Differentiation between Athlete's Heart and Dilated Cardiomyopathy in Athletic Individuals.

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Abstract

Objective: Distinguishing early dilated cardiomyopathy (DCM) from physiological left ventricular (LV) dilatation with LV ejection fraction <55% in athletes ('grey-zone') is challenging. We evaluated the role of a cascade of investigations to differentiate these two entities.

Methods: Thirty-five asymptomatic active males with DCM, 25 male athletes in the 'grey-zone' and 24 male athletes with normal LV ejection fraction underwent NT-proBNP measurement, ECG and exercise echocardiography. 'Grey-zone' athletes and DCM patients underwent cardiovascular magnetic resonance (CMR) and Holter monitoring.

Results: Larger LV cavity dimensions and lower LV ejection fraction were the only differences between 'grey-zone' and control athletes. None of the 'grey-zone' athletes had abnormal NT-proBNP, increased ectopic burden/complex arrhythmias or pathological late gadolinium enhancement on CMR. These features were also absent in 71%, 71% and 50% DCM patients respectively. 95% 'grey-zone' athletes and 60% DCM patients had normal ECG. During exercise echocardiography, 96% 'grey-zone' athletes increased LV ejection fraction by >11% from baseline to peak exercise compared with 23% DCM patients ($p<0.0001$). Peak LV ejection fraction was >63% in 92% 'grey-zone' athletes compared with 17% DCM patients ($p<0.0001$). Failure to increase LV ejection fraction >11% from baseline to peak exercise or achieve a peak LV ejection fraction >63% had sensitivity of 77% and 83% respectively and specificity of 96% and 92% respectively for predicting DCM.

Conclusion: Comprehensive assessment using a cascade of routine investigations revealed that exercise stress echocardiography has the greatest discriminatory value in differentiating between 'grey-zone' athletes and asymptomatic DCM patients. Our findings require validation in larger studies.

Key Questions

What is known about this subject?

Dilated cardiomyopathy (DCM) is a recognized cause of sudden death in young athletes. It is also known that around 11% of healthy endurance athletes develop physiological left ventricular dilatation with a low/borderline left ventricular ejection fraction that may simulate dilated cardiomyopathy. Thus a distinct 'grey-zone' exists between physiological remodelling and dilated cardiomyopathy where erroneous misinterpretation has potentially serious consequences.

What does this study add?

We have demonstrated that failure to increase LV ejection fraction >11% from baseline to peak exercise and inability to augment the LV ejection fraction >63% at peak exercise during exercise stress echocardiography is suggestive of DCM with high sensitivity of around 80% and specificity >90%. Additionally, we used a composite of routine investigations to derive an algorithm to help clinicians to differentiate between athletes with a physiological increase in LV size and borderline or low baseline LV ejection fraction ('grey-zone') and DCM. The algorithm has a sensitivity of 94.1%, specificity of 83.3%, positive predictive value of 88.9% and negative predictive value of 90.9% in predicting DCM.

How might this impact clinical practice?

An erroneous diagnosis of DCM in an athlete with a physiologically increased LV size and borderline or low resting LV ejection fraction may lead to unnecessary disqualification from sport. Conversely, an erroneous diagnosis of athlete's heart in an individual with morphologically mild DCM deprives the individual of prognostic medications and provides false reassurance which may culminate in progressive deterioration of LV function and an

exercise related sudden death. Our findings and proposed algorithm will aid cardiologists and sports physicians when assessing active individuals with LV dilatation and LV ejection fraction<55% ('grey-zone'). Although our results are promising, the numbers are relatively small and require validation in a larger cohort.

Key words:

Athlete’s heart; dilated cardiomyopathy; exercise stress echocardiography;

Abbreviations:

CPET	Cardiopulmonary exercise test
CMR	Cardiovascular Magnetic Resonance
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
LV	Left ventricular
NT-proBNP	N-terminal pro-brain natriuretic peptide
pV02	Peak oxygen consumption
TDI	Tissue Doppler Imaging

INTRODUCTION

Dilated cardiomyopathy (DCM) is a rare but recognised cause of sudden cardiac death in athletes[1]. A small proportion of endurance athletes show enlarged left ventricular (LV) cavities with borderline/low LV ejection fraction[2] which overlaps with the phenotypic expression of morphologically mild DCM. Differentiation between these entities is an important focus of the sports cardiology and imaging societies. Expert opinion suggests that comprehensive assessment including the electrocardiogram (ECG), advanced imaging such exercise stress echocardiography, 2-D strain imaging and the presence of late enhancement on cardiovascular magnetic resonance imaging (CMR) is necessary to differentiate these 2 entities[3,4]; however data regarding utility of such investigations in this context is limited. We sought to evaluate the role of conventional investigations to differentiate between physiological adaptation in healthy athletes with LV dilatation and LVEF<55% ('grey-zone') and active asymptomatic individuals with DCM.

METHODS

The data, analytical methods, and study materials will not be made available to other researchers for the purpose of reproducing the results or replicating the procedure. Researchers interested in the data, methods, or analysis can contact the corresponding author for more information. Patients and public were not involved in the design, conduct, reporting or dissemination plans of our research.

Study subjects:

Patients with Dilated Cardiomyopathy

Asymptomatic male patients with non-ischaemic DCM were recruited from two tertiary cardiomyopathy centres in London. Dilated cardiomyopathy was defined as systolic

impairment in association with LV enlargement (either LV end-diastolic dimension >58mm or LV end diastolic volume of >150mls,equating to 2 standard deviations above the mean, as per the American Society of Echocardiography)[5].Left ventricular impairment was defined as LV ejection fraction <55%. Exclusion criteria included ischaemic heart disease, hypertension, valvular disease, LV ejection fraction<35% and poor echocardiographic windows. In individuals who exercised more than 5 hours of exercise per week, DCM was confirmed by the presence of DCM in a first degree relative, remodelled severe LV systolic dysfunction or late enhancement on CMR. Thirty-five individuals who fulfilled these criteria agreed to participate in the study.

Healthy athletes with LV dilatation and LVEF<55% ('grey-zone')

In the United Kingdom, the charity Cardiac Risk in the Young (CRY) subsidises pre-participation cardiovascular evaluations for elite professional and national sporting organisations. Over the period 2015-2017, 8006 athletes were evaluated by CRY. Additionally, the sports cardiology unit at St George's Hospital is a quaternary referral centre for athletes from centres throughout the country. Twenty-five asymptomatic athletes with phenotypic features resembling DCM were recruited from these sources. The 'grey-zone' was defined as an athlete with LV enlargement and borderline ejection fraction (<55%) who exercised for ≥8 hours per week. Athletes with a family history of DCM were excluded.

Athlete controls

A control cohort of 24 healthy asymptomatic male athletes with normal LV geometry matched to athletes with an increased LV cavity and LV ejection fraction <55% for age and sporting discipline were recruited through the CRY screening programme.

Study protocol

Participants underwent health questionnaire, NT-proBNP, 12-lead ECG, baseline and exercise echocardiogram and cardiopulmonary exercise testing (CPET). Beta-blockade-was held for 48 hours prior to exercise testing. 'Grey-zone' athletes and DCM patients also underwent a CMR and 24 hour Holter monitor.

Health Questionnaire:

The health questionnaire contained questions regarding cardiovascular symptoms, family history and exercise activity.

NT-proBNP

Blood samples for NT-proBNP were obtained from participants during resting conditions. Analysis was performed within 2 hours of extraction at room temperature using a Cobas 8000 E602 Module Immunochemistry Analyser (Roche Diagnostics, Basel, Switzerland).

Electrocardiography

12-lead ECG was performed in the supine position in a quiet room using a GE Marquette Hellige (Milwaukee, WI) ECG machine with a paper speed of 25mm/s as described[6]. Electrocardiograms were interpreted in accordance with international guidelines[7].

Twenty-four hour Holter

Twenty-four hour ambulatory ECG monitoring was performed using Life Card CF Holters (Spacelabs Healthcare). A high ventricular ectopic (VE) burden >500 beats/24 hours[8] or the presence of non-sustained ventricular tachycardia (NSVT) were considered abnormal. The presence of NSVT was defined as ≥3 consecutive beats of >120ms[9].

Echocardiography

Two-dimensional transthoracic echocardiography was performed by 2 board accredited sonographers using a commercially available, portable ultrasound system (Vivid E9, GE Healthcare, Milwaukee, Wisconsin) with a 1.5 – 3.6 MHz phased array transducer. Conventional views were obtained and measurements made as per the American Society of Echocardiography[5]. Pulsed-wave Doppler recordings were obtained to assess transmitral Doppler and Tissue Doppler Imaging (TDI) was acquired at the lateral and septal mitral annulus[10]. M-mode echocardiography was used to assess the tricuspid annular plane systolic excursion (TAPSE).

Speckle Tracking Imaging

Speckle tracking imaging was performed using a designated speckle tracking package (GE EchoPAC Clinical Workstation Software (Pollards Wood, UK)) to obtain global LV longitudinal strain (GLS) in the 2-,3-,4- chamber views then averaged accordingly. A normal GLS value was <-17%[5].

Stress echocardiography

Exercise echocardiography was conducted on a semi-recumbent cycle ergometer (Lode Angio with Echo Cardiac Stress Table, Groningen, Netherlands) according to a ramp protocol of 20 W/min to volitional exhaustion. Standard apical, parasternal short and long-axis images and transmitral Doppler and TDI of the lateral wall were acquired at baseline and peak exercise. Left ventricular volumes and ejection fraction were calculated using the Simpson's Biplane method[5]. Intravenous contrast was not required as all subjects had good endocardial definition.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed in an upright position with a COSMED E100w cycle ergometer (Rome, Italy) using a ramp protocol 20-30 W/min to volitional exhaustion. Breath-by-breath gas exchange analysis was performed using a dedicated COSMED Quark CPEX metabolic cart (Rome, Italy). Peak oxygen consumption (pVO_2) was calculated in ml/kg/min.

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance imaging was performed using methods described and analysed using semi-automated software[11] . All measurements were recorded as absolute values and indexed to body-surface area as per the DuBois-DuBois formula[12]. Delayed enhancement images were acquired after administration of gadolinium diethylenetriamine pentaacetate. Isolated late gadolinium enhancement (LGE) at the right ventricular insertion was not considered pathological as this is a common finding in healthy endurance athletes[8].

Statistical analysis:

Analyses were performed using SPSS (Version 25.0 IBM Corp). Shapiro-Wilk Test and analysis of histograms were performed to assess for normality. Continuous variables are presented as mean ± standard deviation or median and interquartile ranges. Comparison of 2 groups was by unpaired Student's t-tests or Mann-Whitney-U tests. Comparisons of more than two groups were performed by one-way ANOVA (with Bonferroni post-hoc test) or Krushal-Wallis (with Dunn's post hoc test) where appropriate. Categorical variables were presented as percentages and were compared using Fisher Exact Tests or Chi Squared Test. Receiver operating characteristic (ROC) curve analysis was performed to test the sensitivity of the echocardiographic variables in predicting DCM. Athlete was considered a negative

test, whereas DCM was considered a positive test. Optimal cut-off values, defined by the best compromise between sensitivity and specificity, were calculated by the Youden's Index using Medcalc 19.0.7. Inter-reader variability was assessed by intra-class correlation coefficients. Statistical significance was defined for p-values<0.05. Forward step-wise logistic regression was used. Stress echocardiographic variables with an area under the curve (AUC) >0.7 as identified by the ROC curve were included in the model.

To determine sample sizes, we estimated using a previous study of exercise radionuclide angiography which showed those with contractile reserve (representing athletes) had an increase in LVEF of 5±6% and those with poor outcome (representing DCM) had a change of LVEF of 0±5%[13]. Using these assumptions, we calculated we needed at least 21 in each cohort to provide 80% power. To allow for a margin of error we aimed to recruit at least 30 DCM patients and match them for age and baseline LVEF with the 'grey-zone' athletes (α=5%, 1-β=80%, n=21).

Ethics:

Full ethical approval was granted by the Chelsea Research Ethics Committee, London UK and participants provided informed written consent.

RESULTS

Demographics

Patients with DCM

The DCM patients were aged 39.5±13.4 (18-68) years. The majority (88.6%) were white. All patients were in NYHA Class 1 and exercised for an average of 4(2-8)hours per week.

Twenty-four (68.8%) were on beta-blockers and 23 (65.7%) on ACE-inhibitors or angiotensin II receptor blockers. Three patients (8.6%) had an implantable cardioverter-defibrillator in-situ. Fifteen patients (42.9%) had familial DCM, 3 (8.6%) had anthracycline induced DCM, 4 (11.4%) had post-viral DCM and 15 (42.9%) had idiopathic DCM.

Athletes

Athletes with an enlarged LV and baseline LV ejection fraction <55% ('grey-zone athletes') (32.3± 10.4; range 18-58 years) and control athletes (36.7±7.7; 22-48) were of similar age; however 'grey-zone' athletes were younger than DCM patients (p=0.035). The majority (>90%) were white. 'Grey-zone' athletes and control athletes exercised for a mean of 14.0(10-20) and 10(8.5-14.75)hours per week respectively and participated primarily in endurance sports. 'Grey-zone' athletes participated in cycling (n=8), endurance running (n=10), triathlon (n=3), rowing (n=3) and rugby (n=1). Control athletes competed in cycling (n=15); triathlon (n=2), endurance running (n=6) and rowing (n=1).

Electrocardiography

All participants were in sinus rhythm. Fourteen (40%) DCM patients had an abnormal ECG (some with multiple abnormalities) compared with 2 (8.0%) 'grey-zone' athletes and 1 (4.2%) control athlete (p=0.0007). Among the DCM cohort, 4 had left bundle branch block, 2 had pathological q waves, 2 had ST-segment depression, 5 had T-wave inversion and 4 had ≥ 2 ventricular extrasystoles. None of these abnormalities were seen in either athletic cohort. Ten (28.6%) DCM patients had an abnormal Holter of which 5 (14.3%) showed > 500 ventricular extrasystoles, 2 (5.7%) revealed isolated NSVT and 3(8.5%) had both. None of the 'grey-zone' athletes had an abnormal Holter.

NT-proBNP

There was no significant difference in median NT-proBNP between the 3 groups [50(26-262) pg/ml in the DCM group, 33.0 (23.5-57.5)pg/ml in the 'grey-zone' and 28(17.5-42)pg/ml in the athlete controls (p=0.131)]. Ten (28.6%) DCM patients had a NT-proBNP>125pg/ml (upper limit of normal)[14] compared with none of the athletes.

Baseline Echocardiography

There were no significant differences in the LV end-diastolic dimensions or ejection fraction between 'grey-zone' athletes or DCM patients. Both groups had a larger LV cavity compared with control athletes but there were no differences between the groups in left atrial indexed volume or LV mass. LA dilatation was observed in 12 (48.0%) grey-zone athletes, 16 (66.7%) control athletes and 12 (34.3%) of DCM patients. Diastolic dysfunction was noted in 5 DCM patients (2 grade I, 2 grade II and 1 grade III). None of the athletes had diastolic dysfunction. Both athletic cohorts showed significantly higher TDI measurements compared with DCM patients. Lateral S' wall was higher in both athletic groups compared to DCM patients. All the 'grey-zone' athletes and 28 (80.0%) DCM patients had a lateral E' $\geq$ 10 cm/s. Twenty (80%) 'grey-zone' athletes and 15 (42.9%) DCM patients had an S' wave$\geq$10 cm/sec.

Table 1: Baseline echocardiographic characteristics.

	DCM (n=35)	Healthy athletes with LV dilatation and LVEF<55% 'grey-zone'(n=25)	Athlete controls (n=24)	P value
LAVi (ml/m2)	29.2(24.4-35.2)	33.7 (30.0-37.5)	35.6 (31.3-40.7)	0.081
LVEDD (mm)	60.3±2.2*	59.3±2.3*	53.3±3.3	<0.0001
LVEDD/BSA	28.6±3.6	29.8±2.0	28.2±2.7	0.137
LVESD (mm)	45.7±5.5*	41.8±3.4*	35.3±3.7	<0.0001
LVESD/BSA	21.7±3.6	21.0±2.2	18.7±2.4	<0.0001
LV Mass (g)	209.8±58.1	200.3±47.9	180.6±30.4	0.081
Baseline LVEDV (ml)	185.27±31.2*	185.0 ±20.4*	152.4±22.9	<0.0001
Baseline LVESV (ml)	97.9±22.8*	92.7±12.0*	64.4±11.7	<0.0001
Baseline SV (ml)	87.3±16.3	92.6±12.0	88.1±13.7	0.346
LV ejection fraction (%)	47.6±5.4*	49.9±2.5*	58.3±2.3	<0.0001
TAPSE (mm)	22.2±4.0	23.6±3.2	24.5±4.1	0.059
RVD1 (mm)	40.2±5.6‡	45.4 ±4.6	41.4±5.0‡	0.001

RVD2 (mm)	27.6±5.1	31.9. ±5.5	29.5±5.5	0.010
Mitral E wave (cm/s)	0.71±0.20	0.52±0.15	0.88±0.17	0.487
Mitral A wave (cm/s)	0.52±0.15	0.44±0.14	0.46±0.10	0.094
Mitral E/A ratio	1.53±0.62	1.97±0.66	1.93±0.97	0.096
Lateral E' (cm/s)	13.7±4.8	17.2±4.4†	17.1±3.3†	0.008
Lateral S' (cm/s)	8.8±2.3	11.4±2.3†	11.7±1.9†	<0.0001
Lateral E/E'	5.99±2.32	4.33±1.35†	4.53±1.03†	0.004
Average E/E'	6.75±1.91	5.24±1.61†	5.30±1.26†	0.007

BSA=body surface area; LA=left atrial; LAVi=left atrial volume indexed; LV=left ventricular; LVEDD=left ventricular end-diastolic dimension; LVEDV=left ventricular end-diastolic volume; LVESD=left ventricular end-systolic dimension; LVESV=left ventricular end-systolic volume; RVD1=right ventricular basal dimension; RVD2=right ventricular mid-cavity dimension; RVD3=right ventricular longitudinal dimension 3; SV=stroke volume; TAPSE=tricuspid annular plane systolic excursion.=non-significant between the DCM patients and athletes in the 'grey-zone'; †= non-significant between 'grey-zone' and control athletes. ‡non-significant between DCM and athlete controls*

Speckle Tracking Imaging

Average GLS was highest in athlete controls (-17.4±1.9%), followed by 'grey-zone' athletes (-16.0±2.1%) and DCM patients (-13.6±3.0%) $p<0.0001$. A significant proportion of 'grey-zone' athletes (n=17; 68%), 14 (n=14; 58.3%) control athletes and 27 (n=27; 79.4%) DCM patients had GLS values outside the normal range (<-17%).[5]

Exercise echocardiogram

All cohorts demonstrated improvement in indices of diastolic (E') and longitudinal systolic function (S') at peak exercise, however the athletes showed a greater improvement in lateral S' compared with DCM patients (Table 2)Change in LV ejection fraction≤11% and peak LV ejection fraction≤63% were considered the optimal 'cut-off' to distinguish between DCM and 'grey-zone' athletes (Table 3).All but one of the 'grey-zone' athletes (96.0%) failed to increaseLV ejection fraction >11% as did 19 (79.2%) control athletes (Figure 1) compared with only 8 (22.9%) DCM patients. All athlete controls and 23 (92.0%) 'grey-zone' athletes achieved a peak LV ejection fraction>63% compared with only 6 (17.1%) DCM patients (Figure 2). Thirty (85.7%) DCM patients failed to increase LV ejection fraction by >11% or achieve a peak ejection fraction > 63%. Combining the inability to achieve a peak exercise LVEF>63% and a change in LVEF>11% exercise echocardiography had a sensitivity of 85.7% and specificity of 92.0%.

Table 2: Stress echocardiographic characteristics.

	DCM (n=35)	Athlete in the 'grey-zone' (n=25)	Athlete controls (n=24)	P value
Total Watts	234.6±48.0	308.6±59.6*	293.5±59.6*	<0.0001
Peak LVEDV (ml)	176.3±40.3†	167.4±17.5†	140.7±22.8	<0.0001
Peak LVESV (ml)	86.2±34.7†	56.2±11.3†	40.3±4.9	<0.0001
Peak SV (ml)	90.1±22.8	111.2 ±15.6	101.8±17.9	<0.0001
Peak LV ejection fraction (%)	52.0.±11.5	67.6 ±3.9*	71.4±3.4*	<0.0001
Change in LV ejection fraction (%)	4.9±8.9	17.7 ±4.1	13.1±3.1	<0.0001
Peak mitral E wave	1.34±0.28	1.30±0.27	1.46±0.24	0.217
Peak Lateral E' (cm/s)	21.5±5.5	23.6±5.2	23.8±5.8	0.266
Peak Lateral E/E'	6.6±2.3	5.9±2.0	5.86±1.84	0.463
Peak S' (cm/s)	15.6±5.0	22.1±6.1*	22.5±6.6*	<0.0001
Peak SBP (mmHg)	189.5±26.7	210.3±24.7*	202.3±27.2*	0.007
Peak DBP (mmHg)	98.0 ±11.0	102.3 ±13.9	94.1±14.50	0.018

Peak HR (bpm)	148.6±15.4‡	162.2 ±11.1	150.6±9.7‡	0.01

*bpm=beats per minute; BP=blood pressure; DBP= diastolic blood pressure; HR=heart rate; LV=left ventricular; LVEDV=left ventricular end-diastolic volume; LVESV=left ventricular end-systolic volume; SBP=systolic blood pressure; SV=stroke volume. * non-significant between 'grey-zone' and control athletes.†=non-significant between 'grey-zone' and DCM ‡non-significant between DCM and athlete controls*

Cardiovascular Magnetic Resonance

All but 1 DCM patient and 1 athlete with a dilated LV and LVEF >55% ('grey zone') underwent a CMR. Pathological late gadolinium enhancement was observed in 17 (50.0%) DCM patients (mid wall n=12 and subepicardial n=5) compared with none of the 'grey-zone' athletes (supplementary Table 1).

Cardiopulmonary exercise testing:

There were no significant differences in cardiopulmonary parameters between either athletic group and both achieved superior results compared to DCM patients (supplementary Table 2). A significant proportion (n=25; 71.4%) of DCM patients had a normal pV02[15] with 7(20%) achieving a pV02 of >120% predicted. Of these 7, all had ventricular arrhythmias on Holter and 6 had the late enhancement on CMR.

Discriminating ability of echocardiographic parameters

Receiver-operator characteristic curve analysis showed peak LV ejection fraction ≤63% (AUC 0.904; p<0.0001) and change LV ejection≤11% (AUC 0.906; p<0.0001) predicted DCM with good sensitivity and excellent specificity (Table 3). Step-wise logistic regression model including a change in LV ejection fraction ≤ 11%, peak LV ejection fraction ≤ 63%, peak stroke volume ≤ 94 ml and peak S'≤ 21 cm/s as predictors of DCM, revealed a that change in LV ejection fraction ≤11% independently predicted DCM. The final model had a Nagelkerke R^2 of 0.677.

Table 3: Receiver operator characteristic curve analysis evaluating biomarkers and structural and functional stress echocardiographic parameters to distinguish betweendilated cardiomyopathy and athletic adaptation.

Variable	Optimal 'cut-off'*	AUC	Sensitivity	Specificity	P value
NT-proBNP	>75 pg/ml	0.645	48.6%	96.0%	0.045
E' Lateral Peak	<25cm/s	0.638	78.8%	48.0%	0.066
S' Lateral Peak	≤21cm/s	0.792	84.4%	64.0%	<0.001
Stroke Volume Peak	≤94ml	0.754	62.9%	96.0%	<0.001
LV Ejection Fraction	≤63%	0.904	82.9%	92.0%	<0.0001
Change in left ventricular ejection fraction from baseline to peak exercise	≤11%	0.906	77.1%	96.0%	<0.0001

*AUC=area under the curve; LV=left ventricular.*Value calculated by Youden's Index as best compromise between sensitivity and specificity*

Inter-observer variability

Agreement between observers for the echocardiographic variables was assessed on a random sample of 40 stress echocardiograms using intra-class coefficient between the primary observer and an independent observer blinded to the initial readings and other results. The intra-class coefficients for the assessment of baseline LV ejection fraction, the difference between baseline to peak LV ejection fraction and peak LV ejection fraction were 0.734, 0.877and 0.899 respectively.

DISCUSSION

To our knowledge, this is the first study which has comprehensively assessed the utility of a cascade of investigations to differentiate between the athletes with an enlarged LV and LV ejection fraction<55% ('grey zone') and morphologically mild DCM. Our results reveal the combination of investigations including NT-proBNP, electrocardiogram, Holter and CMR will fail to diagnose DCM>30% of cases. Whereas NT-proBNP>125 pg/ml was highly specific for DCM, most affected active patients had normal values. The electrocardiogram has a sensitivity of 90[16]% and 80%[17] in hypertrophic and arrhythmogenic cardiomyopathy respectively; however only 40% of our active individuals with DCM demonstrated abnormal electrocardiograms[7]. Although, beyond the scope of this paper, genetic testing may have a role in resolving this diagnostic conundrum, however it is limited by the relatively high cost and low yield for results.

Indices of diastolic and longitudinal function.

Baseline echocardiographic markers of systolic and diastolic function as assessed by E' and S' at the lateral mitral annulus had a sensitivity of 51.4% and 88.6% respectively in

differentiating between ‘grey-zone’ athletes and DCM patients. Although GLS was higher in the ‘grey-zone’ athletes compared to DCM patients, over 50% had low values[5]. Interpretation of these results is challenging because currently there is no clear consensus on ‘normal’ GLS values athletes with a borderline or low LV ejection fraction. A meta-analysis by Beaumont et al[18], reported that GLS values in athletes ranged from -16.5 to-23.3% and were lower in endurance athletes. Our results suggest that GLS may be of limited value in this context as low values may not be pathological. Further research is required on the spectrum of GLS values in endurance athletes with borderline or mildly depressed LV function at rest.

Exercise stress echocardiography

Our results demonstrate the importance of exercise echocardiography in differentiating between these entities. Failure to increase LV ejection fraction by>11% from baseline to peak exercise is a useful marker of impaired contractile reserve. Only 6 patients with DCM were able to generate a LV ejection fraction >63% at peak exercise compared to more than 90% of the ‘grey-zone’ athletes and all of the athletic controls and therefore the inability to achieve a peak LVEF>63% is an additional marker of pathology. The sensitivity of either of these parameters was around 80% and the specificity around 90%. Combining these parameters to define a ‘normal’ test reduces the false negatives to 5(14.2%) with only 2 (8%) false positive results.

There is limited data used to define contractile reserve in health and this has predominantly focused on pharmacological and non-echocardiographic methods[13,19,20] . We used exercise echocardiography as it is more physiological and exercise echocardiography is readily available to the physician. Our findings are in-keeping recent study using exercise CMR

which also found that a failure to increase LV ejection fraction by >11% at peak exercise predicted DCM[21].

Cardiopulmonary exercise testing

Although all but one of the 'grey-zone' athletes showed normal pV02, we observed normal $pV0_2$ in three quarters of the DCM cohort. Additionally, superior pV02 >120% predicted was seen in a fifth of our cohort which is similar to a published study looking athletes with hypertrophic cardiomyopathy[22]. All of the individuals with a pV02>120% predicted had ventricular arrhythmias and most had late enhancement on CMR. Therefore, highly trained individuals may have excellent functional capacity despite significant pathology

Cardiovascular Magnetic Resonance

In our study, CMR identified pathological LGE in only 50% patients with DCM, suggesting that baseline CMR at rest is not enough on its own to exclude pathology which gives further importance to the role of stress echocardiography in this setting. Although we did not utilise T1 and T2 mapping techniques, data suggests these techniques may be useful in distinguishing athlete's heart from DCM[23].

Algorithm

Based on our findings, we have produced a clinical algorithm with diagnostic thresholds to aid physicians when assessing highly active individuals with a dilated LV and a LV ejection fraction <55% (Figure 3) and demonstrated its utility using our data (Figure 4). The 2 individuals without CMR have been excluded from analysis. The combination of NT-proBNP, ECG and Holter monitoring would confirm DCM in <60% of cases. An additional exercise echocardiogram, would result in a diagnosis in 31 (91.2%) cases. A subsequent

CMR could exclude pathology in another 3% of cases without impact on false positives. The algorithm has a sensitivity of 94.1%, specificity of 83.3%, positive predictive value of 88.9% and negative predictive value of 90.9%. More than 70% of our DCM patients had a normal pV02 therefore we would not recommend this investigation in isolation.

Limitations

Study participants were predominantly white and exclusively male therefore results may not readily be applicable to female athletes or the black athletic population. Given the rarity of patients with DCM who are asymptomatic and athletes in the 'grey-zone', the numbers studied are relatively small. The algorithm was derived and assessed in the same cohort which may result in over optimistic results, therefore larger studies are required to validate our findings. Due to the cross-sectional nature of the study we are unable to confidently exclude the development DCM in the 'grey-zone' athletes in the future.

CONCLUSION

When attempting to differentiate between physiological LV enlargement with a borderline/low baseline LV ejection fraction from mild DCM, a combination of NT-proBNP, electrocardiogram, Holter monitoring, baseline echocardiographic and CMR parameters have a modest discriminating value; however exercise echocardiography has good sensitivity and excellent specificity.

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Figure titles and legends:

Figure 1:

(a) Change in LV ejection fraction from baseline to peak exercise in the healthy athletes with LV dilatation and LVEF<55% (the 'grey-zone') (left), athlete controls (centre) and individuals with morphologically mild DCM (right). Each circle represents an individual and the horizontal line represents the mean and the 95% confidence intervals. Almost all the athletes in both cohorts increase the LV ejection fraction by >11% compared to the DCM cohort who demonstrate a heterogenous response. DCM=dilated cardiomyopathy; LVEF=left ventricular ejection fraction.

(b) The change in ejection fraction from baseline to peak exercise. The healthy athletes with LV dilatation and LVEF<55% ('grey-zone)' are on the left, the DCM cohort on the right and the control athletes in the centre. All the athletes demonstrate an increase in LV ejection fraction compared to the DCM patients who show a heterogenous response.

DCM=dilated cardiomyopathy; LVEF=left ventricular ejection fraction.

Figure 2: Peak exercise LV ejection fraction. This figure shows peak exercise LV ejection fraction from baseline to peak exercise in the healthy athletes with LV dilatation and LVEF<55% ('grey-zone') (left), control athletes (centre) and DCM cohort (right). Each circle represents an individual and the horizontal line represents the mean and the 95% confidence intervals. All the athlete controls and almost all the 'grey-zone' athletes increase their LV

ejection fraction to >63% from baseline to peak exercise which is in contrast to the DCM cohort. DCM=dilated cardiomyopathy; LVEF=left ventricular ejection fraction

Figure 3:

This figure outlines a simple algorithm to aid physicians when assessing active individuals with LV dilatation and LVEF <55%. On the left are the changes that would support physiological adaptation and on the right those that suggest pathological remodelling. The electrocardiogram was interpreted as per the international recommendations in athletes[7].

CMR=cardiovascular magnetic resonance; DCM=dilated cardiomyopathy; LV=left ventricular; LVEF=left ventricular ejection fraction; LBBB=left bundle branch block; LGE=late gadolinium enhancement; NSVT=non-sustained ventricular tachycardia; TWI=T-wave inversions; VEs=ventricular extrasystoles

Figure 4:

The figure demonstrates the utility of the step-wise clinical algorithm for differentiating between physiological adaptation and morphologically mild DCM in apparently healthy individuals with LV dilatation and LVEF<55%. The number and percentages of both cohorts with abnormal investigations is shown with the cumulative true negative and true positive results on the extreme right and left respectively. The overall sensitivity of the algorithm is 94.1% with a specificity of 83.3%. The positive predictive value is 90.3% with a negative predictive value of 94.7%.

CMR=cardiovascular magnetic resonance; DCM=dilated cardiomyopathy; ECG=electrocardiogram; LV=left ventricular; LVEF=left ventricular ejection fraction; NPV=negative predictive value; NT-proBNP=N-terminal pro-brain natriuretic peptide; PPV=positive predictive value; TN=true negatives; TP=true positives