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Physiological determinants of the variation in left ventricular mass from early adolescence to late adulthood in healthy subjects

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Summary

Background: The physiological determinants of left ventricular mass (LVM) measured by cardiac magnetic resonance (CMR) imaging are not well defined as prior investigators have studied either adults or adolescents in isolation or have not strictly excluded hypertension or accounted for the effects of exercise habits, haemodynamic, demographic, or body shape characteristics.

Methods: A total of 102 healthy volunteers (12–81 years, 53 males) underwent CMR. All parameters [unstandardized and adjusted for body surface area (BSA)] were analysed according to gender and by adolescence versus adulthood (adolescents <20 years, adults ≥20 years). The influence of haemodynamic factors, exercise, and demographic factors on LVM were determined with multivariate linear regression.

Results: LVM rose during adolescence and declined in adulthood. LVM and LVMBSA were higher in males both in adults (LVM: 188 ± 22 g versus 139 ± 21 g, P<0·001; LVMBSA: 94 ± 11 g m^{-2} versus 80 ± 11 g m^{-2}, P<0·001) and in adolescents when adjusted for BSA (LVM: 128 ± 29 g versus 107 ± 20 g, P = 0·063; LVMBSA: 82 ± 8 g m^{-2} versus 71 ± 10 g m^{-2}, P = 0·025). In adults, systolic blood pressure (SBP) and self-reported physical activity increased while meridional and circumferential wall stress were constant with age. Multivariate regression analysis revealed age, gender, and BSA as the major determinants of LVM (global R^2 = 0·69).

Conclusions: Normal LVM shows variation over a broad age range in both genders with a rise in adolescence and subsequent decline with increasing age in adulthood despite an increase in SBP and physical activity. BSA, age, and gender were found to be major contributors to the variation in LVM in healthy adults, while haemodynamic factors, exercise, and wall stress were not.

Introduction

Several factors may influence left ventricular mass (LVM) including age, resting blood pressure, frequency of physical training and biological alterations in growth and sex hormones.

The variation in LVM with age in healthy individuals has been shown in cross-sectional studies by independent investigators to increase (Linzbach & Akuamoa-Boateng, 1973; Lakatta *et al.*, 1987; Wei, 1992), or slightly decrease in men but stay the same in women (Olivetti *et al.*, 1995). In one study (Hees *et al.*, 2002), LVM was shown by CMR to decrease in men but stay the same in women, whereas echocardiography showed a mild, non-significant increase in LVM for both men and women. These conflicting results may be explained by several factors including subject selection, measurement technique and study population size. Taken together, these previous findings indicate that the variation in LVM with age in healthy individuals is not completely established.

LVM is often assessed in the clinical setting using two-dimensional echocardiography although this technique may be limited by variable image quality, reconstruction of three-dimensional structures using geometric assumptions, and potential measurement error (Gosse *et al.*, 1990; Germain *et al.*, 1992; Bottini *et al.*, 1995; Gottdiener *et al.*, 1995). In contrast,

cardiac magnetic resonance (CMR) imaging assessment of LVM is generally not affected by these factors and may therefore more accurately and reproducibly measure differences in LVM within study populations (Bellenger *et al.*, 2000). Although several investigators (Lorenz *et al.*, 1999; Marcus *et al.*, 1999; Hees *et al.*, 2002; Salton *et al.*, 2002; Alfakih *et al.*, 2003) have defined CMR normal ranges of LVM in limited age ranges, none have examined the normal physiological trend of these parameters over a wide age range in healthy individuals without risk factors for cardiovascular disease and accounted for the effect of haemodynamic factors and exercise activity on these trends.

We therefore sought, using a prospective and cross-sectional study design, to explore the normal variations in LVM in completely healthy volunteers from early adolescence to the eighth decade of life and to examine the relative influence of factors such as exercise frequency, blood pressure, left ventricular wall stress, and body habitus on these findings.

Methods

Study population and study design

The study population consisted of 102 healthy volunteers prospectively recruited from the local community (82 adults, age 20–81 and 20 adolescents, age 12–16 years). On inclusion, all subjects had a normal ECG and blood pressure [systolic blood pressure (SBP) ≤140 mmHg and diastolic blood pressure (DBP) ≤90 mmHg] (1999 World Health Organization, 1999; Ramsay *et al.*, 1999) and had no clinical history of systolic or diastolic hypertension. Subjects with previous or current cardiovascular, systemic, or metabolic disease (e.g. diabetes mellitus, renal failure, connective tissue disorders, etc.) or treatment with medication (except for oral contraceptives or hormonal replacement therapy) were excluded from study. Body mass index was not a factor influencing inclusion. CMR imaging was performed within 4 weeks after inclusion with image analysis undertaken by independent observers blinded to subject characteristics. Physical activity in adults was assessed by questionnaire where subjects reported the number of sessions of prolonged walking, physical training, or aerobic activity undertaken each week. Physical activity of the adolescent group was not assessed. The investigation protocol and procedures were approved by the local research ethics committee. Written informed consent was obtained from all subjects prior to inclusion.

Blood pressure

SBP and DBP were non-invasively obtained within 10 min after the CMR imaging examination in the supine position using a sphygmomanometer with a cuff size appropriate for arm diameter. Systolic pressure was recorded upon hearing the first Korotkoff sound and diastolic measurement between the fourth and fifth Korotkoff sounds.

Cardiac magnetic resonance imaging protocol

All subjects were imaged in the supine position using a 1·5 T system (Magnetom Vision, Siemens, Erlangen, Germany) with a 25 mT m^{-1} gradient and a phased-array body coil. Standard scout images were used to locate the orthogonal planes of the heart. End-expiratory ECG triggered short-axis fast gradient echo images were then acquired throughout the left ventricle from the base (atrioventricular valve plane) to the apex. Typical imaging parameters were time to repetition (TR) of 100 ms (giving an effective phase interval of 50 ms after echo sharing), time to echo (TE) 4·8 ms, slice thickness 10 mm, field of view (FOV) 350–420 mm, acquisition matrix 126 × 256, flip angle 20°. The number of cardiac phases per acquisition was determined as the integer obtained from the RR interval divided by TR. Nine to 12 slices were required to completely cover the left ventricle, depending on heart size. Image acquisition time for the left ventricle was approximately 10 min per subject.

Cardiac magnetic resonance image analysis

Tracing of endocardial and epicardial contours

All measurements were undertaken manually without the aid of automated image analysis software. Left ventricular endocardial and epicardial measurements (Scion Image Beta 4·0·2, Scion Imaging Corporation) in each image frame were calculated in the short-axis views to minimize partial volume effects (Wu *et al.*, 2001). End-diastolic and end-systolic frames were identified according to ventricular blood pool area. At the base of the left ventricle, the aortic outflow tract below the valve was included in volume measurements. The free papillary muscles were included for LVM assessment (Pennell, 2002). In the basal region of the heart where the left atrium was seen, only the portion of the slice that could be identified as left ventricle was included for measurement (Fig. 1).

Left ventricular mass

The difference in area between the endocardial and epicardial contours multiplied by the slice thickness (10 mm) represented myocardial volume for a given slice. LVM was obtained by calculating the sum of all myocardial slice volumes and multiplying by the myocardial specific gravity (1·05 g cm^{-3}). LVM was also adjusted for body surface area (LVMBSA). Left ventricular meridional stress was calculated using the equation $\sigma_m = (1{\cdot}35P \times R_i)/[2h(1 + h/2R_i)]$, where σ_m is meridional stress, 1·35 is the conversion factor from mmHg to g cm^{-2}, P is cuff SBP, R_i is the minor semi-axis (inner radius of the left ventricle) and h is the posterior systolic wall thickness (Grossman *et al.*, 1975). Left ventricular circumferential stress was obtained using the equation $\sigma_c = (1{\cdot}35P \times R_i/h)(1 - (R_i^3/(a^2(2R_i + h))))$, where variables are as above and a is the major semi-axis (half the distance between inner apex and mitral valve in diastole) (Sandler & Dodge, 1963).

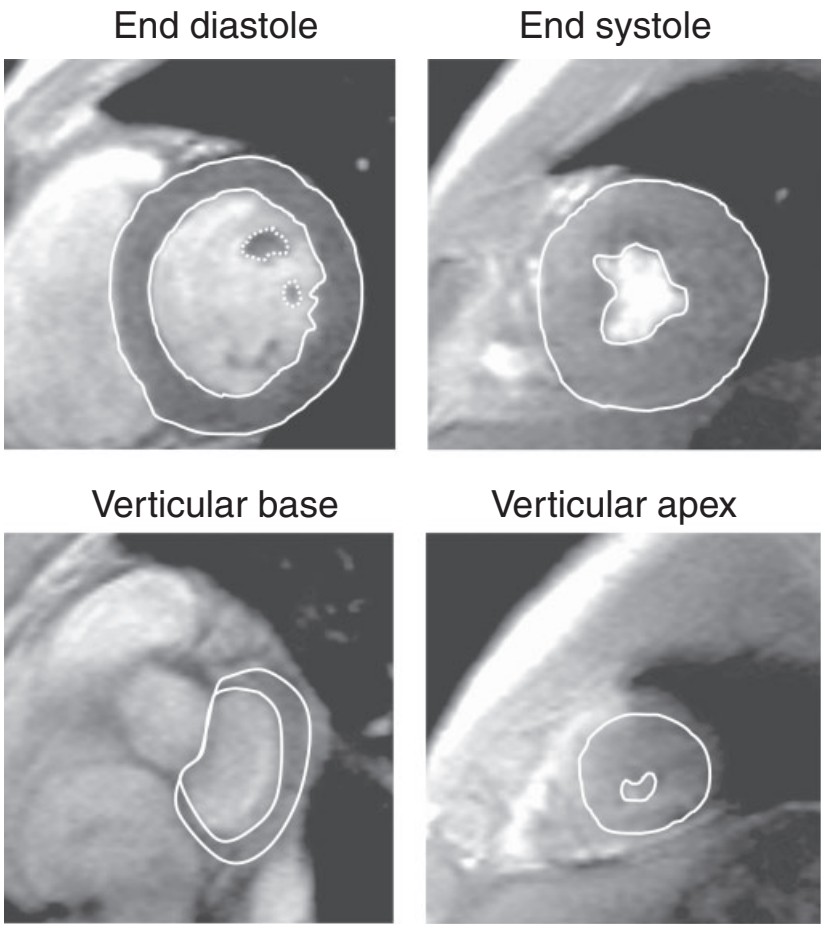

Figure 1 Delineation of the left ventricular borders in the short axis plane. Both the endocardial and epicardial borders are outlined manually for both left ventricular volume and mass measurements (solid lines). Papillary muscle measurements are only included for mass measurements (dashed lines). In some cases, the most basal image plane of the left ventricle (lower left) was slightly oblique to the left ventricular short axis plane resulting in non-circumferential profiles of the myocardium. In these situations left ventricular mass and volumes were assessed from only this partial profile. Delineation of the most apical slice (lower right) often resulted in very small endocardial areas.

Inter-observer variability

A subset of 20 subjects were analysed by two readers, blinded to each other's results, to examine inter-observer variability.

Statistical analysis

SPSS (version 11.5) was used for all statistical calculations. A P-value less than 0·05 was considered to indicate a statistically significant difference. Values are expressed as mean ± SD. Unpaired Student's *t*-test was used to test for significance between groups. Inter-observer variability was calculated by intraclass correlation coefficient (ICC) (Shrout & Fleiss, 1979) and R^2 from Pearson's correlation. BSA was calculated using a previously described technique (Mosteller, 1987). Pearson's correlation coefficient was used to determine the relationship, in adults, between LVM and age, demographic, haemodynamic, and body shape predictors. Spearman's correlation coefficient was used for the relationship between LVM and gender. Multiple stepwise linear regression was used for multivariate analysis of the variation in LVM in the adult population. Curve estimation and 95% prediction intervals of LVM and LVMBSA were defined using commercial software (Matlab curve fitting toolbox, Matlab version R13, Mathworks). The most appropriate curve fitting algorithm for LVM and LVMBSA was identified as the rational polynomial of the form $P(x)/Q(x)$ where both numerator and denominator were at most of the second degree and which had the highest adjusted R^2 and lowest root mean square (RMS) of the error. The rational polynomial describing the prediction interval was determined by fitting the same polynomial as for LVM and LVMBSA to the numerically calculated prediction interval values for each age.

Results

Population description

Table 1 displays the baseline characteristics of the adult and adolescent subjects. Within adults, females displayed lower average body height, weight, and BSA. All measures of blood pressure were similar between genders and within accepted normal limits (1999 World Health Organization, 1999; Ramsay *et al.*, 1999). No significant differences were observed for all variables between genders in the adolescent population. Five of 38 adult females (13%) medicated with an oral contraceptive and five of 38 adult females (13%) medicated with hormonal replacement therapy.

Table 1 Baseline characteristics of the adult and adolescent study populations according to gender (mean ± SD).

	Adults			Adolescents		
	Male	**Female**	***P*-value**	**Male**	**Female**	***P*-value**
Number	44	38		9	11	
Age (years)	46 ± 17	48 ± 17	0·52	14 ± 2	13 ± 1	0·22
Height (m)	1·81 ± 0·07	1·68 ± 0·06	<0·001	1·63 ± 0·13	1·59 ± 0·08	0·46
Weight (kg)	80 ± 9	66 ± 13	<0·001	55 ± 14	50 ± 6	0·33
BSA (m^2)	2·00 ± 0·14	1·75 ± 0·18	<0·001	1·56 ± 0·26	1·48 ± 0·12	0·38
BMI (kg m^{-2})	24·5 ± 2·4	23·4 ± 3·9	0·09	20·2 ± 2·6	19·7 ± 1·9	0·58
SBP (mmHg)	123 ± 9	123 ± 11	0·87	108 ± 10	108 ± 9	0·97
DBP (mmHg)	74 ± 7	73 ± 8	0·44	61 ± 3	61 ± 8	0·85
σ_m (g cm^{-2})	53 ± 14	58 ± 18	0·14	64 ± 16	59 ± 18	0·54
σ_c (g cm^{-2})	151 ± 30	163 ± 38	0·13	169 ± 33	160 ± 34	0·58

BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; SBP, systolic blood pressure; σ_c, circumferential wall stress; σ_m, meridional wall stress.

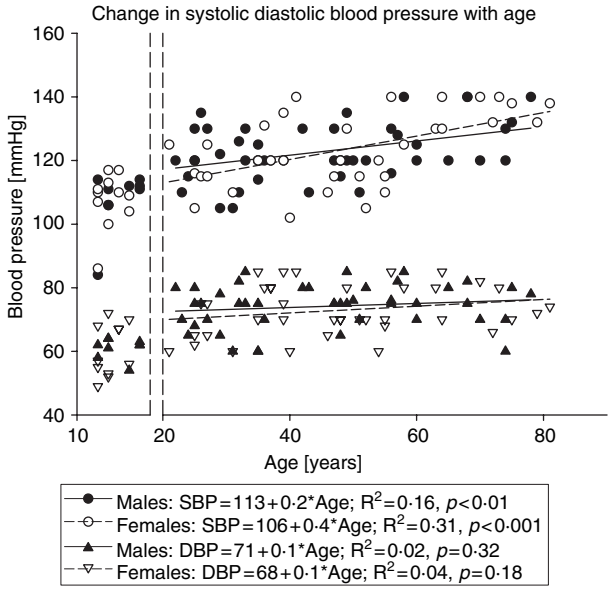

Figure 2 Systolic and diastolic blood pressures in the study population. Regression lines (solid: male, dashed: female) are shown for the adult subjects (right of axis break). Systolic blood pressure increases with age in adults while diastolic blood pressure remains essentially the same. Values are also shown for the adolescent subjects (left of axis break).

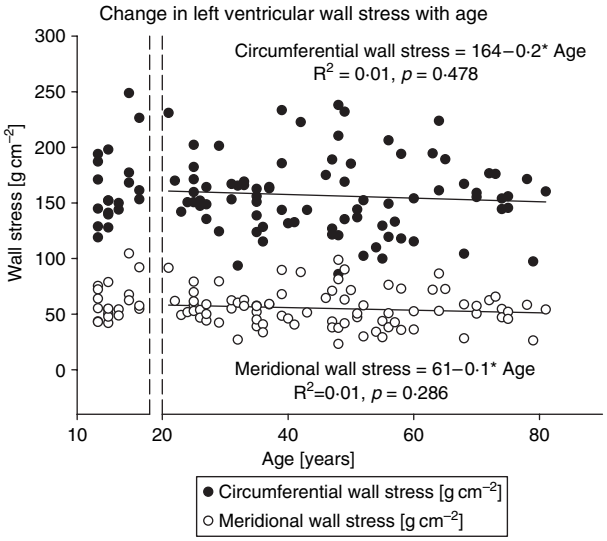

Figure 3 Meridional and circumferential left ventricular wall stresses in the study population. Regression lines are shown for the adult subjects (right of axis break).

Variations in blood pressure, left ventricular wall stress and exercise frequency with age

In the adult population, both males and females increased in SBP with age (males: $R^2 = 0{\cdot}16$, $P<0{\cdot}01$; females: $R^2 = 0{\cdot}31$, $P<0{\cdot}001$). However, there was no increase with age in DBP in the adult population (males: $R^2 = 0{\cdot}02$, $P = 0{\cdot}32$; females: $R^2 = 0{\cdot}04$, $P<0{\cdot}18$). Importantly, despite these variations, both systolic and diastolic blood pressures were still within the inclusion criteria as previously stated (Fig. 2). Both circumferential and meridional wall stress were constant in the adult population over a wide age range ($R^2 = 0{\cdot}01$, $P = 0{\cdot}478$, and $R^2 = 0{\cdot}01$, $P = 0{\cdot}286$, respectively) (Fig. 3). Self-reported physical exercise in the adult population was undertaken on average 2·4 ± 1·9 days $week^{-1}$ and increased with age ($R^2 = 0{\cdot}09$, $P = 0{\cdot}007$).

Regression analysis to identify determinants of left ventricular mass

Univariate predictors of LVM included gender, age and BSA (Table 2). Despite increasing SBP and exercise frequency with age in the study population, these factors were not significant determinants of LVM either in the male or female adult groups. Meridional and circumferential left ventricular wall stress were not significant contributors to LVM.

Multivariate analysis confirmed the associations of decreasing LVM with increasing age and increasing LVM with increasing BSA and male gender (global $R^2 = 0{\cdot}69$).

Table 2 The effect of the studied variables on left ventricular mass in adults.

	Univariate analysis		Multivariate analysis	
	R^2	*P*-value	β	*P*-value
Gender	0·59	<0·001	0·53	<0·001
Age	0·09	0·01	0·21	<0·01
Exercise	0·00	0·79		
Height	0·42	<0·001		
Weight	0·42	<0·001		
BSA	0·48	<0·001	0·33	<0·001
BMI	0·14	<0·001		
SBP	0·00	0·59		
DBP	0·00	0·93		
σ_m	0·00	0·82		
σ_c	0·00	0·69		
			Global $R^2 = 0{\cdot}69$	

BMI, body mass index; BSA, body surface area; β, the standardized beta coefficient reflecting the relative effect of each respective variable; DBP, diastolic blood pressure; SBP, systolic blood pressure; σ_c, circumferential wall stress; σ_m, meridional wall stress.

Age variations in left ventricular mass by age and gender

In both males and females, LVM and LVMBSA showed a similar variation with age with a marked increase during teenage years and steady decline thereafter (Fig. 4). The formulas describing the LVM and LVMBSA variation with age were: male $LVM = (-1{\cdot}209 \times age^2 + 279{\cdot}0 \times age - 2646)/(age - 6{\cdot}401)$ (adjusted R^2=0·65, RMS = 19·7), female $LVM = (-0{\cdot}5739 \times age^2 + 178{\cdot}1 \times age - 1821)/(age - 9{\cdot}397)$ (adjusted R^2 = 0·38, RMS = 19·4), male $LVMBSA = (-0{\cdot}5507 \times age^2 + 136{\cdot}1 \times age - 361{\cdot}9)/(age + 3{\cdot}36)$ (adjusted R^2 = 0·20, RMS = 10·1), and female $LVMBSA = (-0{\cdot}2260 \times age^2 + 93{\cdot}54 \times age - 1018)/(age - 10{\cdot}86)$ (adjusted R^2 = 0·18, RMS = 10·0), respectively. In the adolescent group, males had a trend toward higher LVM than females (128 ± 29 g versus 107 ± 20 g, P = 0·063) which was significant when adjusted for BSA (82 ± 8 g m^{-2} versus 71 ± 10 g m^{-2}, P = 0·025). In the adult population both the LVM and LVMBSA were significantly higher in the male population (LVM: 188 ± 22 g versus 139 ± 21 g, P<0·001; LVMBSA: 94 ± 11 g m^{-2} versus 80 ± 11 g m^{-2}, P<0·001).

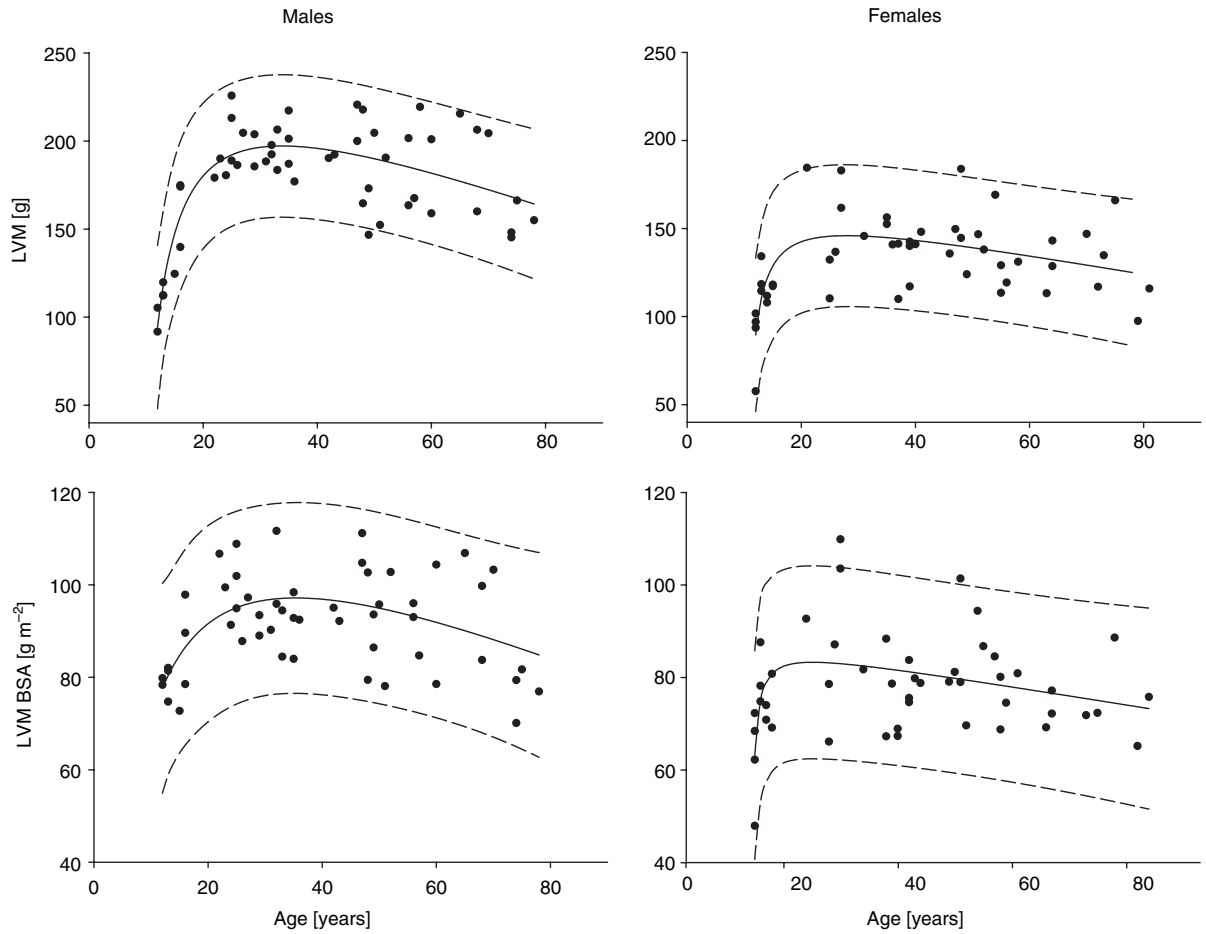

Figure 4 Scatterplots demonstrating the variation in left ventricular mass (LVM) and left ventricular mass adjusted for body surface area (LVMBSA) with age in males (left) and females (right). Solid lines represent rational polynomial curve fitting of scatterplots and dashed lines 95% prediction intervals of these fits. For details and formulas see text.

Inter-observer variability

The variability of LVM measurements was 0·5 ± 4 g between readers ($R^2 = 0{\cdot}98$, ICC 0·98).

Discussion

The major finding of this study is that age, gender, and BSA are the major determinants of LVM in healthy, normotensive humans. Specifically, LVM demonstrates an increase in adolescence and subsequent decline during adult life to a level that is approximately 80% of early adulthood despite increasing blood pressure and exercise activity in our study population.

Earlier observations of variations in left ventricular mass

Autopsy studies

In contrast to the present study, several autopsy studies examining LVM in humans have reported a uniform *increase* in both total cardiac mass and LVM with age (Lakatta *et al.*, 1987; Wei, 1992), with one study reporting an increase of total myocardial mass of 1·5 g $year^{-1}$ (Linzbach & Akuamoa-Boateng, 1973). However, many of the subjects included in these studies were exposed to covariates that are known to influence LVM such as diabetes and hypertension. A subsequent autopsy study (Olivetti *et al.*, 1995) described the effect of age on LVM in a healthy population and demonstrated a steady decline with age among men. The values of normal LVM in this autopsy study showed a decrease in males from approximately 200–150 g throughout adult life. These findings agree closely with the present study. Our female population, however, also showed a decline in LVM during adult life similar to that found in males. By comparison, this age-related decline in LVM in females was not found in the autopsy study by Olivetti *et al.* (1995).

Non-invasive imaging

The mainstay of non-invasive clinical LVM assessment has been two-dimensional echocardiography (Levy *et al.*, 1990) and normal ranges of LVM have been in use for some time (Devereux *et al.*, 1986). The geometrical assumptions inherent in this approach are based on wall thickness uniformity throughout the ventricle (rarely so in pathological ventricles) which make no attempt to account for the significant ventricular length reduction (approximately 10% over the full adult age range) with age (Hees *et al.*, 2002). Such methodological shortcomings may result in an overestimation of LVM. Indeed, the major echocardiographic studies that have defined normal ranges have demonstrated an *increase* in LVM with age (Gerstenblith *et al.*, 1977; Shub *et al.*, 1994). Furthermore, interpretation of serial clinical examinations of LVM assessment with two-dimensional echocardiography may be limited by interstudy and inter-observer variability (Germain *et al.*, 1992). During adolescence the normal evolution of LVM with age is less well explored although differences between children and adults have been described (Daniels *et al.*, 1988). Other non-invasive techniques including three-dimensional echocardiography (Gopal *et al.*, 1994, 1997) and computerized tomography (Wachspress *et al.*, 1988) have overcome many of the shortcomings of two-dimensional echocardiography although no reference values for normal subjects have been established in a large population.

The main advantage of LVM assessment with CMR is its relative freedom from many of the confounding factors described with other imaging modalities. Several studies (Lorenz *et al.*, 1999; Marcus *et al.*, 1999; Hees *et al.*, 2002; Salton *et al.*, 2002) examining LVM in normal subjects with CMR have now been published, although varying by their inclusion criteria and study design. A large cross-sectional study from a wider adult age range (21–96 years) was recently published (Hees *et al.*, 2002). The authors suggested a 10% decrease in LVM in men throughout adult life attributable to decreased ventricular length. Notably, the LVM values described in our study are consistent with those in the corresponding age groups and study populations in the above studies. The results presented in our study of normal subjects extend upon these findings of variations in LVM with age in both genders in the adult population and demonstrate the age related patterns of LVM from early adolescence to late adulthood, and in particular, the rapid evolution of these parameters during adolescence.

Potential biological explanations for varying left ventricular mass with age

Approximately 70% of the age variations in LVM within our adult population could be explained by age, BSA, and gender. Potentially, a decrease in SBP and DBP with age may result in lower myocardial mass. However, SBP and to a lesser extent, DBP increased with age and therefore this hypothesis seems unable to provide a physiologically intuitive explanation for the LVM decrease with age. Frequent exercise may also affect LVM (Morganroth *et al.*, 1975) although our population appeared to exercise more often with increasing age and the observed decrease in LVM with age would appear to counter this hypothesis. However, the decline in LVM with age observed in our study could potentially be explained by other mechanisms. A variation in sex hormones with age has been reported and suggested to likely be an important determinant of LVM (Hayward *et al.*, 2001). Noteably, the variation in LVM found in the male and female populations of our study mirror closely these reported age-related variations in testosterone and oestrogen. The direct relationship of growth hormone to LVM is also well described (Colao *et al.*, 2001; Khan *et al.*, 2002). Both integrated and pulsatile growth hormone secretion decrease rapidly during the teenage years and continue to slowly decline thereafter throughout life in both men and women (Carlson *et al.*, 1972; Finkelstein *et al.*, 1972; Dudl *et al.*, 1973). Although our study has not directly assessed this

hypothesis, these landmarks in growth hormone expression are reflected in the pattern of LVM variation throughout life in both genders in this study. Our study showed a rapid increase of LVM and dimensions during the teenage years and subsequent steady decrease with age. Taken together, our findings of gender, age, and BSA as major determinants of LVM may, in part, reflect the influence of growth and sex hormones on these factors.

Reproducibility of measurement

The reproducibility of CMR LVM measurement obtained in our study was consistent with previously reported inter-observer studies (Germain *et al.*, 1992; Bottini *et al.*, 1995). This level of variability would result in approximately a 4 g error in measurement of LVM and therefore acceptable for clinical use and would not, by itself, seem to significantly influence the trends of LVM values with age found in this study. Interstudy variability was not assessed in the present study but CMR LVM has previously been shown to be highly reproducible with an interstudy variability of approximately 4% (Semelka *et al.*, 1990).

Limitations

The study was planned to overcome limitations experienced in previous studies. Despite this, the present study has not included subjects less than 10 years of age or older than 90 years of age and therefore the present study cannot predict findings in these extremes of age. In addition, this study was undertaken in Swedish subjects from suburban Sweden and therefore results may not be applicable in all racial groups.

Women on oral contraceptives or hormonal replacement therapy were not excluded from the study. However, since it has been previously shown that there is no difference in LVM between healthy women on either oral contraceptives (George *et al.*, 2000) or hormonal replacement therapy (Voutilainen *et al.*, 1993), this is not likely to alter the results.

The criteria used to exclude subjects with hypertension were the same for both adolescents and adults, although normal ranges of blood pressure may differ between the extremes of subject age in this study. Also, physical activity was evaluated by self-assessment as opposed to objective measurement, and this is a limitation. The greater amount of physical activity in older age subjects might reflect a selection bias. However, this increase in activity with age may also be seen as an expected consequence of having the absence of disease as an inclusion criterion.

Furthermore, the values provided in this study are appropriate for studies undertaken using similar gradient echo sequences. To highlight this issue, recent evidence (Plein *et al.*, 2001; Thiele *et al.*, 2001; Alfakih *et al.*, 2003) suggests that implementation of balanced steady-state free precession based sequences may result in consistently lower LVM and greater LV volumes although this difference is likely to be systematic in nature and does not alter the physiological significance of these findings.

Conclusions

The major finding of this study is that age, gender, and BSA are the major determinants of LVM in healthy, normotensive humans. Specifically, LVM demonstrates an increase in adolescence and subsequent decline during adult life to a level that is approximately 80% of early adulthood despite increasing SBP and exercise activity in our study population. In adults, approximately 70% of the variations in LVM may be explained by age, gender, and BSA. These findings also demonstrate the need for age and sex specific normal ranges during CMR examinations.

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