CARDIOVASCULAR MEDICINE

Left ventricular growth response to exercise and cigarette smoking: data from LARGE Heart

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Heart 2006;**92**:1784–1788. doi: 10.1136/hrt.2006.088294

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Accepted 14 June 2006
Published Online First 27 June 2006

Background: Increasing left ventricular mass is a risk factor for cardiovascular morbidity and mortality.
Objective: To examine the possible association of smoking with the left ventricular growth response in men.
Methods: Left ventricular mass was measured in 309 army recruits before and after an identical 12-week physical training programme. Left ventricular mass was determined using cardiovascular magnetic resonance.
Results: Left ventricular mass increased with training (mean (standard deviation (SD)) 3.83 (10.81) g, $p<0.001$). By univariate analysis, exercise-induced change in left ventricular mass was positively associated with cigarette smoking (mean (SD) 1.69 (11.10) g *v* 4.76 (10.23) g for non-smokers *v* ex- and current smokers, respectively; $p=0.026$), whereas age, height, diastolic and systolic blood pressure (SBP), alcohol consumption or indices of physical activity were not significantly associated with change in left ventricular mass. Multivariate analysis showed body weight, smoking status and SBP to be independent predictors of left ventricular mass (incremental $R^2=3.4\%$, $p=0.004$; $R^2=4.9\%$, $p=0.024$; and $R^2=1.7\%$, $p=0.041$, respectively).
Conclusions: Cigarette smoking and SBP are associated with exercise-induced left ventricular growth in young men. The positive association of smoking with changes in left ventricular mass is surprising, given the limited exposure of these subjects to smoking, and although these data do not prove causation, they are of great interest to those trying to uncover the drivers of left ventricular hypertrophy, as well as to those examining the possible ill-effects of smoking in the young.

Left ventricular mass varies greatly between people,[1–4] with increasing mass representing an independent risk factor for the development of cardiovascular disease,[2 5 6] even among otherwise healthy people.[7–9] Thus, the identification of factors that influence the left ventricular growth response is of considerable interest. To date, most studies were based on elderly people[10] or patients with disease,[11] most were cross-sectional in nature and only a few have examined young healthy people[12] or prospective growth responses.[13 14] One of the goals of the Lichfield Army Recruit Growth in Exercise Heart Study (LARGE Heart) was to elucidate the environmental factors that alter exercise-induced left ventricular growth responses in Caucasian men. As such, it represents the third in a series of studies that have examined the left ventricular growth response of army recruits to a homogeneous physical training programme. The first study exclusively examined genetic determinants of physiological left ventricular growth,[14] and the second was a pharmacogenomic study.[13] The use of an exercise or physiological model of left ventricular hypertrophy to understand pathological hypertrophy is justifiable:

1. pathological LV hypertrophy is slow to develop, limiting the scope for longitudinal studies;
2. large prospective studies on left ventricular hypertrophy are few and plagued by confounders (especially influential in an older population);
3. the stimuli for pathological left ventricular hypertrophy may be diverse in cause and severity; and
4. the mechanisms underlying the left ventricular growth response show considerable overlap, regardless of the growth stimulus,[15] making results from the exercise model relevant to pathological left ventricular hypertrophy.

The ''environmental'' component of the LARGE Heart study specifically sought to assess whether any relationship existed between exercise-induced left ventricular growth and cigarette smoking. Additionally, we examined the role of known predictors of left ventricular mass such as age, height, weight and specifically blood pressure, in determining changes in left ventricular mass in response to a defined stimulus.

METHODS

Study participants

Participants were consecutive Caucasian men recruited to the Army Training Regiment, Lichfield, UK between July 2002 and April 2004. All participants successfully completed an army medical examination before undergoing a 12-week period of intensive physical training.

Before training, height and weight of the participants were recorded. At interview, cigarette smoking history and alcohol consumption were documented. A questionnaire was used to assess physical activity and to confirm smoking history documented earlier during interview. Smoking history included smoking status (current, ex-smokers or non-smokers), consumption (number of cigarettes per day and duration of smoking) and time since cessation. Alcohol consumption was recorded as the number of units of alcohol

Abbreviations: CMR, cardiovascular magnetic resonance; CPD, cigarettes smoked per day; DBP, diastolic blood pressure; LARGE Heart Study, Lichfield Army Recruit Growth in Exercise Heart Study; SBP, systolic blood pressure

consumed per week, estimated by the participant. Physical activity assessment listed the sports previously undertaken and those currently undertaken; 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 three factors: the number of sports participated in, whether the participant continued to play that sport and the level the sport was played to; this score was used as the primary measure of physical activity.

At the start (pre-) and end (post-) of the training period, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 20 min of supine rest using an automated unit (In Vivo, Philadelphia, Pennsylvania, USA), the mean of two readings (2 min apart) being used in subsequent analysis.

At the end of training (at interview), smoking habit during training was documented.

Assessment of left ventricular mass

The availability of participants before training was limited to a 12-h period, during which time as many randomly selected volunteers as possible were imaged. A mobile 1.5-T Siemens Sonata cardiovascular magnetic resonance (CMR) scanner (Siemens, UK) applied previously described protocols[16] with validated reproducibility.[17 18]

Image analysis was carried out by JRP who was blinded to other study data, using CMR tools (Cardiovascular Imaging Solutions, London, UK). Unadjusted left ventricular mass before and after training, change and percentage change in unadjusted left ventricular mass were used in statistical analysis. Images of poor quality (such as those with respiratory or movement artefacts) were prospectively excluded from analysis.

Statistical analysis

Data were analysed using STATA V.8. Left ventricular mass, body weight and SBP before and after training required natural log transformation to normalise distribution; geometric means and approximate standard deviations (SDs) are reported for these variables. Alcohol consumption was converted into a categorical variable because of its skewed distribution. Mean unadjusted values (and SDs) were initially calculated for pre-training, post-training and exercise-induced change in left ventricular mass with respect to categorical variables (smoking status and alcohol consumption). p Values have been calculated from analysis of variance unless otherwise stated. Pearson correlation coefficients were determined individually for bivariate associations between pre-training, post-training change and percentage change in left ventricular mass, and age, height, weight, SBP and DBP. The independent association with exercise-induced change in left ventricular mass was determined for each of these potential covariates using stepwise regression modelling.

RESULTS

Study participants

In all, 1430 participants were invited to participate in the study, of whom 897 volunteered. Of the 541 participants who had left ventricular mass measured before training, 336 had complete magnetic resonance imaging studies after training. Of these, image quality was unacceptable in 27 and hence paired (pre-training and post-training) left ventricular mass data were available in 309 participants.

Left ventricular mass before training

Anthropometric, demographic and lifestyle data, and left ventricular mass before training were similar for participants included and those excluded. Univariate analysis showed left ventricular mass before training (baseline) to be positively associated with age, height, weight, alcohol consumption, DBP, SBP and indices of physical activity, and to be negatively associated with smoking. Multivariate analysis confirmed indices of physical activity, weight and SBP to be independently associated with left ventricular mass before training.

Change in left ventricular mass

Training was associated with a significant increase in left ventricular mass; mean left ventricular mass was 164.5 (SD 24.6) g and 168.5 (SD 23.6) g before and after training, respectively, whereas the mean of individual changes was 3.83 (SD 10.81) g, $p<0.001$ by paired t test. Mean percentage exercise-induced change in left ventricular mass was 2.64% (SD 6.59%), $p<0.001$ and mean change in left ventricular mass indexed to body surface area was 2.07 (SD 5.66) g/m^2, $p<0.001$. Neither body mass nor SBP changed significantly (mean of individual changes 0.50 (SD 5.11) kg, $p = 0.49$; and 0.1 (SD 14.4) mm Hg, $p = 0.96$, respectively, by paired t test), although a small reduction in DBP was detected (−2.3 (SD 9.5) mm Hg $p<0.001$ by paired t test).

By univariate analysis (tables 1 and 2), age, height, DBP, SBP, alcohol consumption or indices of physical activity were not significantly associated with unadjusted or percentage change in left ventricular mass. However, after stratifying SBP before training, levels >140 mm Hg seemed to be associated with a trend for greater mean increase in left ventricular mass in response to training (3.66 (SD 10.85) g *v* 3.45 (SD 10.85) g *v* 6.92 (SD 10.35) g for mean SBP ⩽120 *v* 120.5–140 *v* >140 mm Hg, respectively, $p = 0.311$). Change in left ventricular mass did not differ between current and ex-smokers (mean 4.94 (SD 10.37) g *v* 4.03 (SD 9.86) g, respectively; $p = 0.697$); however, mean change in left ventricular mass for these participants (current and ex-smokers) was significantly greater than that among non-smokers (4.76 (SD 10.23) g *v* 1.69 (11.10) g, respectively; $p = 0.026$, and 3.21% (6.28%) *v* 1.37% (6.69%), respectively; $p = 0.029$).

During training, none of the non-smokers began smoking, whereas 17 (14%) of the current smokers stopped and 11 (47%) of the ex-smokers restarted. No evidence suggested that these changes in smoking status during training altered the change in left ventricular mass over and above the pre-training smoking status. Similarly, unadjusted changes in left ventricular mass were unrelated to changes in body weight ($R^2 = 0.04$, $p = 0.79$), DBP ($R^2 = 0.009$, $p = 0.89$) or SBP ($R^2 = 0.05$, $p = 0.42$). The same held true for change in left ventricular mass adjusted for BSA and percentage change in left ventricular mass.

Subsequent multivariate analysis showed weight, SBP and smoking status (table 3) to be independent predictors of exercise-induced change in left ventricular mass ($R^2 = 3.5\%$, 1.7% and 4.9%, respectively). A history of smoking (whether ex or current) was significantly associated with a greater increase in left ventricular mass in response to training ($p = 0.024$). Finally, pre-training SBP, although not significantly associated with change in left ventricular mass in univariate analysis, was found to be an independent predictor of exercise-induced change in left ventricular mass on multivariate analysis. Further multivariate analysis suggests that independently, pre-training SBP is positively associated with body weight ($p<0.001$) and negatively associated with smoking ($p = 0.002$), possibly explaining the non-significant association found on univariate analysis.

The association of smoking with change in left ventricular mass was explored further in ex and current smokers combined, by examining the effect of cigarettes smoked per day (CPD) and the duration of smoking. The mean change in

Table 1 Left ventricular mass before and after training (both log transformed), and exercise-induced change and percentage change in left ventricular mass according to smoking status and alcohol consumption

		Pre-training LV mass (g)		Post-training LV mass (g)		Change in LV mass (g)		% Change in LV mass	
	n	Mean (SD)*	p Value	Mean (SD)*	p Value	Mean (SD)	p value	Mean (SD)	p Value
Smoking status									
Non-smokers	119	166.2 (24.9)	0.279	167.6 (24.5)	0.303	1.69 (13.50)		1.37 (7.64)	
Ex-smoker	24	156.8 (23.8)		160.9 (23.6)		4.03 (9.86)	0.079	2.78 (6.12)	0.086
Current smoker	99	163.7 (22.8)		168.8 (21.8)		4.94 (10.37)	0.026‡	3.31 (6.35)	0.029‡
Alcohol consumption (units/week)									
0	81	160.6 (27.9)	0.065	166.3 (26.7)	0.107	5.46 (11.42)	0.217	3.79 (7.04)	0.169
1–10	131	163.8 (22.4)		166.9 (20.4)		2.78 (10.57)		2.08 (6.53)	
⩾11	96	169.1 (24.0)		172.8 (24.8)		3.81 (10.58)		2.39 (6.21)	

LV, left ventricular.
*Geometric mean (SD).
‡p Value for (non-smokers) *v* (ex-smokers and current).

left ventricular mass was 3.9 (SD 9.6) g *v* 13.3 (SD 13.7) g for current smokers <20 *v* ⩾20 CPD, respectively; p = 0.005, whereas mean change in left ventricular mass was 3.7 (SD 9.7) g *v* 4.4 (SD 9.8) g *v* 14.0 (SD 11.4) g for those who have smoked for <4 *v* 4–8 *v* >8 years, respectively; p = 0.011. Finally, there was a significant correlation between smoking burden (CPD×duration of smoking) and percentage change in left ventricular mass (R = 0.257, p = 0.004). The use of percentage (rather than raw) change in left ventricular mass, the exclusion of ex-smokers and finally the exclusion of outliers did not significantly alter these findings.

DISCUSSION

This longitudinal study examined the influence of environmental and physiological factors on the human left ventricular growth response to a controlled exercise stimulus. The data show that a history of cigarette smoking is associated with an exaggeration in such growth, and that SBP has a similar positive association.

In this study, past (ex) or current cigarette smoking was associated with a greater left ventricular growth response. A ''catching up'' phenomenon might be postulated, where those with lowest left ventricular mass before training have most to gain. This does not seem to be the case, with both unadjusted and percentage change in left ventricular mass being related to smoking status. In addition, we have evidence to support a dose-dependent effect with duration of smoking, CPD and lifelong smoking burden, all having a positive association with change in left ventricular mass. These data are consistent with other studies; smoking and left ventricular mass seem to be positively related in older populations[19–21]; however, this is the first study to show this association in young people. The exposure of the participants to smoking in our study is relatively limited in comparison to that of a middle-aged ''lifelong'' smoker; hence it may seem casual to suggest that such limited exposure could cause an accentuated left ventricular growth response to exercise. However, in young participants, a similar association has been shown between smoking and aortic SBP. Mahmud and Feely[22] used applanation tonometry to assess aortic blood pressure and stiffness in 41 young adult smokers (mean age 22.7 (SD 4) years) and 116 non-smokers matched for age, height, weight and sex. They found that both aortic SBP and stiffness were considerably greater in smokers.[22] Interestingly, they could not show a difference in brachial artery blood pressure between the groups; a similar observation was made in our study. Such a disparity has been attributed to greater pulse pressure amplification occurring in non-smokers.[22] Thus, smokers in our study may well have had greater aortic SBP and arterial stiffness compared with non-smokers, resulting in a greater left ventricular workload and thus growth response in smokers in comparison to their non-smoking counterparts.

At least 4000 components of cigarette smoke may contribute to its association with cardiovascular disease.[23] Despite this, only a few of these components have been examined as a potential effector in the pathogenesis of cardiovascular disease, including carbon monoxide,[24] polycyclic aromatic polycarbons[25] and nicotine.[26] The exact mechanisms underlying the clear association of cigarette

Table 2 R^2 from analysis of variance, which represents the percentage variation in pre-training, post-training (both log transformed), exercise-induced change and percentage change in left ventricular mass (g), which is explained fitting a univariate model with each variable

	Pre-training LV mass (g)*		Post-training LV mass (g)*		Change in LV mass (g)			% Change in LV mass	
	R^2	p Value	R^2	p Value	R	R^2	p Value	R^2	p Value
Age (years)	2	0.01	3	0.002	0.06	0.4	0.294	0.01	0.556
Height (m)	16	<0.001	14.3	<0.001	−0.088	0.8	0.122	0.1	0.068
Weight* (kg)	46.6	<0.001	42.6	<0.001	−0.112	1.3	0.049	2.7	0.004
Pre-DBP (mm Hg)	2.4	0.006	2.5	0.006	−0.012	0.01	0.837	0.04	0.708
Pre-SBP* (mm Hg)	9.3	<0.001	12.2	<0.001	0.040	0.2	0.487	0.01	0.847
Physical activity score*	3.3	0.005	2.3	0.018	−0.092	0.8	0.154	0.08	0.160

DBP, diastolic blood pressure; LV, left ventricular; SBP, systolic blood pressure.
*Log transformed

Table 3 Results of stepwise regression modelling on exercise-induced change in left ventricular mass (final model shown, including only significant predictors of left ventricular mass)

Variable	Incremental R^2 (%)*	Standardised β-coefficient	p Value
Weight (kg)†	3.5	−2.009‡	0.004
Pre SBP (mm Hg)*	1.7	1.504‡	0.041
Smoking status			
Non-smoker	4.9	—	0.024
Ex-smoker		2.9	
Current smoker		3.947	

SBP, systolic blood pressure.
Predictors with $p<0.05$ are presented.
Note that the overall R^2 for the model containing all variables is 6.5%.
*The incremental R^2 shows the additional variability in exercise-induced change in left ventricular mass explained by adding the variable to a model that contains all other variables listed.
†Required log transformation to normalise distribution.
‡The β-coefficient is for a 1 SD increase in continuous variables (on the transformed scale where specified).

smoking with cardiovascular disease have not been clarified.[27] In theory, cigarette smoke may drive cardiovascular disease and left ventricular hypertrophy through several pathways. Smoking may reduce arterial vasodilative function through reduced nitric oxide availability.[28 29] Cigarette smokers have derangements in lipid profile[30] likely to encourage the development of atherosclerosis. Finally, smoking may cause insulin resistance,[31] a possible risk factor for the development of left ventricular hypertrophy.[32 33] The direct effect of cigarette smoking on the myocardium has received little attention. In vitro, nicotine stimulates proliferation of endothelial cells[34] and vascular smooth muscle cells.[35] However, such an effect has yet to be investigated in cardiomyocytes. Similarly, in rats, chronic inhalation of carbon monoxide induces cardiac hypertrophy,[36] and left ventricular growth in response to myocardial infarction also seems to be greater in rats exposed to carbon monoxide.[37]

Thus, in theory, there are several possible mechanisms through which smoking may influence left ventricular growth in our study of young men. However, it is possible that the association of smoking with left ventricular growth may be a product of confounders. In this study, we have documented possible modifiers of left ventricular growth such as previous physical activity (and included them in our stepwise regression); however, we have not been able to record previous dietary intake, a factor possibly different in smokers and well known to alter cardiovascular risk.

The change in left ventricular mass seen in this study in response to training seems to be small. However, most of the studies examining the change in left ventricular mass in response to exercise have used echocardiography, which is a less reproducible method of assessing change in left ventricular mass.[38] Perhaps data from our two previous studies examining exercise-induced left ventricular growth in army recruits serve as a good example of this. The first study used echocardiography and showed a mean (SD) change in left ventricular mass of 30.4 (35.5) g (n = 140).[14] The second used CMR and observed a mean change in left ventricular mass of 8.4 (SD 14.3) g (n = 141).[13] In similar subjects experiencing near identical exercise regimens, the change in left ventricular mass differed by over threefold. We believe that such a disparity reflects a reduction in reproducibility associated with the use of echocardiography to assess changes in left ventricular mass.[38] At least two explanations show why mean change in left ventricular mass is less in our study than that seen in the second study (3.8 *v* 8.4 g). The training stimulus in this study may have been less intense. Secondly, in our study we used a ''Fast Imaging with Steady-state free Precession'' CMR sequence in contrast with the second study, which used ''Fast Low-Angle Shot''.[17] The relatively small changes in left ventricular mass are comparable with those seen in our second study using CMR.[13] By using previously published interstudy reproducibility data for the CMR unit used in this study,[17] power calculation suggests that we can detect a 1.46% difference in change in left ventricular mass between groups with ⩾119 participants (80% power, 95% confidence), a magnitude within the differences observed between smoking status groups.

Our study found that 40% of the participants were current smokers; a high prevalence of smoking may seem surprising, given the prevalence of smoking in the UK population[39]; however, such data are consistent with our previous experience in studying similar groups over the past decade. Similarly, the relatively high proportion of ex-smokers (11%) recorded might seem unexpected among those so young; however, over one quarter had ceased smoking ⩽2 months before the start of training (data not presented), suggesting an anticipatory effect related to recruitment. Thus, we may even consider many of the ex-smokers to behave in a similar fashion to current smokers, and data on exercise-induced change in left ventricular mass are certainly consistent with this notion (table 2).

Our study does have limitations. We could not obtain biochemical confirmation of smoking status, nor determine the accuracy of self-reported estimates of smoking intensity, alcohol consumption or exercise history. Although being unique in study design, and of large scale, expanded numbers would allow dissection of mechanistic relationships to be more readily carried out. In addition, and as for all such studies, further studies are warranted among those of different age, race and sex. Similarly, we must emphasise that these data apply to physiological left ventricular growth. Such factors may be of differing importance when considered in the context of pathological left ventricular growth.

We have shown for the first time using a longitudinal model, in a large number of participants using CMR, that cigarette smoking and blood pressure are positively associated with exercise-induced change in left ventricular mass. Although several cross-sectional studies show a similar association with left ventricular mass, the uniformity of stimulus and prospective nature of our study make these data unique. The positive association of smoking with change in left ventricular mass is surprising, given the limited exposure of these participants to smoking, and although these data do not prove causation, they are of great interest to those trying to uncover the drivers of left ventricular hypertrophy, as well as to those examining the possible ill effects of smoking in the young.

ACKNOWLEDGEMENTS

We thank the army recruit volunteers at Lichfield, the hospitality and cooperation of the staff at the Army Training Regiment Lichfield, particularly the staff of the Medical Reception Station, the staff of the Officer's Mess and the commanding officer. We also thank Alliance Medical Limited, who provided the mobile CMR scanner, and especially recognise the hard work of the scanning technicians.

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Competing interests: This work was supported by an unconditional educational grant from Aventis UK, to whom we express our thanks.

Ethical approval: This study complies with the Declaration of Helsinki, and the Defence Medical Services Clinical Research Committee provided appropriate ethical approval. Written informed consent was obtained from all participants.

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