

Left Ventricular Wall Thickness and the Presence of Asymmetric Hypertrophy in Healthy Young Army Recruits Data From the LARGE Heart Study

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Background—To use cardiovascular magnetic resonance to investigate left ventricular wall thickness and the presence of asymmetrical hypertrophy in young army recruits before and after a period of intense exercise training.

Methods and Results—Using cardiovascular magnetic resonance, the left ventricular wall thickness was measured in all 17 segments and a normal range was calculated for each. The prevalence of asymmetrical wall thickening was assessed before and after training and defined by a ventricular wall thickness ≥ 13.0 mm that was $>1.5\times$ the thickness of the opposing myocardial segment. Five hundred forty-one men (mean age, 20 ± 2 years) were recruited, 309 underwent repeat scanning. Considerable variation in wall thickness was observed across the ventricle with progressive thickening on moving from the apex to base ($P<0.001$) and in the basal and midcavity septum compared with the lateral wall (11.0 ± 1.4 versus 10.1 ± 1.3 mm; $P<0.001$). Twenty-three percent had a maximal wall thickness ≥ 13.0 mm, whereas the prevalence of asymmetrical wall thickening increased from 2.2% to 10% after the exercise-training program. In those who developed asymmetry, the wall thickness/diastolic volume ratio remained normal (0.09 ± 0.02 mm \cdot m² \cdot mL⁻¹), indicative of a remodeling response to exercise.

Conclusions—In a cohort of healthy young white men, we have demonstrated that wall thickness frequently measures ≥ 13.0 mm and that asymmetrical wall thickening is common and can develop as part of the physiological response to exercise. A diagnosis of hypertrophic cardiomyopathy in young athletic men should, therefore, not be made purely on the basis of regional wall thickening. (*Circ Cardiovasc Imaging*. 2013;6:262-267.)

Key Words: cardiovascular MRI ■ exercise ■ hypertrophic cardiomyopathy ■ left ventricular hypertrophy ■ wall thickness

The differentiation between physiological left ventricular (LV) hypertrophy secondary to exercise and hypertrophic cardiomyopathy (HCM) is a complex and increasingly common clinical dilemma.¹ Overdiagnosis of HCM can lead to the premature discontinuation of a professional sporting career, whereas underdiagnosis may place individuals at risk of sudden cardiac death during strenuous physical exertion. Currently, physiological and pathological forms of hypertrophy are differentiated using a variety of diagnostic algorithms and echocardiography.^{2,3} However, uncertainty frequently persists and physicians are frequently turning to cardiovascular magnetic resonance (CMR) to resolve such cases. This technique offers superior spatial resolution, better visualization of the lateral wall, and apex and is unlimited by echocardiographic windows; however, a normal range for wall thickness measurements is lacking and the echo cutoff of 13 mm is frequently used.⁴

Both the pattern and the degree of wall thickening are important in establishing a diagnosis of HCM. Although concentric patterns of wall thickening are more commonly associated with an increased afterload and an athletic heart, HCM is traditionally associated with regional and asymmetrical increases, most commonly in the ventricular septum. According to the recent American College of Cardiology Foundation/American Heart Association guidelines, HCM is usually recognized by a regional increase in LV wall thickness ≥ 15.0 mm, with measurements of 13 and 14 mm considered borderline.⁵ However, such asymmetrical wall thickening has also been described in both aortic stenosis and hypertension,⁶⁻⁸ and we postulated that it might develop in response to strenuous physical training as well.

The aims of this study were, therefore, to investigate CMR wall thickness measurements in a group of young healthy men and to assess whether asymmetrical wall thickening might develop as part of the physiological response to exercise.

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Methods

Study Recruits

Recruits were enrolled in the LARGE Heart study, as previously described.^{7,9} In brief, 541 consecutive healthy young white men army recruits were prospectively studied at entry to the British Army Training Regiment, Lichfield, United Kingdom, between July 2002 and April 2004. Recruits with an established diagnosis of hypertension, diabetes mellitus, cardiomyopathy, and those on regular medication were excluded. Army recruits are routinely screened for clinical signs or a family history of cardiomyopathy or sudden death at an early stage and were referred to a cardiac specialist when this was suspected. Ethical approval was granted by the Defense Medical Services Clinical Research Committee and written informed consent was obtained from all participants. This study was conducted in accordance with the Declaration of Helsinki.

Baseline Data

Data relating to medical history, smoking status, medication use, and alcohol consumption were collected. Recruit height and weight were recorded and body surface area estimated using the Mosteller formula, $\text{body surface area} = (\text{height (cm)} \times \text{weight (kg)}) / 3600)^{0.5}$.

British army regulations require all new army recruits to demonstrate a prespecified level of physical fitness at enrollment. This includes the static lift of a weighted bag (between 15 and 40 kg), carrying two 20 kg water carriers more than 150 m within 2 minutes and a 1.5 mile run in <12 minutes 45 s. For the purposes of this study, each participant also underwent an independent assessment of physical activity as described previously.^{9,10} This listed the sports undertaken currently and in the near past; the period of participation (in years); the hours played per week; and the level of participation (leisure, or for school or county). For simplicity, a physical activity score was generated based on 3 factors: the number of sports participated in, whether the recruit continued to play that sport, and the level the sport was played to; this score was used as the primary measure of physical activity.

Physical Training Regime

All recruits underwent an identical 12-week period of intensive strength and endurance training. This involved more than 40 hours of physical exercise per week with an average energy expenditure of >5000 calories per day. A mixture of aerobic and anaerobic exercise was performed, including running, swimming, push ups, pull ups, sit ups, and marching with weighted backpacks (up to 35 lbs).

CMR Assessment of LV Wall Thickness

CMR was performed both at baseline and after the physical training regime using a mobile 1.5 Tesla Siemens Sonata CMR scanner and applying protocols described previously.^{11,12} All images were acquired using a steady state-free precession sequence.

Image analysis was manually performed by one investigator (P.L.) blinded to other study data, including whether scans were pre-

post exercise, using CMRtools (Cardiovascular Imaging Solutions, London, UK). The maximal LV wall thickness was calculated in end diastole in each of the 17 segments of the myocardium, excluding right ventricular trabeculations. Three measurements were taken and the average of these values was used (Figure 1). Basal readings were taken on short-axis views just beneath the LV outflow tract, whereas midcavity measurements were made using short-axis images at the level of the papillary muscles. Finally, apical readings and that of the true apex were made on 2- and 4-chamber views (Figure 1).

Measurements of LV mass and volume were made and indexed to body surface area as described and reported previously.^{9,10} Subsequently, these were used to derive the LV mass/volume ratio (*M/V*) as the CMR equivalent of the relative wall thickness⁸ and the wall thickness/volume ratio (maximal end-diastolic wall thickness divided by the indexed LV end-diastolic volume) as a measure of wall thickness in relation to cavity size.¹³ The latter has been demonstrated to be a useful discriminator between wall thickening due to exercise and pathological thickening related to cardiomyopathy or conditions associated with an increased afterload.¹³

Reproducibility Studies

Twenty recruits were selected at random from the cohort. Having established the methodology for LV wall thickness measurements, all scans from these recruits were analyzed independently by 2 trained observers (P.L. and S.P.) to provide measures of interobserver reproducibility. To assess intraobserver variation, P.L. repeated the analyses at least 2 months later to minimize recall bias.

Asymmetrical Wall Thickening

The prevalence of asymmetrical wall thickening was defined as a ventricular wall thickness ≥ 13.0 mm that was $>1.5\times$ the thickness of the opposing myocardial segment. Its presence was assessed in each army recruit both before and after the period of physical training.

Statistics

Wall thickness measurements were presented as mean \pm SD. The 95% upper limit of normal for each segment was calculated as the mean \pm 2 SD. Differences between wall thicknesses in different regions of the ventricle were assessed using Student paired *t* test and an ANOVA that accommodated the recruit as a random factor. Differences in recruit characteristics between those with and without asymmetrical wall thickening were sought using unpaired sample *t* test. Paired *t* tests were used for comparison between pre- and post-training data. The 95% normal range for differences between repeated measures of LV wall thickness (the limits of agreement) was estimated by multiplying the SD of the mean of the differences by 1.96. Intraclass correlation coefficients with 95% confidence intervals were calculated for intra- and interobserver variation. Data were analyzed using SPSS software version 17.0 (SPSS Inc, Chicago, IL). A 2-sided *P*<0.05 was regarded as statistically significant.

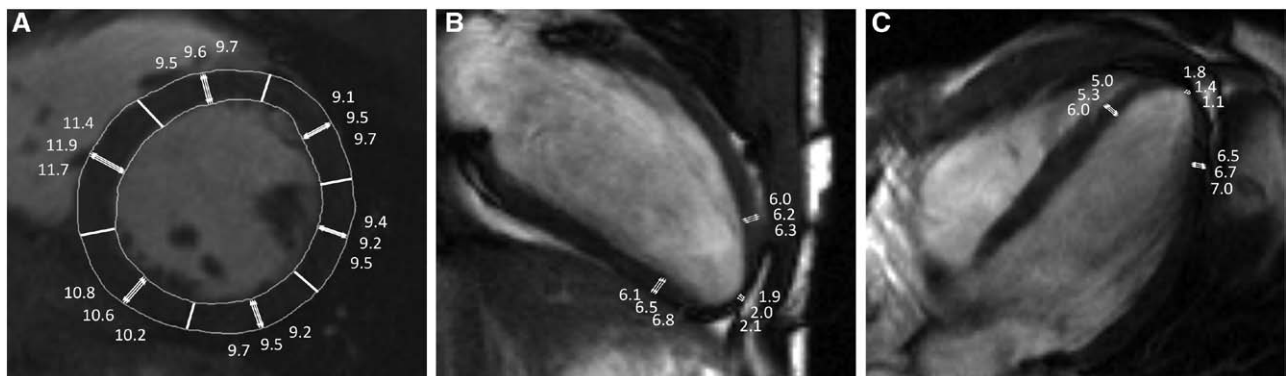


Figure 1. Method for wall thickness measurements at the basal, midcavity, apical levels, and at the true apex. Three measurements were taken of the thickest region in each segment and then averaged. Right ventricular trabeculations were excluded.

Table 1. Baseline Recruit Characteristics of the Whole Cohort (n=541) and Among Those Who Completed the Physical Exercise Regime (n=309)

	Whole Cohort	Cohort That Completed Exercise Regime
Number	541	309
Age, y	20±2	20±2
Height, m	1.78±0.06	1.78±0.06
Weight, kg	72±10*	73±10
Alcohol consumption, U/wk	6 (1–14)†	6 (0–14)†
Systolic blood pressure, mmHg	123±12*	122±18*
Diastolic blood pressure, mmHg	66±8	70±11
Body mass index, kg/m ²	23±3	23±3
Smoking status		
Never smoked	201 (49%)	99 (41%)
Ex-smokers	47 (11%)	120 (49%)
Current smokers	165 (40%)	24 (10%)
Physical activity score	4.6±3.6*	6.8±5.3*

Values represent mean±SD.

*Geometric mean±approximate SD.

†Median (interquartile range).

Results

Study Recruits

CMR studies were obtained in 541 men army recruits (age, 20±2 years) before the physical training program and repeated afterward in 309 recruits (age, 20±2 years). Baseline characteristics of these 2 groups were similar (Table 1). None of the recruits had a history of hypertension or cardiovascular disease and none were clinically suspected of having an underlying cardiomyopathy. One hundred sixty-five recruits (40%) were current smokers, 47 (11%) were ex-smokers, and none were on medication.

Reproducibility

Among the 20 recruits selected, 340 paired measurements of LV wall thickness were performed by P.L., displaying excellent measures of intraobserver reproducibility, with no fixed or proportional biases and narrow limits of agreement ±0.99 mm. This was true at all levels of the ventricle (base, midcavity, and apex; Table 2). Overall, the intraclass correlation coefficient value for these measurements was 0.98. Interobserver agreement was similarly good with a mean difference of 0.07 mm, limits of agreement of ±1.03 mm, and an intraclass correlation coefficient value of 0.99 (Table 2).

Baseline Data

LV Wall Thickness

There was significant variation in wall thickness across the 17 segments of the myocardium (Figure 2; Table 3). LV wall thickness gradually decreased on progression from base to the apex (base, 10.3±1.0 mm; midcavity, 10.2±0.9 mm; apical, 7.3±1.0 mm; apex 2.3±0.6 mm; $P<0.001$). At the basal and midcavity levels, the mean wall thickness was greater in the septum than the lateral wall (11.0±1.4 mm versus 10.1±1.3 mm; $P<0.001$). One hundred twenty-five recruits (23%) were found to have a wall thickness ≥13.0 mm, which was most commonly observed in the septum (87%). Forty-six (9%) had a maximal wall thicknesses ≥14.0 mm and in 14 recruits (3%) it was ≥15.0 mm. Overall, in 4 of the 17 LV segments, the 95% upper limit of normal wall thickness exceeded 13.0 mm. The 95% upper limit of normal for the mid inferoseptum was 14.1 mm (Table 3). Two percent of the cohort (12 of the 541 recruits) fulfilled criteria for asymmetrical wall thickening even before the physical training regime (Figure 3).

Response to Physical Training

After exercise training, the prevalence of asymmetrical wall thickening increased so that it was present in 10% of the cohort (31 of 309 recruits), most commonly affecting the midcavity inferoseptum (74%) (Figure 3). In these recruits, the maximal wall thickness increased from 12.7±1.1 mm pretraining to 14.1±0.9 mm post-training ($P<0.001$), but in contrast to the rest of the cohort indexed LV mass and end-diastolic volumes did not change ($P=0.71$ and $P=0.61$, respectively; Tables 4 and 5). M/V also did not change with exercise in this subgroup or in the cohort as a whole. Although there was a small increase in the wall thickness/volume ratio in recruits who developed asymmetrical wall thickening, this ratio remained normal in all cases (<0.15 mm·m⁻²·mL⁻¹), suggestive of an exercise-induced remodeling response (Tables 4 and 5).¹³ Electrocardiograms were only available in 3 of the 31 recruits but again were not suggestive of HCM.

There was no difference in the baseline characteristics of recruits who did and did not develop asymmetrical wall thickening, with the exception of the body mass index, which was marginally higher in the former (24±3 versus 23±3 kg/m; $P=0.02$; Tables 4 and 5). Only 3 of the recruits with asymmetrical wall thickening post exercise had it at baseline and in each the degree of regional wall thickening increased further after training.

Discussion

In a cohort of young army recruits, we have demonstrated significant regional variation in LV wall thickness and that more

Table 2. Intra- and Interobserver Reproducibility Statistics (Top and Middle Panels) for LV Wall Thickness Measurements

	Intraobserver Reproducibility				Interobserver Reproducibility			
	Mean Difference	SD of Difference	95% Limits of Agreement	ICC	Mean Difference	SD of Difference	95% Limits of Agreement	ICC
Overall	−0.02	0.50	−1.00 to 0.98	0.98	0.07	0.53	−0.96 to 1.10	0.99
Basal segments	0.02	0.58	−1.12 to 1.16	0.92	0.05	0.46	−0.86 to 0.95	0.98
Midcavity segments	−0.02	0.38	−0.77 to 0.73	0.96	0.14	0.52	−0.88 to 1.15	0.96
Apical segments	−0.04	0.53	−1.09 to 0.99	0.97	0.02	0.60	−1.16 to 1.20	0.98

ICC indicates intraclass correlation coefficient; and LV, left ventricular.

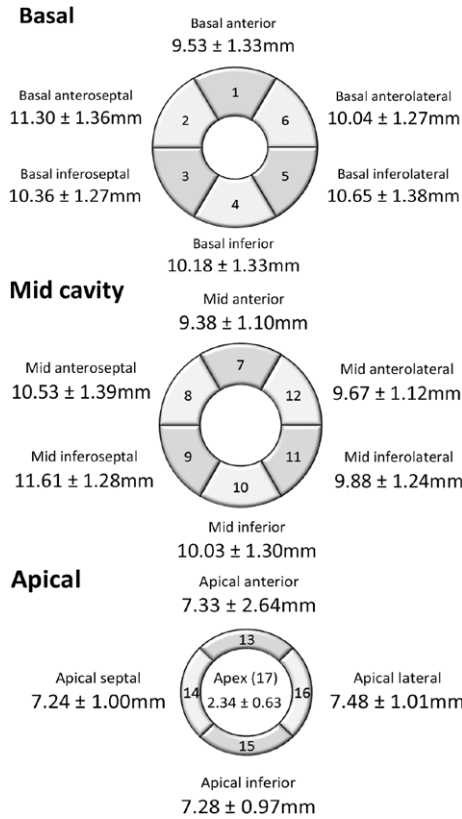


Figure 2. Baseline wall thickness measurements in each of the 17 segments of the myocardium among a cohort of young healthy army recruits (mean±SD).

than one fifth of our recruits had a wall thickness equal or in excess of 13.0 mm, when measured using CMR. Furthermore, the prevalence of asymmetrical wall thickening increased in response to the physical training program, suggesting that in about one tenth of individuals, this develops as part of the physiological response to exercise. These observations have important implications for the diagnosis of HCM in young, fit men.

Wall Thickness Measurements

We have demonstrated excellent inter- and intraobserver reproducibility in our wall thickness measurement for all regions of the myocardium with limits of agreement of 1 mm.

In line with previous studies,¹⁴ significant regional variation was observed in these measurements with progressive thinning of the LV wall on moving from base to apex, and comparing the

Table 3. Ninety-Five Percent Upper Limit of Normal Wall Thickness for All 17 Segments of The Left Ventricle Measured Before Physical Training

	Left Ventricular Wall Thickness in all 17 Myocardial Segments mm		
	95% Upper Limit	95% Upper Limit	
Basal anterior (1)	12.1	Mid inferoseptal (9)	14.1
Basal anteroseptal (2)	14.0	Mid inferior (10)	12.6
Basal inferoseptal (3)	12.9	Mid inferolateral (11)	12.3
Basal inferior (4)	12.8	Mid anterolateral (12)	11.9
Basal inferolateral (5)	13.4	Apical anterior (13)	12.5
Basal anterolateral (6)	12.5	Apical septal (14)	9.2
Mid anterior (7)	11.5	Apical inferior (15)	9.2
Mid anteroseptal (8)	13.3	Apical lateral (16)	9.5
		Apex (17)	3.6

lateral wall to the septum. However, the 95% upper limit of normal wall thickness was >13.0 mm in 4 of the 17 LV segments. This is in sharp contrast to previous echocardiographic studies. Indeed even among elite sportsmen and women, wall thicknesses ≥13 mm have only been described in 1% to 2%.^{2,15,16} This is likely to reflect the greater sensitivity of CMR to regional increases in wall thickness than echocardiography, which has been demonstrated in several previous studies examining different cardiac conditions.^{8,17} However, the nature of our cohort may have also contributed. Given the entry requirements of the British army, it is likely that our population had a high level of baseline physical fitness, so that many of the recruits are likely to have had an athletic heart even before training and therefore increased wall thickness measurements. Given this concern, our normal range should not be considered representative of the population as whole and further studies are required to define such a range in more sedentary individuals. Nevertheless, our results do indicate that given the regional variation, a universal cutoff is unlikely to be appropriate for all segments of the myocardium and that CMR wall thickness measurements of 13 to 15 mm are observed quite commonly in young athletic men who are not infrequently screened for HCM.

Asymmetrical Wall Thickening

Before training, asymmetrical wall thickening was present in 2% but increased dramatically to 10% after the period of intensive physical exercise. In these recruits, the maximal wall thickness

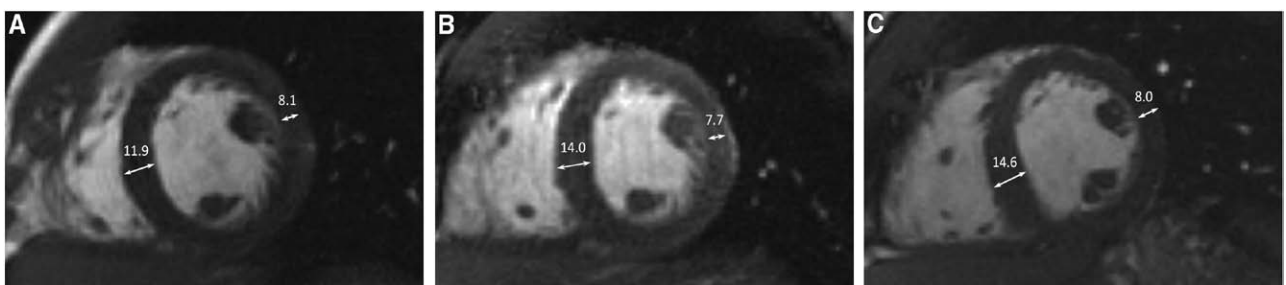


Figure 3. Short-axis steady state-free procession images in end-diastole. **A,** Pretraining measurements showing normal septal to lateral wall ratio and left ventricular wall thickness. **B,** Post-training measurements showing asymmetrical wall thickening in the same recruit. **C,** Example of asymmetrical wall thickening after training in another recruit.

Table 4. Comparison of Recruits Who Did and Did Not Have Asymmetrical Wall Thickening After Army Training

Baseline Characteristics	Recruits With Asymmetrical Wall Thickening After Exercise (n=31)	Recruits Without Asymmetrical Wall Thickening (n=277)	P Value
Age, y	20±3	20±2	0.57
Systolic blood pressure, mm Hg	122±10	122±19	0.98
Diastolic blood pressure, mm Hg	73±6	69±11	0.07
Body mass index, kg/m ²	24.0±2.5	22.9±2.5	0.02
Alcohol consumption, U	4.4±6.7	3.4±5.6	0.38
Smoking (pack years)	1.5±2.8	1.1±2.0	0.38
Physical activity score	6.1±4.4	6.9±5.4	0.49

increased from 12.7 to 14.1 mm and was not observed outwith the septum. However, in contrast to the rest of the cohort and previous descriptions of exercise-induced remodeling, there was no change in the indexed LV mass or volumes, underlining that this response represents an unusual form of adaption.

The explanation for why some recruits developed asymmetrical wall thickening remains unclear. There were no other clinical markers in these recruits to indicate a diagnosis of HCM. No recruit had symptoms, a family history, or physical signs suggestive of cardiomyopathy, and in the few recruits where electrocardiograms were available, these were also within normal limits. Furthermore, the wall thickness/diastolic volume ratio, which is considered to be a useful discriminator between wall thickening due to exercise and that related to an increased afterload or cardiomyopathy,¹³ was normal in all our recruits. It, therefore, seems unlikely that exercise was simply unmasking an underlying cardiomyopathy in these recruits, particularly given the frequency with which asymmetry was observed. More likely in certain individuals, asymmetrical wall thickening seems to occur as part of the normal physiological response to exercise, albeit with key differences to the previously reported patterns of adaption. On the basis of these results, we would, therefore, urge caution in diagnosing HCM based on borderline increases in regional wall thicknesses (13–15 mm), particularly in young and physically fit men.

LV Mass/Diastolic Volume Ratio

As previously reported, we have confirmed in a large cohort of army recruits that LV mass increases with exercise; however, our analysis of the LV mass/volume ratio (*M/V*) in this study add further insight. Importantly, we have demonstrated that *M/V* did not change after exercise, indicating that the increase in mass

is balanced by changes in ventricular volume. Furthermore, the wall thickness/volume ratio remained normal in all subjects supporting the role of these 2 parameters as useful discriminators between exercise-induced and other forms of hypertrophy.

Limitations of Study

The advantage of concentrating on a young cohort of adults is that we can ensure that conditions such as hypertension, coronary artery disease, or diabetes mellitus will not have influenced our results. However, as discussed, our cohort is likely to have a higher level of physical conditioning at baseline than the general population, making it unlikely that our reference range will be more widely applicable. Further work is therefore required to establish a true normal range for wall thickness in both sexes and ideally across a range of ages and ethnicities.

Dawson et al¹⁸ have recently published wall thickness measurements in 20 cases, aged 20- to 30-year olds (10 men) that seem slightly lower than ours (eg, basal anterolateral, 9.0±2.5 versus 10.0±1.3 mm). Again this may reflect the high baseline levels of physical fitness of our army recruits or simply the low numbers in their cohort.

Electrocardiograms were not performed routinely in our cohort, which is a limitation when attempting to differentiate hypertrophy due to exercise and that related to HCM. Nevertheless, we think that given the results of the wall thickness/volume ratio and the screening that army recruits undergo before their recruitment, we can be satisfied that asymmetrical wall thickening was observed as part of a physiological remodeling response to exercise and not a manifestation of cardiomyopathy.

Table 5. Baseline Characteristics Shown to CMR Indices Both Before and After Exercise

CMR Indices	Pre-training	Post-training	P Value	Pre-training	Post-training	P Value	P Value*
End-diastolic volume, mL	160.4±26.1	158.9±25.2	0.61	156.0±26.6	160.0±27.1	<0.01	0.84
Indexed end-diastolic volume, mL/m ²	82.6±10.7	81.7±9.6	0.60	82.7±11.2	84.8±11.4	<0.01	0.16
LV mass, g	171.2±19.7	171.9±19.2	0.75	165.8±25.2	170.0±24.5	<0.01	0.68
LV mass index, g/m ²	87.7±6.5	88.1±6.5	0.71	87.8±10.3	90.0±10.1	<0.01	0.15
Mass/volume, g/mL	1.07±0.12	1.09±0.14	0.56	1.07±0.13	1.07±0.13	0.84	0.56
Maximal wall thickness, mm	12.7±1.1	14.1±0.9	<0.01	12.2±1.2	12.3±1.1	0.13	<0.01
Lateral wall thickness, mm	9.4±0.7	9.0±0.5	0.01	9.2±0.8	9.2±0.8	0.11	0.39
Wall thickness/diastolic volume ratio, mm · m ⁻² · mL ⁻¹	0.08±0.02	0.09±0.02	<0.01	0.08±0.01	0.08±0.02	0.07	<0.01

CMR indicates cardiovascular magnetic resonance; and LV, left ventricular.

*P values comparing after exercise values in the recruits with asymmetrical wall thickening with postexercise values in the rest of the cohort.

Conclusion

In a population of young men army recruits, we have demonstrated significant regional variation in LV wall thickness and that it is common for this to exceed the traditional normal cutoff of 13.0 mm. In addition, we have provided evidence that asymmetrical wall thickening occurs as a common response to exercise. These observations indicate that in young athletic individuals being investigated for HCM, a diagnosis should not be made simply on the basis of a borderline CMR increase in regional wall thickness.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The differentiation between physiological left ventricular hypertrophy secondary to exercise and hypertrophic cardiomyopathy is a complex and increasingly common clinical dilemma. Regional increases in wall thickening are an important component of current diagnostic algorithms for hypertrophic cardiomyopathy, although asymmetrical patterns of wall thickening have also been described in the context of hypertension and aortic stenosis. We sought to investigate whether asymmetrical patterns might also develop as part of the physiological response of the left ventricle to exercise. Cardiovascular magnetic resonance was performed in male army recruits before (n=541) and after (n=309) an identical and rigorous physical training program. On the baseline scans, we demonstrated significant regional variation in wall thickness and that dimensions ≥ 13.0 mm were common (present in 23% of recruits). Furthermore, we observed that although asymmetrical wall thickening was present at baseline in only 2% of our population, it increased to $>10\%$ after a uniform exercise regimen. None of the subjects were otherwise suspected of having hypertrophic cardiomyopathy, suggesting that asymmetrical wall thickening occurs in a subgroup of the population as part of the physiological response to exercise. We would, therefore, urge caution in making a diagnosis of hypertrophic cardiomyopathy in young athletic men purely on the basis of regional wall thickening. Interestingly, the mass/volume and wall thickness/diastolic volume ratios remained normal in all the recruits after exercise, indicating that these parameters may prove more useful discriminators.