Multimodality imaging in the characterization and risk-stratification of cardiac disease and CRT recipients

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Risk stratification of genetic, dilated cardiomyopathies associated with neuromuscular disorders: role of cardiac imaging

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ABSTRACT

The etiology of dilated cardiomyopathy (DCM) can be grouped as either genetic or non-genetic. More than 50 pathogenic genes have been described, with sarcomeric and lamin A/C mutations being the most common. Mutation carriers for genetic DCM are often asymptomatic until cardiac disease manifests with heart failure, arrhythmias or sudden cardiac death. Preventive strategies are promising, but can only be applied and tested adequately if genetic DCM can be diagnosed at an early stage. Early diagnosis of mutation carriers that may develop overt DCM requires advanced imaging techniques that can detect subtle structural and functional abnormalities. Advanced echocardiographic techniques such as tissue Doppler imaging and speckle tracking strain analysis permit early detection of functional abnormalities, whereas cardiovascular magnetic resonance (CMR) techniques provide information on tissue characterization and myocardial energetics that may be altered at an early stage. Furthermore, nuclear imaging techniques provide information on cellular function (metabolism, perfusion). Once the diagnosis of overt DCM has been established, various imaging parameters such as echocardiography-based myocardial mechanics and CMR-based tissue characterization have shown incremental benefit to left ventricular ejection fraction in risk-stratification. Further research is required to understand how imaging techniques may help to choose management strategies which could delay progression when instituted early in the course of the disease. The present article reviews the role of imaging in the risk-stratification of genetic DCM in general, with specific emphasis on DCM associated with neuromuscular disorders.

INTRODUCTION

Dilated cardiomyopathy (DCM) is defined as "left ventricular (LV) or biventricular systolic dysfunction and dilation that are not explained by abnormal loading conditions or coronary artery disease".[1] Ischemic heart disease is therefore excluded by definition, and etiologies of DCM are divided into two major groups: genetic and non-genetic.[1] The distinction between genetic and non-genetic DCM is sometimes less clear, since the likelihood of certain non-genetic etiologies (e.g. chemotherapy) of causing DCM can be superimposed on the genetic susceptibility of an individual.[1]

More than 50 pathogenic genes have been described, with sarcomeric and lamin A/C mutations being the most common, but defects of the desmosome, nucleus, mitochondrion, lysosome and ion channels are also associated with the development of DCM.[2,3] More than one pathogenic mutation may be present in a single individual, and this may be (at least in part) responsible for the large variation in penetrance of many of the genetic defects causing DCM.[4]

The clinical manifestations of a genetic defect can vary from being "preclinical" (mutation carrier without clinical manifestations, LV dilation without hypokinesia or arrhythmias) to "clinical" (hypokinetic but non-dilated cardiomyopathy or DCM).[1] The entity of hypokinetic but non-dilated cardiomyopathy has recently been formally defined as "hypokinesia without significant LV dilation".[1]

Early diagnosis of mutation carriers who may develop overt DCM requires advanced imaging techniques that detect subtle structural and/or functional abnormalities. Advanced echocardiographic techniques such as tissue Doppler imaging and speckle tracking strain analysis permit early detection of functional abnormalities, whereas cardiovascular magnetic resonance (CMR) techniques provide information on tissue characterization and myocardial energetics that may be altered at an early stage. Furthermore, nuclear imaging techniques provide information on cellular function (metabolism, perfusion). The evidence supporting these imaging techniques in the diagnosis and risk-stratification of patients with DCM is accumulating, specifically in DCM associated with neuromuscular disorders (genetics and extracardiac features: Table 1).[5-7] The present article reviews the role of imaging in the early diagnosis and risk-stratification in established disease of patients with DCM associated with neuromuscular disorders.

EARLY DIAGNOSIS OF VENTRICULAR DYSFUNCTION IN DCM ASSOCIATED WITH NEUROMUSCULAR DISORDERS

Early diagnosis is integral to the process of risk-stratification in DCM, since patients often remain asymptomatic until cardiac disease manifests with heart failure, life-threatening arrhythmias or sudden cardiac death.[8,9] The onset or progression of ventricular systolic dysfunction and the development of myocardial fibrosis may be slowed by early initiation of therapy resulting eventually in improved prognosis.

Examples include: the early use of systemic steroids, angiotensin-converting enzyme (ACE)-inhibitors or beta-blockers in patients with Duchenne muscular dystrophy (DMD).[10-16] Barber et al.[16] demonstrated in 462 patients with DMD that every year of steroid treatment decreased the probability of developing cardiomyopathy (defined by abnormal LV fractional shortening or ejection fraction (EF)) by 4%. Additionally, in a randomized, double-blind study of 56 DMD patients with normal LVEF, ACE-inhibitors delayed the onset of LV systolic dysfunction (P=0.02).[11] In a similar fashion, either an ACE-inhibitor or a beta-blocker improved LV fractional shortening in patients with DMD and Becker muscular dystrophy and cardiac involvement (P<0.05).[15] Experimental therapies hold promise of influencing disease processes when initiated early, e.g. the membrane sealant poloxamer (which repairs damaged biologic membranes), growth hormone treatment or gene therapy in DMD.[17-19] Approaches to early diagnosis have focused on advanced imaging techniques to demonstrate abnormalities of cardiac structure, and mechanical as well as cellular function.

Table 1: Neuromuscular diseases which are associated with genetic, dilated cardiomyopathies (DCM).[5-7]

Disorder	Abnormal gene/ protein; chromosome	Mode(s) of transmission	Clinical features (extracardiac)
Duchenne muscular dystrophy	Dystrophin; Xp21	X-linked recessive	• Proximal, skeletal muscle weakness • Respiratory failure
Becker muscular dystrophy	Dystrophin; Xp21	X-linked recessive	Similar to Duchenne muscular dystrophy, but more benign course
Emery-Dreifuss muscular dystrophy	• Emerin; Xq28, Xq26 • Lamin A/C; 1q21	• X-linked recessive • Autosomal dominant • Autosomal recessive	• Contractures, e.g. Achilles tendons and elbows • Humero-peroneal muscle weakness & wasting
Limb-girdle muscular dystrophy	• FKRP, 19q • Lamin A/C; 1q22	• Autosomal recessive • Autosomal dominant	Weakness of shoulder and pelvic girdles
Myotonic dystrophy	• DMPK; 19q13 (type I) • ZNF9; 3q21 (type II)	Autosomal dominant	• Skeletal muscle weakness, e.g. facial, sternocleidomastoid and intrinsic muscles of hand • Myotonia (slow relaxation after contraction) • Non-muscular, e.g. cataracts, insulin resistance
Friedreich ataxia	FXN; 9q13	Autosomal recessive	• Ataxia of gait and limbs • Abnormal reflexes: absence of deep tendon reflexes and extensor plantar responses • Loss of position and vibration sense in lower limbs

DMPK: myotonic dystrophy protein kinase, FKRP: fukutin-related protein, FXN: frataxin, ZNF9: zinc finger protein 9.

Cardiac structure

Increased extracellular matrix and fibrosis of the myocardium are the hallmark of changes in the cardiac structure in DCM. Myocardial late gadolinium enhancement (LGE) allows the non-invasive detection of replacement myocardial fibrosis with CMR imaging.[20] Segmental LGE has been demonstrated in individuals with DMD and Becker muscular dystrophy before the onset of LV or right ventricular systolic dysfunction, and may therefore indicate early disease (Figure 1).[20-24] Similarly, segmental LGE has been visualised in carriers of lamin A/C mutations and in patients with myotonic dystrophy and preserved LVEF.[25-28] Segmental LGE has also been detected in mitochondrial diseases with cardiac involvement (chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome) but normal LV systolic function.[29]

However, in early phases of DCM, reactive fibrosis (increase of interstitial space by deposition of collagen) rather than replacement fibrosis is present. This reactive fibrosis is detected with T1 mapping CMR imaging techniques. For example, longitudinal relaxation is described by a T1 recovery curve, and the time constant (when 63% of recovery has occurred) of such a curve can be represented by a pixelwise, colour-coded map (a T1 map).[30] Increased reactive fibrosis will result in long T1 times in native T1 maps (acquired without the use of a gadolinium-based contrast agent). In contrast, when T1 maps are registered after gadolinium-based contrast media administration, the T1 times are shorter in segments with increased fibrosis as compared to normal myocardium.[31]

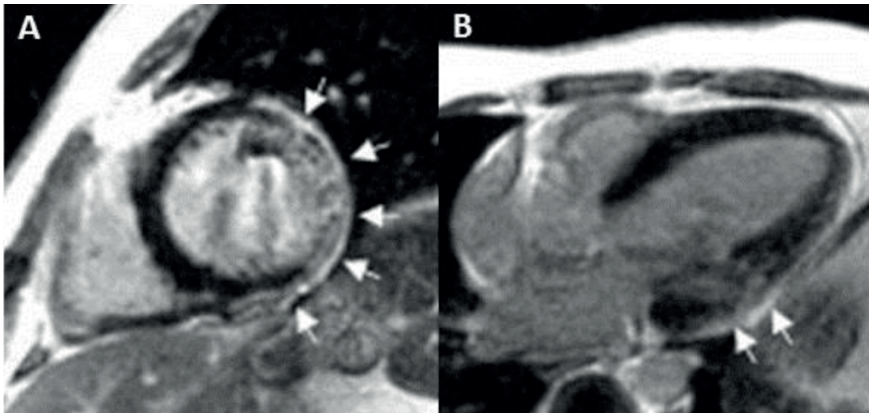

Figure 1: Cardiac magnetic resonance with late gadolinium enhancement (LGE) in a patient with Becker muscular dystrophy. Transmural fibrosis in the lateral free wall of the left ventricle in a short-axis view (indicated by arrows) (A) and a horizontal long-axis view (B). Adapted with permission from Yilmaz et al.[21]

Different CMR sequences are employed in T1 mapping, e.g. modified Look-Locker Inversion (MOLLI) recovery and shortened MOLLI (ShMOLLI).[30] The extracellular volume fraction (ECV) of the myocardium, which is a measure of the size of the extracellular space, can be calculated from the native myocardial and precontrast blood T1 values, the post-contrast myocardial and blood T1 values, as well as the haematocrit.[32] Interstitial, reactive myocardial fibrosis, re-

presenting an early form of myocardial damage, can be both diagnosed and quantified by T1 mapping and ECV calculation.[33] An elevated ECV was found in lamin A/C mutation carriers with normal LV systolic function, and even in some individuals without LGE. ECV may therefore be an even more sensitive marker of early disease than LGE.[34] An elevated ECV and native T1 values have also been documented in patients with DMD and normal LV systolic function (including some without LGE) (Figure 2).[35-37] T1 mapping may be particularly suited to the investigation of cardiac involvement in myotonic dystrophy, since fibrosis is most frequently diffuse, rather than localised, in this condition.[38] Postcontrast T1 values were significantly lower in a group of individuals diagnosed with type 1 and type 2 myotonic dystrophy and normal LV systolic function, compared to controls.[38] Segmentally-increased ECV and focal lipid deposits have been described in patients affected with type 2 myotonic dystrophy and preserved LV systolic function – including regions without LGE – supporting the concept that reactive, diffuse fibrosis is a very sensitive marker of cardiac involvement.[28]

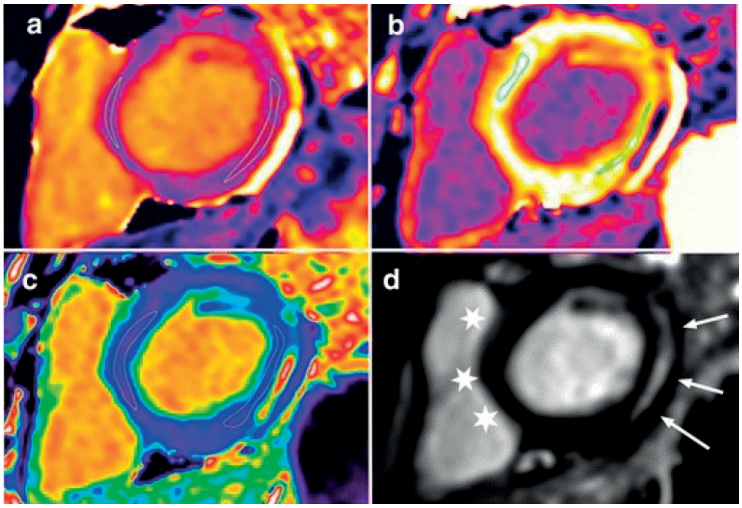

Figure 2: Cardiac magnetic resonance T1 mapping in a patient with Duchenne muscular dystrophy, demonstrating fibrosis of the lateral wall in short-axis views. The images show a native T1 map of the left ventricle (a) a post-contrast T1 map, (b) an extracellular volume (ECV) map, and (c) late gadolinium enhancement (LGE), with arrows indicating LGE of the lateral wall and stars denoting normal, septal myocardium (d). Reproduced with permission from Olivieri et al.[35]

Myocardial tissue characterization can also be performed with echocardiography by analysis of the reflected ultrasound signal, which is known as integrated backscatter (IBS). Two parameters are generally measured in the anteroseptal and posterior walls of the left ventricle which include the magnitude of cyclical variation and the IBS intensity (both expressed in dB).[39,40] A decrease in the magnitude of cyclical variation denotes an increase in myocardial collagen content, even though it can be influenced by myocardial water content, myofibril architecture and contractility, while the degree of IBS intensity shows a correlation with myocardial fibrosis.[39,40]

In a study of 25 patients with DMD, the IBS intensity was higher, and the magnitude of cyclical variation lower, in the outer half of the LV myocardium compared to controls, suggesting epicardial fibrosis.[39] Similarly, a lower magnitude of cyclical variation and a higher IBS intensity were noted in 20 children with DMD, compared to age-matched controls (Figure 3).[41]

Mechanical function

Although LVEF is the measure of choice to characterize LV systolic function, subtle changes in myocardial function can be detected with more sensitive measures based on deformation and tissue velocity imaging. Myocardial deformation can be quantified by strain, which reflects a unitless measure of change in dimension.[42] Echocardiographic strain imaging is most commonly performed with speckle tracking echocardiography. Myocardial "speckles", which arise from the interaction of ultrasound and myocardium, are identified by imaging software and their displacement followed from frame to frame.[42] Strain is most commonly reported in the longitudinal, radial or circumferential directions of LV deformation and can be reported at segmental level (pertaining only to one segment of the ventricle) or global level (reflecting all segments of the ventricle).[43] Global LV longitudinal strain is the deformation parameter which has been most extensively studied, and demonstrates the best reproducibility. Myocardial strain imaging has demonstrated value in both the early diagnosis and risk-stratification of various cardiac diseases, including genetic and non-genetic cardiomyopathies.[43] Different CMR techniques can also be employed to measure strain, e.g. myocardial tagging and feature tracking.[44,45]

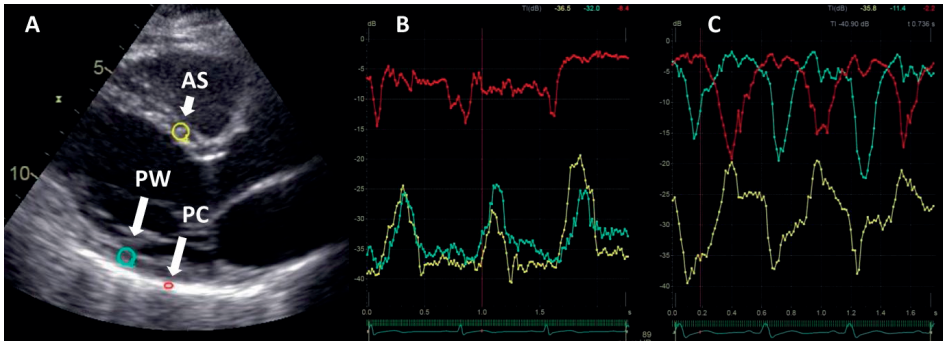

Figure 3: Integrated backscatter (IBS) in a patient with Duchenne muscular dystrophy. Assessment of the basal anterior septum (AS), basal posterior wall (PW) and pericardium (PC) by placement of regions of interest on a parasternal, long-axis view (A). Tracking of IBS during three cardiac cycles with color coding: anterior septum (yellow curve), posterior wall (blue curve) and pericardium (red curve) in a normal individual (B). The cyclic variations of IBS are clearly visible. IBS values of the posterior wall (blue curve) are similar to the pericardium (red curve) in a patient with Duchenne muscular dystrophy, suggesting myocardial fibrosis (C).

Impaired LV longitudinal, circumferential and radial strain, as well as reduced longitudinal and radial strain rates (using speckle tracking echocardiography) have been reported in individuals with DMD and normal LVEF on echocardiography or CMR.[46-51] Impaired segmental LV systolic

and diastolic radial strain rates were noted in patients with Becker muscular dystrophy and a normal LVEF.[52] Reduced LV segmental, circumferential strain (despite normal LVEF) was observed in patients with Emery-Dreifuss muscular dystrophy due to lamin A/C mutations.[53] An abnormal transmural LV strain pattern (comparing endo-, mid- and epicardial strain values) was identified in patients with DMD and preserved LVEF.[54]

The myocardial tissue velocity can be determined by tissue Doppler echocardiography during both systole and diastole.[55,56] Systolic myocardial tissue velocity is a reflection of longitudinal LV function, which is caused by endocardial fibre shortening, while diastolic myocardial tissue velocity is a surrogate of early diastolic, LV relaxation.[57] Impaired LV systolic and diastolic myocardial tissue velocities are markers of early cardiac disease and have been associated with outcome in various cardiac disorders.[57-60] Systolic and diastolic LV tissue velocities are reduced in patients with DMD and Friedreich ataxia who display a normal LVEF.[47,48,61-63] Similarly, systolic and diastolic LV tissue velocities are impaired in patients with myotonic dystrophy with a normal LVEF.[64,65]

In a normal heart, LV endocardial velocity (measured with tissue Doppler imaging) is greater than epicardial velocity, which reflects the rate of increase in wall thickening with contraction. The myocardial velocity gradient is the difference in myocardial velocity between the endo- and epicardium, divided by the myocardial wall thickening, and is an index of regional myocardial function.[66] Abnormal myocardial velocity gradients were identified in the interventricular septum, as well as the posterior wall of the left ventricle, in patients with Friedreich ataxia, DMD and Emery-Dreifuss muscular dystrophy (in the presence of a lamin A/C mutation) and preserved LV systolic function.[53,67,68]

Cellular function

Phosporus-31 magnetic resonance spectroscopy (^{31}P-MRS) allows non-invasive examination of cardiac energetics by quantification of high-energy phosphate metabolites.[69] Altered cardiac energetics are early markers of cardiomyopathy, often preceding morphological and overt functional abnormalities. Evaluation of LV myocardial metabolism can be obtained on a cellular level with ^{31}P-MRS.[70] Current 1.5T and 3T scanners do not allow voxel sizes with a spatial resolution which is high enough to produce spectra of individual myocardial segments (according to the American Heart Association 17-segment model) and subsequently, a volume of interest is placed in either the anterior LV wall or the interventricular septum.[71,72] Peaks in the ^{31}P-MR spectra reflect the concentrations of the three phosphorous atoms of adenosine triphosphate (ATP), i.e. γ-ATP, α-ATP and β-ATP, as well as phosphocreatine (PCr) (Figure 4).[69] From the ATP and PCr concentrations, the ratio of PCr to ATP can be calculated, which is influenced by abnormal cardiac metabolism in disease states. The reaction equilibrium of the creatine kinase reaction favours the synthesis of ATP rather than PCr, leading to a reduction in PCr when ATP demand is in excess of ATP supply – the consequence of which is a decrease in the PCr:ATP ratio.[69]

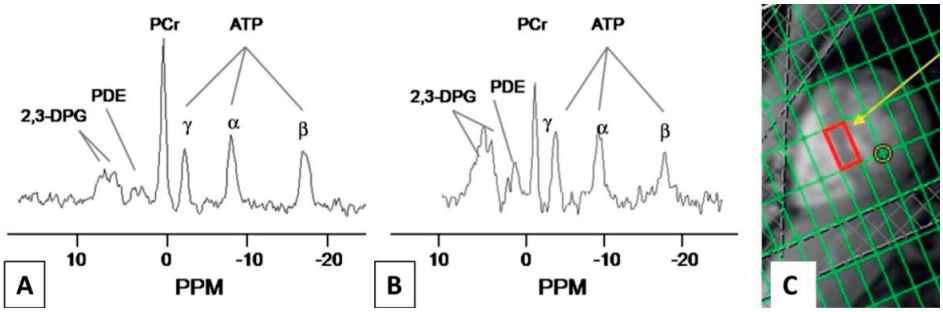

Figure 4: ^{31}P-magnetic resonance spectroscopy. The spectrum of a healthy individual, demonstrating peaks for 2,3-diphosphoglycerate (2,3-DPG), phosphodiesters (PDE), phosphocreatine (PCr), γ-adenosine triphosphate (ATP), α-ATP and β-ATP (A). Reduced PCr:ATP ratio in a patient with dilated cardiomyopathy (B). Region of interventricular septum in a short-axis view (red box, indicated by yellow arrow) for which quantification of myocardial metabolites is performed with ^{31}P-magnetic resonance spectroscopy (C). PPM: parts per million. Adapted with permission from Holloway et al.[71]

Some carriers of Xp21 mutations (the gene encoding dystrophin, causing DMD and Becker muscular dystrophy) with normal LV wall thickness, systolic and diastolic function, nevertheless manifest a reduced PCr/ATP.[73] Abnormal cardiac energetics, diagnosed with ^{31}P-MRS, may therefore also be a signal of early cardiac involvement in such patients. Similarly, a reduced myocardial PCr/ATP has been detected in patients with myotonic dystrophy, Friedreich ataxia and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome – all without evident structural or functional heart disease.[7,70,74] Additionally, ^{31}P-MRS can be used to interrogate skeletal muscle energetics, thereby allowing a comprehensive assessment of cardio-neuromuscular disorders.[70]

Nuclear imaging can also evaluate the cellular integrity and function. Global and regional myocardial perfusion can be visualised with gated imaging with single-photon emission computed tomography (SPECT).[75] Dystrophin-deficient myocardium is more vulnerable to pressure overload than normal myocardium, particularly in the LV inferior wall which is exposed to greater wall stress than other segments of the left ventricle.[8] Patients with DMD and Becker muscular dystrophy may show myocardial perfusion defects in the LV inferior wall on ^{99m}technetium SPECT imaging.[8] In addition, the myocardial cells of the LV apical segments are rich in dystrophin protein and may also show myocardial perfusion defects (Figure 5). This technique has not only shown potential for the early identification of cardiac involvement, but also for monitoring treatment response to systemic steroid therapy in DMD.[8] After a follow-up period of two years in patients with DMD who received systemic steroids, a significant improvement in myocardial perfusion was detected while no change was evident in LV dimensions or LVEF.[8] Positron emission tomography (PET) imaging, using ^{13}N-ammonia as tracer, can image myocardial perfusion, as well as ^{99m}technetium SPECT; the advantage of PET over SPECT is that PET permits absolute quantification of processes, whereas SPECT provides semiquantitative measurements.[75] Furthermore, myocardial metabolism can be investigated with ^{18}F-fluorodeoxyglucose

(FDG) PET.[75] Patients with DMD and normal LVEF have shown reduced myocardial perfusion in the LV posterobasal and posterolateral segments on ^{13}N-ammonia PET, whereas the uptake of ^{18}F-FDG was increased, suggesting the presence of regional metabolic alteration in uptake and trapping, a reduction in regional blood flow or both.[76]

RISK-STRATIFICATION IN ESTABLISHED DISEASE

Once a diagnosis of genetic DCM has been established, risk-stratification is of paramount importance. Risk may entail ventricular arrhythmias, incident heart failure or sudden cardiac death. Various imaging parameters of myocardial structure and function have been identified which may be useful in risk-stratification.

Cardiac structure

LGE of the interventricular septum (denoting myocardial fibrosis), was associated with ventricular arrhythmias in a cohort of lamin A/C mutation carriers with a normal LVEF (LGE was present only in patients experiencing ventricular arrhythmias, P=0.007), and may therefore help to risk-stratify these individuals, who are at high risk of ventricular arrhythmias and sudden cardiac death.[27] Patients with Friedreich ataxia and cardiac involvement experienced more frequent cardiac symptoms in the presence of LGE: after 12 months of follow-up, 3 of 14 (20%) patients with LGE experienced cardiac events, while no events were recorded in LGE-negative patients (P=0.1).[77] Not only the presence of LGE, but also the extent thereof may be important in the quantification of risk: transmural LGE in patients with DMD or Becker muscular dystrophy was an independent predictor of ventricular tachycardia and hospitalization for heart failure (hazard ratio (HR) 2.89; 95% confidence interval (CI) 1.09-7.68; P=0.033) regardless of preserved or reduced LVEF.[78]

The presence of LGE in patients with DMD has been associated with the development of heart failure symptoms and impaired LVEF (64±6% in LGE-negative patients vs. 57±7% in LGE-positive patients; P=0.014), while the extent of LGE has been correlated with the degree of decline in LVEF over time (2.2±0.31% decline per year in LGE-positive patients vs. 0.21±0.22% decline per year in LGE-negative patients; P=0.34).[79,80] LGE is therefore a potential marker of not only the presence of heart failure, but also of its progression.[79,80]

An increased ECV has been associated with arrhythmias (odds ratio (OR) 1.97; 95% CI 1.21-32.22; P=0.032) in patients with Becker muscular dystrophy, while the presence of LGE per se (considered in a binary fashion) was not.[81] While the presence of LGE is useful in the diagnosis of cardiac involvement in Becker muscular dystrophy, quantification of ECV may have more utility in risk-stratification.[81]

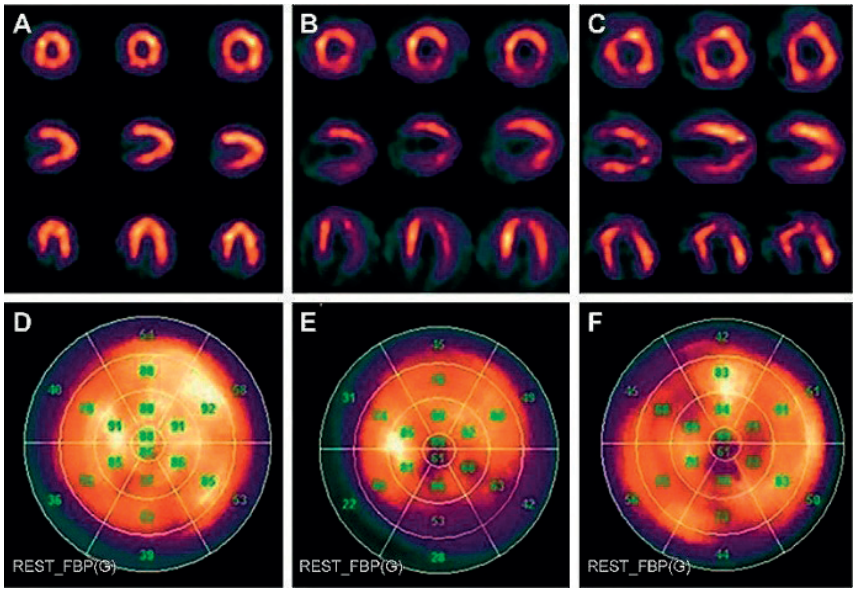

Figure 5: Myocardial perfusion defects at rest assessed with ^{99m}technetium single-photon emission computed tomography in three patients with Duchenne muscular dystrophy. Cross-sectional myocardial perfusion images are displayed in A-C panels (short-axis, horizontal long-axis and the vertical long axis from top to bottom) and the polar maps are presented in panels D-F. The patient presented in panels A and D shows normal myocardial perfusion whereas the patients in panels B/E and C/F show perfusion defects in the inferior and apical segments. REST_FBP: filtered back projection images acquired at rest, (G): gated. Reproduced with permission from Zhang et al.[8]

Mechanical function

In 88 patients with DMD or Becker muscular dystrophy and cardiac involvement, an LVEF <45% independently predicted ventricular tachycardia and hospitalization for heart failure (HR 0.94; 95% CI 0.89-0.97; P=0.001).[78] Similarly, an LVEF <45% was associated with appropriate implantable cardioverter-defibrillator therapy and sudden cardiac death (HR 4.4; 95% CI 1.7-11.0; P=0.021) in lamin A/C mutation carriers.[82]

However, in patients with preserved LVEF, strain imaging may refine the risk-stratification of these patients. Longitudinal, septal (averaged from four septal segments) strain, measured with speckle tracking echocardiography, was reduced when compared to longitudinal strain in non-septal segments of the LV in 41 lamin A/C mutation carriers (Figure 6).[27] In the same study, reduced septal strain correlated with the PR-interval on electrocardiography (R=0.41, P=0.03), while a prolonged PR-interval was associated with ventricular arrhythmias (P<0.001).[27]

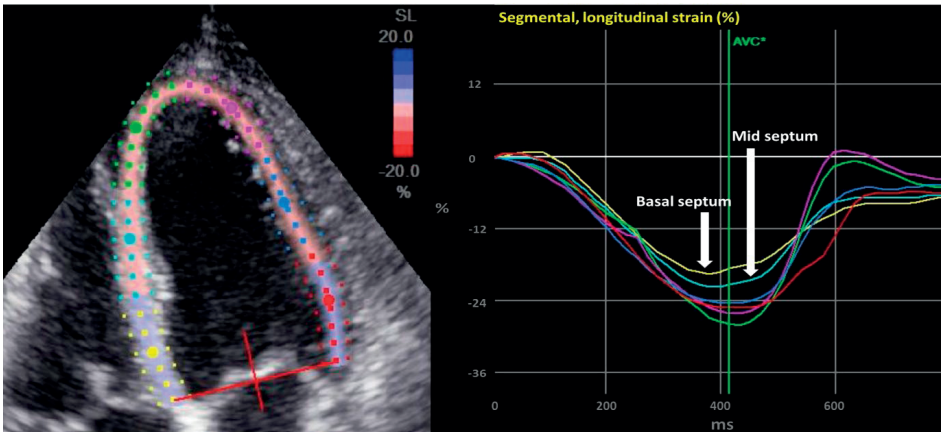

Figure 6: Impaired septal strain in a patient with lamin A/C mutation. Longitudinal strain is assessed with 2-dimensional speckle tracking echocardiography in the apical 4-chamber view. Different myocardial segments are indicated by different colours. White arrows identify impaired strain curves from the inferoseptal basal and midventricular myocardial segments. AVC: aortic valve closure.

In addition, LV mechanical dispersion measures the standard deviation of the time to peak systolic deformation of 16-17 segments of the left ventricle, and is an application of strain imaging performed with speckle tracking echocardiography.[83,84] LV mechanical dispersion is an indicator of the degree of mechanical heterogeneity, and has been associated with ventricular arrhythmias in a number of different cardiac pathologies.[83,85,86] Increased mechanical dispersion has been reported in lamin A/C mutation carriers with ventricular arrhythmias as compared with mutation carriers without ventricular arrhythmias (49±14 ms vs. 38±10 ms; P=0.02), while LVEF alone could not distinguish between individuals with and without ventricular arrhythmias (Figure 7).[87]

CLINICAL INTEGRATION OF CARDIAC IMAGING IN RISK-STRATIFICATION OF GENETIC DCM ASSOCIATED WITH NEUROMUSCULAR DISORDERS

Position statements on the diagnosis, risk-stratification and treatment of DCM (including the role of genetic testing) have been published by the American Heart Association and the European Society of Cardiology.[1,9,88] Based on the abovementioned position statements, an algorithm can be proposed which integrates cardiac imaging modalities into the risk-stratification of genetic DCM (Figure 8).

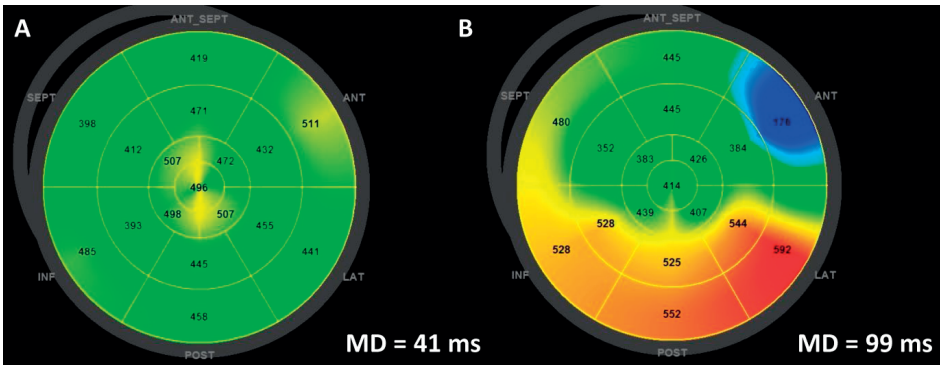

Figure 7: Segmental mechanical dispersion (MD) displayed in a parametric map of the left ventricle. In a lamin A/C mutation carrier without ventricular arrhythmias, all segments are activated simultaneously (panel A). A patient with a lamin A/C mutation and ventricular arrhythmias, in whom late activation of the inferior and posterior and segments (orange-red areas) is present, resulting in increased mechanical dispersion (MD) (panel B).

Although there are no specific position statements for genetic DCM associated with neuromuscular disorders, the principles are similar, and therefore, it can be applied to these genetic conditions. This algorithm (Figure 8) includes both early diagnosis and risk-stratification of established disease. In general, it is not recommended to screen children before the age of 10-12 years.[88] There are two approaches to screening family members of an index patient (the proband) with genetic DCM: genetic and clinical cascade screening. Genetic cascade screening involves testing family members for the specific mutation present in the proband. If the result is negative, no risk exists for development of the specific, genetic DCM, and further screening is not required.[88] If: i) genetic screening is not available, ii) the mutation is present, or iii) no disease-causing mutation can be found in the proband, clinical cascade screening is indicated. This involves history-taking, physical examination, a 12-lead ECG and transthoracic echocardiography.

If the LVEF is reduced (≤50%) or the LV end-diastolic diameter or volume is increased, the presence of disease is established.[1] Genetic testing to risk-stratify patients with established disease is of limited utility, except in lamin A/C mutations, which portend a high risk.[88] Advanced cardiac imaging can be used to further risk-stratify these individuals by means of early diagnosis: LV longitudinal strain and mechanical dispersion can be derived from routinely-acquired, 2-dimensional echocardiographic data without additional cost. When echocardiography does not provide a definitive answer regarding the presence/absence of disease, or when the echocardiographic window is suboptimal, CMR can be considered.

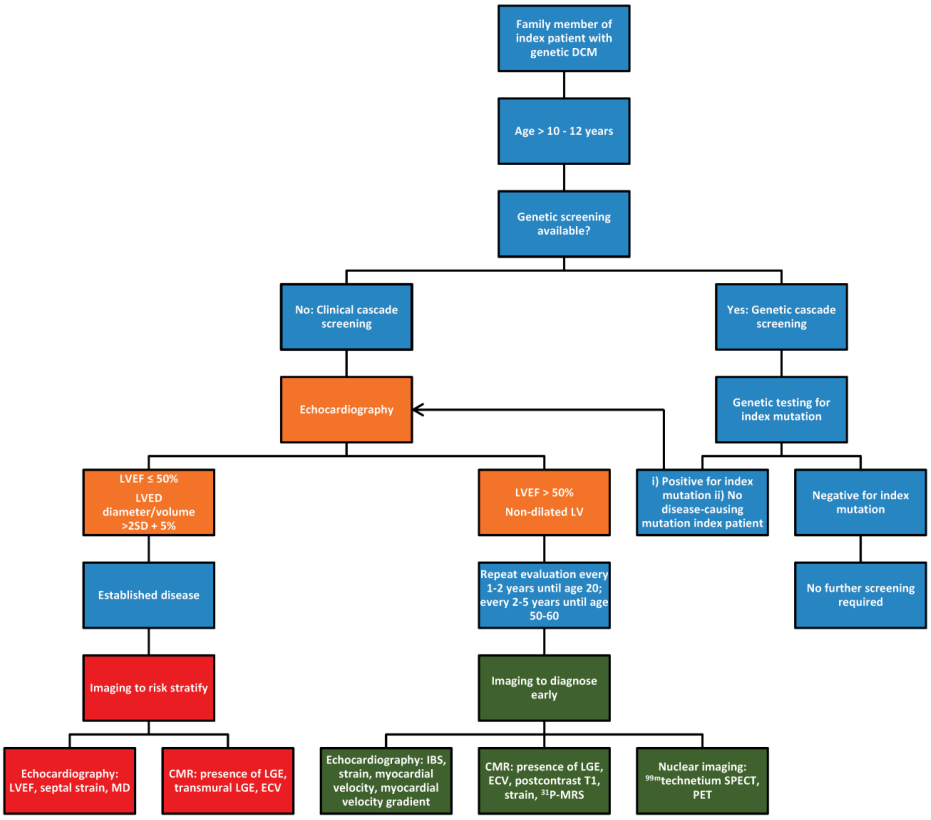

Figure 8: Proposed algorithm for integration of cardiac imaging in risk-stratification of genetic, dilated cardiomyopathy (DCM). Color coding denotes the following: blue = guideline-directed approach for risk-stratification, orange = guideline-based role for imaging, red = suggested role of imaging in risk-stratification for established disease, green = suggested role of imaging for early diagnosis.

If the LVEF is preserved (>50%) and/or the left ventricle is not dilated, clinical cascade screening has to be repeated at 1-2 yearly intervals until the age of 20 years, and every 2-5 years until the age of 50-60 years.[88] Transthoracic echocardiography is included in each screening event. For the risk-stratification of established disease, assessment of IBS, strain and myocardial velocities on clinically acquired echocardiographic data could help identify patients with increased risk of progression of the disease or ventricular arrhythmias. However, the impact of these measures on the clinical management of the patients is still being evaluated. Similar to risk-stratification for established disease, CMR can be performed when uncertainty remains. If contrast is administered for LGE, post-contrast T1 maps and ECV calculation can be performed. Strain imaging and ^{31}P-MRS are promising but still considered investigational techniques. Nuclear imaging techniques can be considered if requested for additional indications, e.g. exclusion of coronary artery disease as potential cause of cardiomyopathy.

The clinical applicability of various imaging techniques is summarized in Table 2. In general, the reproducibility of imaging parameters is good in genetic DCM (Table 3). In the absence of studies comparing different imaging modalities and parameters for risk-stratification of genetic DCM, a specific order of testing cannot be recommended currently, and the sequence of imaging modalities will depend more on the availability, cost and concomitant indications, as discussed above.

Table 2: Summary of imaging techniques and their clinical applicability.

Substrate	Imaging modality	Imaging technique	General use
Cardiac structure	**CMR**	LGE	Routine
		Native T1 mapping	Investigational
		Post-contrast T1 mapping	Investigational
		ECV	Investigational
	Echocardiography	IBS	Investigational
Mechanical function	**Echocardiography**	LVEF	Routine
		LV global longitudinal strain	Investigational
		LV global circumferential strain	Investigational
		LV systolic myocardial tissue velocity	Investigational
		LV diastolic myocardial tissue velocity	Investigational
		LV myocardial velocity gradient	Investigational
		Mechanical dispersion	Investigational
	CMR	CMR circumferential strain	Investigational
Cellular function (metabolism, perfusion)	**CMR**	^{31}P-MRS (metabolism)	Investigational
	Nuclear imaging	^{99m}technetium SPECT (perfusion)	Routine
		PET (perfusion, metabolism)	Routine

CMR: cardiac magnetic resonance imaging, ECV: extracellular volume fraction, IBS: integrated backscatter, LGE: late gadolinium enhancement, LV: left ventricular, LVEF: left ventricular ejection fraction, PET: positron emission tomography, ^{31}P-MRS: phosphorous-31 magnetic resonance spectroscopy, SPECT: single-photon emission computed tomography.

CURRENT STATE OF KNOWLEDGE AND FUTURE PERSPECTIVES

Even though the diagnostic role of cardiac imaging is well defined for genetic DCM, there are two evident research opportunities, where imaging will play a pivotal role: the prediction of outcome with imaging parameters and the benefit of early therapy in the prevention (or inhibition of progression) of genetic DCM. Lack of data regarding early therapy may be partly ascribed to the absence of effective, directed therapies. Prospective trials will be required to obtain evidence that any directed therapy or standard heart failure therapy (e.g. ACE-inhibitors)

improves patient outcomes when started early in the course of the disease. Treatment effects have generally been evaluated with only conventional functional imaging parameters (e.g. LV fractional shortening or LVEF), although LV global longitudinal strain has been employed to measure the effect of enalapril and carvedilol in patients with DMD and Becker muscular dystrophy.[15]

Despite various imaging parameters providing data on risk-stratification in established disease, prospective studies are also necessary to determine if these data will translate into improved outcomes, e.g. when used for guidance of primary prevention implantable cardioverter defibrillator (ICD) placement.

Few studies have systematically studied multimodality imaging in a single mutation or disease entity in order to compare their relative usefulness in early diagnosis or risk-stratification, or to compare a single technique between different etiologies of genetic DCM.

In summary, the following steps are required before cardiac imaging parameters can guide therapy for genetic DCM. Both conventional (LVEF) and novel (LV strain) parameters have to be evaluated for their ability to predict long-term outcome (development of symptoms, decrease in LV systolic function, ventricular arrhythmias and mortality), especially in asymptomatic mutation carriers. Furthermore, a variety of therapies (ACE-inhibitors and ICD) have to be evaluated for their abilities to influence the course of disease, either when instituted early in asymptomatic mutation carriers or in established disease that has been risk-stratified with imaging techniques. Moreover, the impact of such therapies can be measured by imaging (for example change in ECV) or mortality endpoints and, finally, multicentre studies will be required.

Employing imaging markers as therapeutic targets may prove especially useful, since obtaining long-term follow-up of uncommon cardiomyopathies in multicentre studies, will be challenging. Two lines of evidence suggest that imaging parameters could be useful as therapeutic targets. First, pharmacotherapy (beta-blockers and systemic steroids) has been shown to reverse LV remodeling in genetic DCM (DMD and Becker muscular dystrophy).[13,14] This likely reflects an inhibitory effect on myocardial fibrosis, and T1 mapping CMR techniques (including calculation of myocardial ECV) have the potential to reflect a treatment effect. In addition, early therapy has been proven to delay the onset or slow the progression of systolic dysfunction in some types of genetic DCM, e.g. systemic steroids and ACE-inhibitors in patients with DMD.[10,11] Parameters from imaging techniques could therefore be used to guide therapy.

Table 3: Reproducibility of various imaging techniques.

Substrate	Imaging modality	Imaging technique	Reproducibility for genetic DCM
Cardiac structure	**CMR**	LGE	K=0.75; P<0.001
		Native T1 mapping	-
		Post-contrast T1 mapping	ICC for inter-observer agreement=0.997; 95% CI 0.994-0.999
		ECV	• ICC for intra-observer agreement=0.957; P<0.001 • ICC for inter-observer agreement=0.963; P<0.001
	Echocardiography	IBS	-
Mechanical function	**Echocardiography**	LVEF	• ICC for intra-observer agreement=0.80; 95% CI 0.47-0.94 • ICC for inter-observer agreement=0.77; 95% CI 0.48-0.93
		LV global longitudinal strain	• ICC for intra-observer agreement=0.72 • ICC for inter-observer agreement=0.78
		LV global circumferential strain	• ICC for intra-observer agreement=0.91 • ICC for inter-observer agreement=0.88
		LV systolic myocardial tissue velocity	• Intra-observer mean percentage variation=6.7-9.2% for systolic indices • Inter-observer mean percentage variation=3.8-6.8% for systolic indices
		LV diastolic myocardial tissue velocity	• Intra-observer mean percentage variation=5.6-11.8% for diastolic indices • Inter-observer mean percentage variation=6.6-9.9% for diastolic indices
		LV myocardial velocity gradient	• Mean intra-observer difference=8.2±5.3% (interventricular septum) and 8.0±6.9% (posterior wall) • Mean inter-observer difference=9.3±44% (interventricular septum) and 8.8±3.8% (posterior wall)
		Mechanical dispersion	-
	CMR	CMR circumferential strain	-
Cellular function	**CMR**	^{31}P-MRS	-
	Nuclear imaging	^{99m}Tc-MIBI/SPECT (perfusion)	-
		PET	-

CI: confidence interval, CMR: cardiac magnetic resonance, ECV: extracellular volume fraction, IBS: integrated backscatter, ICC: intraclass correlation coefficient, LGE: late gadolinium enhancement, LV: left ventricular, LVEF: left ventricular ejection fraction, PET: positron emission tomography, ^{31}P-MRS: phosphorous-31 magnetic resonance spectroscopy, ^{99m}Tc-MIBI/SPECT: technetium 99m-methoxyisobutylisonitrile single-photon emission computed tomography.

CONCLUSIONS

Genetic DCM represents a substantial proportion of DCM. Affected individuals are at high risk of complications, and strategies to identify disease early and effectively risk-stratify these patients are needed. A variety of cardiac imaging modalities have proven their ability to identify disease early and they have shown promise in risk-stratification. Further research is required to apply imaging techniques to the evaluation of management strategies which could delay progression when instituted early in the course of disease.

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