The value of cardiac MRI versus echocardiography in the pre-operative assessment of patients with Duchenne muscular dystrophy


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Abstract

Background/purpose: Duchenne muscular dystrophy (DMD) related cardiomyopathy is associated with significant perioperative mortality. Cardiac MRI (CMR) has not previously been systematically evaluated as pre-operative assessment tool for heart function in DMD. Our aim was to establish whether CMR versus echocardiography contributes to pre-operative assessment.

Methods: Case records were retrospectively reviewed of 35 consecutive DMD boys who underwent evaluation for surgical procedures between 2010 and 2013. Results: Echocardiography revealed a median left ventricular (LV) shortening fraction (SF) of 29% (range: 7–44). 37% of boys (13/35) had abnormal SF <25%, 66% (23/35) showed hypokinesia and 26% (9/35) had LV dilatation. CMR revealed a median left ventricular ejection fraction (LVEF) of 52% (range: 27–67%). 57% of boys (20/35) had abnormal LVEF <55%, 71% (25/35) had hypokinesia, and 82% late gadolinium enhancement. Extensive versus minimal late gadolinium enhancement was associated with reduced left ventricular ejection fraction (48% vs 58%; p = 0.003) suggesting more severe cardiomyopathy. Although echocardiography shortening fraction correlated with CMR ejection fraction (rs = 0.67; p < 0.001), three-quarter of echocardiography studies had suboptimal scanning windows and in 26% measurements significantly over- or underestimated left-ventricular function compared to CMR.

Conclusion: Our findings clearly demonstrate the added value of CMR versus echocardiography in assessing DMD-cardiomyopathy. Particularly when echocardiographic scanning windows are suboptimal, CMR should be considered to allow accurate pre-operative cardiac assessment.

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1. Introduction

Duchenne muscular dystrophy (DMD) is one of the most severe muscular dystrophies, affecting one in 5000 newborn boys.\(^1,2\) It is caused by mutations in the dystrophin gene which leads to deficiency of the protein dystrophin affecting skeletal and cardiac muscle function.\(^3,4\) Without treatment, progressive degeneration of muscle tissue will eventually lead to loss of ambulation by 13 years and death in young adulthood due to respiratory, orthopaedic, and/or cardiac complications.\(^1\) Following the advances in DMD care including corticosteroids, respiratory, cardiac and orthopaedic interventions, life expectancy has increased significantly.\(^5\)–\(^8\) Longer survival is associated with higher incidences of cardiomyopathy and an increasing number of deaths in DMD are now attributed to poor cardiac function.\(^9\)–\(^11\)

Orthopaedic complications such as ankle deformities and scoliosis affect the functional abilities of boys with DMD and often require tenotomy or spinal surgery.\(^8,12\) However, major surgical procedures pose an increased risk of perioperative morbidity and mortality due to anaesthetic reactions, exacerbation of respiratory failure or worsening of cardiomyopathy.\(^13\)–\(^15\) It is now recommended that preoperative cardiac assessment is performed to minimise the risk of any cardiac complications occurring during surgery.\(^14,16\) In the past 5 years, two patients died perioperatively in our hospital, having had apparently normal echocardiographic screening assessment. This led to a comprehensive review of clinical practice and the addition of cardiac MRI to the preoperative cardiac assessment, aimed at identification of high-risk patients which are potentially missed by echocardiography.

Echocardiography is the imaging modality used most frequently to determine the presence of cardiomyopathy.\(^10,17\) However, the performance of an echocardiogram can be technically challenging in this group of patients due to scoliosis and chest deformities, resulting in suboptimal imaging and inaccurate interpretation.\(^10\)

Recently cardiac magnetic resonance (CMR) imaging has been used more frequently to assess cardiac function in DMD.\(^18\)–\(^20\) CMR is a non-invasive, objective technique allowing 3-dimensional volumetric analysis and accurate measurement of left ventricular ejection fraction (LVEF), and the degree of wall motion abnormalities (hypokinesia). CMR is also capable of characterising the myocardium. By giving a gadolinium-based, extracellular contrast and using late gadolinium enhancement (LGE) imaging techniques, focal areas of interstitial change, or myocardial fibrosis can be depicted. There is evidence of LGE in Muscular Dystrophy patients with otherwise normal ejection fraction, suggesting that myocardial fibrosis might occur prior to the onset of decreased systolic function; thus allowing earlier detection of cardiac abnormality than would be possible by echocardiography alone.\(^18\)–\(^21\) Similarly previous work has shown that conventional echocardiography is inferior in detecting early myocardial dysfunction compared to tissue Doppler imaging.\(^22\) These findings suggest that CMR may be more sensitive than conventional echocardiography in assessing cardiac function in DMD.

To our knowledge CMR has not previously been systematically evaluated as a tool for pre-operative assessment of cardiac function in DMD. Our aim was to establish whether adding CMR to echocardiography contributed to the cardiac assessment for patients with DMD undergoing surgical procedures.

2. Materials and methods

We retrospectively reviewed the case records of 35 consecutive DMD patients who underwent pre-operative assessment at the Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London from 2010 to 2013. Patients were assessed for a range of surgical procedures including spinal and lower limb surgery.

Clinical data obtained from structured medical records review included clinical, histological and genetic diagnosis of DMD, functional ability (age at loss of ambulation), medication history (corticosteroids and use of cardio-protective drugs such as ACE inhibitors, beta blockers or diuretics) and type of surgery proposed (spinal or lower limb). As part of the pre-operative assessment echocardiogram and cardiac MRI were documented.

Echocardiography was performed in the cardiology department at Great Ormond Street hospital under institutional protocol. Factors measured included cardiac shortening fraction (SF%), regional wall motion abnormalities (hypokinesia present or not), and presence of left ventricular dilation. An SF less than 25% was defined as abnormal. Scan results were reviewed by a senior paediatric cardiologist (MF) and expert in this field, who qualitatively categorised the image quality as being either good or suboptimal and confirmed the accuracy of results. MF was blinded to the CMR results.

Cardiac MRI (CMR) detailed left and right end diastolic volume (EDV in ml), end systolic volume (ESV in ml), stroke volume (SV in ml/beat), LV and RV EF% and cardiac output. An LVEF less than 55% was defined as abnormal. The ventricular volumes were indexed for body surface area and related to normal values, giving EDV (ml/m\(^2\)) with Z-score and ESV (ml/m\(^2\)) with Z-score.\(^23\) Wall motion abnormalities were categorised as follows: 1 = none seen, 2 = basal infero-lateral wall hypokinesia only and 3 = more extensive hypokinesia.

Late gadolinium enhancement (LGE) was graded in a binary manner, by distribution: 0 = no LGE or LGE in basal infero-lateral wall only vs 1 = LGE involving any more extensive area, including basal lateral and infero-lateral wall, inferior wall and septum. CMR reports were reviewed by a senior paediatric cardiologist and expert in this field to confirm accuracy and standardisation (MH). MH was blinded to the Echocardiography results.

2.1. Statistical analysis

Patients with missing data were excluded via case-wise deletion from the relevant analyses.

Correlations between echocardiography and CMR data were calculated via Spearman’s correlation coefficient \(r_s\). We only included cases where echocardiography and CMR took
place within 3 months of each other. Chi-square statistics were used to determine categorical differences between groups. Comparisons of continuous variables were performed using the Mann–Whitney U test and values expressed as median and range.

All analyses were performed using SPSS statistical software version 21.0 at a significance level of 5% (SPSS Chicago). This study was approved by the Great Ormond Street Hospital institutional board (No: 1219).

3. Results

35 DMD patients aged 12–18 years (median 15.0) underwent pre-operative assessment for a total of 35 procedures. These were 33 spinal and 2 lower limb surgeries.

The diagnosis of DMD was confirmed by genetic testing and/or muscle biopsy in all cases. All boys were non-ambulant at the time of pre-operative assessment and the age at loss of ambulation was at a median of 10.0 years (range 6–15).

29 out of 35 (83%) had been on steroid therapy at any one time. A number of boys had been on cardio-protective medication including 24/34 (71%) on ACE inhibitors, 9/34 (27%) on beta-blockers and 3/34 (9%) on diuretics.

3.1. Echocardiography data

Echocardiography revealed a median left ventricular (LV) shortening fraction (SF) of 29% (range: 7–44). 37% of boys (13/35) had abnormal SF <25%, 66% (23/35) showed hypokinesia and 26% (9/35) had LV dilatation.

3.2. CMR data

CMR revealed a median left ventricular ejection fraction (LVEF) of 52% (range: 27–67%). 57% of boys (20/35) had abnormal LVEF <55%, 71% of boys (25/35) had hypokinesia, of which 28% (10/35) was basal infero-lateral hypokinesia only and the remaining 43% (15/35) showed extensive wall hypokinesia. Gadolinium was given in 17 out of 35 cases (49%). In the remaining cases contrast was refused by the patient or IV access could not be obtained. The group receiving gadolinium contrast (median LVEF = 53.5%; range 43–67%) did not differ significantly in cardiac function from the group not receiving gadolinium contrast (median LVEF = 52%; range 27–66%; p = 0.757). Focal late gadolinium enhancement (LGE) was seen in 82% (14/17) of boys suggesting myocardial interstitial change. The LGE was distributed as follows: basal infero-lateral wall only in 21% (3/14), and more extensive LGE in 79% (11/14). Fig. 1 illustrates exemplary CMR imaging findings.

3.3. Correlation between echocardiography and CMR data

Echocardiography SF correlated significantly with CMR LVEF (rs = 0.67; p < 0.001; Fig. 2). Increasing severity of hypokinesia on CMR correlated with reduced CMR LVEF (rs = −0.64; p < 0.001) and reduced echo SF (rs = −0.47; p = 0.004).

We used the Teichholz formula to calculate echocardiography EF from the M-mode data and performed a direct comparison with the MRI EF via Bland–Altman analysis (Fig. 3).

The Bland–Altman plot confirms that the mean difference of both methods is close to zero, indicating that the two methods are not systematically producing different results and the differences between measurements lie within the limits of agreement in approximately 95% of the time. There are two outliers with marked differences both of whom had suboptimal image quality. Equally both of those with the lowest mean EF values (<32%) had suboptimal image quality; whereas those with the highest mean EF values (>66%) both had good image quality. At high mean EF values there might be a trend for echocardiography measurements being more often greater than the equivalent CMR measurements.

We were further interested to examine whether the degree of LGE was associated with left ventricular dysfunction. For this purpose we compared two groups: one group (n = 10) with no or focal-basal LGE and a second group (n = 7) with extensive LGE. Those with extensive LGE had significantly lower LVEF (median = 48%; range 43–58%) compared to the group with no or focal-basal LGE (median = 58%; range 50–67%; p = 0.003). Extensive LGE was associated with reduced LVEF (<55%) in all but one case (who had a normal LVEF of 58%); whereas most individuals with no or focal-basal LGE had normal LVEF ≥55%. No patient with no or focal-basal LGE had an LVEF <50%.

Comparing the echocardiography data between groups, the group with extensive LGE had a significantly lower SF (median = 21%; range = 15–32%) compared to the group with no or focal-basal LGE (median 32.5%; range = 25–44%; p = 0.003).

3.4. Differences between echocardiography and CMR findings

Although functional echocardiography and CMR data tended to correlate, we observed a significant number of inconsistent findings. Nine individuals (26%) had particularly discrepant results: seven (20%) had evidence of cardiac dysfunction on CMR that was not detected on echocardiography; and in two cases the echocardiogram measured worse cardiac function than CMR recorded. Table 1 illustrates these discrepant cases in more detail. Importantly, twenty-seven of the 35 echocardiography scans (77%) had suboptimal image quality due to limited acoustic windows.

To work towards logical clinical use of this data, and given the varying image quality seen on echocardiography we were interested to know how useful SF measurements are to discriminate between normal LVEF ≥55% and reduced LVEF <55% as measured by CMR. We found that no abnormal LVEF (<55%) was noted in cases where SF was above 33%.

4. Discussion

This is the first study evaluating the potential value of CMR in the pre-operative assessment for patients with DMD. Our findings clearly demonstrate the added value of CMR compared to echocardiography. We found that echocardiographic assessment of systolic function generally correlated...
with that measured via CMR; however, a number of discrepancies were noted. Three-quarters of echocardiography studies had suboptimal scanning windows and measurements more often overestimated rather than underestimated left ventricular function compared to CMR. We were able to show that widespread late gadolinium enhancement of the LV myocardium on CMR is associated with reduced LVEF, and we suggest that this may be an early indicator of the potential for poor cardiac function or poor myocardial reserve.

DMD patients that undergo major surgery are subject to significant perioperative morbidity and mortality. Cardiac complications are prominent, and heart function should be assessed prior to surgery. During pre-operative planning it is crucial to have valid parameters by which to assess an
individual’s risk, increased during the stress of prolonged anaesthesia, by haemodynamic changes and blood loss. Echocardiography has been the most widely used imaging tool to evaluate cardiac function in DMD. However, echocardiography can be technically challenging, particularly in DMD patients with significant thoracic deformities presenting for scoliosis surgery. In our series three-quarters of patients had poor scanning windows resulting in suboptimal image quality. A previous study evaluating the imaging quality of echocardiography among 31 DMD patients age 11–34 equally showed that imaging was challenging as it was never possible to directly measure EF due to the absence of normal intercostal spaces. Therefore echocardiography data may not always accurately reflect cardiac function. CMR in contrast is not affected by acoustic windows or lung artefacts and may enable a more comprehensive and accurate evaluation of the myocardium.

We observed a clinically significant number of discrepant results between the two imaging modalities. Prior to the introduction of CMR, our centre experienced two fatalities due to post-operative cardiac failure in boys that had not been anticipated at increased risk, as the pre-operative echocardiography showed a normal SF<25% and LVEF<55%.

Fig. 3 – Bland–Altman plot. Mean EF = mean ejection fraction (EF) values; Difference EF = differences in EF measurements of echocardiography and CMR studies; Filled circles = good echocardiography image quality; Unfilled circles = suboptimal echocardiography image quality.

Table 1 – Differences in echocardiography and CMR findings in selected patients.

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<th>No</th>
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SF = shortening fraction, LV = left ventricular, EF = ejection fraction, LGE = late gadolinium enhancement, abnormal SF<25% and LVEF<55% are highlighted in bold.
expected when using echocardiography, particularly when the acoustic windows and image quality is poor.

Clinically, myocardial dysfunction in DMD is often unrecognised, due to the lack of physical activity in affected patients.\textsuperscript{17} However histologically there is progressive fatty replacement of myocytes and a distinct pattern of myocardial fibrosis leading ultimately to a generalized dilated cardiomyopathy.\textsuperscript{26} Tissue Doppler echocardiography (TDE) demonstrated that cardiac tissue velocities and strain rate can identify early myocardial dysfunction in young asymptomatic boys with DMD without conventional echocardiography showing signs of dilated cardiomyopathy.\textsuperscript{22,25,27,28} TDE offers a more objective measure to quantify regional and global LV function by using myocardial velocity data and should be considered to evaluate cardiac function in this group of patients particularly if CMR is not available.\textsuperscript{27–29}

LGE has been used as an indicator of myocardial fibrosis and recent evidence suggests that increased LGE is associated with worsening LVEF.\textsuperscript{18–21} Our results confirm that individuals with extensive LGE had worse LVEF compared to those with no or basal LGE. In a recent large study of DMD patients, over a third had LGE, the youngest being 7.6 years old. The occurrence of LGE increased significantly with age and its presence was associated with poor LVEF. A regional distribution pattern emerged, with LGE affecting basal free wall segments first followed by septal involvement, the latter being associated with even lower LVEF. Ultimately, progressive heart failure and death were associated with widespread and particularly septal LGE involvement.\textsuperscript{19} The authors conclude that the time course and distribution of LGE may be a useful clinical biomarker for DMD-associated cardiac disease. Further evidence has emerged showing that particularly an impaired LVEF and a “transmural” pattern of LGE appear to predict the occurrence of adverse cardiac events in DMD patients.\textsuperscript{20}

The question remains how to clinically interpret findings of low grade LGE when this is mostly associated with normal cardiac function, or the rare case with extensive LGE but relatively preserved LVEF? LGE is based on the delayed wash-in and wash-out of gadolinium in myocardial areas with increased extracellular space due to fibrosis.\textsuperscript{30} Cardiac function might be preserved for many years in DMD, even with fibrosis, and given the decreasing levels of physical activity with age, individuals may not display clinical symptoms unless they are exposed to additional stress such as anaesthesia/surgery. In a patient with normal LVEF, the presence of extensive LGE might indicate an individual with a higher risk for deterioration under the stress of prolonged anaesthesia; compared to an individual with normal heart function. Currently no prospective studies have been performed to evaluate the outcome in these specific cases. The independent implications of LGE on post-operative outcome are still difficult to predict and prospective studies are required to assess this in the future.

5. Conclusion

Our findings clearly demonstrate the added value of CMR versus echocardiography in assessing DMD-cardiomyopathy. Particularly when echocardiographic scanning windows are suboptimal, CMR should be considered to allow accurate preoperative cardiac assessment. Further studies are required to evaluate the risk implications of CMR late gadolinium enhancement on intraoperative myocardial function.

6. Limitations

There are several limitations to this study. The study was performed at a single tertiary paediatric centre and is therefore subject to selection bias. Echocardiography scans were performed by experienced examiners, however inter-observer variability may occur. In order to reduce any systematic bias, scan results were reviewed and categorised by a senior paediatric cardiologist (MF). Not all individuals who underwent CMR could be given gadolinium contrast due to practical difficulties of its application. However this group of patients did not differ significantly in their cardiac function compared to those that received gadolinium contrast.

Conflict of interest

None.

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REFERENCES