

Table 1. Baseline population characteristics

	% (n) mean±SD Total n=154
Women	41.9% (65)
Age	43.7±13.3
NYHA class	1.2±0.4
Palpitations	21.7% (33)
Syncope	6.6% (10)
Chest pain	3.9% (6)
Respiratory dysfunction	65.6% (99)
Need of NIV	24.5% (37)
Moderate/Severe Mitral valve disease	0.7% (1)
LVEF (%)	62±8
Diastolic dysfunction	19.6% (30)
Known Atrial fibrillation	9.8% (15)
History of Atrial Flutter	3.3% (5)

Legend. NYHA: New York Heart Association. NIV: non-invasive ventilation. LVEF: left ventricular ejection fraction.

Table 2. ECG and electrophysiological characteristics

	% (n) mean±SD Total 202
PR (ms)	204±44
QRS (ms)	108±21
LBBB (%)	9.4% (19)
RBBB (%)	10.4% (21)
1^{st} degree atrioventricular block (%)	52.0% (105)
SR at baseline (%)	96.5% (195)
AH (ms)	115±31
HV (ms)	63±14
AVN WCL (ms)	485±170
AVN ERP (ms)	375±134

Legend. LBBB: left bundle branch block. RBBB: right bundle branch block. SR: sinus rhythm. AVN: atrioventricular node; WCL: Wenckebach cycle-length. ERP: effective refractory period.

Table 3. Univariable and multivariable analysis predictors of HV≥70ms

	All EPS		Only 1st EPS	
	Univariable	Multivariable	Univariable	Multivariable
	OR, 95%CI	OR, 95%CI	OR, 95%CI	OR, 95%CI
Male	0.41, 0.21-0.80	-	0.49, 0.23-1.04	-
Age	0.99, 0.97-1.01	-	1.00, 0.97-1.03	-
Chest pain	0.97, 0.18-5.16	-	1.27, 0.22-7.19	-
Syncope	1.25, 0.33-4.80	-	1.08, 0.27-4.39	-
Palpitation	0.62, 0.31-1.27	-	1.60, 0.71-3.64	-
NYHA	1.66, 0.88-3.11	-	2.04, 0.95-4.38	-
Use of NIV	2.47, 1.27-4.80	-	2.28, 1.04-5.02	-
PR	1.01, 0.99-1.01	-	1.01, 0.99-1.01	-
QRS	1.05, 1.03-1.07	-	1.04, 1.02-1.06	-
PR>230ms	2.04, 0.96-4.32	2.47, 1.01-6.06	2.92, 1.21-7.09	2.99, 1.11-8.09
QRS≥112ms	7.27, 3.67-14.41	7.94, 3.85-16.37	5.95, 2.75-12.89	5.98, 2.64-13.585
LVEF	1.00, 0.96-1.05	-	0.99, 0.95-1.04	-
Diastolic dysfunction	0.72, 0.33-1.5	-	1.16, 0.48-2.78	-

Legend. EPS: electrophysiological study. NYHA: New York Heart Association. NIV: non-invasive ventilation. LVEF: left ventricular ejection fraction.

Figure 1. Normal 12-lead ECG (A; speed 25mm/s) in a subject with prolonged HV interval of 72ms at EPS (B; speed 100mm/s). Note the AH interval of 92ms.

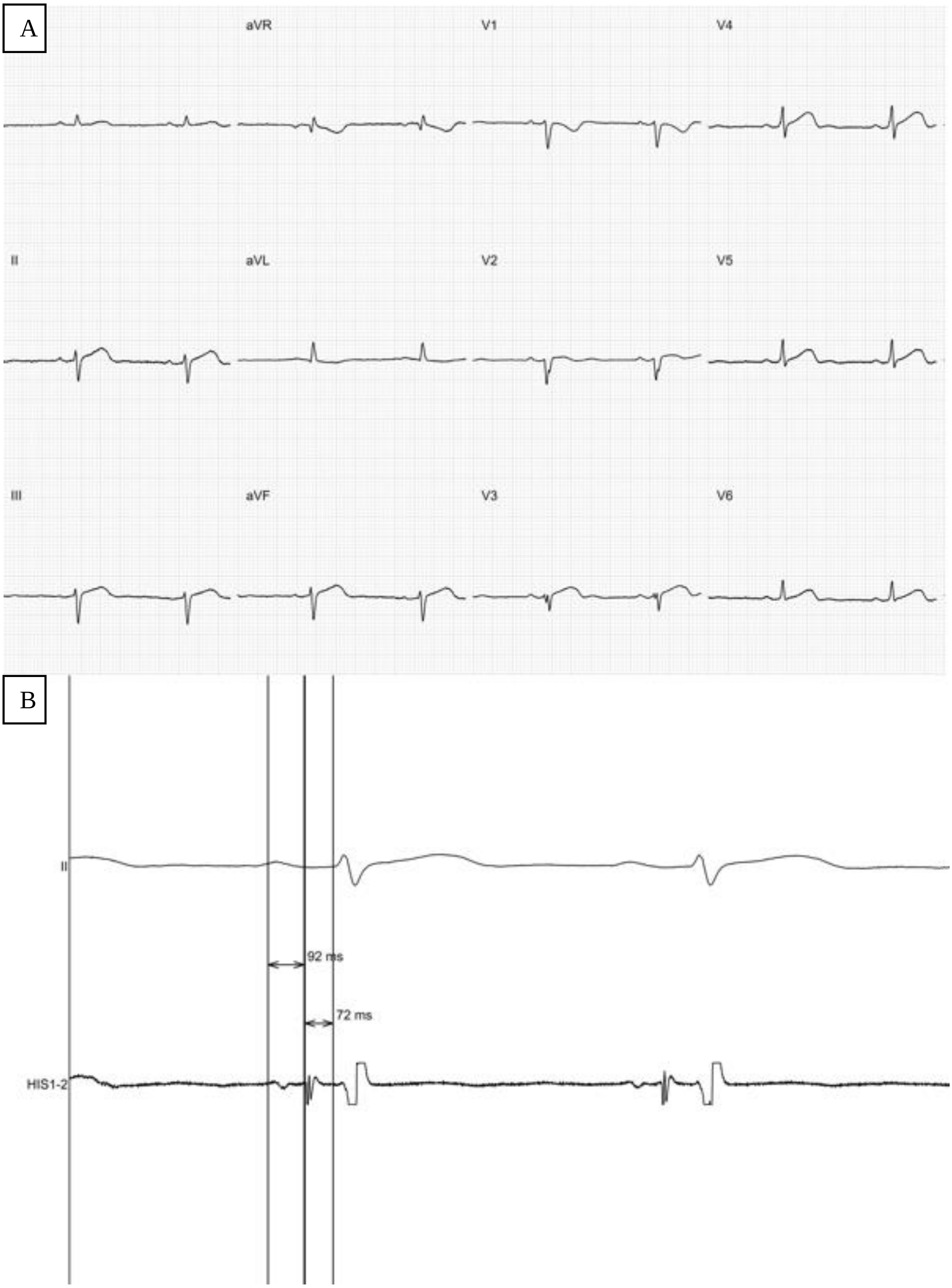


Figure 2. 12-lead ECG (A; speed 25mm/s) showing PR=280ms and QRS=150ms in a subject with normal HV interval on EPS (B; speed 100mm/s). Note the AH interval of 186ms.

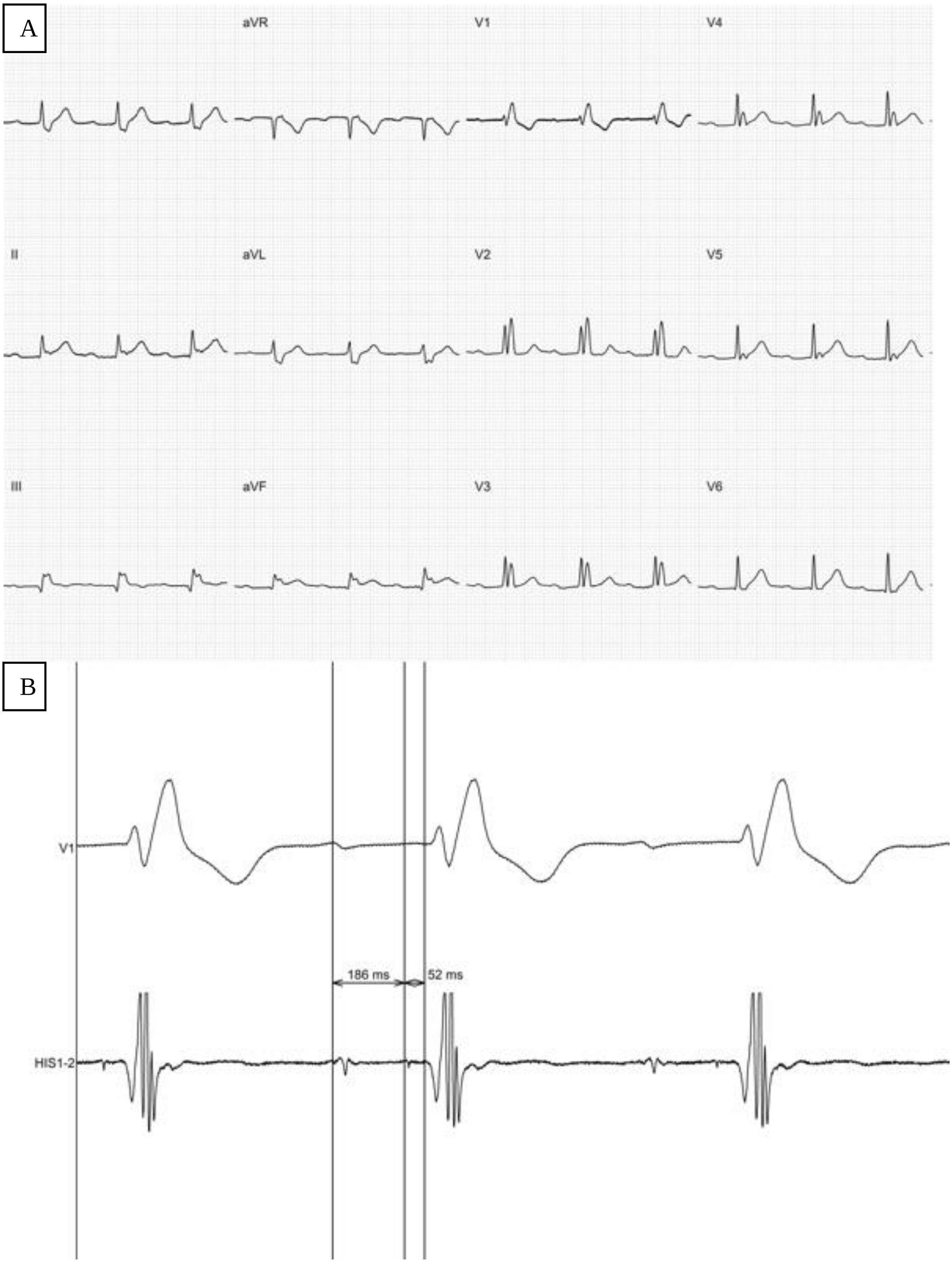
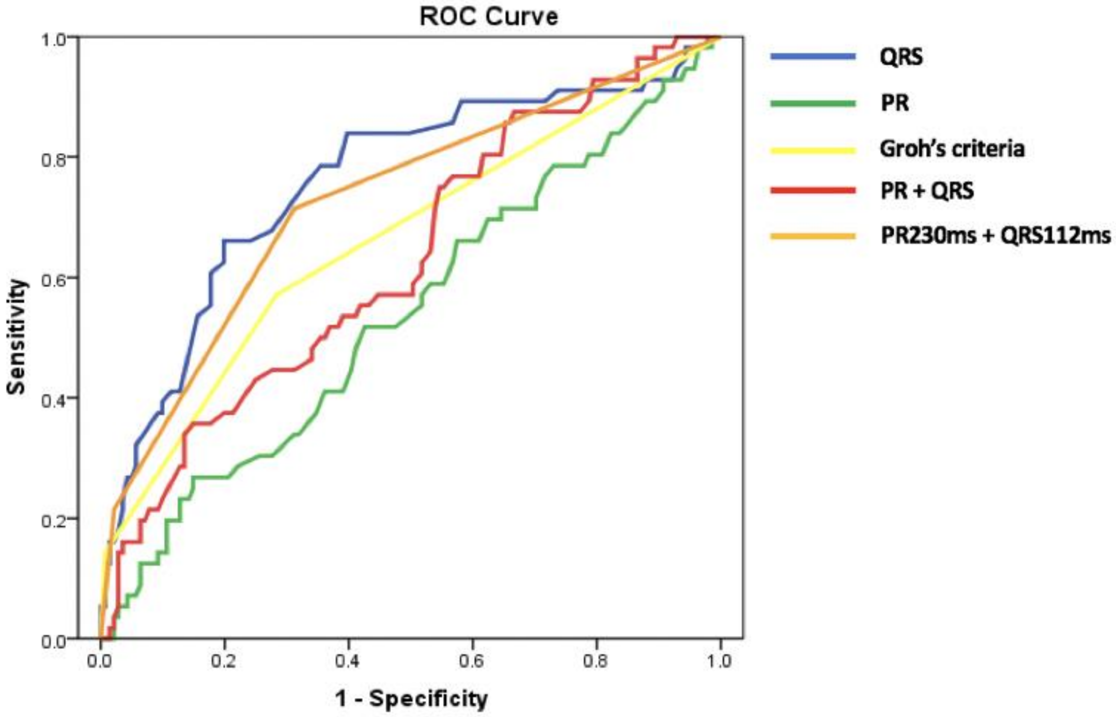


Figure 3. Incidence of HV≥70ms according to each ECG parameter

ECG Parameter	% HV≥70ms	N° of ECGs
PR+QRS≥320ms	35%	79
PR+QRS<320ms	24%	118
Groh score of 0	19%	125
Groh score of 1	37%	67
Groh score of 2	89%	9
PR≥200ms	30%	105
PR<200ms	27%	93
PR≥230ms	36%	42
PR<230ms	27%	156
PR≥240ms	40%	25
PR<240ms	27%	173
QRS≥112ms	54%	69
QRS<112ms	15%	132
QRS≥100ms	37%	129
QRS<100ms	13%	72
QRS≥120ms	58%	52
QRS<120ms	18%	149
PR≥230ms and/or QRS≥112 ms	43%	93
PR≥230ms + QRS≥112 ms	67%	18
PR<200ms + QRS<100ms	6%	35
PR<200ms + QRS<110ms	15%	59
PR<200ms + QRS<120ms	16%	70
PR≥200ms and/or QRS≥100ms	34%	164
PR≥200ms and/or QRS≥110ms	35%	139

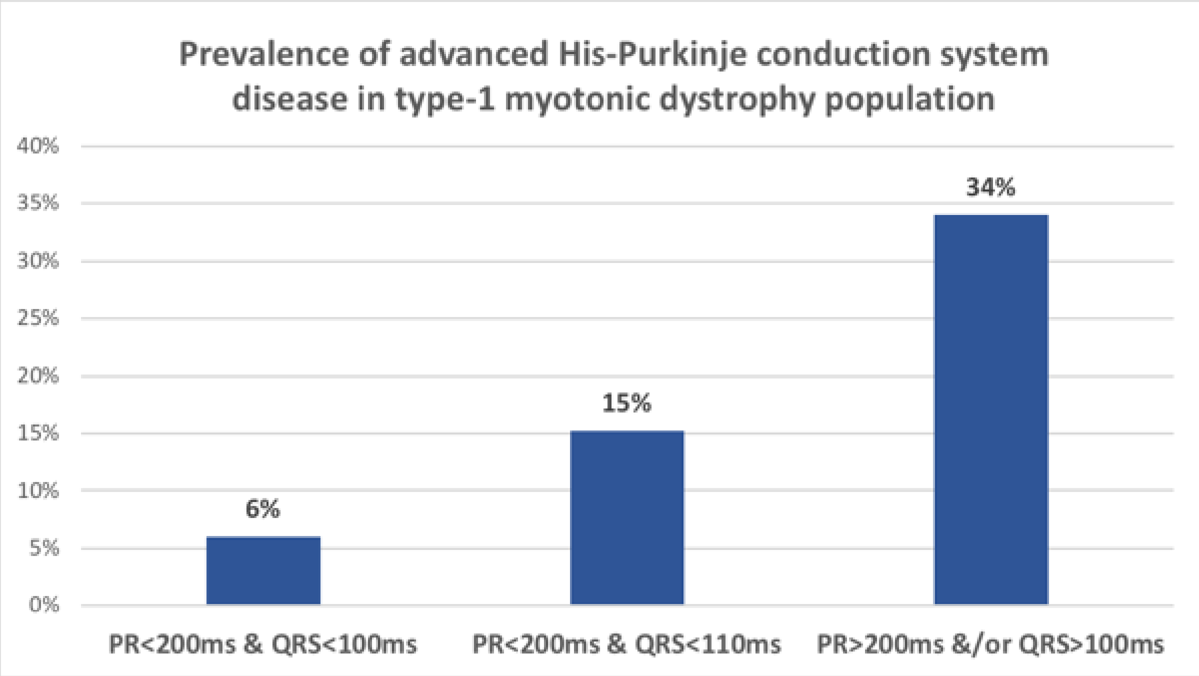
Legend. "Groh score" was defined as number of high-risk criteria according to Groh et al [5]: any rhythm other than sinus, 2^{nd} or 3^{rd} degree atrioventricular block, PR≥240ms, and/or QRS≥120ms.

Figure 4. ROC curve- discriminative capacity of different ECG criteria for HV≥70ms



Legend. AUC of the different ECG criteria for HV≥70ms for one or multiple electrophysiological studies. QRS: 0.759; 95%CI, p<0.001; 0.679-0.838. PR: 0.539; 95%CI, p=0.388; 0.449-0.630. Groh's criteria: 0.662; 95%CI, p<0.001; 0.573-0.751. PR+QRS: 0.629; 95%CI, p=0.044; 0.543-0.715. PR230+QRS112: AUC 0.727; 95%CI, p<0.001; 0.645-0.809**. Note.** A sub-analysis including only the first electrophysiological study performed in each patient showed similar values: QRS: 0.737; 95%CI 0.639-0.834, P<0.001. PR: 0.590; 95%CI 0.486-0.693, P=0.092. Groh's criteria: 0.670; 95%CI 0.567-0.774. PR+QRS: 0.666; 95%CI 0.570-0.763, P=0.002; PR230+QRS112 : 0.720, 0.622-0.817, P<0.001.

Central Illustration



- 15.2% of type 1-myotonic dystrophy patients with normal baseline ECGs have advanced His-Purkinje conduction disease (HV≥70ms) at electrophysiology study
- Conversely, the vast majority of those with minor ECG abnormalities (PR≥200ms and/or QRS≥100ms) do not have a prolonged HV interval
- Permanent pacemaker insertion based on ECG criteria alone therefore carries a risk of unnecessary device implantation in some and omitting other patients who may benefit
- Electrophysiology testing should be mandatory to guide pacemaker insertion in the type 1-myotonic dystrophy population