International Journal of Cardiology 184 (2015) 600–608

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Myotonic dystrophy and the heart: A systematic review of evaluation and management

J.K. Lau [a], R.W. Sy [a], A. Corbett [b,1], L. Kritharides [a,*,1]

[a] Department of Cardiology, Concord Repatriation General Hospital, University of Sydney, Hospital Road Concord, Sydney, NSW 2139, Australia
[b] Department of Neurology, Concord Repatriation General Hospital, University of Sydney, Hospital Road Concord, Sydney, NSW 2139, Australia

ARTICLE INFO

Article history:
Received 29 October 2014
Received in revised form 11 February 2015
Accepted 3 March 2015
Available online 5 March 2015

Keywords:
Myotonic dystrophy
Arrhythmia
Pacemaker
Electrocardiogram
Electrophysiology

ABSTRACT

Myotonic dystrophy (MD) is a multisystem, autosomal dominant disorder best known for its skeletal muscle manifestations. Cardiac manifestations arise as a result of myocardial fatty infiltration, degeneration and fibrosis and present most commonly as arrhythmias or conduction disturbances. Guidelines regarding the optimal cardiac management of patients with MD are lacking. The present article provides a summary of the pathophysiology of cardiac problems in patients with MD and provides a practical approach to contemporary cardiac monitoring and management of these patients with a focus on the prevention of complications related to conduction disturbances and arrhythmias.

Methods: A literature search was performed using PubMed and Medline. The keywords used in the search included "myotonic dystrophy", "cardiac manifestations", "heart", "arrhythmia", "pacemaker" and "defibrillator", all terms were used in combination. In addition, "myotonic dystrophy" was searched in conjunction with "electrophysiology", "electrocardiogram", "echocardiograph", "signal averaged electrocardiograph", "magnetic resonance imaging" and "exercise stress testing". The titles of all the articles revealed by the search were screened for relevance. The abstracts of relevant titles were read and those articles which concerned the cardiac manifestations of myotonic dystrophy or the investigation and management of cardiac manifestations underwent a full manuscript review.

1. Introduction

Myotonic dystrophy (MD) is the most common inherited muscular dystrophy in adulthood with an incidence of 1 in 8000 [1]. Cardiac involvement is an important cause of premature death in these patients. Despite being relatively common, guidelines regarding optimal investigation, management and follow-up of cardiac issues, particularly in asymptomatic patients with MD are lacking. The aim of this study was to comprehensively review the literature regarding cardiac manifestations of MD and to propose an evidence-based protocol for investigation, management and follow-up of asymptomatic cardiac abnormalities with a focus on arrhythmic manifestations.

2. Pathophysiology

2.1. Genetic basis

The genetic basis of MD type 1 is a mutational expansion of cytosine, thymine, guanine (CTG) repeats in the 3′ untranslated region of the Myotonic Dystrophy Protein Kinase (MDPK) gene, a serine–threonine protein kinase on chromosome 19. A normal allele contains between 5 and 35 repeats whereas alleles in patients with MD type 1 may contain up to 4000 CTG repeats. The disease is transmitted across generations in an autosomal dominant fashion with incomplete penetrance, variable phenotypic expression and somatic mosaicism. Anticipation, where increased number of CTG repeats in subsequent generations is associated with earlier onset and increased severity of disease, is well recognised [2] and more marked with maternal transmission. The disease is divided into two types based on both genetic and clinical criteria, with type 1 being most common. MD 2 arises from mutations affecting a CCTG repeat on the zinc finger protein 9 gene on chromosome 3 and is milder than MD 1. This review will focus on MD type 1.

The CTG expansion size may increase with age, vary between tissues and correlate with the extent and rate of progression of cardiac disease [2–5], however, the correlation with clinical cardiac disease has not

* Corresponding author at: Department of Cardiology, Concord Hospital, Hospital Road Concord, Sydney NSW 2139, Australia.
E-mail addresses: jerrett.lau@gmail.com (J.K. Lau), raymond.sy01@gmail.com (R.W. Sy), alastair.corbett@sydney.edu.au (A. Corbett), leonard.kritharides@sydney.edu.au (L. Kritharides).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2015.03.069
0167-5273/

been universally observed [6–10]. There appears to be a more consistent association between cardiac conduction disturbances and age, duration of neurological disease and male gender than with CTG repeats [11]. Peripheral blood leucocyte DNA can underestimate CTG repeat lengths relative to skeletal and cardiac muscle DNA where expansion lengths may be up to 13-fold longer [1,12,13].

2.2. Mechanisms

The expanded CTG repeat sequences are transcribed into RNA but not translated, accumulating in the nucleus and disrupting the splicing of pre-messenger RNA into mature mRNA of a number of genes including those coding for the muscle specific chloride channel and also the insulin receptor [14]. Impairment of intercellular impulse propagation has been implicated in the cardiac conduction manifestations of the disease. MDPK in the myocardium is localised to the intercalated discs and animal models of MDPK deficiency demonstrate compromised conduction at the level of the atrioventricular node and of the His–Purkinje system [1].

2.3. Clinical presentation and pathology

In its classical form, most patients with MD type 1 present in the 2nd to 4th decades with skeletal myotonia, progressive muscle weakness and wasting. Axial, distal limb and facial muscles are predominantly affected. However, MD is a multi-system disorder involving the endocrine (diabetes, thyroid disease, hypogonadism), central nervous (cognitive impairment, attention disorders), respiratory (hypoventilation, obstructive sleep apnoea), gastrointestinal (dysphagia, gall stones, pseudo bowel obstruction), ophthalmologic (cataracts), genitourinary (micturition disturbances) and cardiovascular systems [15,16].

Muscle biopsy is not necessary for the diagnosis but histopathological changes include a marked increased variation in fibre diameter, severely atrophic fibres with pyknotic nuclei, minimal contractile elements and ring fibres with a sarcolemmal band of cytoplasm with or without a sarcoplasmic mass [17]. A variety of nonspecific histopathological findings have been reported in MD-related cardiac disease. These include interstitial fibrosis, degeneration, fatty infiltration, myocyte hypertrophy, variation in myocyte size and focal myocarditis with lymphocyte infiltration. In addition, muscle fibre re-arrangement and focal vacuolar myocyte degeneration may be seen [13,18–22]. Early and extensive involvement of the conduction system is a common finding.

Patients with MD have higher tumour necrosis factor alpha (TNF-α) levels than do healthy controls and the level of TNF-α correlates with disease severity, CTG repeat expansion size, PR intervals and the presence of ventricular late potentials on the signal averaged ECG [23]. It remains unclear whether TNF-α plays a role in the pathogenesis of MD or is a marker of disease activity [23]. Higher levels of TNF-α have also been found in Becker and Duchenne muscular dystrophy and may prove to be a useful marker of disease stage and activity if correlations with clinical endpoints are demonstrated.

3. Clinical cardiac manifestations

The early stages of cardiac involvement in MD are typically clinically silent. Phenotypic variability results in a wide spectrum of clinical manifestations even amongst members of the same family [24].

3.1. Cardiac contributions to reduced life expectancy

Patients with MD have a reduced life expectancy with a mean age at death of 53 years and a mortality rate approximately 7.3 times that of an age-matched general population [25]. The cause of death is respiratory failure in approximately 40% of cases and cardiac in origin in approximately 30% of cases [25–27]. Predictors of mortality include older age, male gender and ECG conduction defects [28], while conduction disease on a surface ECG and a past history of atrial fibrillation are predictors of sudden death [29].

3.2. Arrhythmias

The most common cardiac manifestations of MD are arrhythmic. Cardiac fibrosis and fatty infiltration most commonly affect the His–Purkinje system but may also involve the sino-atrial and atrioventricular (AV) nodes. These provide a substrate for conduction block, ectopic activity and re-entrant arrhythmias and can present with palpitations, syncope and sudden cardiac death (0.56% per year of follow-up) [24,30]. A meta-analysis of 1828 patients with MD revealed 1st degree AV block in 28.2%, QTc >440 ms in 22.0%, QRS >120 ms in 19.9%, frequent premature ventricular contractions in 14.6%, atrial fibrillation/flutter in 5.0%, right bundle branch block in 4.4%, left bundle branch block in 5.7% and non-sustained ventricular tachycardia in 4.1% [30].

Traditionally bradyarrhythmias, with asystole or bradycardia-induced ventricular fibrillation [15], were thought to be the main mechanisms of sudden death in patients with MD. Primary ventricular tachyarrhythmias are increasingly recognised in these patients, possibly responsible for a proportion of cases of sudden death in patients with pacemakers [1,31,32]. Male patients with MD are at higher risk of both atrial and ventricular tachyarrhythmias as well as bradyarrhythmias, as are those patients who are older and who have greater muscular disability and symptoms [33]. There is also a positive association between age and the need for device implantation.

3.2.1. Tachyarrhythmia

The most common tachyarrhythmias are atrial (atrial tachycardia, atrial fibrillation and atrial flutter) and the predisposition is probably due to regions of atrial fibrosis [15]. Monomorphic and polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) due to classic re-entry circuits are promoted by fibrotic foci, fatty infiltration as well as triggered activity [31,34]. Delayed conduction in the His–Purkinje system also predisposes patients to bundle branch re-entry tachycardia, an unusual form of ventricular tachycardia due to re-entry occurring exclusively within the bundle branch system [1,35]. This requires specific pacing and pharmacological protocols during EP study for identification and may be cured by catheter ablation of either the right or left bundle [31,35]. Ventricular tachycardia arising from the left anterior or posterior fascicles has also been reported [36] as has QT interval prolongation and torsade de pointes [37]. Sudden cardiac death may result from ventricular tachycardia or ventricular fibrillation [9].

3.2.2. Sleep and arrhythmia in MD

While most cases of arrhythmias are not precipitated by sleep apnoea, episodes of apnoea and desaturation can be a precipitant for both atrial and ventricular tachyarrhythmias [38]. There have been studies suggesting reduction in arrhythmias with the use of continuous positive airway pressure in the obstructive sleep apnoea syndrome [39].

Bradycardia during sleep is well described in the healthy population, particularly in younger patients and athletes. Holter monitors during sleep may identify higher grades of conduction disturbance than an ECG while awake. Specifying the degree of conduction disturbance during sleep at which intervention is required in this population is challenging.

3.3. Left ventricular dysfunction and other structural abnormalities

MD may also be associated with left ventricular hypertrophy (LVH), left ventricular (LV) dilatation, left ventricular systolic dysfunction and mitral valve prolapse [40,41]. Similar to other patient populations, left ventricular impairment and heart failure impacts on patient prognosis.

The prevalence of LV systolic dysfunction in patients with MD varies widely, ranging from apparently normal M mode and 2D echocardiography [42], to LVH, LV dilatation and LV systolic dysfunction with prevalence of 19.8%, 18.6% and 14.0% respectively [43]. Left ventricular systolic dysfunction was found to be associated with increasing age, CTG repeat length, PR >200 ms and QRS >120 ms [43]. In addition mitral valve prolapse, left atrial enlargement and LV non-compaction/hypertrabeculation have been observed [43–46]. At 9.2 years follow-up, documented left ventricular systolic dysfunction or heart failure were associated with a 3.9-fold increased risk of all cause death and a 5.7 fold increased risk of cardiac death in patients with MD [47].

Subclinical myocardial systolic dysfunction is common and its identification often requires additional imaging techniques, such as myocardial strain or tissue velocity analysis on echocardiography [48], or assessment of augmentation of ejection fraction with exercise [49]. Diastolic dysfunction analogous to skeletal muscle myotonia can also be seen in MD [1] and may manifest as impaired early myocardial relaxation [50], or heart failure with preserved ejection fraction.

LV dyssynchrony has been observed even without conduction abnormalities [51]. This can increase early diastolic cavity tension and reduced stroke volume, causing subendocardial ischaemia even in the absence of epicardial coronary disease [51].

3.4. Microvascular dysfunction

Microvascular dysfunction and reduced coronary flow reserve has been described in MD patients with chest pain, and some of these patients have positive thallium imaging but angiographically normal coronary arteries [1,13]. Reduced global and regional coronary flow reserve has been proposed to be due to smooth muscle dysfunction, similar to that seen in the urinary and digestive tracts in patients with MD. Global coronary flow reserve, demonstrable with positron emission tomography with ^{15}oxygen-labelled water, has been shown to correlate inversely with the DNA mutation size and is possibly due to small vessel dysfunction [52].

3.5. Autonomic dysfunction

Autonomic dysfunction is an uncommonly considered feature of MD. A mixed, predominantly parasympathetic cardiac dysfunction occurs, which is not associated with a peripheral neuropathy or related to CTG repeat expansion size [16]. Heart rate variability during deep breathing, a marker of parasympathetic function, is significantly reduced in patients with MD compared to normal controls [16]. It remains uncertain whether changes in the autonomic nervous system accompany degeneration of the myocardium and conduction system.

4. Clinical investigations

The management of overt cardiac manifestations does not differ significantly from patients without neuromuscular disorders. For example, pacemakers should be implanted in patients with symptomatic bradycardia as well as asymptomatic high-grade (type II and complete) atrioventricular heart block. Likewise, defibrillators should be considered in patients with documented sustained ventricular arrhythmias [53] according to their overall prognosis from the MD.

However, the risk stratification and the timing of prophylactic interventions in asymptomatic patients without documented arrhythmias remain controversial. Although conduction system disease typically progresses slowly over many years before becoming symptomatic [15,27], the rate of progression can occasionally be rapid and life threatening. Additionally, cardiac arrhythmias can occur early in the disease course, before conduction disease is clinically apparent and in the absence of significant neuromuscular impairment [14].

Initial screening for cardiac involvement should include a 12 lead ECG, echocardiogram and Holter monitoring regardless of symptom status. Clinicians should have a low threshold for investigating symptoms or asymptomatic ECG findings [53,54]. Patients presenting with symptoms indicative of arrhythmias should be considered for invasive electrophysiological studies.

4.1. Electrocardiogram

Approximately 65% of patients with MD have ECG abnormalities, the most common being prolongation of the PR interval and the QRS duration [15,24,41]. QRS prolongation appears to progress with age, approximately at the rate of 0.54 ms/year, and prolongation of the PR interval and QRS duration are correlated [10]. There may also be prolongation of the QT interval, low P wave amplitude and non-specific ST–T changes. In patients with MD with a normal ECG, the earliest time to detection of a conduction abnormality on annual ECG recordings was greater than 4 years, and a 3rd yearly ECG MD patients with a normal ECG has been proposed [28].

There is a correlation between the degree of PR and QRS prolongation and patient age as well as CTG repeat length [55]. This finding suggests a time-dependent degenerative process in the conduction system of patients with MD. See Fig. 1.

Of all available investigations, no investigation correlates more closely with clinical events than the surface ECG. The QTc, PR, QRS intervals, II or II degree AV block and atrial tachyarrhythmias are important markers of adverse outcome including sudden death and all-cause mortality (Table 1). The Groh criteria (defined as a rhythm other than sinus, PR interval >240 ms or QRS duration >120 ms or second/third degree heart block) [26], have been shown to be a predictor of sudden death.

4.2. Ambulatory Holter monitoring

Up to 32% of MD patients with a normal ECG may have arrhythmias and conduction abnormalities detectable on Holter monitoring [10]. A 24 h recording revealed at least one abnormality in 93% of patients with MD with mild to moderate neuromuscular manifestations [56]. The most common abnormalities demonstrated were first-degree heart block (in 70%) and a corrected QT interval of greater than 460 ms (in 33%). Sinus node dysfunction, severe atrioventricular heart block and ventricular arrhythmias were uncommon in mild MD.

Repeat Holter studies may prompt changes in management. In one study of 36 patients with MD, serial Holter monitoring resulted in pacemaker implantation in 11 patients [57]. Heart rate variability and turbulence (the biphasic acceleration and deceleration of sinus rhythm following a premature ventricular contraction) assessed by Holter monitor have also been shown to be useful in MD. Heart rate variability is reduced, especially in those with longer CTG repeats, increasing age and longer PR interval [4]. Heart rate turbulence is also reduced, and has been associated with inducibility of ventricular arrhythmias in patients with MD [58]. Heart rate turbulence has been used for risk stratification in populations with prior myocardial infarction and patients with non-ischaemic cardiomyopathy [59,60].

4.3. Implantable loop recorder

Implantable loop recorders (ILR) have the capacity to detect rare arrhythmias because of their duration of monitoring and have been

Fig. 1. Case: The following serial ECGs are from a man with MD followed for over 10 years. He had a dual chamber pacemaker implanted at age 40 after an unexplained fall with likely syncope, at that time having apparently normal left ventricular function. At age 50, he has developed moderately severe LV impairment and is now being considered for biventricular pacing and defibrillator implantation (CRT-D device upgrade). The ECGs demonstrate progressive PR and QRS prolongation. (a) Age 40, PR = 178 ms and QRS = 102 ms. (b) Age 47, PR = 197 ms and QRS = 126 ms. (c) Age 50, PR = 200 ms and QRS = 166 ms.

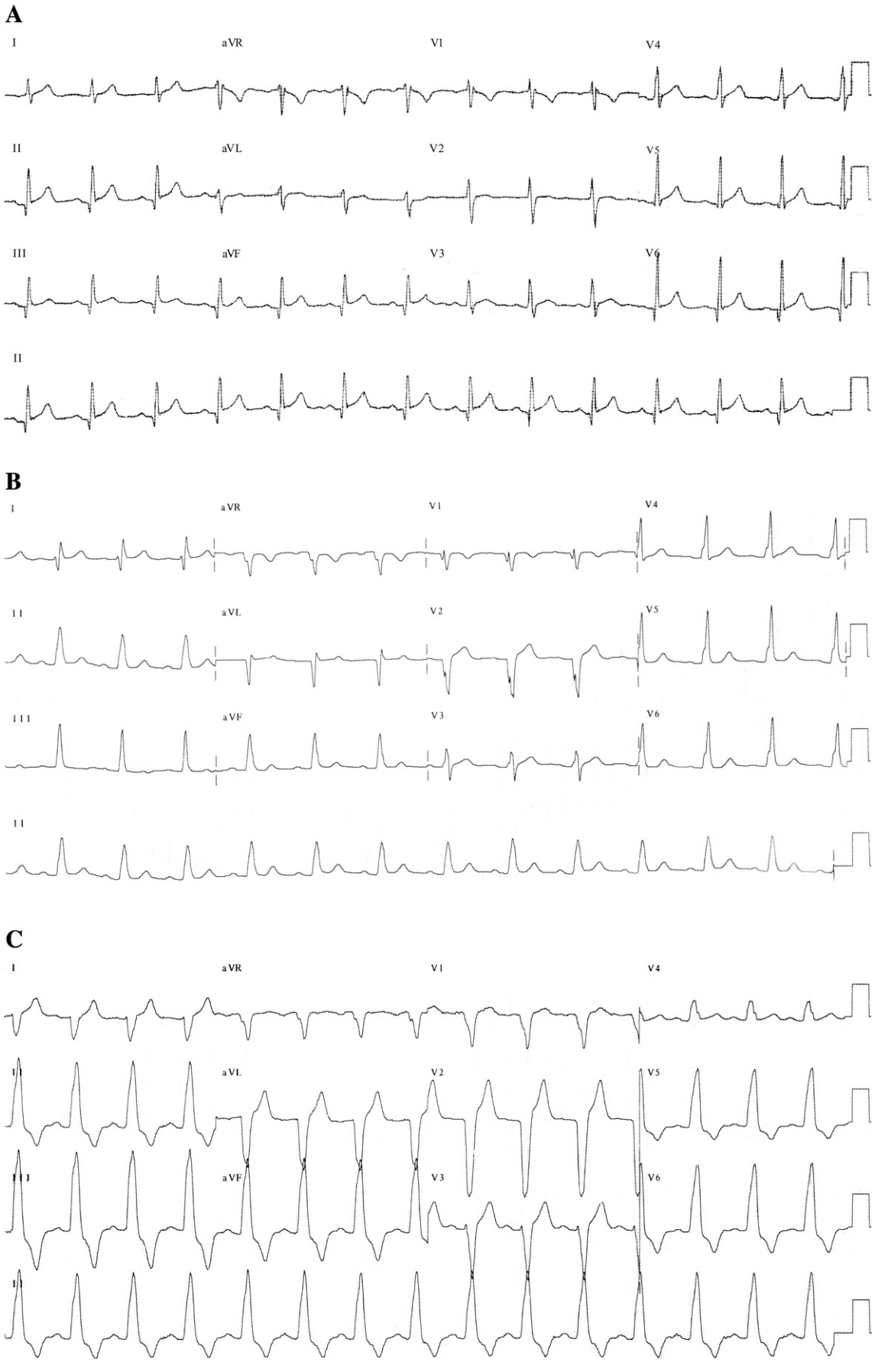
A
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
B
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
C
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Table 1
Electrocardiogram.

Parameter	Findings in MD	Reference
Conduction intervals and atrial arrhythmias	PR >240 ms, QRS >120 ms, second or third degree heart block ("Groh criteria") or a history of atrial tachyarrhythmias: • Associated with increased risk of mortality (cardiac and all cause) • Conduction abnormalities are associated with LV impairment, heart failure and family history of sudden death • Conduction abnormalities predict pacemaker implantation and atrial tachyarrhythmias	[20,26,28,83,84]
PR and QRS combined	PR and QRS combined duration >320 ms predicted long-term (17 years) mortality	[85]
QTc	QTc interval >450 ms associated >3-fold increased risk of sudden death or need for pacemaker implantation on long-term follow-up	[8]

used in small studies of patients with MD [61,62]. In predominantly asymptomatic patients, the ILR recorded arrhythmias (such as asystole and VT) that led to device implantation in 4 of 7 patients. In each case, the Holter monitor was inconclusive. With increasing availability and affordability, it is likely that ILRs will prove useful in detecting both symptomatic an asymptomatic arrhythmias in these patients. They may have a complementary role for risk stratification, especially in those patients unable or unwilling to undergo invasive EP study.

4.4. Echocardiogram

As indicated in Section 3.3, the assessment of LV dysfunction yields varying results in patients with MD, and the prevalence of subclinical disease is underestimated. Echo techniques such as tissue Doppler and speckle strain analysis may allow detection of myocardial dysfunction not detected by 2D echocardiography (summarised in Table 2). Cardiac magnetic resonance (CMR) imaging also has an emerging role and is described in Section 4.7 below.

Lower systolic and diastolic tissue velocities can be demonstrated compared to controls. Spectral Doppler analyses also indicate diastolic impairment in patients with MD in the absence of LVH, indicating a specific abnormality of myocardial relaxation. Abnormal right ventricular tissue Doppler analysis has been found in the absence of LV abnormality, possibly reflecting a greater disposition of the RV to decompensation. Diastolic dysfunction appears to correlate with increasing age and the duration of neurological symptoms.

Calculation of the myocardial performance index (MPI) and speckle strain echocardiography can detect subclinical myocardial dysfunction not apparent on 2D echocardiography. The MPI has been shown to be a sensitive predictor of LV dysfunction and the development of heart failure in other populations and may prove to be of clinical utility in patients with MD.

4.5. Signal averaged ECG

The signal averaged ECG (SAECG) detects late potentials which reflect regions of slowed conduction in diseased or scarred myocardium potentially capable of supporting re-entry circuits. They are more frequent in patients with MD than in the healthy population and are more likely to be a reflection of delayed activation of myocardium through a diseased His–Purkinje system than a marker of ventricular arrhythmias [63]. Although late potentials on a SAECG have been correlated with an increased risk of complete AV block [64], there appears to be no association with ventricular arrhythmias or sudden death in MD [63].

Table 2
Echocardiogram.

Parameter	Findings in MD	Reference
Tissue Doppler	Lower longitudinal and radial systolic velocities (S′), longer time to peak systolic velocity	[13,48]
	Systolic velocities correlate inversely with age, QRS duration and severity of neurologic manifestations, but not with number of CTG repeats	
	Lower early diastolic velocity (E′) and atrial velocity (A′) even with normal LV systolic function	[7]
	Lower E′ and E′/A′ ratios and higher E/E′ at lateral tricuspid annulus	[7]
Spectral Doppler	Lower peak transmitral early (E) velocities, lower peak atrial (A) velocities, prolongation of the deceleration time of the E wave and increased isovolumic relaxation time compared to healthy controls	[2,7,13,23,86]
	Correlation between parameters of diastolic dysfunction with age and duration of neurological symptoms	[2]
Speckle tracking	Significantly lower LV peak strain rate and lower mean strain rate	[87]
	Early diastolic dysfunction detected by a lower E/A strain rate	
	Lower global longitudinal strain compared to controls, despite normal ejection fraction	[88]
	Higher radial strain in patients with MD	
	Right atrial speckle tracking analysis correlates with regions of low voltage on electroanatomical mapping	[34]
Myocardial performance index	MPI (isovolumic relaxation time + isovolumic contraction time / ejection time) of LV and RV are higher in patients with MD than normal subjects	[86]
	High discriminating ability to distinguish between the hearts of MD patients and those without MD	[87]

In a study of patients with MD, late potentials were sensitive for predicting ventricular arrhythmias but had poor specificity and positive predictive value for identifying patients with ventricular tachycardia with high false positive rates [65]. There was no difference in 12 lead ECG or echocardiographic findings between those with and those without late potentials on the SAECG and late potentials were a poor predictor of sudden death.

It has been generally concluded that the SAECG should not be used to identify patients with MD who are at risk of ventricular arrhythmias or sudden death [5,63,65].

4.6. Electrophysiology study

Although there is a reasonable correlation between intracardiac and surface measurements of cardiac conduction intervals [66], patients with MD with a normal PR interval on the surface ECG can have a prolonged HV interval at EP study (masked by a short AH interval) [66]. The most common conduction abnormality in MD is a prolonged HV and the only reliable method to measure the HV interval is with an invasive EP study [66]. A HV interval of >70 ms or the finding of non-physiological infra-nodal conduction block may indicate the need for pacing. However, patients with an initially normal EP study still require follow-up as conduction disease can be expected to progress with age and the duration of illness. Serial EP studies are not a straightforward option because of their invasiveness and finite procedural risk. This risk is compounded by the need for sedation or anaesthetic in the context of MD-related respiratory muscle weakness.

In a cohort of 25 patients with an initially normal HV interval on EP study, a second EP study at an average of 91 months later showed an average increase in HV interval by 1.2 ms/year [67]. Interestingly, the

rate of progression does not correlate with the initial HV interval on serial EP studies [68]. New conduction disease on the surface ECG is strongly associated with progressive HV prolongation at repeat EP study.

The inducibility of atrial arrhythmias at EP correlates positively with prolonged AH intervals, but this invasive measurement does not correlate with P wave duration or clinical factors such as muscle weakness [66]. The only factor that has been found to correlate with the inducibility of ventricular arrhythmia during EP study is young age [66,69]. The prognostic value of inducible VT in patients without documented spontaneous VT is uncertain [1]. However, in the context of literature regarding the significance of VT inducibility in other cardiac diseases [70], the finding of inducible monomorphic VT at EP study should initiate a discussion regarding ICD implantation, especially if there is concomitant left ventricular dysfunction or gadolinium-enhancement on CMR.

Electroanatomical mapping can detect areas of myocardial scarring with higher sensitivity than gadolinium-enhancement on cardiac magnetic resonance imaging when tested against endomyocardial biopsy [71]. However, the technique is time-consuming and the increased dwell-time of catheters may be associated with thromboembolic complications.

Overall, the role of EP studies in risk stratification of MD patients still requires further investigation. It is reasonable to consider discretionary EP testing in selected patients with baseline ECG or Holter abnormalities and/or symptoms to guide device therapy. Further prospective studies to confirm the prognostic value in this cohort are required, especially with respect to the significance of VT inducibility.

4.7. Magnetic resonance imaging

Cardiac magnetic resonance (CMR) imaging is an accurate and highly reproducible technique for assessment of cardiac volumes, function, mass and fibrosis, with inter-study reproducibility superior to 2D echocardiography [9]. It is also a superior modality for studying the right ventricle [72].

In patients with MD, CMR can facilitate the detection of systolic dysfunction, left ventricular hypertrophy, right ventricular hypertrophy, ventricular dilatation, areas of fatty infiltration, fibrosis and occasionally non-compaction [14,72]. Other studies have reported reduced cardiac volumes and stroke volume [20].

A CMR study of 80 patients with MD (48 with dyspnoea or fatigue on exertion) found either a functional or structural abnormality in 44% [9]. Abnormalities were more frequent in men and older aged patients. LV systolic dysfunction was the most common finding (25% of patients), with LV dilatation, hypertrophy and fibrosis also commonly detected. LV mass indexes were significantly lower than values from healthy volunteers and RV dysfunction was not present without LV dysfunction.

There appears to be no correlation between the extent of fibrolipomatous infiltration on CMR and severity of cardiac contractile dysfunction. However, fatty infiltration is very common in older patients with MD, those with more severe neuromuscular disease and patients with more advanced conduction disease [72]. Although there is a strong association between ECG abnormalities and abnormalities on CMR, 16% of patients with a normal ECG will have myocardial abnormalities on CMR [9].

In a prospective study of patients with MD undergoing invasive EPS, there was a strong correlation between inducibility of ventricular arrhythmias at invasive EPS and increased fatty infiltration, myocardial thinning and hypokinesis or dyskinesis of the RV on CMR [69]. No morphological or contraction abnormalities were detected in patients without inducible ventricular tachyarrhythmias [69]. Hence RV involvement on CMR may be an important marker of ventricular arrhythmic risk.

Both focal and diffuse fibrosis have been reported in MD [9,14,20,64]. Patchy myocardial fibrosis acts as a substrate for ventricular arrhythmias in dilated cardiomyopathy and is also a common finding at autopsy in patients with MD. These findings on CMR may in the future help identify those at highest risk of sudden death [64]. However, at this time, the utility of screening for structural or functional abnormalities with CMR is uncertain, especially in the absence of ECG abnormalities.

5. Evidence for pacing and defibrillator implantation

There has been general support for early treatment of conduction disease in MD patients with pacemaker implantation. Age >40 and significant ECG abnormalities are independent predictors of pacemaker implantation in these patients [28]. While the management of patients who are symptomatic or patients who have documented arrhythmias should not differ greatly from patients without MD, it appears that prophylactic implantation of pacemakers in patients with MD and high risk characteristics leads to improved outcomes [73]. The role of implantable cardiac defibrillators (ICD) in patients with MD is unclear, with the residual incidence of sudden death in MD patients with pacemakers suggestive of a potential benefit. The role of ILRs in detecting arrhythmias is insufficiently established in this population but may have a defined role once more data are available.

In a retrospective, propensity matched analysis of 486 patients with MD and a PR interval >200 ms or a QRS duration >100 ms, patients managed with an invasive strategy (follow-up, 5.9 years) were compared to patients managed with a non-invasive strategy (follow-up, 6.5 years) [73]. The invasive strategy involved an invasive EPS and prophylactic pacemaker implantation if the HV interval was greater than 70 ms and, ICD if appropriate, whereas a non-invasive strategy involved close surveillance and EPS or device implantation only if the patient developed high degree AV block on the surface ECG. Over the follow-up period, the invasive strategy was associated with greater overall survival after adjustment for age, history of SVT, left ventricular ejection fraction, PR interval and QRS duration. An invasive strategy was also associated with a significant reduction in sudden death with an absolute reduction of 13.5% (4.5% vs 18.0%, $p = 0.001$). However, the lack of randomisation raises concerns about selection bias.

In a study of MD patients with a HV interval of greater than 70 ms undergoing prophylactic permanent pacemaker implantation regardless of symptoms, arrhythmias were noted over 53.5 months in 41 of the 49 patients [74]. Complete heart block was detected in 43% of patients, sinoatrial block in 8%, supraventricular tachyarrhythmias in 51% and ventricular tachycardia in 27%. Of the 10 patients who died during the study period, 9 were not due to a primary arrhythmic cause and the cause of death in the other patient was unknown.

In a registry study of 406 patients with MD followed for 9.5 years, 11.3% of whom received a pacemaker and 5.2% received a defibrillator [75], 29% of patients with pacemakers died suddenly, with the most common rhythm discovered being VT/VF. A PR interval ≥240 ms and a QRS ≥120 ms were independent predictors of the development of second or third degree AV block. A QRS ≥120 ms and a history of atrial tachyarrhythmias were associated with resuscitated VT/VF arrests or sudden death. Factors associated with non-sudden death and 'not for resuscitation' status, indicating lesser benefit from prophylactic device implantation, included increased age, severe proximal muscle weakness and clinical heart failure. In this cohort, the decision to implant a device was made predominantly based on surface ECGs rather than invasive EP studies.

In a cohort study of 100 patients with MD, 49 had a permanent pacemaker implanted prophylactically as their HV interval at invasive EP study was >70 ms [76]. A greater number of those who received a pacemaker fulfilled the ECG criteria for predicting sudden death as proposed by Groh [26] than those who did not receive a pacemaker. During mean follow-up of 79 months, there was only one sudden death, representing a six-fold reduction relative to the expected rate reported by Groh [26].

6. Recommendations and conclusions

Based on the available literature, we recommend a practical approach to cardiac investigation with the aim of efficiently identifying those patients with MD at risk of sudden death who would have a prognostic benefit from device implantation (Fig. 2). Furthermore, a multidisciplinary approach is advisable to ensure appropriate patient selection [53,54].

All patients should undergo regular clinical evaluation, ECG, Holter monitoring and echocardiography. Pacemaker implantation should be considered in patients with 2nd and 3rd degree heart block, or prolonged pauses. Patients with documented sustained ventricular arrhythmia or significant LV dysfunction (LV ejection fraction <35%) should be referred for ICD implantation as per standard guidelines.

In asymptomatic patients, given the low cost, safety and clinical utility, the surface ECG should be performed annually and is the mainstay of risk stratification. In our opinion, Holter monitoring should also be performed yearly or second yearly. The development of unexplained presyncope/syncope, or progressive abnormalities on serial testing should prompt relatively urgent discussion regarding invasive investigation and/or device implantation.

Otherwise, it is reasonable to follow general guidelines for the management of myocardial dysfunction and atrial tachyarrhythmias. Although there is no direct evidence for traditional medical therapy (angiotensin converting enzyme inhibitors and beta blockers) for patients with MD, there is general literature on the prevention of heart failure by treatment of patients with left ventricular dysfunction [77–79] and thus should be considered in patients with MD on a case by case basis. Conventional heart failure therapies have been found to slow decline in LV systolic function in patients with Duchenne muscular dystrophy and LV scar demonstrated on CMR [80].

In our experience, beta blockers are often poorly tolerated in patients with MD due to fatigue, whereas angiotensin converting enzyme inhibitors are usually well tolerated and, where therapy is being considered, should be first line for these patients. One should exercise extreme caution in the use of rate controlling and anti-arrhythmic medications. The role of anticoagulation in those with atrial arrhythmias is not well defined, with some literature suggesting a lower risk of stroke than the general population [81]. In the absence of other information patients should be risk-stratified according to CHADS2 or CHADS-Vasc scores and managed appropriately according to contemporary guidelines.

Although prophylactic pacing may also be considered in the setting of asymptomatic first degree heart block (Class IIb recommendation), or fascicular block (Class IIa recommendation) [82], the practice in our centre is to offer further discretionary testing. This includes EP study, loop recorder implantation and/or CMR to patients deemed to be at intermediate risk of sudden death as indicated by the presence of atrial arrhythmias, non-sustained VT, PR interval >240 ms, QRS duration >120 ms, abnormal LV or RV function. We have a low threshold for performing an EP study in this setting. Although progressive change in PR interval, QRS duration or the combination, or the signal averaged and filtered QRS duration, may indicate greater risk for heart block, none of the non-invasive parameters have been found to reliably detect infranodal conduction disease [66]. Therefore, we recommend formal evaluation of the HV interval and permanent pacing is offered to patients with infranodal block or HV interval >70 ms. In addition, the inducibility of VT, especially in the setting of mild left ventricular dysfunction or gadolinium-enhancement on CMR may trigger a discussion about ICDs.

Patients with negative EP studies should be monitored with annual ECGs [29]. Patients at intermediate risk who are unfit or unwilling to undergo an invasive EP study may be offered the option of surveillance with an implantable loop recorder or prophylactic pacemaker implantation. However, we acknowledge that scientific data in this "intermediate-risk" patient sub-group are limited, and potential limitations to consider include patient preference, access to tests and devices, financial costs related to such investigations and the requirement for respiratory anaesthetic support for EP study in some patients.

Echocardiography is an important investigation for all patients with MD and abnormal function risk stratifies patients for risk of cardiac

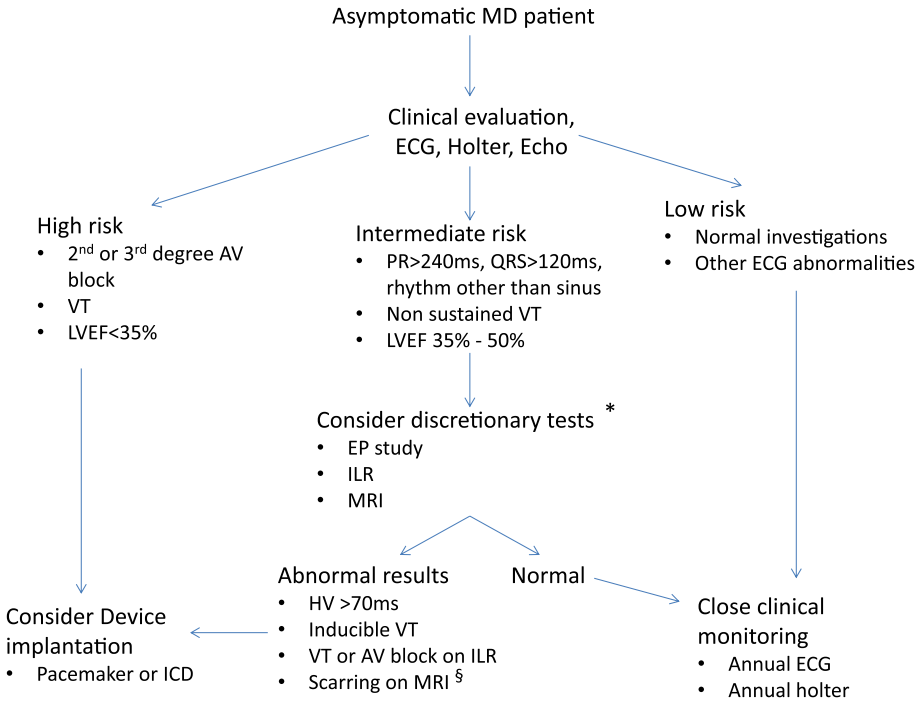

Fig. 2. Suggested flow diagram for the management of asymptomatic patients with myotonic dystrophy. *Patients who are unable or unwilling to undertake discretionary tests such as EP, ILR and MRI could be considered for device implantation based on other clinical parameters and test results (such as progressive ECG change). §Scarring on MRI does not have the same evidence base as HV prolongation at EP study, but in view of the potential for this to represent a pathophysiological substrate for arrhythmias in a range of cardiac conditions, it may evolve into an indication for device implantation in the future.

death. When LV function is normal on 2D images, tissue Doppler can detect early systolic dysfunction and diastolic dysfunction.

Finally, CMR may be useful as an adjunctive tool in detecting subclinical ventricular dysfunction, fibrosis and fatty infiltration, and this information may be used in conjunction with other test results in guidance of device therapy. CMR may become a more powerful risk stratification tool once CMR findings are linked to clinical endpoints.

In conclusion, we have sought to provide a contemporary approach to cardiac evaluation and management of MD patients with a focus on the prevention of complications leading to premature sudden death. We anticipate that further refinement and evaluation of risk stratification models in MD is achievable with collaborative multicentre registries.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] G. Pelargonio, A. Dello Russo, T. Sanna, G. De Martino, F. Bellocci, Myotonic dystrophy and the heart, Heart 88 (2002) 665–670.
[2] Y. Hayashi, U. Ikeda, T. Kojo, M. Nishinaga, H. Miyashita, T. Kuroda, et al., Cardiac abnormalities and cytosine–thymine–guanine trinucleotide repeats in myotonic dystrophy, Am. Heart J. 134 (2 Pt 1) (1997 Aug) 292–297.
[3] P. Melacini, C. Villanova, E. Menegazzo, G. Novelli, G. Danieli, G. Rizzoli, et al., Correlation between cardiac involvement and CTG trinucleotide repeat length in myotonic dystrophy, JACC 25 (1) (1995) 239–245.
[4] B.A. Hardin, M.R. Lowe, D. Bhakta, W.J. Groh, Heart rate variability declines with increasing age and CTG repeat length in patients with myotonic dystrophy type 1, Ann. Noninvasive Electrocardiol. 8 (3) (2003 Jul) 227–232.
[5] N.R. Clarke, A.D. Kelion, J. Nixon, D. Hilton-Jones, J.C. Forfar, Does cytosine–thymine–guanine (CTG) expansion size predict cardiac events and electrocardiographic progression in myotonic dystrophy? Heart 86 (4) (2001 Oct) 411–416.
[6] C. Marchini, R. Lonigro, L. Verriello, L. Pellizzari, P. Bergonzi, G. Damante, Correlations between individual clinical manifestations and CTG repeat amplification in myotonic dystrophy, Clin. Genet. 57 (1) (2000 Jan) 74–82.
[7] M. Parisi, M. Galderisi, M. Sidiropulos, C. Fiorillo, R. Lanzillo, A. D'Errico, et al., Early detection of biventricular involvement in myotonic dystrophy by tissue Doppler, Int. J. Cardiol. 118 (2) (2007 May 31) 227–232.
[8] R. Breton, J. Mathieu, Usefulness of clinical and electrocardiographic data for predicting adverse cardiac events in patients with myotonic dystrophy, Can. J. Cardiol. 25 (2) (2009) e23–e27.
[9] M.C. Hermans, C.G. Faber, S.C. Bekkers, C.E. de Die-Smulders, M.M. Gerrits, I.S. Merkies, et al., Structural and functional cardiac changes in myotonic dystrophy type 1: a cardiovascular magnetic resonance study, J. Cardiovasc. Magn. Reson. 14 (2012) 48.
[10] K. Merlevede, D. Vermander, P. Theys, E. Legius, H. Ector, W. Robberecht, Cardiac involvement and CTG expansion in myotonic dystrophy, J. Neurol. 249 (6) (2002 Jun) 693–698.
[11] M. Šabovič, I. Medica, N. Logar, E. Mandić, J. Zidar, B. Peterlin, Relation of CTG expansion and clinical variables to electrocardiogram conduction abnormalities and sudden death in patients with myotonic dystrophy, Neuromuscul. Disord. 13 (10) (2003) 822–826.
[12] C.A. Thornton, K. Johnson, R.T. Moxley 3rd., Myotonic dystrophy patients have larger CTG expansions in skeletal muscle than in leukocytes, Ann. Neurol. 35 (1) (1994 Jan) 104–107.
[13] D. Vinereanu, B.P. Bajaj, J. Fenton-May, M.T. Rogers, C.F. Madler, A.G. Fraser, Subclinical cardiac involvement in myotonic dystrophy manifesting as decreased myocardial Doppler velocities, Neuromuscul. Disord. 14 (3) (2004 Mar) 188–194.
[14] D. Verhaert, K. Richards, J.A. Rafael-Fortney, S.V. Raman, Cardiac involvement in patients with muscular dystrophies: magnetic resonance imaging phenotype and genotypic considerations, Circ. Cardiovasc. Imaging 4 (1) (2011 Jan) 67–76.
[15] R.O. Bonow, D.L. Mann, D.P. Zipes, P. Libby, Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine 9th Edition, Elsevier Saunders, Philadelphia, 2012.
[16] R.D. Leo, C. Rodolico, C.D. Gregorio, A. Recupero, S. Coglitore, G. Annesi, et al., Cardiovascular autonomic control in myotonic dystrophy type 1: a correlative study with clinical and genetic data, Neuromuscul. Disord. 14 (2) (2004) 136–141.
[17] A.A. Sovari, C.K. Bodine, F. Farokhi, Cardiovascular manifestations of myotonic dystrophy-1, Cardiol. Rev. 15 (4) (2007 Jul–Aug) 191–194.
[18] M.F. Phillips, P.S. Harper, Cardiac disease in myotonic dystrophy, Cardiovasc. Res. 33 (1997) 13–22.
[19] S. Bharati, F.T. Bump, R. Bauernfeind, M. Lev, Dystrophica myotonia. Correlative electrocardiographic, electrophysiologic, and conduction system study, Chest 86 (3) (1984 Sep) 444–450.
[20] E.B. Turkbey, N. Gai, J.A. Lima, R.J. van der Geest, K.R. Wagner, G.F. Tomaselli, et al., Assessment of cardiac involvement in myotonic muscular dystrophy by T1 mapping on magnetic resonance imaging, Heart Rhythm. 9 (10) (2012 Oct) 1691–1697.
[21] N. Uemura, H. Tanaka, T. Niimura, N. Hashiguchi, M. Yoshimura, S. Terashi, et al., Electrophysiological and histological abnormalities of the heart in myotonic dystrophy, Am. Heart J. 86 (5) (1973 Nov) 616–624.
[22] A.M. Thomson, Dystrophia cordis myotonica studied by serial histology of the pacemaker and conducting system, J. Pathol. Bacteriol. 96 (2) (1968 Oct) 285–295.
[23] A. Mammarella, P. Ferroni, M. Paradiso, F. Martini, V. Paoletti, S. Morino, et al., Tumor necrosis factor-alpha and myocardial function in patients with myotonic dystrophy type 1, J. Neurol. Sci. 201 (1–2) (2002 Sep 15) 59–64.
[24] J. Finsterer, C. Stollberger, H. Keller, Arrhythmia-related workup in hereditary myopathies, J. Electrocardiol. 45 (4) (2012 Jul–Aug) 376–384.
[25] J. Mathieu, P. Allard, L. Potvin, C. Prévost, P. Bégin, A 10-year study of mortality in a cohort of patients with myotonic dystrophy, Neurology 52 (8) (1999) 1658–1662.
[26] W. Groh, M. Groh, C. Saha, J. Kincaid, Z. Simmons, E. Ciafaloni, et al., Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1, N. Engl. J. Med. 358 (2008) 2688–2697.
[27] W.J. Groh, Arrhythmias in the muscular dystrophies, Heart Rhythm. 9 (11) (2012 Nov) 1890–1895.
[28] B. Brembilla-Perrot, J.D. Luporsi, S. Louis, P. Kaminsky, Long-term follow-up of patients with myotonic dystrophy: an electrocardiogram every year is not necessary, Europace 13 (2) (2011 Feb) 251–257.
[29] D. Duboc, K. Wahbi, What is the best way to detect infra-Hisian conduction abnormalities and prevent sudden cardiac death in myotonic dystrophy? Heart 98 (6) (2012 Mar) 433–434.
[30] H. Petri, J. Vissing, N. Witting, H. Bundgaard, L. Kober, Cardiac manifestations of myotonic dystrophy type 1, Int. J. Cardiol. 160 (2) (2012 Oct 4) 82–88.
[31] J.L. Merino, J.R. Carmona, I. Fernandez-Lozano, R. Peinado, N. Basterra, J.A. Sobrino, Mechanisms of sustained ventricular tachycardia in myotonic dystrophy: implications for catheter ablation, Circulation 98 (6) (1998) 541–546.
[32] L.E. Grigg, W. Chan, H.G. Mond, J.K. Vohra, W.F. Downey, Ventricular tachycardia and sudden death in myotonic dystrophy: clinical, electrophysiologic and pathologic features, J. Am. Coll. Cardiol. 6 (1) (1985 Jul) 254–256.
[33] P. Cudia, P. Bernasconi, R. Chiodelli, F. Mangiola, F. Bellocci, A. Dello Russo, et al., Risk of arrhythmia in type I myotonic dystrophy: the role of clinical and genetic variables, J. Neurol. Neurosurg. Psychiatry 80 (7) (2009 Jul) 790–793.
[34] P. Ballo, M. Giaccardi, A. Colella, F. Cellerini, F. Bandini, L. Chiodi, et al., Mechanical and electrophysiological substrate for recurrent atrial flutter detected by right atrial speckle tracking echocardiography and electroanatomic mapping in myotonic dystrophy type 1, Circulation 127 (13) (2013 Apr 2) 1422–1424.
[35] J.L. Merino, R. Peinado, J.A. Sobrino, A. Lazarus, J. Varin, Z. Ounnoughene, et al., Sudden death in myotonic dystrophy: the potential role of bundle-branch reentry response, Circulation 101 (5) (2000) e73-e.
[36] M.F. Nageh, Recurrent fascicular ventricular tachycardia in myotonic dystrophy, Europace 8 (5) (2006 May) 336–337.
[37] Y. Umeda, U. Ikeda, J. Yamamoto, H. Fukazawa, Y. Hayashi, H. Fujikawa, et al., Myotonic dystrophy associated with QT prolongation and torsade de pointes, Clin. Cardiol. 22 (2) (1999 Feb) 136–138.
[38] A. Lazarus, J. Varin, G. Jauvert, C. Alonso, D. Duboc, Relationship between cardiac arrhythmias and sleep apnoea in permanently paced patients with type I myotonic dystrophy, Neuromuscul. Disord. 17 (5) (2007 May) 392–399.
[39] J. Harbison, P. O'Reilly, W.T. McNicholas, Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy, Chest 118 (3) (2000 Sep) 591–595.
[40] J.S. Gottdiener, R.J. Hawley, J.A. Gay, R. DiBianco, R.D. Fletcher, W.K. Engel, Left ventricular relaxation, mitral valve prolapse, and intracardiac conduction in myotonia atrophica: assessment by digitized echocardiography and noninvasive His bundle recording, Am. Heart J. 104 (1) (1982 Jul) 77–85.
[41] S. Hiromasa, T. Ikeda, K. Kubota, N. Hattori, M. Nishimura, Y. Watanabe, et al., Myotonic dystrophy: ambulatory electrocardiogram, electrophysiologic study, and echocardiographic evaluation, Am. Heart J. 113 (6) (1987 Jun) 1482–1488.
[42] L. Badano, C. Autore, P.V. Fragola, A. Picelli, G. Antonini, R. Vichi, et al., Left ventricular myocardial function in myotonic dystrophy, Am. J. Cardiol. 71 (11) (1993 Apr 15) 987–991.
[43] D. Bhakta, M.R. Lowe, W.J. Groh, Prevalence of structural cardiac abnormalities in patients with myotonic dystrophy type I, Am. Heart J. 147 (2) (2004 Feb) 224–227.
[44] W.C. Reeves, R. Griggs, N.C. Nanda, K. Thomson, R. Gramiak, Echocardiographic evaluation of cardiac abnormalities in Duchenne's dystrophy and myotonic muscular dystrophy, Arch. Neurol. 37 (5) (1980 May) 273–277.
[45] J. Finsterer, C. Stolberger, W. Kopsa, Noncompaction in myotonic dystrophy type 1 on cardiac MRI, Cardiology 103 (3) (2005) 167–168.
[46] J. Finsterer, C. Stollberger, R. Wegmann, C. Jarius, B. Janssen, Left ventricular hypertrabeculation in myotonic dystrophy type 1, Herz 26 (4) (2001 Jun) 287–290.
[47] D. Bhakta, M.R. Groh, C. Shen, R.M. Pascuzzi, W.J. Groh, Increased mortality with left ventricular systolic dysfunction and heart failure in adults with myotonic dystrophy type 1, Am. Heart J. 160 (6) (2010 Dec) 1137–1141 (41 e1).
[48] K.C. Fung, A. Corbett, L. Kritharides, Myocardial tissue velocity reduction is correlated with clinical neurologic severity in myotonic dystrophy, Am. J. Cardiol. 92 (2) (2003) 177–181.
[49] G.B. Hartwig, K.R. Rao, F.M. Radoff, R.E. Coleman, R.H. Jones, A.D. Roses, Radionuclide angiocardiographic analysis of myocardial function in myotonic muscular dystrophy, Neurology 33 (5) (1983 May) 657–660.
[50] J.S. Child, J.K. Perloff, Myocardial myotonia in myotonic muscular dystrophy, Am. Heart J. 129 (5) (1995 May) 982–990.
[51] P. Lindqvist, S. Morner, B.O. Olofsson, C. Backman, D. Lundblad, H. Forsberg, et al., Ventricular dysfunction in type 1 myotonic dystrophy: electrical, mechanical, or both? Int. J. Cardiol. 143 (3) (2010 Sep 3) 378–384.

[52] D. Annane, P. Merlet, H. Radvanyi, B. Mazoyer, B. Eymard, M. Fiorelli, et al., Blunted coronary reserve in myotonic dystrophy. An early and gene-related phenomenon, Circulation 94 (5) (1996 Sep 1) 973–977.
[53] A.E. Epstein, J.P. DiMarco, K.A. Ellenbogen, N.A. Estes 3rd, R.A. Freedman, L.S. Gettes, et al., ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmic devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons, J. Am. Coll. Cardiol. 51 (21) (2008 May 27) e1–e62.
[54] European Heart Rhythm A, Heart Rhythm S, D.P. Zipes, A.J. Camm, M. Borggrefe, A.E. Buxton, et al., CC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death), J. Am. Coll. Cardiol. 48 (5) (2006 Sep 5) e247–e346.
[55] W. Groh, M. Lowe, D. Zipes, Severity of cardiac conduction involvement and arrhythmias in myotonic dystrophy type 1 correlates with age and CTG repeat length, J. Cardiovasc. Electrophysiol. 13 (5) (2002) 444–448.
[56] M.T. Viitasalo, R. Kala, P. Karli, A. Eisalo, Ambulatory electrocardiographic recording in mild or moderate myotonic dystrophy and myotonia congenita (Thomsen's disease), J. Neurol. Sci. 62 (1–3) (1983 Dec) 181–190.
[57] M.I. Sa, S. Cabral, P.D. Costa, T. Coelho, M. Freitas, J.L. Gomes, Ambulatory electrocardiographic monitoring in type 1 myotonic dystrophy, Rev. Port. Cardiol. 26 (7–8) (2007 Jul–Aug) 745–753.
[58] M. Casella, A. Dello Russo, M. Pace, G. Pelargonio, C. Ierardi, T. Sanna, et al., Heart rate turbulence as a noninvasive risk predictor of ventricular tachyarrhythmias in myotonic dystrophy type 1, J. Cardiovasc. Electrophysiol. 17 (8) (2006 Aug) 871–876.
[59] P. Barthel, R. Schneider, A. Bauer, K. Ulm, C. Schmitt, A. Schomig, et al., Risk stratification after acute myocardial infarction by heart rate turbulence, Circulation 108 (10) (2003 Sep 9) 1221–1226.
[60] P.R. Harris, P.K. Stein, G.L. Fung, B.J. Drew, Prognostic value of heart rate turbulence for risk assessment in patients with unstable angina and non-ST elevation myocardial infarction, Vasc. Health Risk Manag. 9 (2013) 465–473.
[61] C. Stollberger, C. Steger, P. Gabriel, J. Finsterer, Implantable loop recorders in myotonic dystrophy 1, Int. J. Cardiol. 152 (2) (2011 Oct 20) 249–251.
[62] D. Hadian, M.R. Lowe, L.R. Scott, W.J. Groh, Use of an insertable loop recorder in a myotonic dystrophy patient, J. Cardiovasc. Electrophysiol. 13 (1) (2002 Jan) 72–73.
[63] D. Babuty, L. Fauchier, D. Tena-Carbi, P. Poret, J. Leche, M. Raynaud, et al., Significance of late ventricular potentials in myotonic dystrophy, Am. J. Cardiol. 84 (9) (1999 Nov 1) 1099-101 (A10).
[64] S. Nazarian, D.A. Bluemke, K.R. Wagner, M.M. Zviman, E. Turkbey, B.S. Caffo, et al., QRS prolongation in myotonic muscular dystrophy and diffuse fibrosis on cardiac magnetic resonance, Magn. Reson. Med. 64 (1) (2010 Jul) 107–114.
[65] P.V. Fragola, L. Calo, G. Antonini, S. Morino, M. Luzi, D. De Nardo, et al., Signal-averaged electrocardiography in myotonic dystrophy, Int. J. Cardiol. 50 (1) (1995 Jun 2) 61–68.
[66] A. Lazarus, J. Varin, Z. Ounnoughene, H. Radvanyi, C. Junien, J. Coste, et al., Relationships among electrophysiological findings and clinical status, heart function, and extent of DNA mutation in myotonic dystrophy, Circulation 99 (1999) 1041–1046.
[67] B. Lallemand, N. Clementy, A. Bernard-Brunet, B. Pierre, P. Corcia, L. Fauchier, et al., The evolution of infrahissian conduction time in myotonic dystrophy patients: clinical implications, Heart 98 (4) (2012 Feb) 291–296.
[68] E.N. Prystowsky, E.L. Pritchett, A.D. Roses, J. Gallagher, The natural history of conduction system disease in myotonic muscular dystrophy as determined by serial electrophysiologic studies, Circulation 60 (1979) 1360–1364.
[69] O. Vignaux, A. Lazarus, J. Varin, J. Coste, P. Carlier, C. Argaud, et al., Right ventricular MR abnormalities in myotonic dystrophy and relationship with intracardiac electrophysiologic test findings: initial results, Radiology 224 (1) (2002 Jul) 231–235.
[70] S. Kumar, G. Sivagangabalan, S. Zaman, E.B. West, A. Narayan, A. Thiagalingam, et al., Electrophysiology-guided defibrillator implantation early after ST-elevation myocardial infarction, Heart Rhythm. 7 (11) (2010 Nov) 1589–1597.
[71] P. Santangeli, C. Hamilton-Craig, A. Dello Russo, M. Pieroni, M. Casella, G. Pelargonio, et al., Imaging of scar in patients with ventricular arrhythmias of right ventricular origin: cardiac magnetic resonance versus electroanatomic mapping, J. Cardiovasc. Electrophysiol. 22 (12) (2011 Dec) 1359–1366.
[72] L. De Ambroggi, A. Raisaro, S. Marchiano, S. Radice, G. Meola, Cardiac involvement in patients with myotonic dystrophy: characteristic features of magnetic resonance imaging, Eur. Heart J. 16 (1995) 1007–1010.
[73] K. Wahbi, C. Meune, R. Porcher, H.M. Becane, A. Lazarus, P. Laforet, et al., Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease, J. Am. Med.Assoc. 307 (12) (2012) 1292–1301.
[74] A. Lazarus, J. Varin, D. Babuty, F. Anselme, J. Coste, D. Duboc, Long-term follow-up of arrhythmias in patients with myotonic dystrophy treated by pacing, J. Am. Coll. Cardiol. 40 (9) (2002) 1645–1652.
[75] D. Bhakta, C. Shen, J. Kron, A.E. Epstein, R.M. Pascuzzi, W.J. Groh, Pacemaker and implantable cardioverter–defibrillator use in a US myotonic dystrophy type 1 population, J. Cardiovasc. Electrophysiol. 22 (12) (2011 Dec) 1369–1375.
[76] V. Laurent, S. Pellieux, P. Corcia, P. Magro, B. Pierre, L. Fauchier, et al., Mortality in myotonic dystrophy patients in the area of prophylactic pacing devices, Int. J. Cardiol. 150 (1) (2011 Jul 1) 54–58.
[77] D.V. Exner, D.L. Dries, M.A. Waclawiw, B. Shelton, M.J. Domanski, Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the studies of left ventricular dysfunction, J. Am. Coll. Cardiol. 33 (4) (1999 Mar 15) 916–923.
[78] M.A. Konstam, M.W. Kronenberg, M.F. Rousseau, J.E. Udelson, J. Melin, D. Stewart, et al., Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators, Circulation 88 (5) (1993) 2277–2283.
[79] Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors, N. Engl. J. Med. 327 (10) (1992 Sep 3) 685–691.
[80] S.V. Raman, K.N. Hor, W. Mazur, N.J. Halnon, J.T. Kissel, X. He, et al., Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial, Lancet Neurol. 29 (2014 Dec).
[81] J. Finsterer, C. Stollberger, Atrial fibrillation/flutter in myopathies, Int. J. Cardiol. 128 (3) (2008 Aug 29) 304–310.
[82] P.E. Vardas, A. Auricchio, J.J. Blanc, J.C. Daubert, H. Drexler, H. Ector, et al., Guidelines for cardiac pacing and cardiac resynchronization therapy: the Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association, Eur. Heart J. 28 (18) (2007 Sep) 2256–2295.
[83] A.H. Ha, M.A. Tarnopolsky, T.G. Bergstra, G.M. Nair, A. Al-Qubbany, J.S. Healey, Predictors of atrio-ventricular conduction disease, long-term outcomes in patients with myotonic dystrophy types I and II, Pacing Clin Electrophysiol. 35 (10) (2012 Oct) 1262–1269.
[84] P. Kaminsky, B. Brembilla-Perrot, L. Pruna, M. Poussel, B. Chenuel, Age, conduction defects and restrictive lung disease independently predict cardiac events and death in myotonic dystrophy, Int J Cardiol. 162 (3) (2013) 172–178.
[85] S. Morner, P. Lindqvist, C. Mellberg, B.O. Olofsson, C. Backman, M. Henein, et al., Profound cardiac conduction delay predicts mortality in myotonic dystrophy type 1, J Intern Med. 268 (1) (2010 Jul) 59–65.
[86] T. Ozyigit, B. Ozben, H. Oflaz, P. Serdaroglu, Evaluation of biventricular functions with tissue Doppler imaging in patients with myotonic dystrophy, Clin Cardiol. 33 (3) (2010 Mar) 126–131.
[87] A. Di Cori, M.G. Bongiorni, G. Zucchelli, E. Soldati, M. Falorni, L. Segreti, et al., Early left ventricular structural myocardial alterations and their relationship with functional and electrical properties of the heart in myotonic dystrophy type 1, J Am Soc Echocardiogr. 22 (10) (2009 Oct) 1173–1179.
[88] K. Wahbi, S. Ederhy, H.M. Becane, C. Meune, A. Behin, T. Stojkovic, et al., Impaired myocardial deformation detected by speckle-tracking echocardiography in patients with myotonic dystrophy type 1, Int J Cardiol. 152 (3) (2011 Nov 3) 375–376.