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Cardiac Determinants of Heterogeneity in Fitness Change in Response to Moderate Intensity Aerobic Exercise Training:

The DREW Study

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A significant heterogeneity in the cardiorespiratory fitness change in response to exercise training has been reported in well-controlled exercise trials (1). However, the sources of this variability are not well understood. In this study, we sought to examine potential cardiac determinants of fitness change following 6 months of supervised, moderate-intensity endurance training among sedentary, obese post-menopausal women. We hypothesized that phenotypic patterns associated with the low fitness phenotype (2) would be associated with a more attenuated response to exercise training.

The present report is an ancillary study from the DREW (Dose Response to Exercise in Women) trial (3). We examined 147 exercise-training participants who had a baseline transthoracic echocardiogram, as well as fitness testing at baseline and at 6 months follow-up. Change in fitness was defined as the difference in measured peak absolute oxygen consumption ($VO2_{abs}$, LO2/min) from baseline to followup, and study participants were categorized as fitness nonresponders (change in $VO2_{abs} \leq 0$) or responders (change in $VO2_{abs} > 0$) to exercise training. The association between individual echocardiographic parameters and fitness nonresponse to exercise training was assessed using logistic regression analyses with each echo parameter included in separate multivariable models. We also assessed the association between baseline echocardiographic parameters and continuous changes in fitness using multivariable adjusted linear regression analyses. All statistical analyses were performed using SAS for Windows (release 9.2, SAS Institute, Inc., Cary, North Carolina).

A significant heterogeneity was observed after exercise training with more than 30% (n = 46) of participants experiencing no improvement in fitness after training. As expected, fitness responders had lower baseline fitness, and underwent higher dose of exercise training (Figure 1A). Compared with nonresponders, exercise training responders had significantly lower mean baseline inter-ventricular septal thickness (IVST) (11.0 vs. 11.6 mm; p = 0.03), posterior wall thickness (PWT) (11.1 vs. 11.7 mm; p = 0.03), and indexed left ventricular mass (LVmi) (53.2 vs. 59.7 $kg/m^{2.7}$; p = 0.048). Mean baseline relative wall thickness

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(RWT) was also numerically lower for exercise training responders compared with nonresponders (0.51 vs. 0.54; p = 0.25). In multivariable adjusted logistic regression analyses, IVST, PWT, RWT, and LVmi were each found to be significant predictors of nonresponse to exercise training (Figure 1B). Similarly, in multivariable adjusted linear regression analyses, each of these measures also was inversely associated with continuous changes in fitness (IVST: standardized beta = −0.25, p = 0.003; PWT: standardized beta = −0.21, p = 0.01; RWT: standardized beta = −0.19, p = 0.02; LVmi: standardized beta = −0.25, p = 0.002). When LVmi and RWT were included in the same multivariable adjusted logistic regression model, the association between LVmi and fitness nonresponse was attenuated and no longer significant (odds ratio [OR]: 1.42; 95% confidence interval [95% CI]: 0.88 to 2.50) while that of RWT remained associated with nonresponse (OR: 1.68; 95% CI: 1.07 to 2.63).

Finally, we compared the prevalence of nonresponse to exercise training across tertiles of baseline indexed LV mass. There was nearly twice the prevalence of fitness nonresponse to exercise training among the highest indexed LV mass group (40% in Tertile 3), compared with the lowest indexed LV mass group (20% in Tertile 1; p < 0.04).

Taken together, LV wall thickness and mass are important determinants of the heterogeneity in response to exercise training among asymptomatic, low fit individuals. To our knowledge, this is the first study to identify intrinsic differences in cardiovascular phenotype that may contribute to the heterogeneity in exercise responsiveness. The mechanism underlying this association remains incompletely understood. However, we speculate that participants with more normal wall thicknesses and LV mass may be better suited to adapt to exercise with physiological remodeling as compared to those with adverse LV remodeling at baseline.

Our study findings could have important implications. The present study suggests that low fit participants with adverse LV remodeling, who are at a greater risk for nonresponse to exercise, may require alternative exercise training strategies (e.g., higher intensity and/or dose of exercise training) to improve fitness.

Our study represents an important step in this direction with characterization of distinct cardiac phenotypes associated with heterogeneity in response to exercise training. Further studies are needed to characterize the underlying cardiovascular mechanisms and optimal treatment for the nonresponse to moderate-intensity exercise training.

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A

Subject Characteristics	Exercise Training Responders (n = 101)	Exercise Training Non-responders (n = 46)	p Value
Change in Peak absolute VO2 l/min, range	0.14 (0.11)	-0.07 (0.07)	<0.01
Age , years	56.5 (6.2)	57.5 (6.8)	0.437
Exercise Training Groups 4 kcal/kg/week (%) 8 kcal/kg/week (%) 12 kcal/kg/week (%)	 40.6 31.7 27.7	 69.6 19.6 10.9	0.004
African Americans (%)	40.6	45.6	0.38
Body mass index, kg/m²	31.3 (3.4)	32.5 (3.5)	0.02
Baseline exercise systolic BP, mm Hg	178 (20)	181 (24)	0.67
Baseline peak absolute VO2, l/min	1.24 (0.25)	1.34 (0.23)	0.01
Adherence (%) Median (IQR)	100 (99-100)	99.98 (97.1-100)	0.23

B

Echocardiographic Characteristics[a]	Odds Ratio	95% CI
Inter-ventricular Septal Thickness	2.02	1.26 – 3.26
Posterior Wall Thickness	1.92	1.19 – 3.10
Relative Wall Thickness	1.77	1.15 – 2.72
Indexed Left Ventricular Mass[b]	1.70	1.04 – 2.78

[a]Each echo parameter was included in a separate logistic regression analysis model adjusted for age, body mass index, systolic blood pressure, baseline fitness, exercise training dose and adherence to exercise training. [b]Indexed to allometric height.

FIGURE 1. Echocardiographic Determinants of Fitness Response to Exercise Training

(A) Baseline characteristics of study participants stratified by training response. **(B)** Association between baseline echocardiographic measurements and nonresponse to exercise training. Values are mean (SD) or %, unless otherwise noted. BP = blood pressure; CI = confidence interval; IQR = interquartile range; VO2 = volume of oxygen consumed.