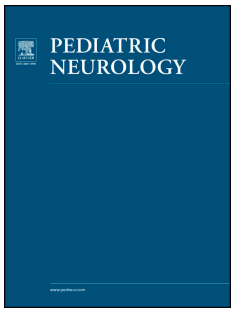

Exercise cardiac magnetic resonance imaging in boys with Duchenne Muscular Dystrophy without cardiac disease

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Complete title: Exercise cardiac magnetic resonance imaging in boys with Duchenne Muscular Dystrophy without cardiac disease

Shorter running title: Exercise cardiac MRI in DMD

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Abbreviations

DMD – Duchenne Muscular Dystrophy
DMD-CM – Duchenne Muscular Dystrophy associated cardiomyopathy
TTE – Transthoracic echocardiogram
CMRI – Cardiac magnetic resonance imaging
ACE-I – Angiotensin converting enzyme inhibitor
BB – Beta blocker
BMI – Body mass index
FFM – Fat free mass
24HABP - 24 Hour Ambulatory Blood Pressure
6MWT - 6 minute walk test
SEM – Standard error of mean
LV – Left ventricular
EF – Ejection fraction
EDV - End Diastolic Volume

ESV - End Systolic Volume

SV – Stroke volume

FS – Fractional shortening

Word count: 4,191

Abstract

Duchenne muscular dystrophy (DMD) is caused by mutations in the *DMD* gene, resulting in cardiomyopathy in all affected children by 18 years. While cardiomyopathy is now the leading cause of mortality in these children, there is ongoing debate regarding timely diagnosis, secondary prevention, and treatment of this condition. The purpose of this study was to use exercise cardiac magnetic resonance imaging (CMRI) in asymptomatic young boys with DMD, to describe their heart function and compare this with healthy controls. We studied 11 boys with DMD aged 8.6–13.9 years, and 11 healthy age- and sex-matched controls. Compared with the controls, boys with DMD had lower ejection fraction at rest (57 vs 63%; p=0.004). During submaximal exercise, they reached similar peak tachycardia, but increased their heart rate and cardiac output only half as much as controls (p=0.003 and p=0.014, respectively). End-systolic volume remained higher in boys with DMD both at rest and during exercise. When transthoracic echocardiograms were compared with CMRI, 45% of the echocardiograms had suboptimal or poor views in the DMD group. Boys with DMD had abnormalities in left ventricular systolic function that was exaggerated by exercise stress. Exercise cardiac magnetic resonance imaging is feasible in a select population of DMD children, and has the potential to unmask early signs of cardiomyopathy.

Key words

Duchenne Muscular Dystrophy; cardiac magnetic resonance imaging; exercise; stress; cardiomyopathy; heart failure

1. Introduction

Duchenne Muscular Dystrophy (DMD) is the most common paediatric neuromuscular condition, affecting 1 in 4700 live male births[1]. It is caused by a number of well documented mutations in the *DMD* gene on the X chromosome (Xp21.1), resulting in the absence of normal functioning dystrophin protein from cardiac, skeletal, and smooth muscle[2]. Lack of dystrophin triggers muscle damage, atrophy, and fibrosis[3-6]. Boys with DMD have progressive skeletal, respiratory, and cardiac muscle weakness, leading to respiratory and cardiac failure. Symptoms of skeletal weakness begin in early childhood, and respiratory and cardiac failure follow in the teenage years[7,8]. Medical therapy including steroid use and respiratory care has improved markedly since the 1960s, increasing the average life expectancy from 14 years in the 1960s to >25 years currently[9-12].

With the increasing average life span, cardiomyopathy has now replaced respiratory failure as the leading cause of death in this population[13]. While DMD-associated cardiomyopathy (DMD-CM) is historically universal in these patients by 18 years[14], the clinical diagnosis is often delayed. This delay is due to limited exercise stress in poorly mobile patients, vague symptomatology, and a subtle, gradual decline in function over time. In addition, there is a discord between the skeletal and cardiac muscle decline in function, as they do not always decline at the same rate[6]. These factors are important, as a delay in the diagnosis of DMD-CM leads to poorer outcomes, including progression of cardiac dysfunction due to lack of intervention, and increased rates of complications during surgery, thromboembolic events, and cardiac mortality[15]. With intervention at the earliest signs of DMD-CM, patients have improved symptomatology, systolic function[16-21], and left ventricular size, as well as delayed onset of clinical DMD-CM[22-25] and overall reductions in cardiovascular mortality[26-28].

Regular cardiac review including non-invasive imaging is currently recommended annually, in order to detect the earliest signs of cardiomyopathy[29]. Transthoracic echocardiogram (TTE) is utilised until children are able to cooperate with the gold-standard cardiac magnetic resonance imaging (CMRI) at age 6–7 years[29]. CMRI is superior to TTE in investigating cardiac structure and function[30], is not restricted by the technical challenges that limit echocardiography windows (e.g. scoliosis, obesity, and seat position), and may therefore allow earlier detection of DMD-CM[31].

There is also interest in additional specialist imaging techniques using CMRI that can identify those children at highest risk for cardiomyopathy. The two main areas are tissue tagging/mapping (further details within section 4.2) and stress imaging.

1.1 Stress imaging of the heart

Stress imaging of the heart is an established technique in cardiac imaging, which uses physiological stressors to increase heart rate and reveal abnormalities that are not apparent at rest. This has been 7demonstrated successfully in paediatric patients using echocardiography[32], but there are limited studies using CMRI. In children, stress echocardiography requires either a pharmacological agent (e.g. dobutamine) or exercise (e.g. a stationary bicycle) to increase myocardial oxygen demand, increase pre-load and blood pressure, which in turn, in susceptible hearts, may unmask ventricular dysfunction[32]. Stress echocardiography can detect early decline in cardiac function prior to changes in ejection fraction, and has been used in children exposed to cardiotoxic medications[33-39] and in congenital heart disease[40-44]. Stress-CMRI (using dobutamine or a specialised CMRI cycle ergometer) has been studied in adults with coronary artery disease, acute coronary syndrome, hypertensive heart disease, dilated and hypertrophic cardiomyopathy[45,46], and is a promising emerging technique in younger patients[47]. Stress

imaging has not been used widely in the DMD population, due to the inherent limitations of echocardiography in this group, and tolerance of pharmacological stressor agents (e.g. dobutamine) in children[32].

Given the challenges of detecting DMD-CM and the significant benefit of early diagnosis, we proposed to investigate the impact of exercise (a physiological stressor) on asymptomatic boys with DMD. We aimed to document the physiological impact of exercise on the cardiac function of DMD patients at high risk of cardiomyopathy, but who were currently asymptomatic. We hypothesised that exercise CMRI in DMD can reveal early signs of DMD-CM, even when patients have both normal screening TTE and CMRI imaging at rest.

2. Materials and Methods

2.1 Sample size

Based on a primary outcome of a change in stroke volume and using a standard deviation of 2.2 ml[47], with power of 0.8 and an alpha of 0.05, 10 subjects were required in each group (DMD and controls) to detect a difference of 2.9 ml between healthy children and participants with DMD. Differences of this magnitude have previously been reported by our group between adolescents with type 1 diabetes and healthy controls using CMRI[48].

2.2. Study population

The New Zealand Neuromuscular Disease Registry database was used to recruit boys with DMD, aged 8 to 18 years, from the upper North Island of New Zealand. Inclusion criteria for DMD participants were: a genetically confirmed diagnosis; symptoms consistent with DMD; be otherwise healthy with no other chronic illnesses; and have a level of fitness would allow participation in the assessments and CMRI scanning. DMD patients did not have to be independently ambulant, but required some muscle strength to move their legs against gravity. Exclusion criteria applicable to all participants were: known cardiovascular disease and pre-existing cardiac dysfunction; a recent fracture or injury (within 8 weeks of enrolment) that prohibited exercise; findings on physical examination that would preclude physical exertion; prescription of an angiotensin-converting enzyme inhibitor (ACE-I) or beta blocker (BB) medication; or a known contraindication to CMRI scanning (e.g. pacemaker and metal fragments in the eye or metal ware not compatible with CMRI).

A total of 72 patients with DMD aged 3–20 years were identified from the database. Of the 29 patients aged 8–18 years in the upper North Island, 18 failed to meet the inclusion criteria (Figure 1). All 11 patients with DMD who met the inclusion criteria and whose families were approached agreed to participate (Figure 1). In addition, healthy age- and sex-matched controls without DMD were recruited from schools within the Auckland region. 4 prospective controls (participants recruited at the same time as the boys with DMD) and 7 historic controls [pre-existing participant data used from our previous study[49]] were recruited for the study. Among the subjects with DMD, all were taking steroid medications and vitamin D supplements; 8 salbutamol suspension; and 1 was taking ataluren as part of a clinical trial.

This study was approved by the Southern Health and Disability Ethics Committee (16/STH/66). All participants, and their parent/legal guardian, provided written informed assent/consent as applicable.

2.3. Physical and Physiological Parameters

All clinical assessments were carried out at the Maurice & Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Weight and height were measured by the same researcher during their first assessment, and body mass index (BMI) was calculated. Three DMD participants were unable to stand, and their supine height was measured instead. Percentage of lean mass, fat-free mass (FFM), body fat, fat mass, as well as gynoid and android percentage of fat, were obtained using whole-body dual-energy X-ray absorptiometry (DXA) scans (Lunar Prodigy 2000; General Electric, Madison, WI). 24-hour ambulatory blood pressure monitoring (24HABP) was performed at home during sedentary activity (OnTrak Ambulatory Blood Pressure Monitor, 2016; Spacelabs Medical Inc., Redmond, WA, USA), with timing of sleep onset/offset recorded by the family.

Non-fasting bloods were taken at baseline for creatine kinase in the DMD group only. For participants who could walk, physical fitness was assessed by the 6-minute walk test (6MWT)[50]. Results of the most recent transthoracic echocardiogram were obtained, and if an assessment had not been completed within the last 6 months, a repeat assessment was arranged.

2.4. Cardiac MRI

2.4.1 Exercise description

Cardiac images were obtained using a 1.5 Tesla MRI scanner (MAGNETOM Avanto; Siemens, Erlangen, Germany) at the Centre for Advanced MRI of the University of Auckland. MRI scans were performed at rest and during low-intensity exercise. This protocol has been adapted from our previous research in submaximal exercise in the MRI[51].

Participants entered the MRI head first, and researchers made sure the participant had enough leg room outside of the magnet to allow leg extension movements freely. The knees of the participants were supported underneath with a foam roller, while their head and shoulders were supported by external foam pads and Velcro straps. This allowed the acquisition of cardiac images during exercise by eliminating movement of the upper body.

Once resting cardiac images were obtained, low-intensity exercise was then performed in the supine position. Participants were instructed to start kicking their legs, i.e. perform contralateral leg extensions; this amounted to a total exercise bout of approximately 15 minutes, with several short rest breaks while the images were taken. Some participants were assisted to maintain the kicking rhythm by a research assistant or guardian. The target heart rate for the exercise was an increase of 30% from baseline. We used a fixed target heart rate for the participants to achieve, in order to reduce left ventricular filling time bias for the EDV and ESV data interpretation[51]. Once this target heart rate was achieved, participants were instructed to stop kicking, and to hold their breath in mid-expiration for 5–7 seconds while images (as described below) were obtained, to avoid respiratory motion artefacts[52,53]. Participants resumed kicking as soon as the image was obtained.

Blood pressure was measured with a digital sphygmomanometer at the start (at rest) and immediately after the leg kicking MRI measurements (exercise). The entire stress-CMRI study (including preparation and set-up) took less than an hour for each participant, and was approximately 20 minutes longer than a standard CMRI.

2.4.2 Image description

Ventricular volumes were calculated from steady-state free-precession cine acquisitions, using three long-axis acquisitions at 0˚, 60˚, and 120˚, and six parallel short-axis acquisitions as previously described[47,48,51,54]. Data were analysed using three-dimensional volumetric modelling software (Cardiac Image Modeller; Auckland MRI Research Group, Auckland, New Zealand), with the analyser blinded to the condition of the participant. Resting images were obtained with 100% phase resolution (256 x 256), so that breath-holds at rest varied from 10-15 seconds in duration. To improve tolerance during exercise exertion, we lowered the resolution to a 66% phase, which shortened post-exercise breath-hold

time[48]. Cardiac indices (left ventricular mass, cardiac output, stroke volume, end-systolic volume, and end-diastolic volume) were subsequently indexed for fat free mass[47,48,55].

2.5. Statistical Analysis

Data were analysed using one-way ANOVA, chi-square tests, Fisher's exact tests, or one-sample t-tests, as appropriate. Blood pressure data were analysed using general linear regression models adjusting for participant's height. A Bland-Altman plot was created to compare mean ejection fraction measured with transthoracic echocardiogram or cardiac magnetic resonance imaging. The presence of fixed bias was determined by the Bland-Altman method using a 1-sample t-test, with limits of agreement derived as (mean ± 1.96 * SD), where SD was the standard deviation of the difference[56].

Statistical analyses were carried out in SPSS v25 (IBM Corp, Armonk, NY, USA). All tests were two-tailed, with statistical significance maintained at $p<0.05$. There were no adjustments for multiple comparisons. Outcome data are reported as means ± standard errors of mean (SEM).

3. Results

3.1 Baseline Data

DMD participants were aged 11.3 years (SD=1.8; range 8.6–13.9 years), with the control group closely matched in age (Table 1). All children were Tanner 1 pubertal stage. The mean duration of steroid use prior to the study was 5.6 years (SD=1.9). Eight (72%) DMD participants were able to stand, and six (54%) were able to walk more than 50 meters. Genetic mutations were predominantly out of frame deletions (n=6); with the remainder premature stop codon (n=2), duplication (n=2), and an essential splice site variant (n=1). Creatine kinase levels had a mean of 7,980 U/L (range 2,924–15,248 U/L) in the DMD group.

Although DMD participants were considerably shorter than controls (-15 cm and -2.1 SDS; both $p<0.001$), they were 14 kg heavier on average ($p=0.015$), so that their BMI was 12.2 kg/m^2 or 2.88 SDS greater (both $p<0.001$; Table 1). This was due to their markedly increased total body fat that was 2.6 times greater and 28 percentage points higher than that of controls ($p<0.001$; Table 1). DMD participants also displayed increased abdominal adiposity, with an android-to-gynoid-fat ratio 41% greater ($p<0.001$; Table 1). However, bone mineral density was 0.11 g/cm^2 lower (-12%; $p<0.001$) in the DMD group (Table 1).

There were 7 DMD participants who completed the 6-minute walk test, but data were summarised for the six participants who walked at least 50 meters. The mean distance covered was 325 ± 67 m. Their heart rate during the test increased by 48 ± 6 %.

3.2. 24-hour ambulatory blood pressure monitoring (24HABP)

This assessment was completed by 10 DMD participants (one participant had incomplete results and was excluded from analysis) and 9 controls (two refused) (Table 2). Compared to controls, DMD participants had markedly higher heart rates in both daytime (+30 bpm; $p<0.001$) and night-time (+28 bpm; $p<0.001$) (Table 2). Similarly, DMD participants had higher systolic blood pressure both during the daytime (+14 mmHg; $p<0.029$) and night-time (+18 mmHg; $p<0.020$) (Table 2). There were no differences in diastolic blood pressure or nocturnal blood pressure dipping (Table 2).

3.3. MRI Cardiac Function

3.3.1 At Rest

Consistent with the 24-hour ambulatory blood pressure results, resting heart rate was 20 bpm higher in the DMD group ($p<0.001$; Table 3). Resting systolic blood pressure was also higher in the DMD group (+15 mmHg; $p=0.028$) (Table 3). Left ventricular mass was similar in the two groups, but when adjusted for total body fat-free mass it was 28% greater in the DMD group participants ($p<0.001$; Table 3). Resting ejection fraction was 6 percentage points lower in the DMD group ($p=0.004$; Table 3). Cardiac output (L/min) was similar in both groups ($p=0.73$), but when corrected for fat-free mass it was 22% higher in the DMD group ($p=0.004$; Table 3). Absolute values for stroke volume were -12 ml lower in the DMD group ($p=0.030$; Table 3). Absolute values for EDV and ESV were similar between groups at rest. There were no differences in stroke volume or end-diastolic volume when adjusted for fat-free mass (Table 3). However, the adjusted end-systolic volume was 25% greater at rest in DMD subjects ($p=0.005$; Table 3).

3.3.2. Submaximal Exercise

When challenged by exercise, both groups reached a similar target heart rate, but the magnitude of the increase in heart rate in the DMD group was less than half that of controls (even though the expressed

level of effort was similar between the same groups) (p=0.003; Table 3). There were no differences between the groups in blood pressure during exercise or in the change from the resting state (Table 3).

While absolute cardiac output (L/min) during exercise was similar in the two groups, the percentage change from rest in cardiac output in DMD participants was nearly half of that displayed by controls (p=0.014; Table 3). When corrected for fat-free mass, there were no statistically significant differences between groups in ejection fraction, stroke volume, or end-diastolic volume during exercise, or in the respective changes from a resting state (Table 3).

End-systolic volume, a marker of ventricular contractility, remained higher in the DMD group during exercise (+41%; p<0.005; Table 3). There was also an 18% reduction in end-systolic volume during exercise compared to the resting state in controls versus 6% in the DMD group (p=0.023; Table 3), further indicating an inability to increase stroke volume in DMD subjects.

3.4. MRI vs Echocardiogram

Transthoracic echocardiogram (TTE) was the previous standard of care for reviewing heart structure and function in patients with DMD[15,57]. The comparisons between global cardiac function using echocardiogram and cardiac MRI imaging techniques for each individual participant are shown in Table 4 and Figure 2. In our participants, real-world TTE imaging had suboptimal or poor-quality views in 45% of the boys with DMD scanned (Table 4). Overall, when both groups were compared, there was no evidence of bias between the two techniques (p=0.60), although there were participants with incongruent results (Table 4). Bland-Altman plot had a mean bias close to 0, with the overall mean difference showing minimal discrepancy between the two methods (-1.6%; Table 4). However, the limits of agreement were relatively wide (-14.9%, 11.7%), indicating wide variability between the two techniques.

4. Discussion

This is the first study to describe a practical technique and document the physiological changes that occur with stress-CMRI in boys with DMD. This study has confirmed that differences exist in ventricular function in children with DMD even when they are asymptomatic. These differences are magnified with even modest physical activity (such as leg raising). Exercise results in both inotropic and chronotropic challenges to the cardiovascular system. These changes may not be detectable at rest

due to the dynamic nature of exercise[58]. Furthermore, exercise testing in adults has predictive value for symptoms and long-term survival[59-62].

The haemodynamic response to exercise in children and adolescents is less well described. Studies that examined boys with DMD are limited, and there are considerable differences in their methodologies that make comparisons difficult[63]. Interpretation of testing is dependent on body surface area, lean mass, age and pubertal stage. However, the expanding literature in this field could provide valuable insights into cardiac function, which cannot be measured using traditional imaging techniques (e.g. trans-thoracic echocardiography or cardiac magnetic resonance imaging) performed at rest.

DMD subjects in our study demonstrated reduced systolic function during exercise stress. Their ability to increase cardiac output from rest to exercise was lower compared with controls. End-systolic volume remained higher in the DMD group, indicating less effective augmentation of left ventricular systolic function This corroborates current literature in children with myocardial dysfunction, where the ability to augment systolic function during exercise becomes impaired. Cardiac dysfunction becomes apparent by a smaller change in end-systolic volume, leading to a decline in stroke volume and cardiac output response[47,48,58,64]. In adolescents with obesity, similar changes in cardiac function during exercise have been reported. They have less heart rate reserve (i.e., reduced ability to generate a maximal tachycardia), and lower cardiac output mediated by lower ESV. However, these changes are generally milder, less severe, and often within the normal range in adolescents with obesity in comparison to patients with other known risk factors for cardiac disease[47,55,65]. This study illustrates the importance of body composition data when interpreting cardiac indices. Often body composition data are not immediately available clinically, but when cardiac imaging results are indexed to FFM, new findings can become apparent as shown by our results.

Our findings also showed that our DMD participants had a higher resting heart rate. There are several possible reasons for this. For example, it may be an adaptive mechanism to maintain cardiac output at rest. One of the earliest and well recognised signs of cardiac dysfunction in DMD is resting sinus tachycardia, which is often present in a large proportion of young DMD patients[66-70]. DMD participants reached the same target peak heart rate as the control groups with exercise. However, the increase in their heart rate with exercise was lower than that of controls. This may be due to a higher heart rate at baseline (possibly an adaptive mechanism to reduced cardiac contractility), or they might have already reached the upper limit of their tachycardic response. We were unable to determine the exact workload generated during exercise, as the DMD participants were too short to access an MRI cycle ergometer[54], which was designed for this purpose. Nonetheless, from clinical observation, there was similar moderate intensity workload in both groups. Beta-2 agonist drugs (e.g. salbutamol and albuterol) are

anabolic, and result in a net increase in muscle size, thought to be due to increased activation of cyclic adenosine monophosphate, which increases muscle protein synthesis[71] and decreases muscle protein degradation[72]. The increase in muscle size is thought to be associated with an increase in muscle strength[73]. Small studies in facioscapulohumeral muscular dystrophy[74,75] and Duchenne muscular dystrophy[76] have shown improved muscle strength after treatment with beta-2 agonists. While beta-2 agonists are not universal therapy in DMD, we offer them to our patients to help maximise muscle function. Side effects of beta-2 agonists include tachycardia, which may be a contributing factor to the resting tachycardia seen in our patient group.

In DMD-CM, left ventricular mass has been shown to increase over time, and with worsening disease[31,77,78]. While the cause of the increasing ventricular mass is not entirely clear, our data are in agreement, indicating DMD subjects had higher left ventricular mass, consistent with early cardiomyopathy.

Transthoracic echocardiogram (TTE) was the previous standard of care for reviewing heart structure and function in patients with DMD[15,57]. In our participants, real-world TTE imaging had suboptimal or poor-quality views in 45% of the boys with DMD scanned. CMRI is the gold standard for investigating cardiac structure and function, and it is becoming more accessible with time, factors which have meant it has superseded TTE in updated standardised care guidelines[29]. Advantages of CMRI are that it is more reliable and reproducible[79], clear images are not restricted by body habitus[30] (important when many of our subjects were markedly overweight), and it has increased sensitivity to detect early changes of cardiomyopathy[31,80]. Disadvantages of CMRI are that it is a lengthier study, can be claustrophobic and more uncomfortable for participants, it is around four times costlier than a TTE to perform, and requires a certain level of coordination and maturity from the participant to perform the breath holds. With the use of a brief educational game, we were able to coach all children suitable to participate in the CMRI without distress. As it is a relatively new technique, longitudinal studies that inform on prognosis are needed.

As discussed above, a stress test may reveal abnormalities in cardiac function that are not apparent at rest[32]. Our study showed that even though both groups had similar cardiac output at rest, the DMD group were not able to increase cardiac output as much as the controls with exercise. This likely represents early systolic dysfunction. Stress tests in children are usually performed with exercise or with an inotropic or chronotropic agent, such as dobutamine. Dobutamine has many side effects (e.g. palpitations, nausea, headache, chills, urinary urgency, anxiety, angina, hypo- and hyper-tension, and arrhythmias), so that sedation is often required for tolerance in children[32]. Submaximal exercise is therefore more appealing for children. While stress testing can be performed using TTE (e.g. tissue

doppler imaging and speckle tracking echocardiography) or CMRI, TTE remains limited by the poor sonographic windows common in DMD.

A stress test in DMD could add valuable information at the time of the initial CMRI scan, potentially adding further information and identifying vulnerable subjects. It could also be useful in other patient groups (e.g. Becker muscular dystrophy or female DMD carriers) at risk of cardiomyopathy[79,81]. These groups have greater muscle strength, which allows them to perform more strenuous exercise, which in turn increases the risk of developing cardiomyopathy[79]. They would be ideal subjects to perform an exercise stress test, and indeed female carriers displayed marked abnormalities during exercise testing[82]. Further research with a larger population group and head-to-head comparisons of existing CMRI techniques (such as T1 mapping) would be helpful in examining the future use of exercise-stress CMRI.

4.1. What are the benefits of this study?

This small pilot was the first study to investigate the effects of exercise stress on young asymptomatic boys with DMD. We have shown that our participants have abnormal cardiac imaging at rest that was exaggerated by exercise stress. We have described a technique that is practical and feasible for other centres to use.

4.2. What are the limitations of this study?

As this was a pilot study, we enrolled only a small number of participants. Nonetheless, the differences in their cardiac imaging when compared with controls showed marked differences. The population group that entered the study was highly selected as we were unable to include boys with poor mobility or cognitive impairment; this limits generalisability of our findings and our ability to extrapolate on the wider use of this technique across all DMD patients. Due to the nature of DMD and treatment with high-dose steroids, this population is difficult to match with healthy controls (particularly with physical parameters such as obesity and short stature). However, we know that while children with obesity can have abnormal cardiac indices when compared with controls, this is usually within the normal range, and unlikely to explain the marked differences in our participant groups. Also, data were adjusted for fat-free mass to control for this, but future larger studies may be able to better differentiate the impact that total fat mass and skeletal mass have on exercise tolerance. Lastly, this study was cross-sectional, and longitudinal studies involving repeated imaging would be helpful to determine those factors that may influence prognosis.

5. Conclusion

This pilot study was the first clinical investigation using exercise CMRI in boys with DMD. We have shown that exercise CMRI is a feasible technique in a select population of DMD children. It can reveal abnormalities in ventricular systolic function, even in young asymptomatic individuals. To monitor cardiac health over time, CMRI is an essential tool due to its highly accurate images that are not distorted by the other factors that often impair echocardiograms. Nonetheless, further studies are needed to assess the value of stress CMRI in the prevention and prognosis of cardiomyopathy in patients with DMD.

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Exercise cardiac magnetic resonance imaging in boys with Duchenne Muscular Dystrophy without cardiac disease

Table 1: Baseline characteristics of children and adolescents with Duchenne Muscular Dystrophy (DMD) and control participants.

		DMD	Control	*P*-value
n		11	11	-
Demography	Age (years)	11.4 ± 0.5	11.2 ± 0.4	0.86
	Age range (years)	8.6 – 13.9	8.5 – 13.0	-
	Ethnicity (New Zealand European)	7 (64%)	11 (100%)	0.09
	Time on steroids (years)	5.6 ± 1.9	N/A	
	Able to walk >50m	6 (54%)	11 (100%)	**0.035**
	Able to stand	8 (72%)	11 (100%)	0.21
Anthropometry	Height (cm)	133.1 ± 1.4	147.8 ± 3.0	**<0.001**
	Height SDS	-1.77 ± 0.27	0.31 ± 0.29	**<0.001**
	Weight (kg)	50.6 ± 4.8	36.8 ± 1.9	**0.015**
	Weight SDS	1.45 ± 0.32	0.02 ± 0.24	**0.002**
	BMI (kg/m^2)	28.9 ± 2.3	16.7 ± 0.3	**<0.001**
	BMI SDS	2.63 ± 0.34	-0.25 ± 0.21	**<0.001**
Body composition	Total body fat (%)	45.8 ± 4.3	17.4 ± 0.7	**<0.001**
	Android fat to gynoid fat ratio	0.86 ± 0.04	0.61 ± 0.03	**<0.001**
	Lean mass (kg)	24.9 ± 3.6	29.3 ± 5.9	**0.049**
	Fat-free mass (% total weight)	55.1 ± 4.2	83.3 ± 1.7	**<0.001**
	Bone mineral density (g/cm^2)	0.84 ± 0.01	0.95 ± 0.01	**<0.001**

P-values for statistically significant differences between groups (at $p<0.05$) are shown in bold.
Data are means ± SEM, n (%) or the range, as appropriate.
BMI, body mass index; N/A, not applicable; SDS, standard deviation score.

Exercise cardiac magnetic resonance imaging in boys with Duchenne Muscular Dystrophy without cardiac disease

Table 2. Parameters from 24-hour ambulatory blood pressure monitoring among children and adolescents with Duchenne Muscular Dystrophy (DMD) and control participants.

		DMD	Control	*P*-value
n		10	9	
Heart rate	Daytime (bpm)	109 ± 3.3	79 ± 2.8	**<0.001**
	Night-time (bpm)	97 ± 3.7	69 ± 2.6	**<0.001**
	Mean (bmp)	104 ± 3.2	76 ± 2.4	**<0.001**
Daytime blood pressure	Systolic (mmHg)	118.6 ± 3.4	104.9 ± 3.6	**0.029**
	Diastolic (mmHg)	74.9 ± 2.9	69.8 ± 3.1	0.31
	Mean arterial pressure (mmHg)	89.4 ± 2.6	80.7 ± 2.8	0.07
Night-time blood pressure	Systolic (mmHg)	111.4 ± 4.2	93.4 ± 4.8	**0.020**
	Diastolic (mmHg)	64.1 ± 3.0	59.7 ± 3.2	0.40
	Mean arterial pressure (mmHg)	80.9 ± 2.8	73.3 ± 3.0	0.13
	Systolic dipping (%)	6.6 ± 2.0	9.6 ± 1.4	0.26
	Diastolic dipping (%)	14.4 ± 2.3	14.2 ± 2.1	0.96

P-values for statistically significant differences between groups (at $p<0.05$) are shown in bold.
Heart rate and dipping data are mean ± SEM; other blood pressure data are model-adjusted means ± SEM, adjusted for participant's height.
bpm, beats per minute

Exercise cardiac magnetic resonance imaging in boys with Duchenne Muscular Dystrophy without cardiac disease

Table 3: Cardiovascular parameters at rest and during submaximal exercise from cardiac magnetic resonance imaging among male children and adolescents with Duchenne Muscular Dystrophy (DMD; n=11) and control participants (n=11).

	At rest			Submaximal exercise			Δ (%)		
	DMD	**Control**	**P-value**	**DMD**	**Control**	**P-value**	**DMD**	**Control**	**P-value**
Heart rate (bpm)	96 ± 3	76 ± 3	**<0.001**	119 ± 2.7	112 ± 1.7	0.06	24.3 ± 2.8	51.0 ± 7.6	**0.003**
Systolic blood pressure (mmHg)	114.6 ± 3.8	99.8 ± 3.8	**0.028**	114.5 ± 4.9	105.9 ± 4.9	0.29	-1.5 ± 3.7	8.3 ± 3.7	0.07
Diastolic blood pressure (mmHg)	66.9 ± 4.7	59.5 ± 4.7	0.35	57.5 ± 5.1	66.8 ± 3.6	0.30	-6.3 ± 5.7	7.5 ± 8.2	0.18
Left ventricular mass (g)	81 ± 4	74 ± 4	0.31	-	-	-	-	-	-
Left ventricular mass (g/kgffm)*	3.10 ± 0.10	2.43 ± 0.08	**<0.001**	-	-	-	-	-	-
Ejection fraction (%)	57.2 ± 1.3	63.2 ± 1.3	**0.004**	60.0 ± 2.0	68.7 ± 1.3	**0.002**	4.8 ± 1.7	8.9 ± 2.0	0.13
Cardiac output (l/min)	5,089 ± 247	4,949 ± 311	0.73	6,578 ± 273	7,783 ± 611	0.09			
Cardiac output (ml/min/kgffm)*	197 ± 8	162 ± 8	**0.004**	256 ± 13	251 ± 8	0.75	30.9 ± 5.4	57.8 ± 8.4	**0.014**
Stroke volume (ml)	53.5 ± 3.0	66.1 ± 4.5	**0.030**	55.6 ± 2.4	69.1 ± 5.0	**0.024**	-	-	-
Stroke volume (ml/kgffm)*	2.06 ± 0.29	2.15 ± 0.06	0.44	2.16 ± 0.10	2.24 ± 0.06	0.50	5.0 ± 2.9	4.7 ± 2.9	0.94
End-systolic volume (ml)	40.2 ± 2.6	38.5 ± 2.8	0.67	37.8 ± 3.2	31.4 ± 2.3	0.12	-	-	-
End-systolic volume (ml/kgffm)*	1.55 ± 0.08	1.25 ± 0.05	**0.005**	1.52 ± 0.11	1.08 ± 0.07	**0.003**	-6.9 ± 2.7	-17.8 ± 3.6	**0.023**
End-diastolic volume (ml)	94 ± 5	105 ± 7	0.20	93 ± 4	102 ± 6	0.25	-	-	-
End-diastolic volume (ml/kgffm)*	3.62 ± 0.14	3.40 ± 0.07	0.20	3.78 ± 0.16	3.52 ± 0.13	0.22	0.2 ± 1.9	-1.3 ± 3.6	0.72

Systolic and diastolic blood pressure data at rest and during submaximal exercise are model-adjusted means ± SEM, adjusted for the participant's height; all other data are means ± SEM.

* These parameters were indexed for fat-free mass in kg (kgffm).

Δ represents the change observed during submaximal exercise in comparison to the resting stage.

P-values for statistically significant differences (at $p<0.05$) between groups are shown in bold.

Exercise cardiac magnetic resonance imaging in boys with Duchenne Muscular Dystrophy without cardiac disease

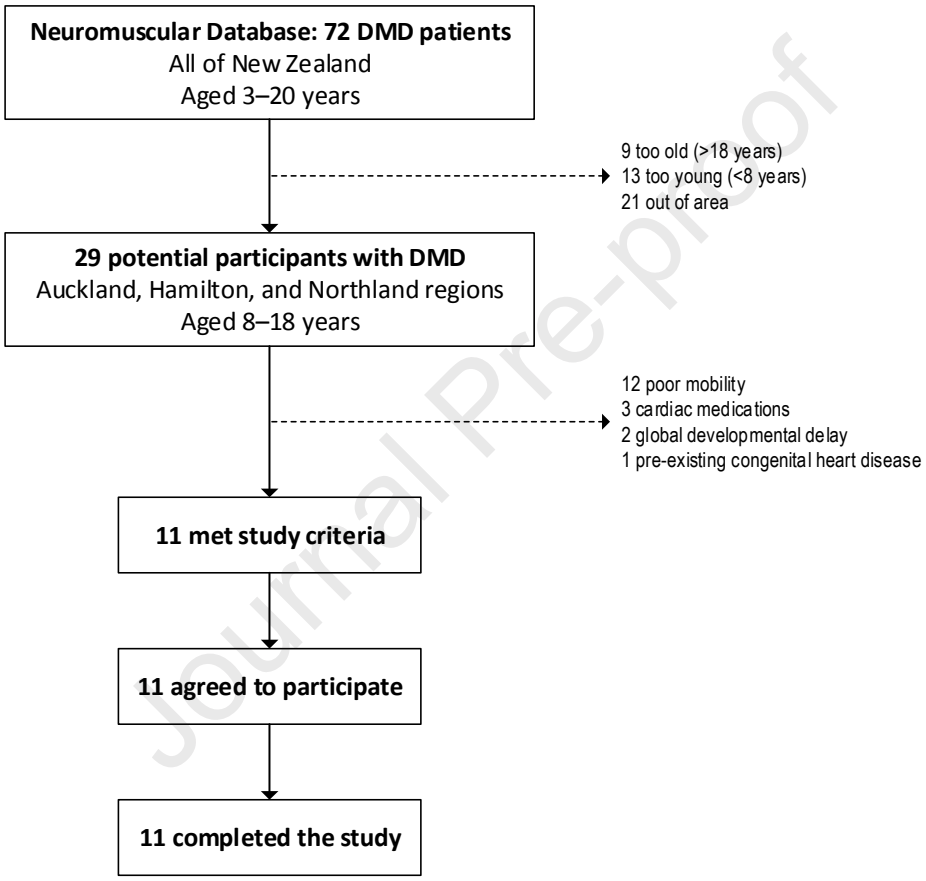
Table 4: Comparison of transthoracic echocardiogram and cardiac magnetic resonance imaging results for global function in study participants with Duchenne Muscular Dystrophy.

Participant	Age (years)	Image quality	TTE FS (%)	TTE LVEF (%)	CMRI LVEF (%)	Difference (TTE vs CMRI) (%)
1	12.3	Suboptimal	33.5	63.0	56.6	-6.4
2	10.0	Poor	22.6	62.5	53.3	-9.2
3	8.6	Good	42.0	68.0	55.6	-12.5
4	13.3	Adequate	32.0	60.0	62.9	2.9
5	13.4	Good	38.8	63.0	62.7	-0.3
6	10.0	Good	25.5	50.0	54.1	4.1
7	9.1	Good	49.0	57.0	59.5	2.4
8	11.3	Poor	25.3	50.0	49.3	-0.7
9	11.3	Poor	29.8	61.0	56.3	-4.7
10	11.7	Adequate	41.0	51.0	62.5	11.5
11	13.9	Suboptimal	33.0	61.0	56.4	-4.6
Mean ± SD			34.3 ± 8.1	58.8 ± 6.1	57.2 ± 4.3	
MD (LoA)†						-1.6 (-14.9, 11.7)*

CMRI, cardiac magnetic resonance imaging; FS, fractional shortening; LVEF, left ventricular ejection fraction; MD (LoA), mean difference and respective 95% limits of agreement; SD, standard deviation; TTE, transthoracic echocardiogram.
† Derived from the Bland-Altman method.
* p=0.60.

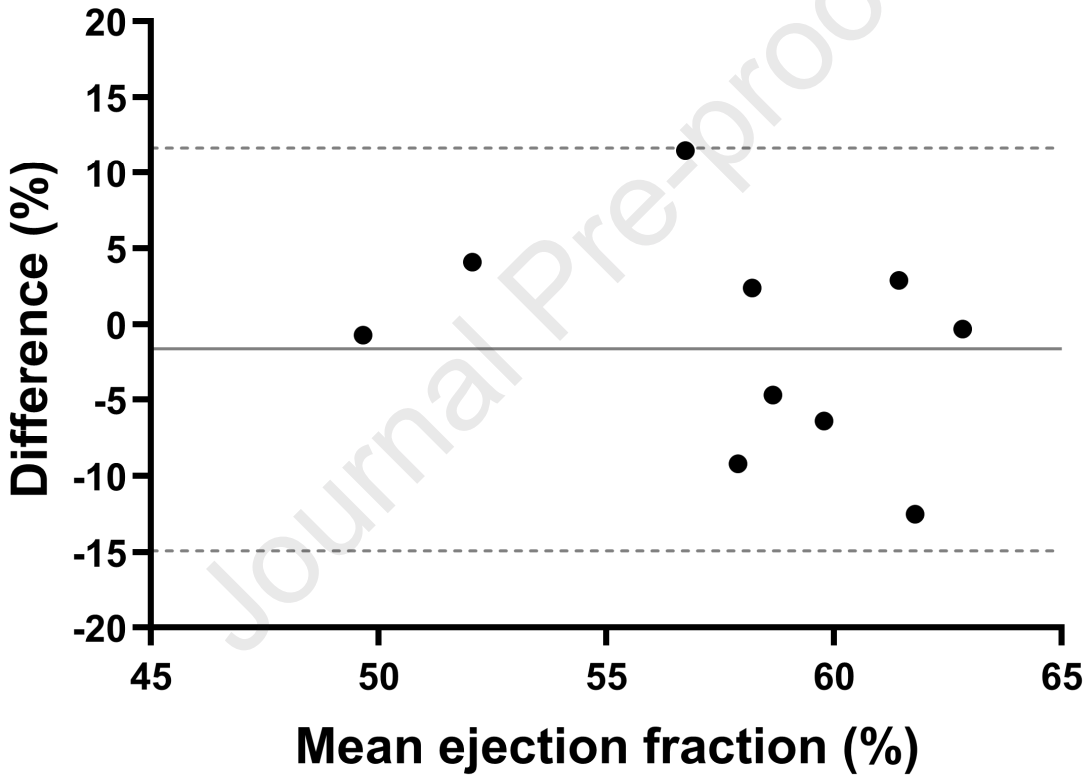
Exercise cardiac magnetic resonance imaging in boys with Duchenne Muscular Dystrophy without cardiac disease

Figure 1. Flow diagram describing the recruitment of participants with Duchenne Muscular Dystrophy (DMD) into the study.



Exercise cardiac magnetic resonance imaging in boys with Duchenne Muscular Dystrophy without cardiac disease

Figure 2. Bland-Altman plot comparing mean ejection fraction measured with transthoracic echocardiogram and cardiac magnetic resonance imaging in study participants with Duchenne Muscular Dystrophy. The horizontal solid grey line represents the mean difference, and the dashed grey lines the upper and lower limits of agreement.



Highlights

- Duchenne muscular dystrophy cardiomyopathy is diagnosed late, with worse outcomes
- Cardiac magnetic resonance has more accuracy and reliability than echocardiography
- Cardiac magnetic resonance is underutilised in Duchenne muscular dystrophy
- Exercise-stress CMRI is feasible in a select group of DMD patients
- Exercise-stress CMRI reveals abnormal cardiac function in asymptomatic children.