Left Ventricular Adaptation to Exercise Training via Magnetic Resonance Imaging: Studies of Twin Responses to Understand Exercise THerapy

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ABSTRACT

MARSH, C. E., H. J. THOMAS, L. H. NAYLOR, L. G. DEMBO, K. J. SCURRAH, and D. J. GREEN. Left Ventricular Adaptation to Exercise Training via Magnetic Resonance Imaging: Studies of Twin Responses to Understand Exercise THerapy. *Med. Sci. Sports Exerc.*, Vol. 54, No. 7, pp. 1095–1104, 2022. **Purpose:** Changes in left ventricular mass (LVM) and end-diastolic volume (EDV) in response to exercise training are important determinants of functional capacity in health and disease, but the impact of different exercise modalities remains unclear. **Methods:** Using a randomized crossover design we studied the impact of resistance (RES) and endurance (END) training using cardiac magnetic resonance imaging in previously untrained monozygotic (MZ) and dizygotic (DZ) twin pairs ($n = 72$; 22 MZ pairs, 14 DZ same-sex pairs; 26.1 ± 5.4 yr). Twins, as pairs, undertook 3 months of RES and 3 months of END training (order randomized), separated by a 3-month washout. **Results:** Group results revealed that END increased LVM ($P < 0.001$) and EDV ($P = 0.007$), whereas RES did not ($P > 0.05$). A higher proportion of individuals responded to END than RES for LVM (72% vs 38%, $P < 0.001$) and EDV (67% vs 40%, $P = 0.003$). Baseline cross-sectional intraclass correlations were higher for MZ than DZ twin pairs for all variables (e.g., LVM heritability = 0.42), but no significant correlations were apparent between pairs for change in any variable in response to either RES or END ($P > 0.05$). **Conclusions:** Our findings indicate that cardiac adaptation in response to exercise is modality-specific and that low responders to one mode of exercise can be high responders to an alternative. Heritability estimates based on cross-sectional data, which suggested a genetic contribution to LVM, do not accord with estimates based on training effects, which indicated limited genetic impact on adaptation in this 3-month study of exercise training. This study has implications for understanding the physiological and health impacts of typically used exercise modalities on cardiac adaptation in previously untrained individuals. **Key Words:** TWINS, HERITABILITY, GENETICS, CARDIAC, MRI

Endurance (END) and resistance (RES) training are commonly prescribed modalities used by health and exercise professionals to induce distinct physiological adaptations. Although these modalities of exercise induce different acute hemodynamic responses (1), their impact on cardiac adaptation in response to training in inactive individuals has not been well described. Previous data from a 6-month exercise intervention study in male subjects indicated that left ventricular mass (LVM) increased after END, but not RES training, and that lean body mass increased in response to both RES (2.3 ± 0.4 kg) and END (1.4 ± 0.6 kg). These data suggested that cardiac morphological adaptation to exercise may be modality-specific (2). However, subjects in that study completed only one form of training (END or RES) and unintentional randomization bias could not be ruled out. A randomized crossover design, where each individual completes both training modes (END *and* RES), separated by a washout period, is an ideal approach to assess adaptation to distinct exercise modalities. In this way, individual responses to each mode of training can be compared within subjects to determine whether response to one mode implies adaptation to the alternative. We designed such an experiment (3) and have recently reported outcomes pertaining to fitness (4), body composition (5), and cerebrovascular function (6).

A classical twin study design, comparing monozygotic (MZ) and dizygotic (DZ) twin pairs, provides a powerful platform to estimate genotypic versus environmental contributions to different human traits (7–9). However, relatively few studies have used

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a twin paradigm to assess training effects on cardiac adaptation (10,11), and these studies either adopted rudimentary imaging approaches or did not exercise train MZ and DZ twins. Cardiac magnetic resonance imaging (CMR) is the contemporary criterion standard for quantifying cardiac morphology in humans (12,13), providing high-resolution three-dimensional imaging for precise volumetric measurement, free from geometrical assumptions (12). Few previous studies of exercise training have used CMR as a modality for assessment of changes in cardiac morphology.

In this randomized crossover study using CMR and a classical twin paradigm, we hypothesized that exercise responsiveness would be modality-specific; that low-responders to one training mode may nonetheless be high responders to the other; and that the genetic contribution to traits based on cross-sectional comparison of twin pairs may not accurately reflect genetic contributions to training. Results of this study will inform the fundamental understanding of cardiac adaptation to exercise training in humans and provide insight into the genetic versus environmental contributions to adaptation resulting from distinct modes of training.

METHODS

Ethical approval. This study was approved by the University of Western Australia Human Research Ethics Committee (RA/4/7031). Written informed consent, which conformed to the Declaration of Helsinki, was obtained from each participant. Full details of the study design and experimental procedures can be found in our protocol article (3), and study registration (ACTRN12616001095459), which was published before subject recruitment.

Participants. Initial CMR cross-sectional testing included 72 subjects (36 healthy same-sex twin pairs, 22 MZ, 14 DZ; age, 26.1 ± 5.4 yr; range, 17–40 yr). After this, 60 individuals (n = 30 pairs, 20 MZ 10 DZ) participated in the training interventions. Two of these individuals were excluded from the concordance results (n = 58 individuals) due to failure to complete their second exercise intervention (RES; Supplemental Fig. 1, Supplemental Digital Content 1, consort diagram, http://links.lww.com/MSS/C534). Inclusion criteria comprised young, healthy individuals who did not meet Australian government guidelines for physical activity (<150 min·wk^{-1}) (14), were nonsmokers, and medication-free. Subjects were, therefore, typical of community-based individuals who might embark on a new exercise regime for health and fitness benefit. A DNA test was administered to verify the zygosity of each twin pair (EasyDNA AU, Springwood, QLD).

Study design. After baseline testing, twin pairs were randomized, together as a pair, to complete either the 3-month RES or END training intervention (see study design in Marsh et al. (3) and Fig. 1). Before crossing over to complete 3 months of the alternate mode (RES or END), participants underwent a 3-month washout period, during which they were instructed to maintain their usual level of activity and diet. We chose a 3-month washout based on recent CMR evidence of regression of athletic hypertrophy within 1 month of detraining (15). Briefly, each intervention consisted of 3 × 1 h sessions per week, for 12 wk, the programs were center-based, supervised by an Accredited Exercise Physiologist/Scientist and progressively overloaded: END training involved 2× running and 1× cycling session per week progressing from 60% to 90% heart rate maximum (based on individual $\dot{V}O_{2max}$ test data); RES training involved alternating between upper/lower body major muscle groups, and each session progressed from 60% to 90% of one-repetition maximum (1-RM).

Comprehensive details of our training approaches, including the ongoing progression and overload of the training intensities are provided in our methods article (3). The 12-wk END program followed a periodized progressive macrocycle plan consisting of three mesocycles of 4 wk each. The first mesocycle, the "general preparatory" phase (weeks 1–4), consisted of low training intensity/volume (walking/jogging at 60% HR, 1–2.5 km

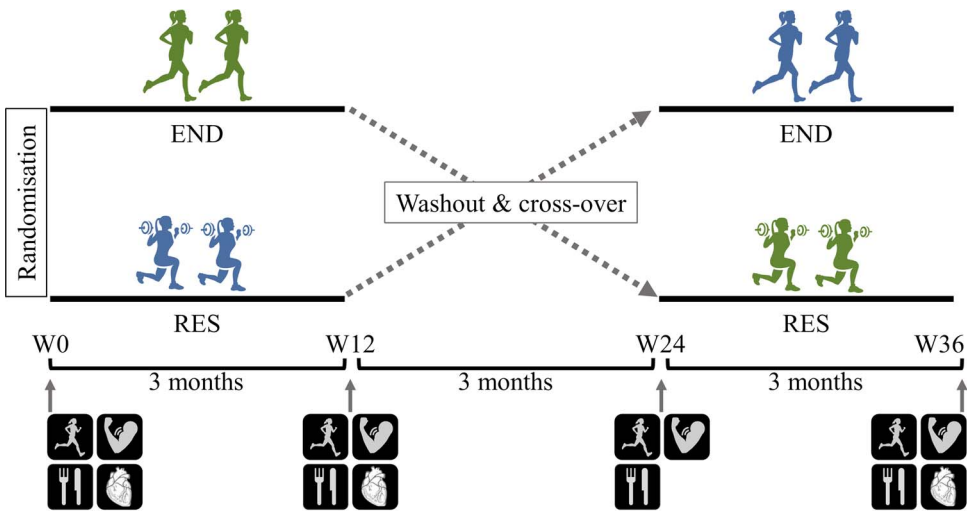

FIGURE 1—Study design. Twin pairs were randomized together to complete 3 months of an exercise intervention (RES or END), followed by 3 months washout period and crossover to complete 3 months of the alternate exercise modality. Outcome measures, including cardiac magnetic resonance imaging, cardiorespiratory fitness and strength, a food diary and physical activity monitoring, were collected in response to training.

running and/or 15–25 min cycling/running) including a long warm-up focusing on running drills, technique and dynamic stretching. The second mesocycle, the "high intensity" phase (weeks 5–8), consisted of higher intensity work with higher HRs (up to 90%), and distance/duration (2.5–5 km running and/or 25–40 min cycling/running). The final mesocycle, the "maintenance and distance" phase (weeks 9–12), consisted mostly of maintaining subthreshold HRs (70%–85%) for longer distance/duration (5–7 km running and/or 40 min in week 9–60 min by week 12 cycling/running). In the mesocycles, a 1:1 structure loading existed with a "hard" loading week followed by an "easier" or "maintenance" week. Within each week, there existed a structured load with a "harder" run session, an "easier" run session and the cycling session was always the longest duration session in each week, adopting many principles from previously published work. The 12-wk RES training program also followed a periodized plan consisting of four mesocycles of 3 wk each. The first mesocycle focused on muscular endurance (weeks 1–3) where intensity was low (60%–70% 1-RM), reps were high (12–15 reps) and rest periods between sets were short (30–60 s), allowing participants to focus on forming good technique habits, condition muscles and assist recovery between sessions. The second mesocycle focused on muscular hypertrophy (weeks 4–6) where intensity increased (70%–75%), reps decreased (10–12 reps), but rest periods remained short between sets (30–90 s). Weeks 7 to 9 were a progressive step between muscular hypertrophy and strength where intensity increased (75%–80%), reps decreased (8–10 reps), and rest periods between sets increased (1–2 min). The last mesocycle focused on improving muscular strength where intensity increased (80%–90%), reps decreased (5 reps) and rest periods between sets increased (3–5 min). Each session focused on one of the five main exercises (two upper body—bench press and standing military press; three lower body—squats, deadlift and leg press) that were rotated, alternating upper and lower body on separate days. There were secondary exercises performed during each session that used muscle groups that were similar to, or would assist in performing, the main exercise of the session (i.e., staggered feet leg press, seated row, lat pulldown). To guide participants' progressions, 1-RM assessments were repeated half way through their 12-wk program.

Outcome measures Briefly, CMR (Magnetom Espree, Siemens, Erlangen, Germany) was completed at week 0 and immediately after each exercise modality (weeks 12 and 36) to assess left ventricular (LV) outcomes, and analyzed with specialized software (ARGUS, Siemens, Supplemental Fig. 2, Supplemental Digital Content 1, analysis of LV image, http://links.lww.com/MSS/C534). The subjects were scanned supine with a posterior phased array spine coil and an anterior flexible phased array body surface coil. Multiplane breath-hold (BH) trueFISP localizers were acquired to obtain the standard cardiac imaging planes. For all sequences the BH times were between 5 and 20 s, dependent on the subject's heart rate. To evaluate functional parameters, BH trueFISP cine images were acquired using a retrogated ECG trigger covering the whole R–R interval. Images of the LV were acquired in short axis plane, perpendicular to the ventricular septum. Between 10 and 12 slices were acquired (6-mm slices/4 mm gap; FoV, 320–350 mm; TR, 37.68; TE, 1.29; flip angle, 70°–80°; resolution, 256 × 166; BW, 930). Cine images of the four-chamber and LV outflow tract were also acquired (6-mm slices; FoV, 300–330 mm; TR, 38.28; TE, 1.32; flip angle, 70°–80°; resolution, 224 × 224; BW, 930).

To assess LV morphology, systemic and pulmonary outflow tracts were autosegmented in individual slices on cine images and then manually adjusted where necessary. Short axis cine loops were inspected to define LV end-diastolic volume (EDV) and end-systolic volume (ESV) frames. The mitral valve markers were automatically displayed on two- and four-chamber cine views but could be manually manipulated if inconsistent tracking occurred throughout the slices. The basal LV slices were taken as the first slice below the level of the mitral valve. Therefore, volumes above the aortic valve and those surrounding the thin myocardial wall in the mitral valve plane were excluded from analysis. Endocardial and epicardial LV borders were automatically contoured (but could be manually manipulated if required), including the septum but excluding the papillary muscles, which were added to LV EDV and LV ESV in accordance with the methods described previously (2). Left ventricular mass was calculated by summing the LV EDV within the epicardial and endocardial borders of the short-axis slices, multiplying the myocardial tissue volume by its specific density (1.05 $g \cdot cm^{-3}$). The LV EDV and LV ESV were used to ascertain stroke volume, ejection fraction, and cardiac output.

To characterize positive and negative change in CMR-based outcomes as a result of each training modality, we used a simple dichotomous criterion of response above, versus below, zero. Because some investigators have argued that measurement variability should be considered when defining responsiveness, we also superimposed (on Fig. 2) the widely cited reproducibility data of Bellenger et al. (12). Concordance graphs (Fig. 3) present each individual's response to both RES and END, with percentages for each quadrant included: concordant +END/+RES (positive responses to both modes based on our criterion of >0) or −END/−RES (≤0 response to either modality), and discordant +END/−RES or −END/+RES (>0 response to only one modality), for RES and END interventions. Supplemental Figure 3, Supplemental Digital Content 1, http://links.lww.com/MSS/C534, individual training responses, presents these data with added detail regarding those individuals who exceeded the random variability limits based on the reproducibility article of Bellenger et al. (12).

As described in our published body composition article (5), dual-energy x-ray (DXA) absorptiometry (Lunar iDXA; GE Healthcare, USA) was used to assess lean mass (LM) at each time point. Standard calibration and quality assurance procedures were used, in line with the equipment documentation (www3.gehealthcare.com). Participants arrived at the laboratory at the same time for each of the measurements (pre-and post-each exercise intervention), usually in the afternoon/evening. Participants were instructed to fast for 3 h, be normally hydrated (i.e., not hyper/hypo-hydrated) and were offered use of the toilet prior to undergoing testing. The intertester and

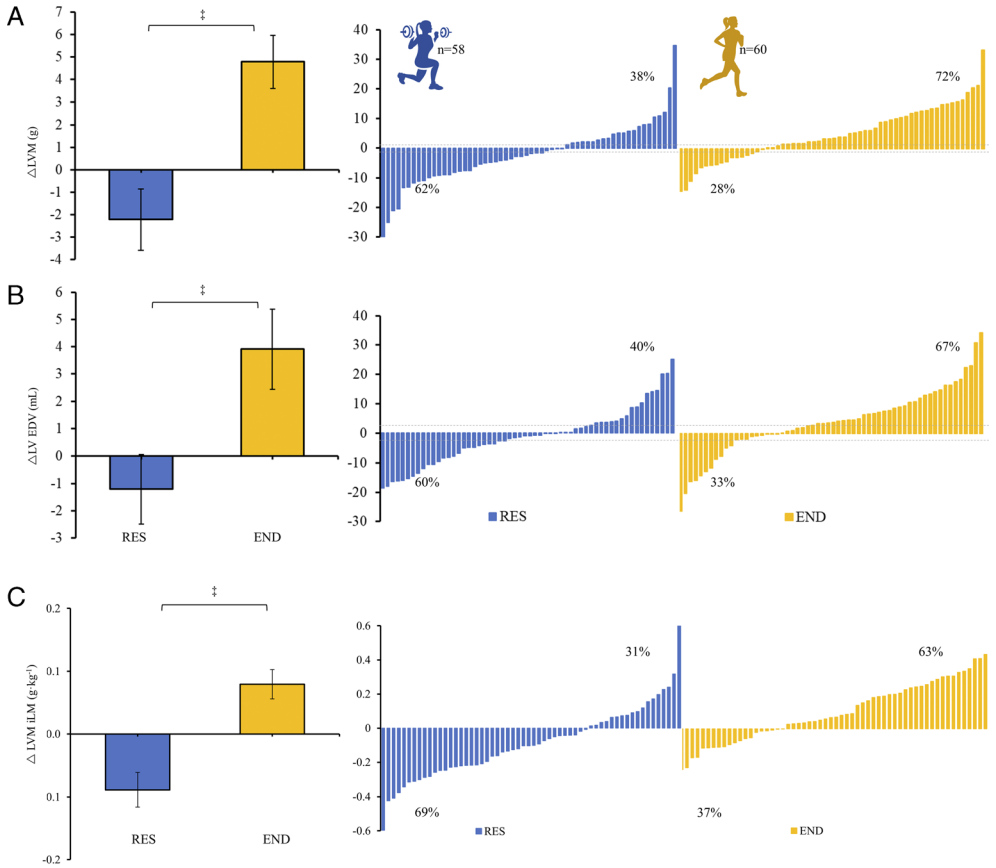

FIGURE 2—Changes (Δ) with RES (blue) and END (yellow) for left ventricular mass (LVM top panel, A), EDV (panel, B) and LVM iLM (panel C) for group responses (left), and individual responses (RES middle, END right) to training. ‡*P* < 0.005. Dotted lines indicate the mean differences for repeated measures using cardiac magnetic resonance imaging based on the widely cited reproducibility study of Bellenger et al. (2000). These data indicate that 95% (for LVM) and 77% (for EDV) of subjects for END training exhibit larger changes than those expected from repeated measures variability. For RES, 95% (for LVM) and 72% (for EDV) of subjects exceeded these variability levels.

intratester reliability results of our machine are very highly repeatable (ICC >0.99 in 52 tested participants). A food diary and physical activity monitor (Actiheart 4; CamNtech Ltd, Cambridge, UK) assessed incidental behavioral change in diet and physical activity at each time point.

To allow for comparison to previous articles, we scaled LVM via simple normalization (Y/X) with body surface area (BSA). However, it has previously been suggested that this form of scaling is flawed and does not provide a robust estimate of the true relationship between body size and heart size (16,17). We therefore used DXA-derived lean body mass to scale LVM. Since George et al. (18) stated that "The relationship between LV mass and lean body mass ($b = 0.90 \pm 0.15$; $r^2 = 0.66$) was linear and geometrically consistent" and concluded that "Lean body mass was the most appropriate variable for simple indexing of LV mass" we undertook analysis on absolute data and also using a simple ratio to lean body mass.

Statistical analysis. Statistical analyses were performed with SPSS 20.0 (IBM Australia Ltd, New South Wales, Australia) and STATA 11 software (StataCorp, College Station, TX). Differences between zygosity (Table 1) were assessed using a linear mixed model that adjusted for twin correlation. Likewise, the effects of the exercise interventions (Table 2) were assessed for each outcome measure using a linear mixed model, which accounted for the repeated nature of the data and pairing within the twins, with age and sex as covariates. For LVM, we additionally performed a linear mixed model analysis using LM as a time varying covariate. A *z* test was used to assess the differences in individual response rates between exercise interventions, and concordance versus discordance for each variable. Significance was $\alpha < 0.05$. We used the highly cited formal CMR reproducibility data of Bellenger et al. (12), who used similar approaches to those in our study, and assuming two-tailed tests and $\alpha = 0.05$, $n = 58$ provides 94% power to detect a change in LVM of 3 g and 99% power to detect a change EDV of 3 mL. Given that a degree of interrater variability and technical variability is inherent in image analysis, we performed additional data verification steps for a subset of individuals who showed larger changes in LVM and EDV with training, as described in Supplemental Appendix, Supplemental Digital Content 2, treatment of potential outliers, http://links.lww.com/MSS/C535.

The comparison of MZ and DZ twin pairs allows the proportion of variation in phenotypes to be determined for additive genetic effects (A; e.g., unmeasured genetic effects) or environmental effects which are shared (C; e.g., growing up in the same household) and/or environmental effects which are unshared

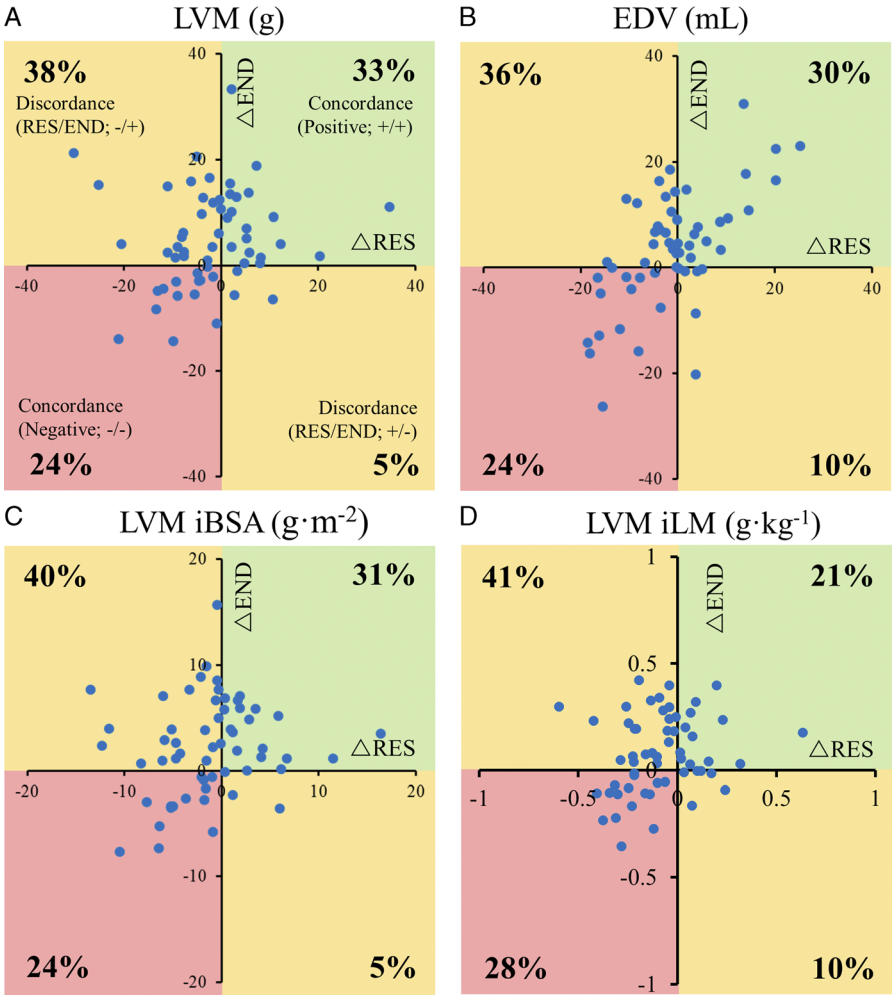

FIGURE 3—Individual subject (n = 58) change (Δ) in response to RES and END training plotted against one another on the x and y axes, respectively. Responses (%) for each quadrant are reported for LVM (A, figure key), EDV; (B), LVM iBSA (C) and LVM iLM (D).

(E; e.g., playing different sports) (19). Mixed-effects models were used to calculate intraclass correlation coefficients (ICC, r) for twin pairs (Table 3). Significant differences between ICC (rMZ vs rDZ) were assessed using the likelihood-ratio test in STATA to compare mixed effects models constraining and not constraining covariances for MZ and DZ pairs to be equal (20). If rMZ was significantly different to rDZ then A, C, E and 95% confidence intervals (Supplemental Table 1, Supplemental Digital Content 1, details of intraclass correlations, http://links.lww.com/MSS/C534) were calculated using the delta method. When rMZ and rDZ were not significantly different, a single model calculated C and E components only. If the DZ ICC was ~0, suggesting possible violation of the equal environments assumption, then a model estimating covariance for MZ but fixing DZ covariance to be zero was fitted.

TABLE 1. Baseline characteristics of participants enrolled in the study.

	MZ	DZ	
	n = 44	n = 28	P
Age (yr)	27.5 ± 6.0	24.2 ± 4.6	0.058
Height (cm)	174.1 ± 6.6	171.0 ± 8.1	0.189
Weight (kg)	76.0 ± 19.1	61.8 ± 10.5	0.003
BSA (m^2)	1.90 ± 0.26	1.71 ± 0.17	0.004
LM (kg)	49.1 ± 9.7	43.5 ± 8.8	0.061
BMI ($kg \cdot m^{-2}$)	24.9 ± 5.5	21.1 ± 2.7	0.003

Data are presented as mean ± SD.
BMI, body mass index.

RESULTS

Participant characteristics. Baseline characteristics are included in Table 1. Daily caloric intake and energy expenditure did not differ between zygosities at baseline ($P > 0.16$) or change across the study ($P > 0.22$), as previously reported (5).

TABLE 2. Left ventricular baseline and response to training group mean changes.

	Baseline	Δres	ΔEnd	RES vs END (P)
LVM (g)	105.4 ± 31.6	−2.2 ± 10.4	4.8 ± 9.1***	<0.001
LVM iBSA ($g \cdot m^{-2}$)	55.9 ± 11.8	−1.3 ± 5.4	2.2 ± 4.5***	<0.001
LVM iLM ($g \cdot kg^{-1}$)	2.17 ± 0.28	−0.09 ± 0.21***	0.08 ± 0.18***	<0.001
EDV (mL)	154.9 ± 30.6	−1.2 ± 9.6	3.9 ± 11.4**	<0.001
ESV (mL)	59.6 ± 15.9	−0.7 ± 8.5	0.8 ± 8.5	0.170
SV (mL)	95.2 ± 18.4	−0.6 ± 9.1	3.1 ± 9.7*	0.005
CO (L)	6.24 ± 1.20	0.00 ± 1.03	−0.02 ± 1.16	0.568
EF (%)	61.8 ± 5.0	0.2 ± 4.7	0.3 ± 4.4	0.944

Data are presented as mean ± SD.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.005$.

TABLE 3. Intraclass correlations and ACE components for MZ and DZ twins, for left ventricular outcomes.

		rMZ	rDZ	*P* rMZ vs rDZ	A	C	E
LVM (g)	CX^{ACE}	0.91*	0.59**	0.008	0.42	0.48	0.01
	ΔRES	0	0				
	ΔEND	0.05	0				
LVM iBSA ($g \cdot m^{-2}$)	CX^{C}	0.87*	0.38			0.88	0.12
	ΔRES	0	0				
	ΔEND	0	0.34				
LVM iLM ($g \cdot kg^{-1}$)	CX^{ACE}	0.95*	0.84*	0.027	0.15	0.80	0.05
	ΔRES	0	0				
	ΔEND	0.10	0.09				
EDV (mL)	CX^{CE}	0.82*	0.71*	0.07		0.79	0.21
	ΔRES	0.09	0				
	ΔEND	0.08	0				
ESV (mL)	CX^{CE}	0.78*	0.74*	0.20		0.77	0.23
	ΔRES	0	0.09				
	ΔEND	0.07	0				
SV (mL)	CX^{CE}	0.75*	0.47***	0.08		0.69	0.31
	ΔRES	0	0				
	ΔEND	0.34	0.29				
CO (L)	CX^{C}	0.34***	0.27			0.43	0.57
	ΔRES	0.11	0				
	ΔEND	0.34	0				
EF (%)	CX^{C}	0.57*	0.31			0.59	0.41
	ΔRES	0	0.23				
	ΔEND	0.27	0.36				

*$P < 0.005$.
**$P < 0.01$.
***$P < 0.05$.
CX, cross-sectional; A, additive genetic effects; C, shared environmental effects; E, individual environmental effects. ^{ACE}ACE method, normal method used when rMZ, rDZ, and likelihood ratio test (*P* rMZ vs rDZ) are significant; ^{CE}CE method, C and E calculated when *P* rMZ vs rDZ is not significant; ^{C}Revised model C, a new method to calculate revised rMZ, when rDZ is not significant. Note: variance components models were not fitted when rMZ nor rDZ were significantly different from 0.

Compliance with completed training sessions was 94% for RES and 95% for END, and the training interventions were effective with specific regards to muscular strength and cardiorespiratory fitness adaptation, as previously reported (4). Briefly, muscular strength increased after RES but not END training (leg press, Δ47.0 vs 3.0 kg, $P < 0.001$; bench press, Δ5.1 vs −0.4 kg; $P < 0.001$), and $\dot{V}O_{2max}$ increased after END but not RES (Δ3.61 vs 0.03 $mL \cdot kg^{-1} \cdot min^{-1}$; $P < 0.001$). In terms of body composition changes for the subjects who had CMR assessed, DXA-derived LM increased after RES (47.8 ± 9.8 kg pre vs 48.9 ± 9.9 kg post; Δ1.08 ± 1.10 kg; $P < 0.001$) and END training (48.3 ± 9.5 kg pre vs 48.6 ± 9.6 kg post; Δ0.28 ± 1.07 kg; $P < 0.05$). The change in LM with training was significantly greater in response to RES than END ($P < 0.001$).

For group mean responses (Table 2, Fig. 2, Supplemental Figures 4 and 5, Supplemental Digital Content 1, http://links.lww.com/MSS/C534), END increased EDV ($P = 0.007$), stroke volume (SV) ($P = 0.01$), LVM ($P < 0.001$), LVM indexed to BSA ($P < 0.001$), and LVM indexed to LM ($P = 0.001$). RES *decreased* LVM indexed to lean body mass (iLM) ($P = 0.001$). When LVM was analyzed with LM as a time varying covariate, the reduction in LM-adjusted LV mass after RES was highly significant ($P = 0.007$ vs unadjusted $P = 0.119$). With END training, the increase in adjusted LV mass remained significant at ($P = 0.009$ vs unadjusted $P < 0.001$). Analysis of cardiac sex differences from the current cohort has previously been published (21).

Was response modality-specific? Individual response to each exercise intervention is plotted in Figure 2, and Supplemental Figures 4 (Supplemental Digital Content 1, BSA-indexed LVM, http://links.lww.com/MSS/C534) and 5 (additional cardiac variables). The response rates (values >0) were higher for END (72%) compared with RES (38%) for LVM ($P < 0.001$), LVM iBSA ($P < 0.001$), LVM iLM ($P < 0.001$), and EDV ($P = 0.003$). Therefore, the magnitude of responsiveness was modality-specific, with a larger LV response to END than RES training for most morphological outcomes. The superimposed measurement variability data indicate that 95% (for LVM) and 77% (for EDV) of subjects for END training exhibited larger changes than those expected from repeated measures variability. For RES, 95% (for LVM) and 72% (for EDV) of subjects exceeded these variability levels.

Was the response of individuals concordant between modalities? Concordance graphs (Fig. 3 and Supplemental Figure 6 (Supplemental Digital Content 1, concordance for additional cardiac variables, http://links.lww.com/MSS/C534)) present each individual's response to both RES and END. Supplemental Figure 3 (Supplemental Digital Content 1, http://links.lww.com/MSS/C534) presents these data with added detail regarding those individuals who exceeded the random variability limits based on the reproducibility article of Bellenger et al. (12).

There were no significant differences between the percentage of individuals who were concordant (57%) versus discordant (43%) for LVM ($P = 0.14$; Fig. 3), LVM iBSA (55% vs 45%, $P = 0.27$; Fig. 3), LVM iLM (49% vs 51%, $P = 0.71$; Fig. 3), or EDV (54% vs 46%, $P = 0.27$; Fig. 3). A higher percentage of individuals were concordant than discordant for ejection fraction (EF) (66% vs 34%, $P = <0.001$), ESV (66% vs 34%, $P < 0.001$), SV (74% vs 26%, $P < 0.001$) and cardiac output (CO) (65% vs 35%, $P < 0.001$); all Supplemental Figure 6 (Supplemental Digital Content 1, concordance for additional cardiac variables, http://links.lww.com/MSS/C534).

Pearson bivariate correlations for individual responses between RES and END training revealed moderate correlations for EF ($r = 0.44$, $P = 0.001$), EDV ($r = 0.63$, $P < 0.001$), ESV ($r = 0.47$, $P < 0.001$), SV ($r = 0.51$, $P < 0.001$), and CO ($r = 0.49$, $P < 0.001$). There were no significant correlations for LVM ($r = 0.11$, $P = 0.41$), iBSA ($r = 0.16$, $P = 0.23$), and iLM ($r = 0.20$, $P = 0.14$). Correlation between LVM and EDV was significant for END training ($r = 0.35$, $P = 0.003$) but not RES training ($r = -0.04$, $P = 0.75$; Supplemental Fig. 7, Supplemental Digital Content 1, correlation of LVM and EDV, http://links.lww.com/MSS/C534).

Heritability of cardiac structure and function. In terms of baseline cross-sectional comparisons between twin pairs (Table 3, Supplemental Fig. 8, Supplemental Digital Content 1, twin pair relationships for LVM, http://links.lww.com/MSS/C534), the intraclass correlation coefficients for monozygotic twins (rMZ) and dizygotic twins (rDZ) were significant for LVM, LVM iLM, EDV, ESV, and SV. Subsequent analysis revealed contributions to variation from additive genetics and shared environment effects for LVM ($A = 0.42$; $C = 0.48$), and predominantly shared environment effects for LVM iLM (0.80), EDV (*0.79*), ESV (0.77), and SV (0.69). A significant

rMZ, but not rDZ, was found for LVM iBSA, EF, and CO. Subsequent analysis revealed predominant contributions from shared environmental effects for LVM iBSA (0.88) and EF (0.59). Contributions to variance were split between shared and unshared environmental effects for CO ($C = 0.43$; $E = 0.57$).

In terms of changes that occurred in LV outcome variables in response to exercise training (Table 3, Supplemental Fig. 8, Supplemental Digital Content 1, http://links.lww.com/MSS/C534), there were no notable or significant rMZ or rDZ coefficients, or differences between these (rMZ vs rDZ) for any outcomes in response to either modality. This is indicative of limited, if any, additive genetic (A) contribution to any LV cardiac adaptations in response to exercise training, with any differences that exist therefore due to environmental factors (C or E).

DISCUSSION

This study used a randomized crossover design to assess changes in LV adaptation to distinct exercise modalities in previously untrained individuals. Both RES and END are widely used in healthy and clinical populations to target distinct physiological adaptations and health benefits. To our knowledge, this is the first study using CMR to assess: (i) the magnitude of response to RES versus END training within subjects, (ii) the concordance of direction of response within individuals for each modality, and (iii) the heritability of exercise training responses using MZ and DZ twin pairs.

Cross-sectional comparisons suggest that long-term training is associated with increased LVM, assessed via CMR, in END athletes (e.g., 35–66 g (22–26)), with one study in older RES athletes (68 ± 4 yr) revealing a 19 g (26) larger LVM compared to nonathletes. However, such cross-sectional comparisons between athletes and controls can be polluted by self-selection bias and scaling issues, and they do not reflect the impacts of exercise training *per se* (27). Few studies have used CMR and actually followed subjects through a training intervention. END training in previously inactive adults of 1 yr (28) and 6 months (2) duration have shown increases in LVM of 35 g and 9 g, and EDV increases of 21 mL and 9 mL. These values exceed the changes we observed in the current study, possibly due to longer or more intensive exercise interventions. A relatively brief, high-intensity training study (16) (10 wk of intensive military training; 5 × 2 h sessions per week) revealed similar results (LVM increase of 9 g) to our previous 6 month END protocol (2). In the current study, we used exercise training prescriptions that were ecologically valid, being consistent with approaches typically adopted for previously exercise-naive individuals. We have demonstrated that 12 wk of training at these levels is sufficient to induce significant eccentric hypertrophy in response to END training (increased LVM by 4.78 g or 4.3%, $P < 0.001$, and EDV by 3.91 mL or 2.5%, $P = 0.007$) whereas, like the Spence et al. (2) study, RES was not associated with significant changes indicative of hypertrophy or remodeling. The latter finding has implications for the "Morganroth" hypothesis (27) relating to exercise modality specificity of ventricular hypertrophy. The study by Bellenger et al. (12) indicates that the variability of CMR measurement from repeated tests in the same individuals is 0.7 g for LVM and 2.5 mL for EDV. Taking these reproducibility data into account, the majority of our subjects responded with changes beyond the measurement error threshold for LVM and EDV.

Only one previous study, to our knowledge, has reported *individualized* CMR-based cardiac adaptation data (in a supplement) (28). This study suggested that 12 months of monitored (but not center-based or directly supervised) mixed-mode END training (running, swimming, cycling and triathlon) induced LVM responses in all 11 subjects (28). Individual results of the present study, including 58 subjects who completed RES and 60 END, indicate that the LVM response to 3 months training was modality-specific (favoring END), and that the percentage of individuals who had low responses (change ≤0) to either modality (24%–38% depending upon the variable of interest) is broadly in keeping with previous studies which have reported low responsiveness in other physiological variables such as fitness, strength, and blood pressure (29–31).

In addition to assessing whether the magnitude of individual response was modality-specific, our crossover study design allowed us to determine concordance/discordance of exercise response *within* subjects to distinct training modalities. Our findings indicate that those who were low responders to RES had a better than even chance of being a higher responder to END, whereas low response to END typically conferred a relatively low chance of responding to RES. These findings reinforce the modality-specificity of training and the observation that different exercise modalities induce specific phenotypic cardiac adaptation.

Our study design and outcome measures allow us to consider the impact of changes in body composition (DXA-derived LM) on LVM, in response to each form of training. There is a literature pertaining to interpretation of the relationship between these variables (16,17,32,33) and how to normalize cardiac dimensions for body size. In a study of military recruits undergoing 10 wk intensive training, within-subjects repeated measures relationships between LM and LVM were used to assess the interdependence of these measures (16). The authors concluded that, after scaling, only about 1/3rd of the change in LVM was accounted for by the change in LM. This runs counter to some other studies (33), which suggested that LV hypertrophy reflects increases in lean body mass (33). The disparity is likely due to problems associated with derivation of scaling indices from between-subject comparisons (e.g., athletes vs controls) rather than repeated within-subjects measures after training interventions. Our findings, in keeping with some previous studies (16), indicate a high level of correlation between absolute measures of LM and LVM at baseline (~$r = 0.9$), but a notable absence of correlation between change in LM and change in LVM as a response to either RES ($r = 0.00$) and END ($r = 0.13$). We observed no change in LVM in response to RES (−2.2 g), despite a significant increase in LM (1.1 kg). In response to END, LVM increased (4.8 g, $P < 0.001$) alongside increases in LM (284 g, $P < 0.05$). These data support our previous

conclusion that distinct forms of exercise induce different forms of LV remodeling (2,27).

By recruiting both MZ and DZ twin pairs we could estimate the genetic versus environmental contributions to cardiac adaptation (34) to distinct training modalities. Previous cross-sectional studies, which have used echocardiography (35–39) or focused on LVM (40), have produced highly variable heritability estimates. Few studies have reported additional LV measures, such as EDV (10,41–44). Our cross-sectional results at baseline revealed higher correlations among MZ than DZ pairs and moderate heritability for LVM (0.42). Remaining variables revealed predominant contributions of shared environmental (C) effects. However, although cross-sectional comparison of MZ and DZ twins can provide heritability estimates of phenotypic traits, exercise intervention studies are required to estimate the contribution of genetics to *trainability*. Our longitudinal crossover study is the first to train same-sex twins contemporaneously at matched intensities. In contrast to our cross-sectional results, there were no notable twin correlations present for changes induced by either training modality. This suggests that cross-sectional heritability estimates are not translatable to actual cardiac training adaptations in terms of genetic contribution to adaptation, and that genetics do not play a dominant role in influencing the magnitude of an individual's cardiac response to exercise training, at least in the short term. Future research should assess the specific individual environmental factors (external factors that are dissimilar within pairs, such as organized sport, daily routines, diet, friendship groups) that are predominant contributors to training adaptation.

As indicated above, it is possible that lifelong training may induce more extreme levels of adaptation than the 3 and 6 month studies we have completed. Although it has been suggested that all individuals respond to exercise if the exercise 'dose' (intensity or frequency) of training is intense enough (45), the current study aimed to investigate the difference between distinct exercise *modes* that were prescribed at typical guideline levels for exercise-naive individuals embarking on an exercise program. Our approach was ecologically valid in this regard (46,47). Another reason for differences between the current study and previous experiments is that we included both female and male participants; previous studies have often studied only men and the inclusion of females may influence the magnitude of responses. Our recent sex differences article specifically addresses this issue (21). A limitation of our study relates to the relatively low number of DZ twin pairs (14 cross-sectional pairs; 10 exercise-trained pairs), which may have influenced the likelihood of finding significant rDZ differences between rMZ and rDZ. When initially recruiting for the study, twin pairs self-reported their zygosity. However, DNA testing revealed that 10 pairs who self-reported as DZ, were in fact MZ. DNA testing to determine zygosity of twin pairs was therefore a major strength of this study, which prevented us misclassifying zygosity, something that is essential to the integrity of twin study analysis but has not previously been done in all twin studies (48). Another strength is that we only included same-sex twin pairs for DZ twins (no male-female pairs), thus eliminating any confounding sex-based hormonal influences (49). We did not include CMR tissue characterization with late gadolinium enhancement due to concerns regarding gadolinium accumulation in healthy volunteers. Nonetheless we used gold standard, reproducible (12) CMR to measure and report on multiple indices of cardiac structure and function in response to distinct exercise modalities in the same individuals. Furthermore we performed additional validation of imaging measures for a subsample of individuals who showed larger changes in LV morphology with training (Supplemental Appendix, Supplemental Digital Content 2, treatment of potential outliers, http://links.lww.com/MSS/C535). Finally, by recruiting and comparing training responses in both MZ and DZ twin pairs, we were able to use twin-based statistical approaches to estimate correlations and the contributions of genetic (A), shared (C), and individual (E) environmental factors.

CONCLUSIONS

This is the first study to compare the individual response and heritability of LV adaptation to distinct exercise modalities using a crossover study design, a classical twin paradigm, and contemporary CMR imaging in previously untrained individuals. Our findings indicate that differences exist between modalities in the magnitude of cardiac adaptation and the proportion of responders. Switching to an alternate form of exercise can induce adaptation in subjects who otherwise may not have benefited from their initial exercise prescription. Our findings also suggest that cross-sectional comparisons between twin pairs produce higher heritability estimates than those associated with actual cardiac adaptation in response to training, where environmental factors have a larger impact. This finding has implications for the interpretation of previous twin studies. Finally, this study provides insight into LV cardiac adaptation responses to distinct modes of training at an individual level and highlights the significance of environmental factors (and lack of genetic contribution) in terms of cardiac adaptation to training.

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