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Exercise cardiac magnetic resonance to differentiate athlete's heart from structural heart disease

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Aims The distinction between left ventricular (LV) dilation with mildly reduced LV ejection fraction (EF) in response to regular endurance exercise training and an early cardiomyopathy is a frequently encountered and difficult clinical conundrum. We hypothesized that exercise rather than resting measures would provide better discrimination between physiological and pathological LV remodelling and that preserved exercise capacity does not exclude significant LV damage.

Methods and results We prospectively included 19 subjects with LVEF between 40 and 52%, comprising 10 ostensibly healthy endurance athletes (EA-healthy) and nine patients with dilated cardiomyopathy (DCM). In addition, we recruited five EAs with a region of subepicardial LV. Receiver operating characteristic fibrosis (EA-fibrosis). Cardiac magnetic resonance (CMR) imaging was performed at rest and during supine bicycle exercise. Invasive afterload measures were obtained to enable calculations of biventricular function relative to load (an estimate of contractility). In DCM and EA-fibrosis subjects there was diminished augmentation of LVEF (5 ± 6% vs. 4 ± 3% vs. 14 ± 3%; $P = 0.001$) and contractility [LV end-systolic pressure–volume ratio, LVESPVR; 1.4 (1.3–1.6) vs. 1.5 (1.3–1.6) vs. 1.8 (1.7–2.7); $P < 0.001$] during exercise relative to EA-healthy. Receiver-operator characteristic curves demonstrated that a cut-off value of 11.2% for ΔLVEF differentiated DCM and EA-fibrosis patients from EA-healthy [area under the curve (AUC) = 0.92, $P < 0.001$], whereas resting LVEF and VO_2max were not predictive. The AUC value for LVESPVR ratio was similar to that of ΔLVEF.

Conclusions Functional cardiac evaluation during exercise is a promising tool in differentiating healthy athletes with borderline LVEF from those with an underlying cardiomyopathy. Excellent exercise capacity does not exclude significant LV damage.

Keywords athlete's heart • dilated cardiomyopathy • exercise • myocardial fibrosis • cardiac magnetic resonance imaging • contractile reserve

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Introduction

Profound left ventricular (LV) dilation with mildly reduced LV ejection fraction (EF) at rest is seen in >10% of elite endurance athletes (EA).[1] Distinguishing this phenotype from true underlying LV systolic dysfunction can be a difficult clinical conundrum[1] with important consequences for competitive sport participation.[2] The two conditions are sometimes considered mutually exclusive based on the assumption that excellent exercise capacity precludes significant pathology. However, we and others have described athletes with significant pathology diagnosed whilst continuing to compete at the highest level.[3–6] Thus, new methods are required to accurately separate health from pathology amongst athletes with ambiguous cardiac function at rest.

Guidelines suggest that exercise assessments of cardiac function can be used to differentiate athlete's heart from cardiomyopathy when resting measures of function appear abnormal.[7] Although a logical premise, there have not been any studies to support this assertion and the accuracy of exercise imaging is uncertain. We have previously demonstrated that real-time cardiac magnetic resonance imaging performed during exercise (ex-CMR) can be used to accurately quantify cardiac function and represents the ideal modality for investigating differences in contractile reserve between normal and diseased myocardium.[8–10]

This study sought to evaluate the cardiac response to dynamic exercise in ostensibly healthy EA with mildly reduced LVEF as compared with a group of non-athletic subjects with mild or early dilated cardiomyopathy (DCM). Furthermore, we tested whether ex-CMR was useful to identify sub-clinical cardiac damage. Therefore, we included a third group of highly trained athletes in whom CMR had incidentally detected significant LV fibrosis while they were still competing at an elite level with normal exercise capacity. We hypothesized that LV contractile reserve would be able to discriminate between healthy athletes and apparently normal athletic subjects with underlying LV damage.

Methods

Subjects

Thirteen EA (all male) with low normal resting LVEF were recruited using a prospective inclusion criterion of LVEF ≤52% measured by CMR, in accordance with previous studies.[1] These EA-healthy athletes were recruited from volunteers responding to advertisements at local triathlon and cycling clubs ($n = 4$) and from individuals referred to our institution ($n = 9$) after screening examinations revealed a mildly reduced LV systolic function in the absence of other signs of structural heart disease (i.e. normal wall thickness, no valvular heart disease, no regional wall motion abnormalities, and no signs of myocardial fibrosis). EA-healthy subjects were included if: (i) they were participating in regular cycling and/or running training of >6 h/week, (ii) they had no history of cardiovascular disease, and (iii) CMR at inclusion confirmed an LVEF ≤52%. Three athletes were excluded because CMR at enrolment revealed a normal LVEF prior to study participation. Therefore, the final EA-healthy cohort consisted of 10 subjects.

Nine patients with mild DCM (eight male) and five EA with fibrosis (EA-fibrosis, all male) were recruited from an existing database in addition to new cases presenting over the study period. The DCM cohort consisted of seven first-degree family members of DCM patients without an identifiable mutation and two patients with partially recovered severe DCM. All subjects had LVEF ≥40 and ≤52% measured by CMR prior to study participation. The cohort of EA-fibrosis subjects consisted of high-level EA in whom significant delayed gadolinium enhancement (11.4 ± 4.7% of LV mass) was detected after screening evaluation revealed pathological T-wave inversion or ventricular arrhythmias, as previously described.[4] Relative to our previous study cohort,[4] only those EA-fibrosis subjects referred to our institution were included in this study, as well as two new cases presenting during the study period. Therefore, the final cohort consisted of five EA-fibrosis subjects. An example of an EA-fibrosis subject is shown in *Figure 1*. All of the EA-fibrosis subjects developed ventricular arrhythmias resulting in exclusion from competitive sports participation.

To ascertain whether significant LV damage and elite exercise capacity could coexist, contractile reserve in the EA-fibrosis cohort was compared against a subset of EA-healthy subjects, matched for exercise capacity.

The study protocol conformed to the Declaration of Helsinki and was approved by the Ethics Committee of UZ Leuven (B322201214035). All subjects provided informed consent.

Study design

Prior to CMR evaluation, a 20-gauge arterial catheter was placed in the radial artery for the measurement of systemic arterial pressures. Subsequently, biventricular volumes were measured during supine cycling exercise using a real-time CMR method that we previously described and validated against invasive standards.[10] In brief, subjects performed supine exercise within the CMR bore using a cycle ergometer with adjustable electronic resistance (Lode, Groningen, The Netherlands). Images were acquired using a Philips Achieva 1.5 T CMR with a five-element phased-array coil (Philips Medical Systems, Best, The Netherlands) at rest and during supine bicycle exercise at 25%, 50%, and 66% of maximal power determined by previous upright cardiopulmonary exercise testing.[10] Steady-state free precession cine imaging was performed without cardiac gating. Imaging parameters were: field of view 320 × 260 mm (approximately), 128 × 128 matrix, flip angle 50°, SENSE factor 2 (Cartesian k-space under-sampling), repetition time 1.8 ms, echo time 0.9 ms, and reconstructed voxel size 2.3 × 2.3 × 8 mm. A 3D stack of 13–18 contiguous 8 mm image slices, covering both ventricles from apex to base, was serially acquired in the short-axis plane and subsequently in the horizontal long-axis plane. All image frames were acquired during free breathing with a temporal resolution of 36–38 ms.

Systemic arterial pressure measurements were continuously recorded during the exercise CMR protocol and analysed off-line using LabChart v6.1.1 (AD Instruments). Using in-house developed software (RightVol, Leuven, Belgium), LV and right ventricular (RV) end-diastolic volumes and end-systolic volumes (EDVi, ESVi) and left atrial and right atrial (LA, RA) maximal volumes and minimal volumes (V_{max}, V_{min}) were calculated by a summation of disks and indexed for body surface area. LVEF and RVEF were calculated as (EDVi–ESVi)/EDVi. Stroke volume was measured as EDVi – ESVi and cardiac index (CI) as the product of SVi and heart rate. If assuming that V0 (zero-volume intercept of the end-systolic pressure–volume relationship) is negligible, a single point LV end-systolic pressure–volume ratio (LVESPVR) can be calculated using the formula (0.9*systolic blood pressure)/LVESV as a surrogate of ventricular elastance.[9,11] LV contractile reserve was defined as a ratio of peak-exercise to resting LVESPVR (subsequently referred to as 'LVESPVR ratio'). Arterial elastance (Ea) was calculated as (0.9*systolic blood pressure)/LVSV.[11] As a measure of global atrial function, atrial total emptying

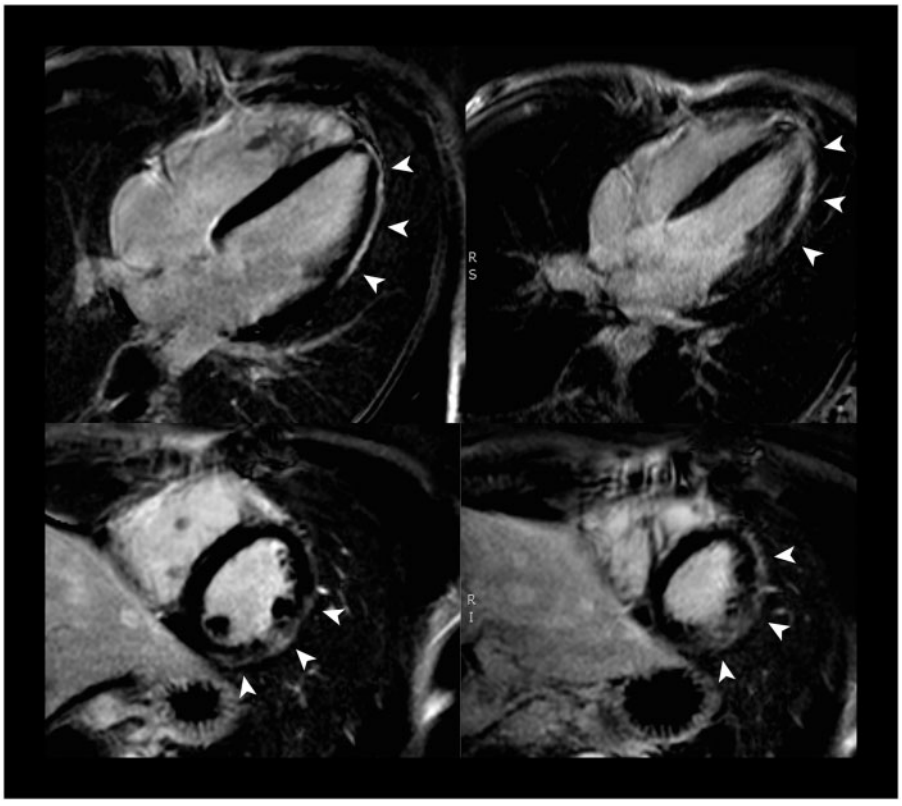

Figure 1 Example of an endurance athlete with significant subepicardial delayed gadolinium enhancement (arrowheads).

fraction (LAEF, RAEF) was calculated as $[(V_{max} - V_{min})/V_{max}]$.[12,13] NT-proBNP was analysed from venous blood samples.

Statistical analysis

Data were analysed using IBM SPSS statistics 22 software. Gaussian distribution of all continuous variables was tested using a Kolmogorov–Smirnov test. Descriptive data for continuous variables are presented as mean ± standard deviation or as medians (25% and 75% percentile) as appropriate. Comparisons between groups for continuous variables were performed by one-way analysis of variance (ANOVA) or the Kruskal–Wallis with Bonferroni or Dunn's test for multiple comparison *post hoc* correction, as appropriate. The Fisher's exact or the χ^2 test was used for categorical variables. To determine the sample sizes, the following estimates were used: in a previous study using exercise CMR, we demonstrated that healthy EA had an 8 ± 6% increase in LVEF from rest to maximal exercise.[9] According to our hypothesis, we predicted that LVEF will not change (0% increase) during exercise in the subjects with underlying LV damage.[14,15] Using these assumptions, a sample size of $n = 9$ was calculated to provide 80% power in detecting impaired LVEF augmentation during exercise in the groups with LV pathology ($\alpha = 5\%$, $1\text{-}\beta = 80\%$, $n = 9$). The biventricular volume response from rest to peak-intensity exercise in the different groups was compared using repeated measures ANOVA with exercise-intensity as within-subject effect and group (DCM vs. EA-fibrosis vs. EA-healthy) as a between-subject effect. Receiver operating characteristic (ROC) curves were constructed to determine the diagnostic accuracy of resting and exercise measures of LV function[16] for distinguishing EA-healthy subjects from both non-athletic and athletic subjects with underlying LV damage (expressed as area and 95% confidence intervals). The 'optimal' cut-off value for each parameter was defined as the value of the parameter that corresponded with the highest sum of specificity and sensitivity. The significance of differences in area under the curve (AUC) of the correlated rest and peak exercise ROC curves was tested using the methodology described by DeLong *et al.*[17] A *P*-value <0.05 was considered statistically significant.

Results

The demographic, clinical characteristics, and cardiopulmonary exercise testing data are presented in *Table 1*. All groups were of similar age and gender. As expected, both EA-healthy and EA-fibrosis cohorts had superior exercise capacity compared with DCM patients. A majority of DCM patients received therapy with a beta-blocker and angiotensin converting enzyme (ACE) inhibitor. All negative chronotropic medication was withheld for at least 24 h prior to exercise testing. NT-proBNP tended to be higher in DCM patients compared with the other groups. Invasive pressure measurement was performed in 20 of 24 study participants (6/10 EA-healthy, 9/9 DCM, and 5/5 EA-fibrosis). All EA-healthy subjects and DCM patients had resting LVEF <55% at the time of the exercise CMR protocol (noting some variability from the measure used for study inclusion). All of the EA-fibrosis subjects had significant delayed gadolinium enhancement (11.4 ± 4.7% of LV mass) as compared with two DCM subjects and none of the EA-healthy subjects. One of the EA-fibrosis subjects also had delayed gadolinium enhancement (DGE) of the RV free wall.

Table 1 Baseline characteristics

	EA-healthy ($n = 10$)	DCM ($n = 9$)	EA-fibrosis ($n = 5$)	ANOVA *P*-value
Clinical				
Age (years)	34 ± 12	44 ± 14	33 ± 8	0.149
BMI (kg/m^2)	23.8 ± 2.3	25.1 ± 3.8	22.0 ± 0.7	0.173
Weight (kg)	77.9 ± 9.2	78.2 ± 16.2	78.1 ± 6.0	0.998
Male, *n*	9	8	5	1.00
Medication				
Beta-blockers, *n*	0	6	1	0.005
ACE inhibitors, *n*	0	6	0	0.001
AR blockers, *n*	0	2	0	0.162
Biochemical				
NT-proBNP (pg/mL)	32 (14–49)	146 (51–320)	57 (19–83)	0.062
CPET				
VO_2peak (mL/min)	4343 ± 760	2253 ± 534*	5343 ± 532*,†	<0.001
VO_2peak (mL/min/kg)	56.2 ± 10.1	29.0 ± 5.3*	68.4 ± 4.2*,†	<0.001
Peak power (watts)	389 ± 70	206 ± 55*	444 ± 56†	<0.001
Peak HR (b.p.m.)	182 ± 8	164 ± 19*	176 ± 6	0.031
CMR at inclusion				
LVEF (%)	49.7 ± 1.9	47.7 ± 5.5	53.0 ± 9.2	0.243
DGE, *n*	0	2	5	<0.001

BMI, body mass index, AR, angiotensin II receptor; CPET, cardiopulmonary exercise testing; DGE, delayed gadolinium enhancement.
*$P < 0.05$ for difference vs. EA-healthy.
†$P < 0.05$ for difference vs. DCM.

Cardiac response to exercise

Resting and peak exercise cardiac haemodynamics are shown in *Table 2*. LV and RV end-diastolic volumes and RV end-systolic volumes were smaller in DCM compared with the EA-healthy and EA-fibrosis, whereas LV end-systolic volumes were similar.

At rest, LVEF was similar in the different groups. In the DCM and EA-fibrosis groups, less augmentation of LVEF (5 ± 6% vs. 4 ± 3% vs. 14 ± 3%; $P = 0.001$; *Figure 2*) and contractility [LVESPVR ratio; 1.4 (1.3–1.6) vs. 1.5 (1.3–1.6) vs. 1.8 (1.7–2.7); $P < 0.001$] was observed during exercise than EA-healthy. This was due to an attenuated reduction in LVESVi (*Figure 3*), whereas the response of LVEDVi was similar in all groups. Exercise-induced changes in Ea were similar between groups (+14 ± 23% vs. +13 ± 21% vs. 27 ± 8%; $P = 0.422$), whereas the change in LVESPVR was greater in EA-healthy compared with DCM and EA-fibrosis (+105 ± 51% vs. +38 ± 17% vs. +53 ± 18%).

In a sub-analysis comparing EA-fibrosis and EA-healthy ($n = 5$), matched for exercise capacity (VO_2peak 68.4 ± 4.2 vs. 64.0 ± 5.9 mL/kg/min; $P = 0.210$), the difference in LVEF reserve remained significant (ΔLVEF 4 ± 3% vs. 14 ± 2%; $P < 0.001$).

DCM patients had higher resting RVEF compared with EA-healthy and EA-fibrosis subjects, the latter groups having similar values. As compared with EA-healthy, the exercise-induced increase in RVEF was diminished in both DCM and EA-fibrosis (ΔRVEF 8 ± 6% vs. 5 ± 5% vs. 14 ± 4%; $P = 0.006$) due to an attenuated reduction in RVESVi ($P = 0.001$ for interaction). Similar to LV functional measures, neither DCM nor EA-fibrosis demonstrated an increase in LAEF or RAEF during exercise, whereas LAEF and RAEF increased in EA-healthy (*Figure 4*).

An example of exercise CMR comparing LV function in a DCM patient with EA-healthy and EA-fibrosis subjects is provided in *Figure 2* and Supplementary data online, *Video S1*.

Diagnostic accuracy to differentiate EA from DCM patients

Receiver-operator characteristic curves demonstrated that cut-off values of 11.2% for the increase in LVEF from rest to peak exercise (AUC = 0.92, $P < 0.001$) had a sensitivity of 93% and specificity of 90% to differentiate EA-healthy from DCM and EA-fibrosis, whereas the LVESPVR ratio of 1.8 (AUC = 0.94; $P = 0.003$) had a sensitivity of 83% and a specificity of 100% patients; *Figure 5*). In contrast, resting LVEF was not predictive (AUC = 0.56, $P = 0.598$). Similarly, VO_2peak was unable to accurately separate the cohorts (AUC = 0.68, $P = 0.128$). The AUC value for ΔLVEF was statistically different from that of resting LVEF ($P = 0.013$) and similar to that of the LVESPVR ratio ($P = 0.879$).

Discussion

The main goal of this study was to determine whether exercise evaluation of cardiac reserve enables differentiation between physiological adaptation to endurance exercise and pathological LV remodelling. Whereas LV systolic function was similar between athletes and DCM at rest, exercise imaging reliably distinguished between healthy athletes and those with pathology (DCM and athletes with LV fibrosis). Importantly, by comparing healthy athletes to elite EA with manifest LV fibrosis, we demonstrated that exercise capacity alone does not

Table 2 Cardiac haemodynamics

		EA-healthy ($n = 10$)	DCM ($n = 9$)	EA-fibrosis ($n = 5$)	*P*-value
Heart rate (b.p.m.)	Rest	66 ± 11	67 ± 8	52 ± 9*,†	0.025
	Peak ex	153 ± 20	142 ± 13	138 ± 20	0.238
Mean arterial pressure (mmHg)	Rest	88 ± 7	90 ± 10	81 ± 11	0.317
	Peak ex	113 ± 14	117 ± 15	109 ± 7	0.580
Ea (mmHg/mL)	Rest	1.9 ± 0.4	2.6 ± 0.6*	1.6 ± 0.4	0.003
	Peak ex	2.1 ± 0.5	2.9 ± 0.3*	2.1 ± 0.3	<0.001
LVEDV (mL/m^2)	Rest	122 ± 18	99 ± 23*	133 ± 11†	0.007
	Peak ex	124 ± 23	104 ± 26	134 ± 15	0.058
RVEDV (mL/m^2)	Rest	124 ± 22	81 ± 18*	125 ± 19†	<0.001
	Peak ex	119 ± 23	77 ± 20*	122 ± 22†	<0.001
LVESV (mL/m^2)	Rest	59 ± 9†	52 ± 15	63 ± 17	0.272
	Peak ex	44 ± 9	51 ± 22	58 ± 17	0.298
RVESV (mL/m^2)	Rest	59 ± 10	34 ± 10*	58 ± 2†	<0.001
	Peak ex	40 ± 9	26 ± 10	51 ± 17†	0.003
LVSV (mL/m^2)	Rest	63 ± 11	47 ± 10*	70 ± 9†	0.001
	Peak ex	81 ± 15	53 ± 9*	76 ± 8†	<0.001
RVSV (mL/m^2)	Rest	64 ± 11	47 ± 9*	67 ± 8†	0.001
	Peak ex	79 ± 15	51 ± 10*	71 ± 7†	<0.001
LVEF (%)	Rest	51.1 ± 2.8	47.7 ± 5.5	53.0 ± 9.2	0.215
	Peak ex	64.8 ± 3.7	52.8 ± 9.5*	57.2 ± 8.9	0.007
RVEF (%)	Rest	51.9 ± 2.1	58.4 ± 6.6*	53.9 ± 3.3	0.017
	Peak ex	66.3 ± 4.0	66.6 ± 5.9	59.0 ± 7.5	0.047
CI (L/min/m^2)	Rest	4.3 ± 1.4	3.1 ± 0.6	3.5 ± 0.5	0.070
	Peak ex	12.3 ± 3.4	7.4 ± 1.6*	10.1 ± 1.1	0.001
LAV_{max} (mL/m^2)	Rest	52 ± 8	46 ± 15	57 ± 11	0.219
	Peak ex	56 ± 18	53 ± 15	61 ± 20	0.745
RAV_{max} (mL/m^2)	Rest	78 ± 9	63 ± 26	95 ± 18†	0.020
	Peak ex	68 ± 22	66 ± 29	76 ± 22	0.755
LAV_{min} (mL/m^2)	Rest	27 ± 5	24 ± 8	36 ± 10†	0.020
	Peak ex	25 ± 8	31 ± 13	36 ± 11	0.202
RAV_{min} (mL/m^2)	Rest	42 ± 8	34 ± 15	59 ± 10*,†	0.003
	Peak ex	26 ± 9	34 ± 18	40 ± 13	0.188

LAV_{max}, left atrial maximal volume; LAV_{min}, left atrial minimal volume; RAV_{max}, right atrial maximal volume; RAV_{min}, right atrial minimal volume; RVEDV, right ventricular end-diastolic volume.
*$P < 0.05$ for difference vs. EA-healthy.
†$P < 0.05$ for difference vs. DCM.

exclude significant LV damage. Therefore, evaluation of contractile reserve may be a useful tool, which can be applied in both athletic and non-athletic populations to separate health from disease.

Although multiple studies reported profound increases in LV and RV mass and volumes due to intensive endurance training, significant variability exists in the extent of cardiac remodelling. In a study on Tour de France cyclists, Abergel *et al.*[1] reported that about one-half of athletes had substantial LV enlargement and 12% had an LVEF <52%, highlighting the diagnostic overlap between health and DCM. Accurate differentiation between these entities is of paramount importance. Incorrectly labelling an athlete with pathology could lead to inappropriate exclusion from sport and, of even greater consequence, failing to identify early pathology will mean that treatments with proven prognostic benefit (e.g. ACE inhibitors) may be delayed, and the patient may be exposed to an increased risk of cardiomyopathy and arrhythmic sudden cardiac death.[2,18] Current diagnostic tests rely on resting assessments and are unproven. Similarly, temporal cessation of sports activity ('detraining') incurs significant periods of uncertainty for the athlete and has not been shown to assist in decision-making. Given that athletic ventricular enlargement has been observed to persist for many years,[19] it is unlikely that short-term detraining could reliably distinguish athletic remodelling from pathology.

Our current results demonstrate that evaluation during exercise facilitates the differentiation between athlete's heart and pathological LV adaptation with considerable accuracy. In both groups with LV pathology, there was impaired contractile reserve characterized by failure to decrease end-systolic volumes and increase LVEF.[20] In contrast, healthy EAs demonstrated a consistent reduction in LV end-systolic volumes and a significant increase in LVEF, irrespective of resting LVEF. Although criticism is often levelled at the load-dependent volume measures and EF, we found no advantage in

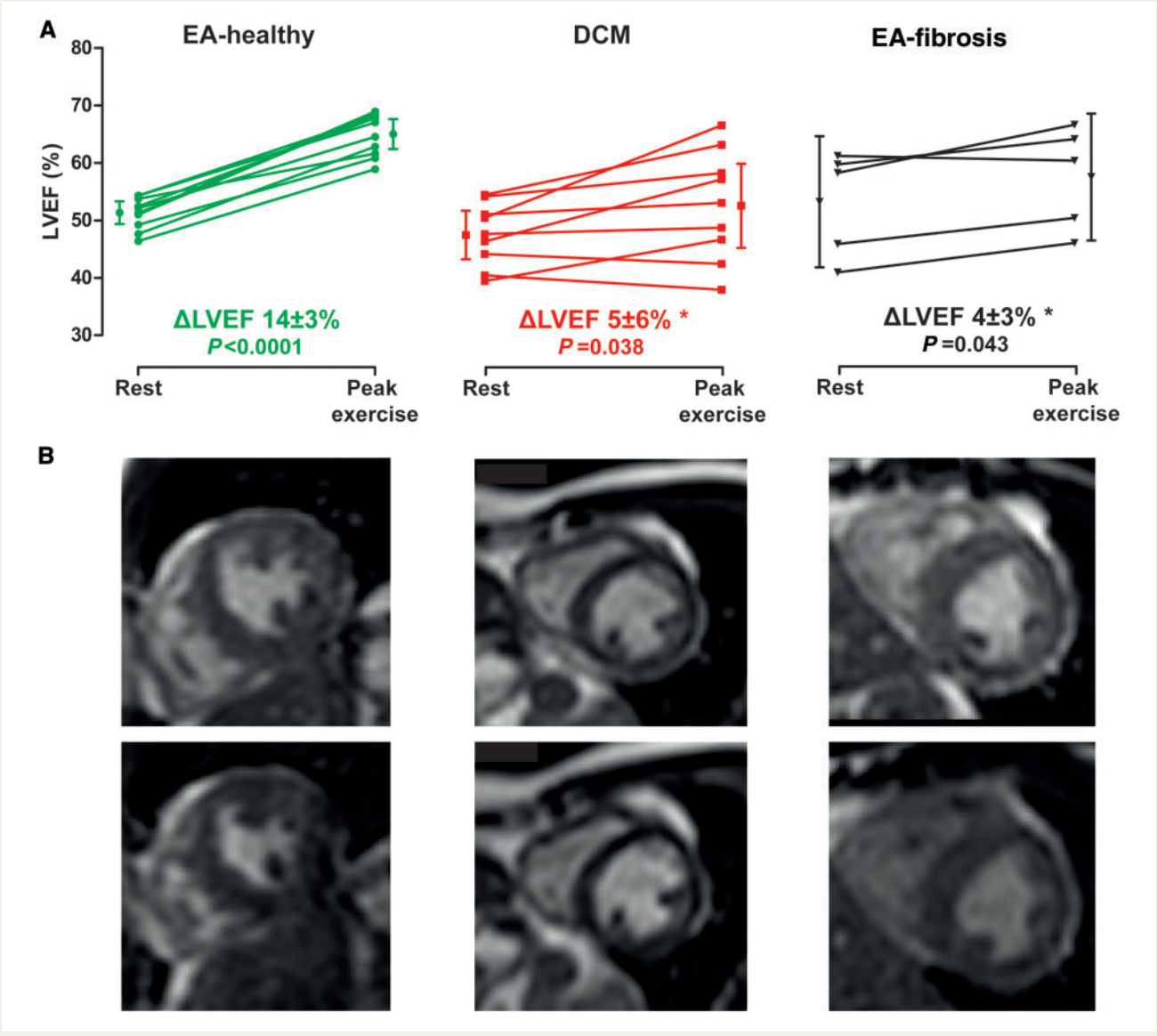

Figure 2 LVEF during exercise. All EA-healthy subjects demonstrate an increase in ΔLVEF during exercise as opposed to DCM patients and EA-fibrosis subjects in whom a heterogeneous response is observed (*A*). Asterisk indicates *P*-value <0.05 for the difference in ΔLVEF vs. EA-healthy. Error bars denote standard deviation. (*B*) End-systolic images at rest and at peak-exercise in a healthy EA, a patient with mild DCM and an EA with fibrosis. In the EA-healthy, LV and RV function augment with exercise. In contrast, LV function fails to augment in the DCM patient and the EA with fibrosis (right image).

combining these measures with invasively derived pressures. The most direct assessment of contractility would be to adjust volumes for pressure, and thus, we assessed the LV end-systolic pressure–volume relationship as a surrogate of contractility. DCM and EA-fibrosis subjects had similar changes in arterial elastance but reduced contractile reserve. Taken together, these findings suggest exercise-induced uncoupling between the LV and the arterial system, as evidenced by impaired augmentation of LVEF, a non-invasive surrogate of ventricular-arterial coupling.[21] Importantly, we demonstrated that purely non-invasive volumetric measures proved as accurate in separating health from disease. This provides obvious advantages for the future utility of these techniques. Future work will have to determine whether exercise echocardiography is as reliable as our CMR evaluation, although image quality and through-plane movement during exercise provide limitations in feasibility and reproducibility.[8]

An important finding of this study is that maximal peak oxygen consumption was paradoxically higher in athletes with LV damage compared with healthy EA, while peak CI was similar in both groups. In combination, these findings suggest that peripheral factors play an important role in the preservation of cardiopulmonary exercise performance despite a reduction in LV contractile reserve. This finding is in keeping with previous data in hypertrophic cardiomyopathy in which exercise testing facilitated the diagnosis in only one-fifth of subjects.[6] The EA with fibrosis in the current study were high-level

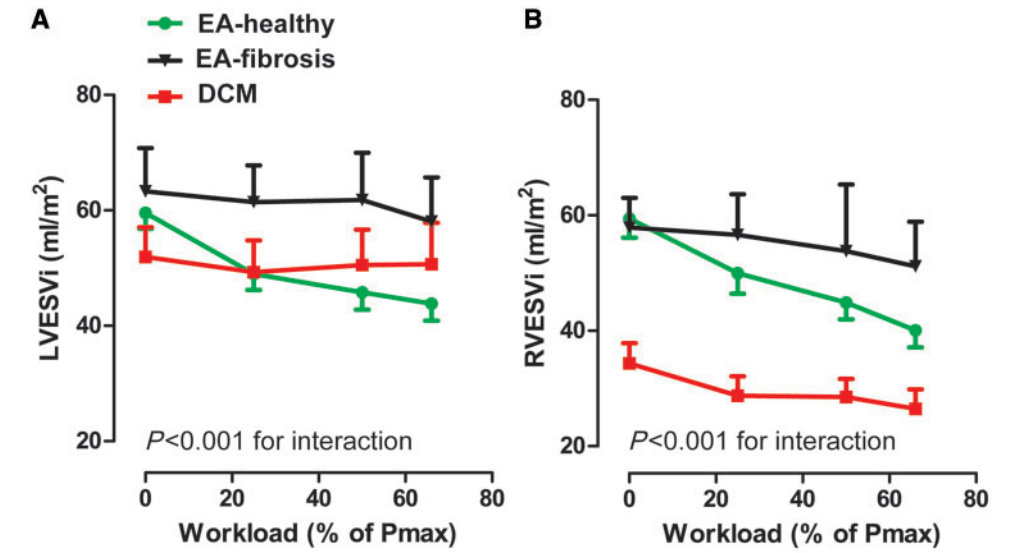

Figure 3 Changes in biventricular end-systolic volume during exercise. Changes in LVESVi (*A*) and RV ESVi (*B*) during incremental exercise are shown for EA-healthy (green), EA-fibrosis (black) and DCM patients (red). *P*-values are shown for the interaction between group and exercise-intensity. Error bars denote standard error of the mean.

competitive athletes as evidenced by their excellent exercise capacity. Hence, all of them had a VO_2peak >60 mL/kg/min. Nevertheless, they all presented with ventricular arrhythmias, either at initial workup or during follow-up, as previously reported, indicating that superb exercise capacity per se does not imply a good prognosis.[4]

Another important finding of this study is that the functional abnormalities during exercise were not restricted to the LV, but also involved the RV and both atria. Previous studies using radionuclide ventriculography or invasive techniques have assessed either the LV[16] or the RV[22] response to exercise in severe DCM. In addition, several studies used pharmacological stress echocardiography or stress CMR to assess LV or biventricular contractile reserve.[23–25] To date, however, no studies have evaluated the response of both ventricles and atria to incremental exercise simultaneously. In keeping with previous data, we found that the increase in RVEF was diminished in the DCM and particularly the EA-fibrosis group compared with healthy EAs. Furthermore, changes in bi-atrial function during exercise mirrored the changes observed in the ventricles, as evidenced by attenuated increases in LA and RA emptying function. This is in line with previous observations revealing that the degree of left atrial dysfunction at rest is greater than expected from the degree of atrial dilatation, thereby suggesting myopathy of the left atrium.[26] Moreover, there is data to suggest that left atrial myopathy may even precede LV myopathy and can be used for early detection and risk stratification in some cases.[27,28] In this context, the normal functional response of both atria to exercise in EAs in the current study provides additional reassurance that the low resting LVEF in EAs is not due to underlying myocardial pathology, but rather represents physiological remodelling.

The findings of this study have clinical implications for subjects at risk for the development of DCM, e.g. asymptomatic family members of patients with severe DCM or prior myocarditis. Due to the design of this study, comparing contractile reserve in EAs and patients with only mild DCM, the degree of resting LV impairment in the DCM group was substantially less profound than in previous studies evaluating contractile reserve in DCM.[14,22,23] As a result, exercise capacity was preserved, NTproBNP was only mildly elevated and the diagnosis of mild DCM was mainly based on a mildly reduced resting LVEF and a high index of suspicion due to disease in other family members. As such, these subjects were well suited for comparison with the EAs because the differentiation from Athlete's Heart would be clinically obvious in patients with severe DCM. Until present, there had been no studies evaluating LV contractile reserve in this subset of DCM patients with mild phenotype despite the recommendation to perform exercise imaging as part of the diagnostic workup.[7] We observed that LV functional reserve in the DCM patients was heterogeneous and independent of resting LVEF. This is consistent with previous data in patients with severe DCM,[14] which suggests that LV contractile reserve may improve clinical risk stratification and guide therapeutic management of these subjects in the early course of the disease. Further studies are required to verify whether those subjects with higher contractile reserve have better outcome as compared with those in whom cardiac function deteriorates during exercise.

Limitations

Firstly, the comprehensive measurements undertaken in this proof-of-concept study and the unique characteristics of the cohorts limited the sample size. The small sample size may have increased the probability of Type II statistical errors while multiple comparisons increase the likelihood of Type I errors. Nevertheless, to date this is the only study to compare exercise measures in EAs and DCM patients. It would have been valuable to include a control group of

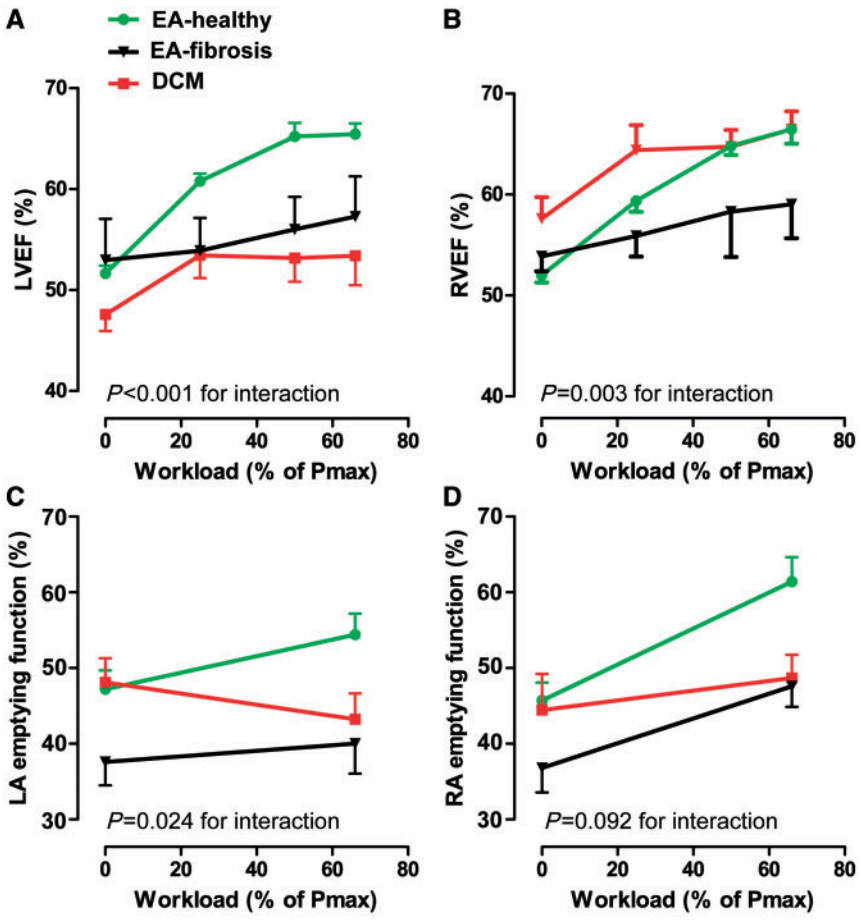

Figure 4 Changes in ventricular and atrial function during exercise. Changes in LVEF (*A*), RVEF (*B*) and LAEF (*C*) and RAEF (*D*) during incremental exercise are shown for EA-healthy (green), EA-fibrosis (black) and DCM patients (red). *P*-values are shown for the interaction between group and exercise-intensity. Error bars denote standard error of the mean.

athletes with established DCM. However, given the low prevalence of DCM amongst athletes, we included a cohort of elite EA with underlying LV damage associated with ventricular arrhythmias. This is the largest cohort to date to assess cardiac function and exercise metrics. The established accuracy of exercise CMR measures enabled us to evaluate meaningful haemodynamic differences even within this modest-sized cohort. The fact that highly significant differences were apparent reinforces the accuracy of ex-CMR and the extent of the physiological differences. Further larger and prospective studies are required to validate the cut-off values reported in this study.

LVESPVR is not equal to end-systolic elastance. Calculation of V0 typically requires the use of invasively derived pressure–volume loops, which was considered far too invasive for the scope of this study. Nevertheless, LVESPVR is considered a valid approximation of end-systolic elastance.[11,29] We cannot exclude that V0 changes during exercise. However, previous studies reported that V0 remains unaltered during exercise or changes in loading conditions.[30,31] As expected, the majority of DCM patients had received treatment including beta-blockers or calcium blockers. This introduces confounders in comparisons with the EAs and control subjects.

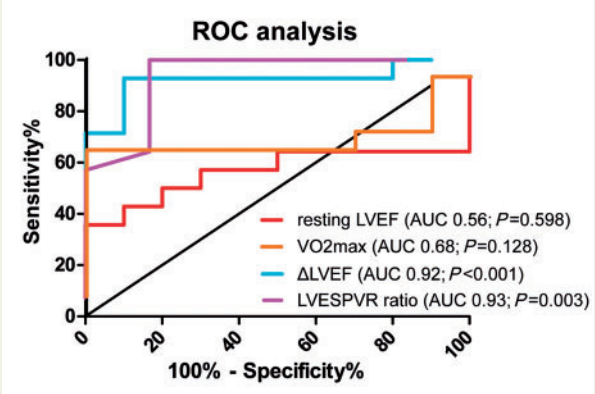

Figure 5 Differentiation between physiological and pathological left ventricular remodelling. Receiver operating curves for the ability of resting and exercise measurements of LVEF and ΔLVEF, peak oxygen consumption (VO_2peak), and contractility (end-systolic pressure–volume ratio) to differentiate healthy EAs with physiological remodelling from DCM patients and EAs with fibrosis.

However, beta-blocker and calcium channel blocking medications were withheld for at least 24 h prior to exercise testing; a period sufficient to exclude any persisting pharmacodynamic effect. Finally, although the cardiac response to exercise in the EAs was similar to previous observations in healthy athletes,[9] longer follow-up is necessary to assess whether the mildly reduced resting LV function is associated with clinical events, e.g. arrhythmias, in the long term. Similarly, larger studies are required to verify whether assessment of contractile reserve provides additional value for risk stratification in DCM patients with mildly reduced LVEF.

Conclusions

Neither exercise capacity nor resting measures of cardiac function are helpful in differentiating healthy athletes with borderline LVEF from those with myocardial impairment or fibrosis. On the other hand, augmentation of biventricular and atrial function during exercise are important tools that can accurately differentiate between physiological and pathological LV remodelling.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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