# Differentiation between Athlete's Heart and Dilated Cardiomyopathy in athletic individuals.

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**Abstract**

**Background:** Distinguishing early dilated cardiomyopathy (DCM) from physiological left ventricular (LV) dilatation with mildly reduced LV ejection fraction ('grey-zone') is challenging. We evaluated the role of a cascade of investigations to differentiate these two entities.

**Methods and Results:** Thirty-five asymptomatic active males with DCM, 25 male athletes in the 'grey-zone' and 24 male athlete controls with normal LV ejection fraction were investigated with NT-proBNP, electrocardiography (ECG) and exercise echocardiography. 'Grey-zone' athletes and DCM patients underwent cardiovascular magnetic resonance and Holter monitoring. Larger LV cavity dimensions and lower LV ejection fraction were the only differences between control and 'grey-zone' athletes. None of the 'grey-zone' athletes had an abnormal NT-proBNP, increased ectopic burden/complex arrhythmias or pathological late gadolinium enhancement. These features were absent in 71%, 71% and 50% of DCM patients respectively. 95% of 'grey-zone' athletes and 60% DCM patients had a normal ECG. During exercise echocardiography, 96% of the 'grey-zone' athletes increased LV ejection fraction by >11% from baseline to peak exercise compared with 23% DCM patients. Peak LV ejection fraction was >63% in 92% 'grey-zone' athletes compared with 17% DCM patients. Failure to increase LV ejection fraction >11% from baseline to peak exercise or achieve a peak LV ejection fraction >63% had a 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.

**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 an enlarged left ventricular (LV) cavity with borderline/low LV ejection fraction[2] which overlaps with the phenotypic expression of morphologically mild DCM. Differentiation between these two entities is an important focus of the sports cardiology and imaging societies. Expert opinion suggests that comprehensive assessment including the electrocardiogram (ECG), advanced imaging and functional assessment 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 ('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.

**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, primary 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 cardiac magnetic resonance imaging (CMR). Thirty-five individuals who fulfilled these criteria agreed to participate in the study.

Athletes in 'the grey-zone'

In the United Kingdom, the charity Cardiac Risk in the Young (CRY) subsidises cardiovascular evaluations for elite sporting organisations (including British rowing and cycling squads and several premier league rugby and soccer teams) as part of pre-participation screening. Over the period 2015-2017, 8006 athletes were screened 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 (as outlined above) who exercised for ≥8 hours per week. 'Grey-zone' athletes were excluded if they expressed cardiovascular symptoms or a family history of DCM.

Athlete controls

An athletic control cohort of 24 healthy asymptomatic male athletes with normal LV geometry matched to the 'grey-zone' athletes 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 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 serum 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 monitoring

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. Images were acquired in the conventional parasternal long-axis and short-axis, and apical views. Standard measurements made and recorded in accordance with protocols specified by the American Society of Echocardiography[5]. Pulsed-wave Doppler recordings were obtained to assess transmitral early (E) and late (A) diastolic filling. 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 and long-axis images and transmitral Doppler and TDI of the lateral wall were acquired at baseline and peak exercise. Loops were stored on designated software for off-line analysis. Left ventricular volumes and ejection fraction were calculated using the Simpson's Biplane method[5]. Contractile reserve was assessed by calculating the change in LV ejection fraction from baseline to peak exercise. 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 imaging 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 was performed to assess for normality of distributions. Continuous variables are presented as mean ± standard deviation, and groups were compared using unpaired Student's t-tests. Categorical variables were presented as percentages and were compared using Fisher Exact Tests. 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. 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 suggesting a fair test were included in the model.

To determine sample sizes, we estimated using 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 the DCMs) 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 ($\alpha$=5%, 1-$\beta$=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 5.3±5.0 hours per week. Most patients were on prognostic medications for heart failure including beta-blockers (n= 24; 68.6%) and ACE-inhibitors or angiotensin II receptor blockers (n =23; 65.7%). Three patients (8.6%) had an implantable cardioverter-defibrillator in-situ. Fifteen patients (42.9%) had familial DCM, 4 who were gene positive. Three (8.6%) had anthracycline induced DCM, 4 (11.4%) had post-viral DCM and fifteen (42.9%) had idiopathic DCM.

Athletes

'Grey-zone' athletes (32.3± 10.4; range 18-58 years) and control athletes (36.7±7.7; 22-48) were similar age; however 'grey-zone' athletes were younger than DCM cohort (p=0.035). As with the DCM cohort, the majority (>90%) were white. 'Grey-zone' athletes and athlete controls exercised for a mean of 15.0±7.5 and 11.4±3.2 hours per week and participated primarily in endurance sports. 'Grey-zone' athletes participated in cycling (n=8, 32%), endurance running (n=10, 40%), triathlon (n=3, 12%), rowing (n=3, 12%) and rugby (n=1, 4%). Control athletes competed in cycling (n=15; 62.5%), triathlon (n=2; 8.3%), endurance running (n=6; 25.0%) and rowing (n=1; 4.2%).

**Electrocardiography**

All participants were in sinus rhythm. Fourteen (40%) DCM patients had an abnormal ECG compared with 2(8.0%) 'grey-zone' and 1 (4.2%) control athlete (p=0.0007). Among the DCM cohort, 4 (11.4%) had left bundle branch block, 2(5.7%) had pathological q waves, 2(5.7%) had ST-segment depression, 5(14.3%) had T-wave inversion and 4(11.4%) had ≥ 2 ventricular extrasystoles. None of these abnormalities were seen in either athletic cohort. Ten (28.6%) DCM patients had an abnormal Holter. Five (14.3%) had > 500 ventricular extrasystoles, 2(5.7%) had isolated NSVT and 3(8.5%) had > 500 ventricular extrasystoles and NSVT. None of the 'grey-zone' athletes had an abnormal Holter.

**NT-proBNP**

Mean NT-proBNP was higher in the DCM patients compared to the 'grey-zone' and control athletes (131.4±158.0 pg/ml versus 39.7±23.2pg/ml. and 33.0±20.7 pg/ml($p<0.0001$)); however there was no difference in NT-proBNP levels between both athlete groups. 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 larger LV end-diastolic dimensions compared with control athletes but there were no differences between the groups in left atrial diameter or LV mass. Transmitral early diastolic filling and mitral E/A ratio was similar in the three groups. Both athletic cohorts showed significantly higher TDI measurements at the mitral valve annulus compared with DCM patients. Lateral S' wall was also significantly higher in both athletic groups compared to DCM patients. All the 'grey-zone' athletes and 28 (80.0%) DCM patients had a lateral E' ≥ 10 cm/s. Twenty (80%) 'grey-zone' athletes and 15 (42.9%) DCM patients had an S' wave≥10 cm/sec. Right ventricular measurements were significantly larger in both athletic groups compared to the DCM patients; however right ventricular function was similar in all groups (Table 1).

***Table 1: Baseline echocardiographic characteristics.***

| | DCM (n=35) | Athlete in the 'grey-zone' (n=25) | Athlete controls (n=24) | P value |
|---|---|---|---|---|
| LA dimension (mm) | 39.5±5.7 | 37.3±5.0 | 37.1±5.8 | 0.160 |
| 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 LVEDV/BSA | 87.5±17.8 | 92.9±11.5 | 80.7±12.2 | <0.0001 |
| Baseline LVESV (ml) | 97.9±22.8* | 92.7±12.0* | 64.4±11.7 | <0.0001 |
| Baseline LVESV/BSA | 46.2±11.6 | 46.6±5.7 | 34.0±5.9 | 0.014 |
| Baseline SV (ml) | 87.3±16.3 | 92.6±12.0 | 88.1±13.7 | 0.346 |
| Baseline SV/BSA | 41.3±9.1 | 46.5±6.7 | 46.7±7.6 | 0.095 |
| 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 |
| RVD3 (mm) | 88.0±14.9 | 95.9±6.2 | 88.6±18.6 | 0.084 |
| Fractional Shortening (%) | 24.1±5.7 | 29.2 ±4.7 | 33.7±6.3 | <0.0001 |
| Mitral E wave (cm/s) | 0.711±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 |
| Deceleration time (ms) | 199.8±44.164 .2 | 206.8±61.2 | 185.7±40.4 | 0.426 |
| 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 |
| Septal E' (cm/s) | 9.0±2.3 | 11.44±3.0† | 12.5±4.2† | 0.001 |
| Septal S' (cm/s) | 7.7±1.3 | 8.4±1.8 | 8.9±1.5 | 0.038 |
| Septal E/E' | 8.24±1.67 | 7.27±2.33† | 6.36±1.94† | 0.035 |
| Average E/E' | 6.75±1.91 | 5.24±1.61† | 5.30±1.26† | 0.007 |

*BSA=body surface area; GLS=global longitudinal strain; LA=left atrial; 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 between 'grey-zone' and control athletes.*

**Speckle Tracking Imaging**

Average GLS was highest in the in the 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. Seventeen (68%) 'grey-zone' athletes, 14 (58.3%) athlete controls and 27 (79.4%) DCM patients had GLS values outside the normal range (<-17%).[5]

**Exercise echocardiogram**

Stroke volume at baseline and peak exercise was higher in both athletic groups than DCM patients (Table 2). All but one of the 'grey-zone' athletes (96.0%) increased LV ejection fraction from baseline to peak by >11% as did 19 (79.2%) control athletes (Figure 1). In contrast, only 8 (22.9%) individuals with DCM increased LV ejection fraction by > 11% (Figure 1). All the athlete controls and 23(92.0%) of '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%. All cohorts demonstrated improvement in indices of diastolic (E') and longitudinal systolic function (S') from baseline to peak exercise, however both athletic groups showed a greater improvement in S' of the lateral wall compared with DCM patients (Table 2).

***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 LVEDV/BSA | 83.4±21.6 | 84.0±8.7 | 75.2±11.1 | <0.0001 |
| Peak LVESV (ml) | 86.2±34.7 | 56.2±11.3 | 40.3±4.9 | <0.0001 |
| Peak LVESV/BSA | 40.7±17.4 | 28.3±6.3 | 21.3±2.8 | <0.0001 |
| Peak SV (ml) | 90.1±22.8 | 11.2 ±15.6 | 101.8±17.9 | <0.0001 |
| Peak SV/BSA | 42.7±11.6 | 55.7±6.9 | 53.9±9.5 | |
| 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 |
| Peak BP product | 28062.9±6314.1 | 34152.7±4985.2* | 30432.5±4373.5.8* | <0.0001 |

*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.*

**Cardiovascular Magnetic Resonance**

All but 1 DCM patient and 1 ‘grey-zone’ athlete 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:**

Athletes achieved a greater work load and pVO2 compared with DCM patients (supplementary Table 2). There were no significant differences in any cardiopulmonary parameters between both athletic groups. 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 this 7, all had ventricular arrhythmias on Holter and all but one had the presence of late enhancement on CMR. None of the patients with DCM achieved a pV02 of ≥57ml/kg/min compared with 10(40%) ‘grey-zone’ athletes.

**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 and cardiopulmonary exercise test parameters to predict dilated cardiomyopathy.***

| Variable | 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.*

**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 physiological 'grey-zone' and morphologically mild DCM. Our results reveal the combination of investigations including NT-proBNP, electrocardiogram, Holter and CMR and will fail to diagnose DCM>30% of cases. Whereas NT-proBNP>125 pg/ml was highly specific for pathological LV systolic impairment, less than a third of our DCM cohort showed these values. The electrocardiogram plays a fundamental role in the diagnosis of hypertrophic and arrhythmogenic cardiomyopathy, in which it is abnormal in 90[16]% and 80%[17] of individuals; however only 40% of our active individuals with DCM demonstrated pathological electrocardiograms[7]

**Indices of diastolic and longitudinal function.**

Baseline echocardiographic markers of systolic and diastolic function as assessed by E' and S' at the lateral wall 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 in the compared to DCM patients, more than half had low values[5]. Our experience suggests that this particular modality has limited value when used in isolation in this context.

**Exercise stress echocardiography**

Our results support the utility of exercise echocardiography in differentiating between these entities. Failure to increase LV ejection fraction by>11% at 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; therefore 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 false positives (8%).

There is limited data used to define contractile reserve in health and this has predominantly focused on pharmacological and non-echocardiographic methods[13,18,19] . 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[20].

**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. Our ROC curves showed that a pV02≤40.7ml/min/kg had a sensitivity of 80.0% and specificity of 92% for predicting DCM. Superior pV02

>120% predicted was seen in a fifth of our cohort which is similar to a published study looking athletes with hypertrophic cardiomyopathy[21].All of the individuals with a pV02>120% predicted had ventricular arrhythmias and most had late enhancement on cardiac MRI. Therefore, highly trained individuals may have excellent functional capacity despite significant pathology

**Cardiovascular Magnetic Resonance**

Cardiovascular magnetic resonance is the gold-standard for the assessment of cardiomyopathy, with mid-wall late enhancement in individuals with an increased LV volume and depressed LV ejection fraction being almost diagnostic for DCM. In our study CMR identified around 50% patients with DCM, suggesting that baseline CMR is less predictive than stress echocardiography in differentiating between physiology and pathology. Although we did not utilise T1 and T2 mapping techniques, preliminary data suggests these techniques are discriminatory in distinguishing athlete's heart from DCM[22].

**Algorithm**

We have produced a clinical algorithm for assessing these individuals (Figure 3). The 2 individuals without cardiac MRI have been excluded from analysis. Our results demonstrate the combination of NT-proBNP, ECG and Holter monitoring would confirm DCM in <60% of cases. An additional exercise echocardiogram, would diagnose in 31 (91.2%) cases. A subsequent CMR could exclude pathology in another 3% of cases without any impact on the false positive results. Overall, 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%. Although

cardiopulmonary exercise testing may add value >70% of asymptomatic 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 the female or black population. Given the rarity of patients with DCM who are asymptomatic and athletes in the 'grey-zone', the numbers studied are relatively small. 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 adaptation 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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Conflicts/disclosures: none

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**Figure titles and legends:**

**Figure 1:**

**(a) Change in left ventricular ejection fraction from baseline to peak exercise in athletes in 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 'grey-zone' athletes 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 'grey-zone' athletes (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:**

The figure reveals a stepwise clinical algorithm for differentiating between physiological left ventricular dilatation and morphologically mild DCM in apparently healthy active young individuals with a dilated left ventricle and borderline/low left ventricular ejection fraction, . 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.

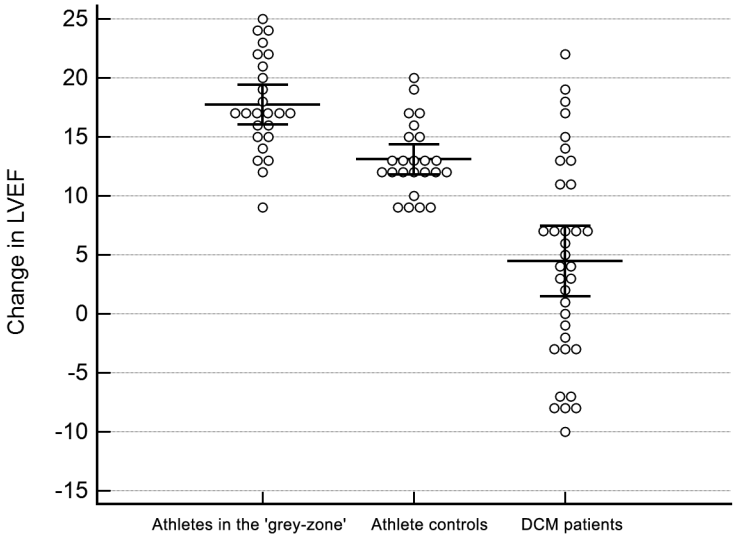


**Figure 1(a): Change in left ventricular ejection fraction from baseline to peak exercise in athletes in the 'grey-zone' (left), athlete controls (centre) and individuals with morphologically mild DCM (right)**. Each circle represents an individual and the horizontal line represents the mean and the 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.

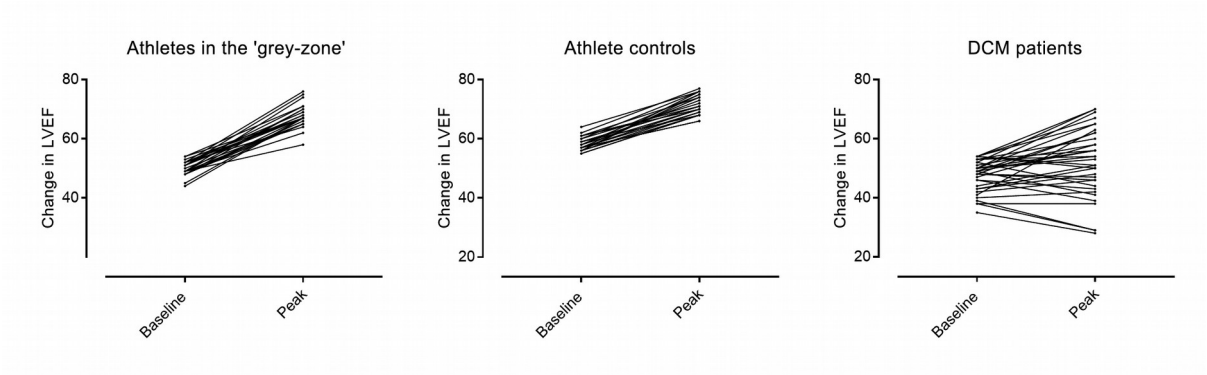


**Figure 1(b): The change in ejection fraction from baseline to peak exercise.** The 'grey-zone' athlete cohort is represented on the left, the DCM cohort on the right and the control athletes in the centre. All the athletes demonstrate an increase in LV ejection fraction compared to the DCM patients who show a heterogenous response.

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

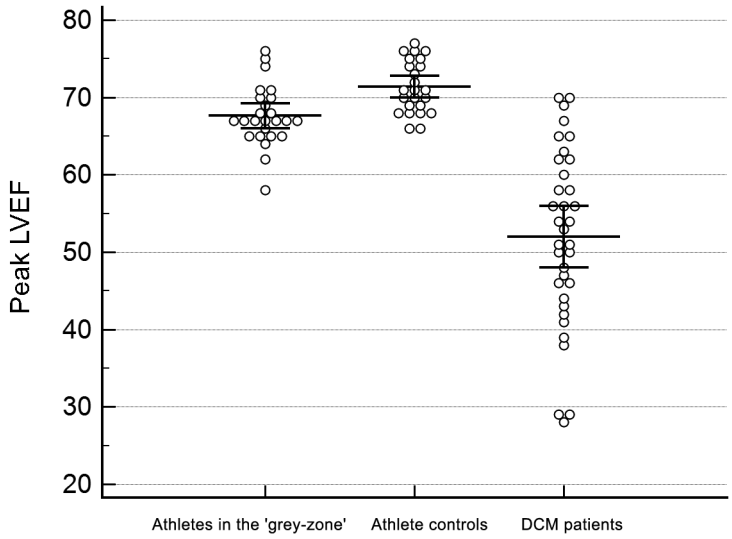


**Figure 2: Peak exercise LV ejection fraction.** This figure shows peak exercise LV ejection fraction from baseline to peak exercise in 'grey-zone' athletes (left), control athletes (centre) and DCM cohort (right). Each circle represents an individual and the horizontal line represents the mean and the 95% confidence intervals. All the athlete controls and all but 2 of the athletes in the 'gray-zone' increase their LV ejection fraction to >63% from baseline to peak exercise which is in contrast to the DCM cohort in which only 4 are able to do this. DCM=dilated cardiomyopathy; LVEF=left ventricular ejection fraction.

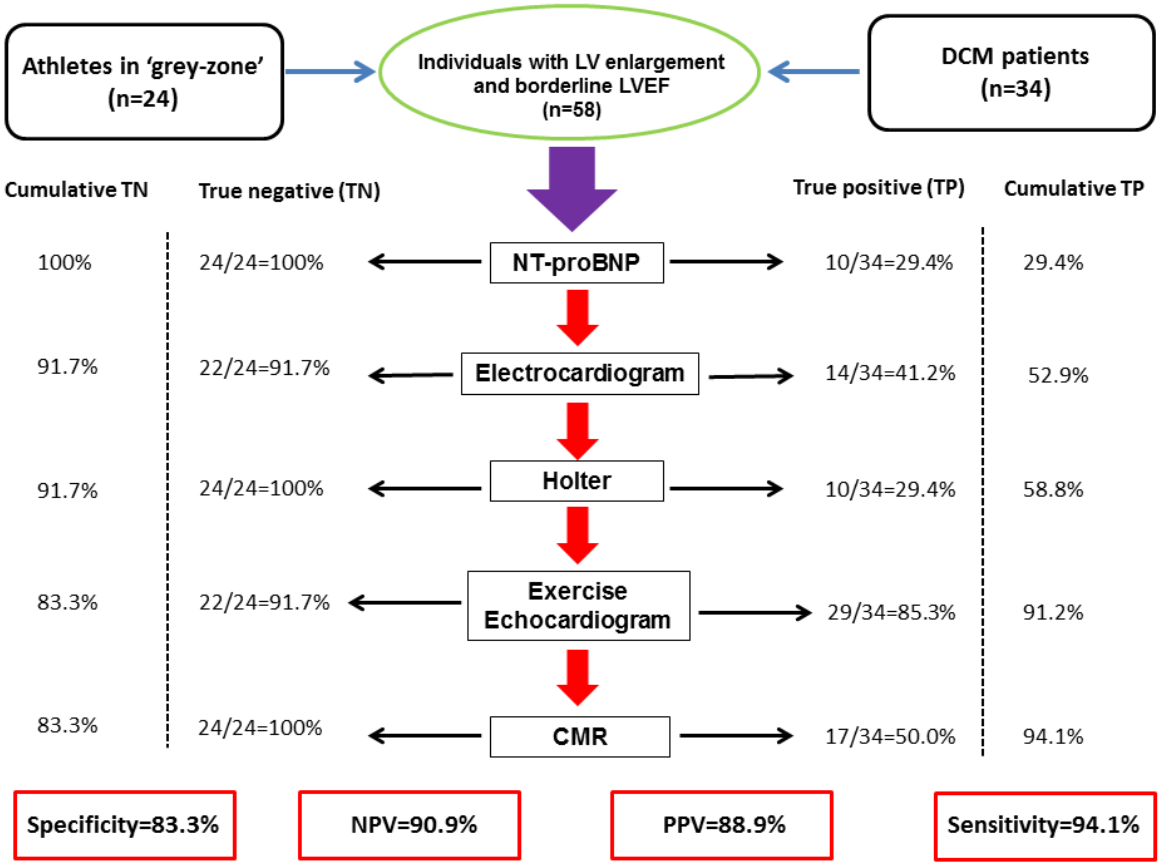


**Figure 3:**

The figure reveals a stepwise clinical algorithm for differentiating between physiological left ventricular dilatation and morphologically mild DCM in apparently healthy active young individuals with a dilated left ventricle and borderline/low left ventricular ejection fraction, based on our findings from this study. The 2 individuals without cardiac MRI have been removed from this analysis. 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 88.9% with a negative predictive value of 90.9%.

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.