Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Establishing Cardiac MRI Reference Ranges Stratified by Sex and Age for Cardiovascular Function during Exercise

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Purpose: To evaluate the effects of exercise on left ventricular parameters using exercise cardiac MRI in healthy adults without known cardiovascular disease and establish reference ranges stratified by age and sex.

Materials and Methods: This prospective study included healthy adult participants with no known cardiovascular disease or genetic variants associated with cardiomyopathy, enrolled between January 2018 and April 2021, who underwent exercise cardiac MRI evaluation. Participants were imaged at rest and after exercise, and parameters were measured by two readers. Prediction intervals were calculated and compared across sex and age groups.

Results: The study included 161 participants (mean age, 49 years ± 14 [SD]; 85 female). Compared with the resting state, exercise caused an increase in heart rate (64 beats per minute ± 9 vs 133 beats per minute ± 19, $P < .001$), left ventricular end-diastolic volume (140 mL ± 32 vs 148 mL ± 35, $P < .001$), stroke volume (82 mL ± 18 vs 102 mL ± 25, $P < .001$), ejection fraction (59% ± 6 vs 69% ± 7, $P < .001$), and cardiac output (5.2 L/min ± 1.1 vs 13.5 L/min ± 3.9, $P < .001$) and a decrease in left ventricular end-systolic volume (58 mL ± 18 vs 46 mL ± 15, $P < .001$). There were statistically significant differences in exercise response between groups stratified by sex and age for most parameters.

Conclusion: In healthy adults, an increase in cardiac output after exercise was driven by an increase in heart rate with both increased ventricular filling and emptying. Normal ranges for exercise response, stratified by age and sex, were established as a reference for the use of exercise cardiac MRI in clinical practice.

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Exercise cardiac MRI is a noninvasive imaging modality that offers high image quality during physiologic stress. It can be undertaken as part of a comprehensive cardiac MRI study of structure, function, and tissue characterization to assess physiologic reserve during maximal exercise. This is typically performed using real-time cine imaging, as well as other cardiac MRI sequences, to assess myocardial strain, aortic flow, or tissue metabolism. The technique has emerging applications across several conditions, including the stratification of patients with pulmonary hypertension, diagnosing athlete's heart, evaluating exercise tolerance in congenital heart disease, and detecting ischemia (1). The use of exercise cardiac MRI offers advantages over exercise echocardiography because of its reliable assessment of systolic and diastolic function, which is less user dependent (2). Use of continuous electrocardiographically triggered imaging eliminates the requirement for breath holding, which may itself affect cardiac filling pressures (3). Physical exercise has a higher diagnostic sensitivity and fewer adverse events compared with pharmacologic stressors and is recommended for stress imaging whenever feasible (4).

Knowledge of the range of normal function in exercise is needed for clinical interpretation (5), but, to our knowledge, no studies to date have reported reference ranges for exercise cardiac MRI. With the widening use of exercise cardiac MRI in both clinical and research domains, there is a need to develop representative values in healthy individuals. It has been established that exercise cardiac MRI is clinically feasible using commercially available exercise equipment and vendor-provided product sequences (6). The purpose of this study is to evaluate the effects of exercise on left ventricular parameters using exercise cardiac MRI in a cohort of healthy adults without known cardiovascular disease or major comorbidities and to establish reference ranges stratified by age and sex.

Materials and Methods

Study Design and Sample

This prospective, observational, single-center substudy was performed at Imperial College London. The overall study aimed to evaluate the role of genetic variation on cardiovascular function in a clinically healthy cohort using cardiac MRI. The current study includes a subcohort of participants for whom exercise cardiac MRI was used to assess functional reserve. This study received research ethics approval from the West London Research Ethics Committee (approval no. 17/LO/0034), and all participants provided written informed consent before study enrollment.

Enrollment was between January 2018 and April 2021. Individuals were randomly selected from a cohort of almost 2000 healthy volunteers who had been recruited by advertisement (7). Participants were eligible for inclusion if they were older than 18 years, had no history of cardiovascular disease, and were genotype negative for inherited cardiac conditions during genetic screening. Exclusion criteria included known or suspected pregnancy, physical limitations that would preclude participants from exercising, and any contraindications to MRI. All participants completed a health questionnaire and underwent assessment of height and weight, blood pressure, and resting 12-lead electrocardiography.

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Abbreviations

EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, HR = heart rate, SV = stroke volume, VO_{2max} = maximum volume of oxygen consumed during exercise

Summary

This study established normal cardiac MRI reference ranges, stratified by sex and age, for left ventricular response to exercise.

Key Points

- In healthy adults, an increase in cardiac output following exercise was driven by an increase in heart rate (64 beats per minute ± 9 [SD] to 133 beats per minute ± 19), increased left ventricular filling (end-diastolic volume, 140 mL ± 32 to 148 mL ± 35), and greater left ventricular emptying (end-systolic volume, 58 mL ± 18 to 46 mL ± 15) (all $P < .001$).
- Sex and age influenced cardiac response to exercise, with male participants achieving greater increase in indexed stroke volume (44 mL/m² ± 8 to 57 mL/m² ± 11 in male participants vs 43 mL/m² ± 9 to 51 mL/m² ± 9 in female patients, $P = .005$) and older individuals demonstrating a reduced heart rate response (in male participants: 123 beats per minute ± 16 among those aged 60–79 years vs 150 beats per minute ± 16 among those aged 20–39 years; in female participants: 121 beats per minute ± 14 among those aged 60–79 years vs 139 beats per minute ± 16 among those aged 20–39 years [both $P < .001$]).
- Exercise testing was readily integrated into a standard contrast-enhanced cardiac MRI protocol.

Keywords

Cardiac, MR Imaging, Heart, Physiological Studies

Image Acquisition

Images were acquired using a 1.5-T MAGNETOM Aera machine (Siemens Healthineers) using a 60-channel cardiac coil. Participants underwent a complete cardiac MRI protocol that included structural and functional imaging, phase-contrast flow assessment, and late gadolinium enhancement (Fig 1), following published guidelines and standards (8). Short-axis cines were then acquired at rest and exercise using a commercially available conventional real-time balanced steady-state free precession sequence. The short-axis sections provided complete coverage from base to apex, allowing for variation in heart size and movement during exercise. Each section was triggered on the electrocardiogram R wave and then acquired free-running for 3 seconds per section. Images were acquired over multiple heart beats, and this enabled a retrospective reconstruction to a predefined number of cardiac phases to simplify subsequent volumetric analysis. Here the output images were reconstructed at the required times using a fifth-order B-spline interpolation of the raw data in the time domain on a pixelwise basis. This approach introduces no bias to volumetric assessment compared with conventional reconstruction (9). Typical acquisition parameters were as follows: repetition time msec/echo time msec, 2.2/0.97; section thickness, 8 mm; section gap, 2 mm; matrix size, 128 × 96; field of view, 360 × 270 mm. The acquisition was accelerated using a phase resolution of 75%, partial Fourier of 6/8, and a generalized autocalibrating partial parallel acquisition factor of 4 with a temporal parallel acquisition reference scan technique. This achieved a temporal resolution of 31 msec.

Exercise Protocol

Participants were instructed to abstain from eating but to drink freely in the 6 hours before their study. Exercise was performed using an MRI-conditional variable-resistance supine ergometer (Lode BV; Fig 2, Movie 1) attached to the scanner table. Participants were asked to grip the handles of the ergometer and coached to keep their torso as stationary as possible during exercise to minimize bulk movement. The exercise protocol was based on a proposed framework for cardiopulmonary exercise testing (10), which is similar to approaches taken for supine exercise cardiac MRI at other centers (1). The target heart rate (HR) for each participant was calculated as 85% of the maximal HR using the Fox equation (220 – age in years) (11).

After resting real-time imaging, the participants were instructed to start exercising while maintaining a cadence of 70–80 revolutions per minute, with an initial minimal workload for 1 minute. While the participants continued to exercise in the bore of the MRI scanner, the workload was increased by 25 W every minute until the target HR was reached or leg exhaustion occurred. Free-breathing real-time imaging began immediately after the cessation of exercise to minimize movement artifacts and electrocardiographic mistriggering.

Image Analysis

In this study, only breath-held cine images and free-breathing real-time images were analyzed. All images were analyzed using cvi42, version 5.16 (Circle Cardiovascular Imaging). End-systolic and end-diastolic frames were manually selected. Subsequently, left ventricular endocardial and epicardial borders were traced using automated deep learning segmentation within cvi42 and were then visually inspected and corrected if necessary (Fig 3; Movies 2, 3) (12). The automated segmentation generally performed well, with only minor manual adjustments, primarily in the apical and basal regions, as needed. Papillary muscles were included in the left ventricular blood pool. Absolute values were indexed to body surface area using the DuBois method. Cardiac output and cardiac index were calculated using the maximal HR achieved. Wall strain was not assessable on the real-time data. Readers were a cardiology fellow (R.S., with 2 years of experience) and a senior cardiology fellow (M.S., with 7 years of experience).

Intraobserver and Interobserver Reliability

Interobserver and intraobserver variability were evaluated to assess reliability of the cardiac MRI measurements. Fifty participants were randomly selected and reanalyzed after an interval of 3 months by the two operators blinded to each other's analysis.

Statistical Analysis

Statistical analyses were performed using R software, version 4.2.1 (R Core Team), and Python, version 3.8.5 (Python Software Foundation). Variables were expressed as percentages if categorical and as means ± SDs if continuous. Bland-Altman plots were used to quantify the agreement between real-time and breath-held cines at rest. Intraclass correlation coefficient was used to assess intra- and interobserver reliability and categorized as poor (<0.5), moderate (0.5–0.75), good (>0.75–0.9), and excellent (>0.9) (13). Reference ranges were defined as the

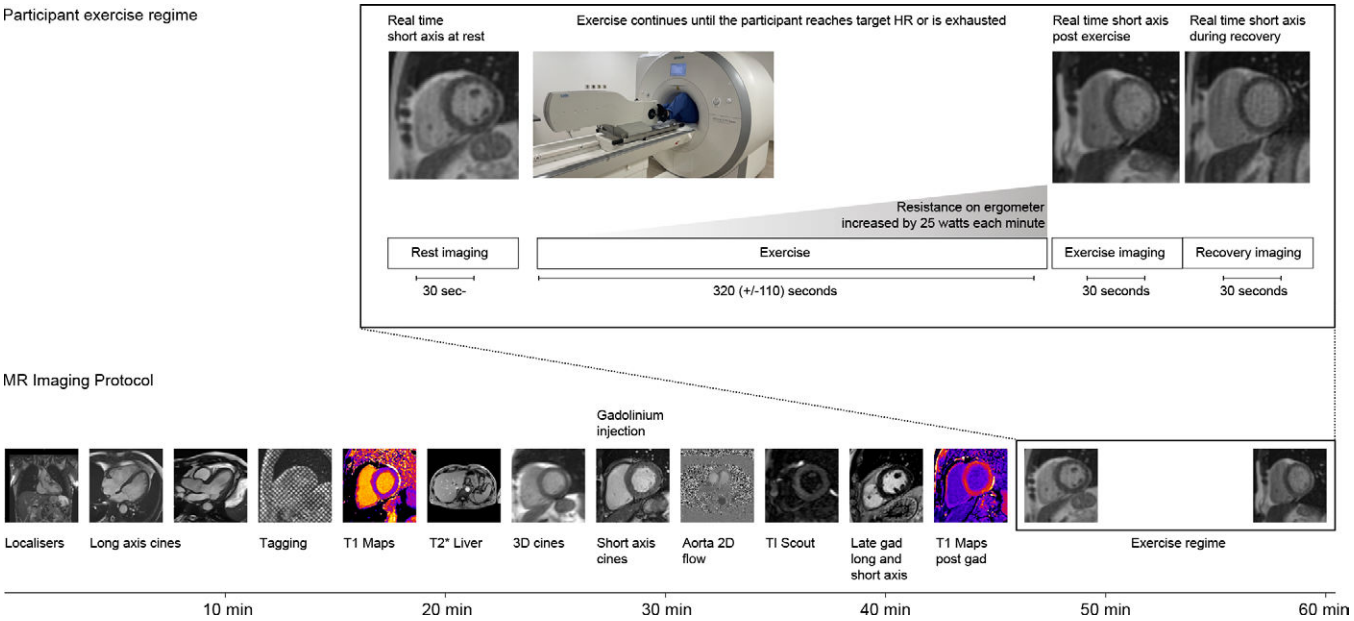

Figure 1: Exercise regimen and imaging protocol used in the study. HR = heart rate, 3D = three-dimensional, 2D = two-dimensional.

Figure 2: Pedal ergometer. Positioning of the bed-mounted MRI-conditional pedal ergometer allows participants to exercise while at isocenter (hand holds not shown). An electromagnetic braking system allows a maximum peak load of up to 300 W. An external control unit displays multiple ergometry parameters in real time.

95% prediction interval of the Student *t* distribution. Ranges were stratified by sex and age groups (20–39, 40–59, and 60–79 years). Comparisons were adjusted for age as a continuous variable unless stratified by age group. Mixed linear models were used to compare left ventricular parameters between rest and exercise and between sexes, and one-way analysis of variance was used to compare parameters across age groups. Post hoc testing used the Tukey honest significant difference test. The *t* tests were two-sided and the analysis of variance one-sided. Adjustments for multiple comparisons were performed using the Benjamini-Hochberg procedure. A *P* value of .05 or less was considered to indicate a statistically significant difference.

Results

Participant Characteristics

A total of 177 healthy, genotype-negative volunteers were enrolled, of whom 161 were included in the substudy (Fig 4). Five participants did not undergo MRI, three participants were excluded because of persistent tachycardia or incidental pleural effusions, and eight were excluded because of poor image quality. The mean age was 49 years ± 14 (SD) (range, 22–77 years); 70% (114 of 161) of participants identified as White, and 53% (85 of 161) identified as female. Baseline characteristics are shown in Table 1. Participants reported the following physical activity levels during enrollment for the original study from which they were drawn: no regular exercise, 7% (12 of 161); light physical activity, 40% (65 of 161); moderate physical activity, 36% (58 of 161); and more than 5 hours of exercise per week, 16% (26 of 161) (14). The real-time images were typically acquired over 27 seconds, during which time there was a mean decrease in HR of 12 beats per minute from peak exercise. Examples of the image quality achieved using the free-breathing real-time sequence immediately after exercise are shown in Movies 2 and 3.

Left Ventricular Reference Values

Reference ranges for absolute and relative change in left ventricular parameters during exercise are stratified by sex and age (male participants, Table 2; female participants, Table 3). The lower values represent the lower end of the 95% prediction interval, the mean values represent the mean change, and the upper values represent the upper end of the 95% prediction interval.

Left Ventricular Response to Exercise

For the cohort as a whole, exercise caused an increase in HR (64 beats per minute ± 9 vs 133 beats per minute ± 19, $P < .001$), stroke volume (SV) (82 mL ± 18 vs 102 mL ± 25, $P < .001$), ejection fraction (EF) (59% ± 6 vs 69% ± 7, $P < .001$), and cardiac output (5.2 L/min ± 1.1 vs 13.5 L/min ± 3.9, $P < .001$). The increase in EF and SV was predominantly mediated by a reduction in end-systolic volume (ESV) (58 mL ± 18 vs 46 mL ± 15, $P < .001$), with a smaller increase in end-diastolic volume (EDV) (140 mL ± 32 vs 148 mL ± 35, $P < .001$).

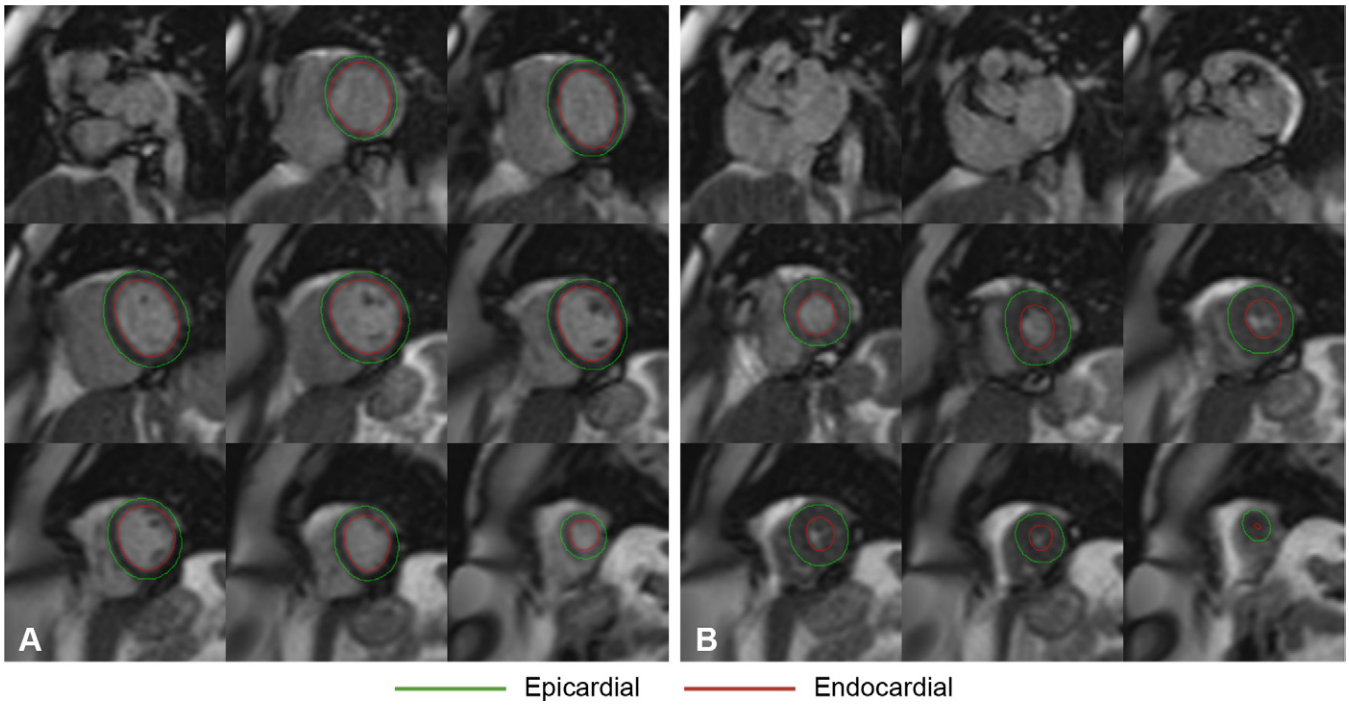

Figure 3: Real-time cine images. Example of exercise real-time short-axis cine images without contrast enhancement in a 52-year-old male participant at **(A)** end diastole and **(B)** end systole. Epicardial contours are shown in green and the endocardial contours in red.

Figure 4: Study flowchart.

Sex Differences

Comparisons between left ventricular parameters at rest and exercise are shown in Tables 4 and S1. Stratified plots of participant-level response to exercise are shown in Figures 5, S1, and S7–S10. In summary, male participants had higher resting indexed EDV (79 mL/m^2 ± 12 vs 70 mL/m^2 ± 13, $P < .001$) and ESV (34 mL/m^2 ± 7 vs 27 mL/m^2 ± 7, $P < .001$) than female participants, as well as a higher HR increase (72 beats per minute ± 22 vs 65 beats per minute ± 18, $P < .001$). Male participants achieved a higher indexed SV (57 mL/m^2 ± 11 vs 51 mL/m^2 ± 9, $P < .001$) through greater left ventricular emptying (change in indexed ESV, −8 mL/m^2 ± 7 vs −4 mL/m^2 ± 5, $P = .001$).

Age Group Differences

Comparisons between left ventricular parameters at rest and exercise stratified by age group are shown in Tables S3–S6 and Figures 6 and S1–S6. In summary, HR response to exercise declined with age in both sex groups (male and female: $P < .01$). Older female participants showed less ventricular emptying (change in indexed ESV in male participants, $P = .07$; in female participants, $P = .012$), but male participants achieved an increase in indexed EDV (male, $P = .035$; female, $P = .6$). There was no evidence of a difference in exercise EF between sexes ($P = .08$), and cardiac index values tended to increase across age groups (male, $P = .07$; female, $P = .006$).

Variability in Stroke Volume Response

In this study, 142 individuals had an increase in their left ventricular SV during exercise and 19 did not. Age and sex distributions were similar across both groups ($P = .86$ for age groups, $P = .47$ for sex). Significant differences were observed in several left ventricular parameters between the two groups.

Table 1: Participant Characteristics

Characteristic	Male Participants			Female Participants		
	20–39 Years (*n* = 26)	40–59 Years (*n* = 32)	60–79 Years (*n* = 18)	20–39 Years (*n* = 24)	40–59 Years (*n* = 35)	60–79 Years (*n* = 26)
Age (y)	32 ± 5	49 ± 6	66 ± 5	31 ± 4	52 ± 5	67 ± 4
White	12 (46)	23 (72)	16 (87)	16 (67)	26 (74)	21 (81)
Weight (kg)	81 ± 13	86 ± 16	85 ± 14	68 ± 12	71 ± 14	63 ± 12
Height (cm)	179 ± 6	179 ± 7	178 ± 5	166 ± 6	163 ± 6	162 ± 6
BSA (m^2)	2.0 ± 0.18	2.05 ± 0.19	2.03 ± 0.17	1.76 ± 0.16	1.77 ± 0.16	1.67 ± 0.14
BMI	25.3 ± 3.6	26.8 ± 4.2	26.7 ± 4.0	24.7 ± 4.2	26.8 ± 5.9	24.3 ± 4.9
Systolic blood pressure (mm Hg)	127 ± 12	132 ± 13	138 ± 17	115 ± 9	123 ± 13	135 ± 22
Diastolic blood pressure (mm Hg)	77 ± 8	83 ± 8	83 ± 11	72 ± 7	79 ± 9	78 ± 10
HR at baseline (beats/min)	62 ± 7	65 ± 13	61 ± 9	66 ± 7	64 ± 7	64 ± 6
HR maximum (beats/min)	150 ± 16	130 ± 20	123 ± 16	139 ± 16	130 ± 12	121 ± 14
Target HR reached	13 (50)	10 (31)	10 (56)	6 (25)	11 (31)	11 (42)
Percentage of target HR reached	94 ± 10	90 ± 13	95 ± 12	88 ± 11	91 ± 9	94 ± 11
Percentage of predicted maximum HR reached	80 ± 8	76 ± 11	81 ± 10	74 ± 9	77 ± 8	80 ± 10
Increase in HR (%)	141 ± 25	118 ± 61	110 ± 37	109 ± 34	103 ± 31	84 ± 28
Decrease in HR during scanning (%)	11 ± 5	11 ± 7	14 ± 7	11 ± 5	12 ± 8	9 ± 7
Maximum wattage (W)	159 ± 31	139 ± 39	126 ± 32	120 ± 26	98 ± 26	83 ± 27
Activity level						
Sedentary	2 (8)	1 (3)	0 (0)	1 (4)	6 (17)	2 (8)
Lightly active	7 (27)	13 (41)	8 (44)	9 (38)	15 (43)	13 (50)
Moderately active	14 (54)	11 (34)	8 (44)	5 (21)	13 (37)	7 (27)
Very active	3 (12)	7 (22)	2 (11)	9 (38)	1 (3)	4 (15)

Note.—Continuous variables are expressed as means ± SDs and categorical variables as numbers of participants, with percentages in parentheses. Heart rate (HR) is reported at rest and peak exercise. BMI = body mass index (calculated as weight in kilograms divided by height in meters squared), BSA = body surface area. Activity levels are defined as follows: sedentary, almost entirely sedentary with no regular exercise; lightly active, light physical activity or exercise for 1 to 3 hours per week; moderately active, physical activity or exercise between 3 and 5 hours per week; very active, engaged in more than 5 hours of exercise per week.

Table 2: Absolute and Relative Reference Ranges for Left Ventricular Parameters on Exercise by Age Group in Male Participants

Variable	20–39 Years			40–59 Years			60–79 Years		
	Lower	Mean	Upper	Lower	Mean	Upper	Lower	Mean	Upper
EDV (mL)	−10 (−5)	0 (0)	9 (6)	11 (6)	18 (11)	24 (16)	0 (0)	11 (7)	21 (14)
EDV/BSA (mL/m^2)	−5 (−5)	0 (0)	5 (6)	5 (6)	9 (11)	12 (16)	0 (0)	5 (7)	10 (14)
ESV (mL)	−26 (−34)	−21 (−27)	−15 (−19)	−20 (−27)	−15 (−20)	−11 (−14)	−18 (−28)	−11 (−15)	−3 (−2)
ESV/BSA (mL/m^2)	−13 (−34)	−10 (−27)	−8 (−19)	−9 (−27)	−7 (−20)	−5 (−14)	−9 (−28)	−5 (−15)	−2 (−2)
SV (mL)	11 (13)	20 (23)	29 (34)	26 (30)	33 (39)	40 (47)	14 (15)	22 (24)	29 (33)
SV/BSA (mL/m^2)	6 (13)	10 (23)	15 (34)	13 (30)	16 (39)	19 (47)	7 (15)	10 (24)	14 (33)
EF (%)	9 (16)	12 (22)	15 (28)	11 (19)	13 (24)	15 (29)	6 (9)	9 (16)	13 (22)
CO (L/min)	9.4 (166)	10.9 (203)	12.4 (240)	8.6 (153)	10.0 (185)	11.5 (217)	7.5 (129)	8.5 (150)	9.5 (170)
CI	4.7 (166)	5.5 (203)	6.2 (240)	4.1 (153)	4.8 (185)	5.5 (217)	3.6 (129)	4.2 (150)	4.8 (170)

Note.—Values represent absolute changes and corresponding percentage changes, in parentheses, from rest to exercise. BSA = body surface area, CI = cardiac index (calculated as CO in liters per minute divided by BSA in square meters), CO = cardiac output, EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, SV = stroke volume.

Table 3: Absolute and Relative Reference Ranges for Left Ventricular Parameters on Exercise by Age Group in Female Participants

	20–39 Years			40–59 Years			60–79 Years		
Variable	Lower	Mean	Upper	Lower	Mean	Upper	Lower	Mean	Upper
EDV (mL)	−1 (0)	4 (3)	11 (8)	−1 (0)	4 (5)	11 (10)	2 (3)	9 (10)	16 (18)
EDV/BSA (mL/m^2)	0 (0)	2 (3)	6 (8)	0 (0)	2 (5)	6 (10)	1 (3)	5 (10)	9 (18)
ESV (mL)	−16 (−31)	−12 (−21)	−8 (−12)	−10 (−23)	−7 (−16)	−4 (−9)	−7 (−15)	−4 (−7)	0 (0)
ESV/BSA (mL/m^2)	−9 (−31)	−7 (−21)	−4 (−12)	−5 (−23)	−4 (−16)	−2 (−9)	−4 (−15)	−2 (−7)	0 (0)
SV (mL	10 (14)	17 (21)	24 (29)	5 (11)	12 (20)	19 (30)	6 (12)	13 (24)	21 (36)
SV/BSA (mL/m^2)	6 (14)	9 (21)	13 (29)	3 (11)	7 (20)	10 (30)	3 (12)	8 (24)	12 (36)
EF (%)	7 (12)	10 (17)	13 (22)	5 (9)	8 (13)	10 (18)	2 (5)	6 (11)	9 (16)
CO (L/min)	7.0 (136)	8.3 (161)	9.7 (185)	5.9 (125)	6.6 (144)	7.4 (162)	4.9 (110)	5.7 (133)	6.5 (155)
CI	4.0 (136)	4.7 (161)	5.4 (185)	3.3 (125)	3.7 (144)	4.2 (162)	2.9 (110)	3.4 (133)	3.8 (155)

Note.—Values represent absolute changes and corresponding percentage changes, in parentheses, from rest to exercise. BSA = body surface area, CO = cardiac output, CI = cardiac index (calculated as CO in liters per minute divided by BSA in square meters), EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, SV = stroke volume.

Table 4: Comparison of Rest versus Exercise Parameters in Male and Female Participants

	Male Participants			Female Participants		
Variable	Rest (n = 76)	Exercise (n = 76)	P Value	Rest (n = 85)	Exercise (n = 85)	P Value
HR (beats/min)	64 ± 11	135 ± 21	<.001	65 ± 7	130 ± 16	<.001
EDV (mL)	160 ± 27	170 ± 32	<.001	122 ± 25	129 ± 25	<.001
EDV/BSA (mL/m^2)	79 ± 12	83 ± 14	<.001	70 ± 13	73 ± 12	<.001
ESV (mL)	70 ± 16	54 ± 15	<.001	47 ± 12	39 ± 12	<.001
ESV/BSA (mL/m^2)	34 ± 7	26 ± 7	<.001	27 ± 7	22 ± 7	<.001
SV (mL)	90 ± 16	116 ± 24	<.001	75 ± 16	89 ± 19	<.001
SV/BSA (mL/m^2)	44 ± 8	57 ± 11	<.001	43 ± 9	51 ± 9	<.001
EF (%)	56 ± 6	68 ± 7	<.001	61 ± 6	70 ± 7	<.001
CO (L/min)	5.7 ± 1.1	15.6 ± 3.7	<.001	4.8 ± 1.1	11.7 ± 3.0	<.001
CI	2.8 ± 0.5	7.7 ± 1.7	<.001	2.8 ± .5	6.6 ± 1.6	<.001

Note.—Data are presented as means ± SDs. Values are adjusted for age. BSA = body surface area, CI = cardiac index (calculated as CO in liters per minute divided by BSA in square meters), CO = cardiac output, EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, HR = heart rate, SV = stroke volume.

Normalized EDV at rest was lower in participants with an SV response (73 mL/m^2 ± 13 vs 82 mL/m^2 ± 12, P = .004), accompanied by an increase in EDV from rest to exercise (11 mL/m^2 ± 12 vs −6 mL/m^2 ± 8, P < .001), and a less pronounced HR response (107% ± 42 vs 128% ± 34, P < .001). In contrast, the change in normalized ESV from rest to exercise did not differ between groups (−6 mL ± 6 vs −4 mL ± 9, P = .23). Activity level had no consistent effect on change in SV.

Data Reliability

Bland-Altman plots (Figs S11–S19) comparing resting real-time imaging with breath-held cines showed good agreement and no measurement bias. Intra- and interobserver reliability testing demonstrated good to excellent agreement for all measured variables (Table S7).

Discussion

This study shows the effects of exercise in healthy volunteers assessed using exercise cardiac MRI and provides corresponding reference ranges stratified by age and sex. In our cohort of 161 adults without known cardiovascular disease (mean age, 49 years ± 14; 85 female), exercise caused an increase in left ventricular cardiac output (5.2 L/min ± 1.1 vs 13.5 L/min ± 3.9, P < .001), SV (82 mL ± 18 vs 102 mL ± 25, P < .001), and EF (59% ± 6 vs 69% ± 7, P < .001). These changes were driven by an increase in HR (64 beats per minute ± 9 vs 133 beats per minute ± 19, P < .001), an increase in left ventricular EDV (140 mL ± 32 vs 148 mL ± 35, P < .001), and a decrease in left ventricular ESV (58 mL ± 18 vs 46 mL ± 15, P < .001). Defining normal ranges for left ventricular parameters will enable exercise cardiac MRI findings to be placed in the context of normal variation

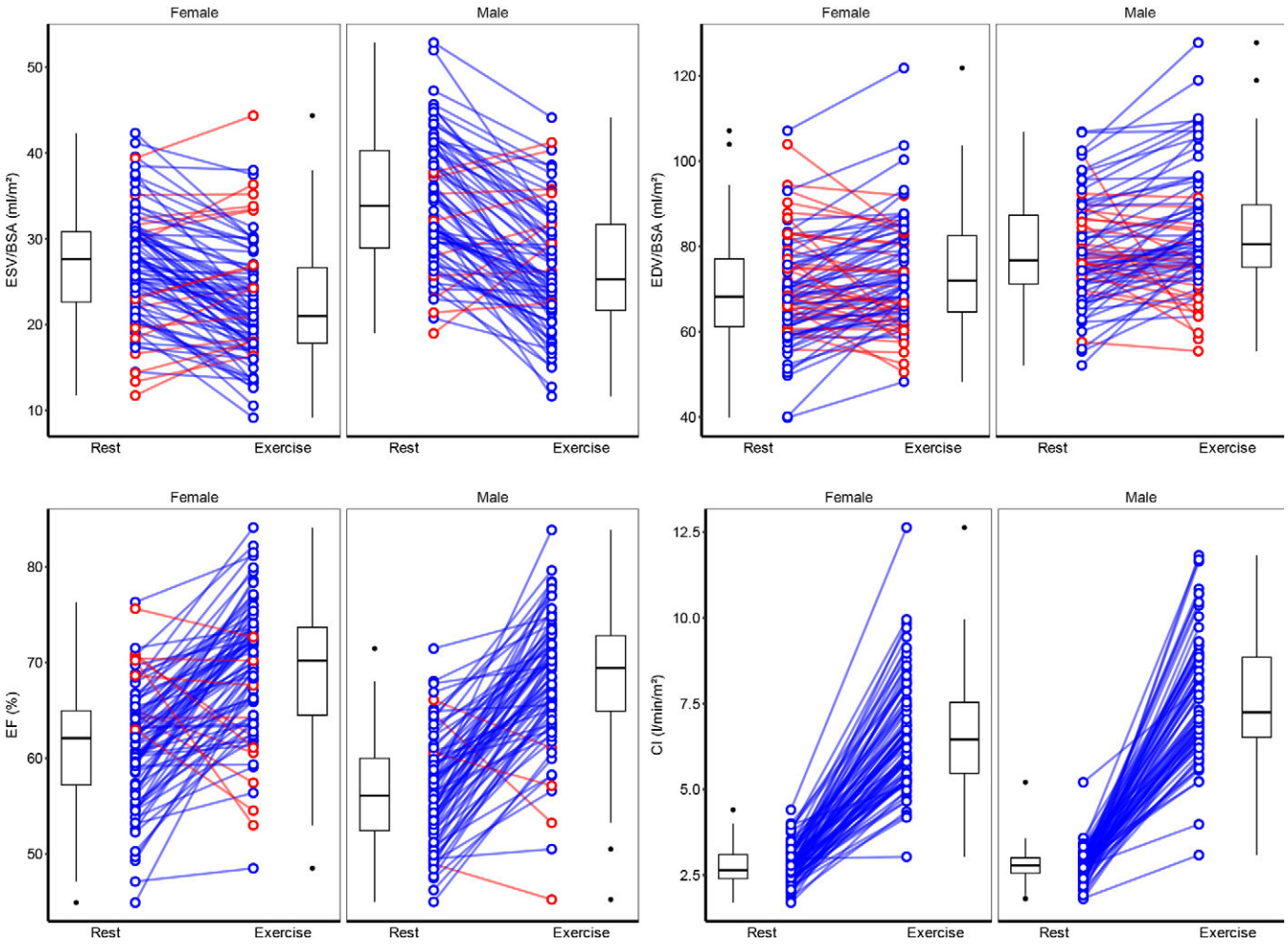

Figure 5: Left ventricular parameters at rest and exercise, stratified by sex, in 161 patients. Lines join corresponding values. Boxes show medians and IQRs, and whiskers show 1.5 × IQRs. Data beyond the whiskers are plotted individually. Individual direction of response shown in blue (same) or red (different) with respect to mean change. BSA = body surface area, CI = cardiac index (calculated as cardiac output in liters per minute divided by BSA in square meters), EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume.

and will facilitate nonpharmacologic quantitative assessment of functional reserve. The availability of this normative data will assist with the clinical interpretation of exercise cardiac MRI as it becomes more widely used in both research settings and clinical practice. The study also highlights sources of individual variation in response to supine exercise, which should be considered when the clinical findings are interpreted.

Cardiac MRI is considered the reference standard for assessing resting cardiac function, and a single examination provides quantitative information about cardiac structure, tissue characteristics, and blood flow (15). Cardiac MRI has multiple class 1 and class 2a recommendations for pharmacologic functional testing (16), and, more recently, exercise cardiac MRI has emerged as a nonpharmacologic assessment of physiologic reserve that is safe and cost-effective (1,17). The Epicardial Delivery of XC011 Gene Therapy for Refractory Angina Coronary Treatment (ie, EXACT) trial showed the potential of using treadmill exercise cardiac MRI in patients at risk for coronary artery disease, demonstrating a strong agreement with coronary angiography and outperforming SPECT/CT (18). In addition, the Evaluating Myocardial Ischemia in Chest Pain Using Exercise CMR (ie, EMPIRE) study showed excellent agreement between supine exercise cardiac MRI and invasive coronary fractional flow reserve (19). The use of exercise cardiac MRI also provides a noninvasive approach to identify heart failure with preserved EF in cases where both clinical and echocardiographic findings are inconclusive (2). Further applications of exercise cardiac MRI include differentiating between athlete's heart and dilated cardiomyopathy (20,21), as well as stratification of patients with pulmonary hypertension (22). Although these trials show that exercise cardiac MRI has diagnostic value in patients with cardiometabolic comorbidities, underlying causes of relative exercise intolerance may cause variation in the ability to reach target HR.

The widening availability and indications for exercise cardiac MRI highlight the need for published normal ranges, which have not previously been reported for this technique (5). Practice varies regarding exercise regimens, imaging protocols, and postprocessing because this is still an emerging technique. For the study sample, we recruited healthy volunteers in the United Kingdom who had been prescreened for cardiovascular disease, including incidental cardiomyopathy-associated rare variants. Study participants had an age range of 21–77 years; there were similar numbers of male and female participants, and 70% of total participants were White. Analyses were stratified by age and sex. We did not have a sufficient sample size to stratify by race and ethnicity. The ranges therefore represent a community-based urban reference population free of known disease.

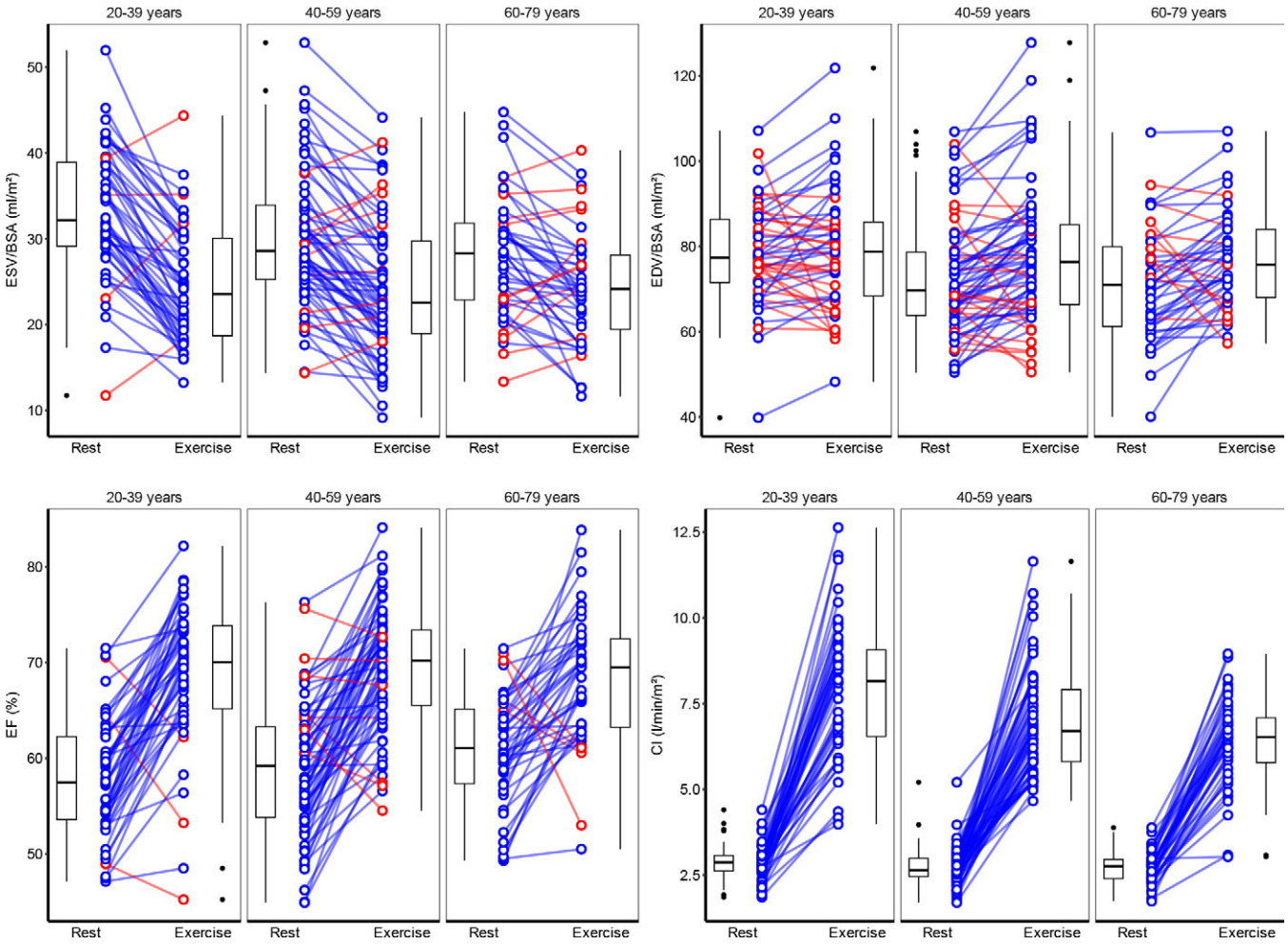

Figure 6: Left ventricular parameters at rest and exercise, stratified by age group, in 161 patients. Lines join corresponding values. Boxes show medians and IQRs, and whiskers show 1.5 × IQRs. Data beyond the whiskers are plotted individually. Individual direction of response shown in blue (same) or red (different) with respect to mean change. BSA = body surface area, CI = cardiac index (calculated as cardiac output in liters per minute divided by BSA in square meters), EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume.

The exercise regimen is based on reaching an age-predicted maximal HR to individualize exercise intensity (23), although some studies have used upright cardiopulmonary exercise testing to adjust target power output (22) or used a single target HR (2). Our protocol has the practical advantage of being personalized while not requiring pretest cardiopulmonary exercise testing. A variety of exercise equipment and protocols are available, including treadmill exercise outside the magnet. Although MRI-conditional cycle ergometers are expensive and currently less widely available, they offer a means of accurately controlling exercise intensity while inside the bore of the magnet, with immediate imaging reducing potential sources of variability. Only 5% of participants who underwent exercise cardiac MRI were excluded from subsequent analysis. Imaging protocols for exercise cardiac MRI favor real-time imaging because the patient is free breathing after exercise. Although accelerated real-time sequences continue to be developed to improve temporal resolution and mitigate motion artifact (24), we used a product sequence that is widely available, shows strong agreement with gated cine sequences, and achieves good reproducibility. To facilitate analysis of end-diastolic and end-systolic frames at real-time imaging, we used a reconstruction that produces a consistent number of frames, but this can also be readily achieved without interpolation. For postprocessing, we initially used widely available commercial software for automated assessment, followed by manual refinement. The overall protocol is broadly generalizable and reflects current practice.

A consistent response to exercise has been shown in meta-analyses of exercise cardiac MRI across different field strengths, exercise protocols, and imaging techniques (6). Our cohort demonstrated a robust response to supine exercise, with almost a 250% increase in cardiac output, achieving at least the maximal response to similar protocols (20). Although only 38% of participants achieved their target HR during exercise, this finding is consistent with previous studies comparing stress protocols, in which no participants achieved criteria for maximum volume of oxygen consumed during exercise (VO_{2max}) while exercising supine, whereas all participants did so when upright (6,25). Such hemodynamic differences between supine and upright exercise suggest that a protocol-specific HR goal may be appropriate. Overall, EDV showed only a modest and variable increase during exercise, whereas HR significantly increased and ESV decreased. Older adults, with a reduced HR response and less systolic reserve, relied on greater ventricular filling to maintain exercise cardiac output. Higher HR in younger adults during exercise, with decreased filling time, could account for the limited increase in EDV during physical activity (26). In

the oldest age groups, a decline in diastolic relaxation could also contribute to a blunted increase in cardiac output (27). Male participants had higher indexed resting and exercise volumes than female participants and a greater absolute and relative response to exercise, findings consistent with those of other studies (28). The increase in HR was similar between sexes, and a higher exercise SV in male participants was achieved through greater left ventricular emptying. Although 88% of participants showed a combined increase in SV and HR, a minority relied on an increase in HR alone during exercise. Previous exercise studies have shown that changes in cardiac index are predominantly driven by HR (6,29), although we show a variable contribution by SV that is age and sex dependent. With respect to rising VO_2, a progressive increase, a plateau with a secondary increase, a flat plateau, and a plateau with a drop in SV have all been reported (30). Some of this variability in healthy adults may be explained by aerobic fitness levels, reflecting the relationship between parameters of fitness (VO_{2max}) and myocardial contractility (EF or SV) with the pattern of exercise dependence of SV. We also demonstrated that it was feasible to incorporate exercise cardiac MRI into a full clinical protocol, including tissue characterization and late enhancement, which could be completed within 60 minutes with a low technical failure rate. Although the study included only healthy volunteers, this finding suggests exercise cardiac MRI could be incorporated into routine cardiac MRI practice. Suitable quality control measures would be recommended that may include validating accelerated cine sequences, ensuring that artifacts do not affect volumetry across exercise intensities, and ensuring that segmentation approaches are accurate and manually corrected if necessary.

Our study had limitations. First, our cohort comprised mainly White participants, which could limit the generalizability of our reference ranges to persons of other racial and ethnic groups. Second, baseline fitness and lifestyle can significantly affect cardiac function even in nonathletes, and our cohort represented a healthy urban population that included those performing regular exercise (14). Third, the study was conducted at a single center, and we did not assess variability due to other scanners or protocols. We used widely available sequences and analysis, but emerging sequences to increase temporal and spatial resolution might achieve better reliability and functional characterization (33). Images were acquired immediately after peak exercise, during which time HR decreased modestly. Acquisition times were similar to those reported in published studies of in-scanner exercise cardiac MRI and also obviated delays in transfer compared with treadmill protocols (1). Fourth, we did not assess test-retest performance because of the effects of fatigue and could not recall participants for a repeat visit. Fifth, we used self-reported measures of physical activity that have acceptable validity when compared with VO_{2max} (32). A normal-values study in almost 500 healthy young adults using the same analysis software had similar resting values (eg, male/female indexed left ventricular EDV of 89/78 mL/m^2 vs 79/70 mL/m^2 and left ventricular ESV of 32/27 mL/m^2 vs 35/28 mL/m^2) (33). Finally, the higher end-diastolic values in our analysis may be due to including papillary muscles in the cavity volume, and the method of volumetry may influence the values obtained.

In conclusion, this study establishes the normal response to exercise assessed by exercise cardiac MRI and provides left ventricular adult reference ranges in a community-based cohort. Quantitative evaluation of exercise cardiac MRI using these normative data will enable better differentiation between health and disease in clinical practice.

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