Original Article

Interventricular Septum Thickness Predicts Future Systolic Hypertension in Young Healthy Pilots

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Left ventricular hypertrophy (LVH) has been associated with hypertension, although debate exists as to whether LVH is caused by elevated blood pressure (BP) or is a risk factor for its development. The present study evaluates the association between left ventricular structure and the development of hypertension in a young healthy population. We followed young healthy Israeli Air Force aviators from initial echocardiography at the start of their military service to a mean of 7.5 ± 3.0 years. Data collection included annual BP measurements, height, weight, smoking habits, and lipid profile. We monitored 500 Air Force men with a mean age of 20.5 ± 3.3 (range, 17–40) years and baseline BP of $125 \pm 13/74 \pm 8$ mmHg. Systolic BP during follow-up was associated with baseline systolic BP, interventricular septum (IVS) thickness, and ejection fraction, whereas diastolic BP was associated only with baseline diastolic BP and body mass index. The probability that the systolic BP during follow-up would be higher than the median was twice that in those with an IVS thickness greater than the median. In conclusion, IVS thickening was associated with long-term elevation of systolic BP. Therefore, it seems that IVS thickening is not merely a result of long-term BP elevation, but may predict the development of systolic hypertension. (*Hypertens Res* 2008; 31: 15–20)

Key Words: echocardiography, normotensives, blood pressure

Introduction

Elevated blood pressure (BP) and obesity are risk factors that affect the structure and function of the left ventricle (1–3). Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular disease (4, 5).

The association between hypertension and left ventricular mass (LVM) has been clearly demonstrated in several studies (1, 6–9). Lauer *et al.* demonstrated that systolic BP, and to a lesser degree diastolic BP, are independent markers associated with increased LVM (9). Harpaz *et al.* evaluated a group of healthy subjects and showed that isolated interventricular septum (IVS) hypertrophy, even in the presence of a normal LVM, is associated with hypertension (8). Yet, it is a matter

of debate whether BP is a risk factor for the development of LVH or merely a result of it. Several studies, mainly in children, have shown that increased LVM may precede hypertension (10–14). de Simone *et al.* followed a group of 132 subjects without hypertension for 4.7 years, during which 15 (11%) developed hypertension. Those who developed hypertension were found to have a greater LVM at baseline compared with their normotensive counterparts (11). These results were the basis for the hypothesis that LVH may in fact be a risk factor for the development of hypertension (10–14). Yet, data regarding the significance of LVH in the future development of hypertension in young, healthy subjects are scarce. The aim of this study was to evaluate the significance of LVM on the future development of hypertension in healthy normotensive subjects.

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Table 1. Baseline Subjects' Characteristics and Echocardiographic Values

Variable	Mean±SD	Median	Range
Age (years)	20.5±3.3	19	17–40
Baseline SBP (mmHg)	125±13	120	90–180
Baseline DBP (mmHg)	74±8	75	50–120
Baseline HR (beats/min)	68±13	66	34–160
Height (cm)	178±6	178	157–193
Baseline weight (kg)	67±8	67	48–97
Baseline BMI (kg/m ²)	21.3±2.1	21.1	16.6–30.6
Total cholesterol (mg/dL)	165±32	160	95–279
Triglycerides (mg/dL)	81±42	71	19–337
LDL cholesterol (mg/dL)	103±33	100	22–226
HDL cholesterol (mg/dL)	52±12	50	25–116
End-diastolic dimension (cm)	5.1±0.4	5.1	4.0–6.5
End-systolic dimension (cm)	3.1±0.4	3.1	2.3–4.4
Interventricular septum thickness (cm)	0.9±0.1	0.9	0.6–1.2
Posterior wall thickness (cm)	0.9±0.1	0.9	0.6–1.2
Left atrium (cm)	3.4±0.4	3.4	2.0–4.5
Ejection fraction (%)	77±6	78	59–84
Left ventricular mass index (g/m ²)	103.2±19.7	101.6	54.3–182.9
Relative wall thickness	0.35±0.05	0.35	0.27–0.53

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Methods

Subjects

The study population consisted of 500 consecutively examined Israeli Air Force aviators. These healthy subjects underwent baseline evaluation and routine echocardiography prior to their enlistment and were then evaluated annually. The evaluation included BP, height, weight, and lipid profile. Subjects whose echocardiographs were inconclusive for technical reasons were excluded from the study, as were those with significant cardiac defects. Subjects who did not have at least 1 year of BP follow-up were also excluded.

BP Measurements

BP was measured at every visit twice in the sitting position following 2 min of rest using a sphygmomanometer, and the mean of the measurements was recorded. The BP was measured in the same arm every visit by skilled physicians who were unaware of the echocardiographic findings.

Echocardiographic Evaluation

Echocardiography was performed by an HP SONOS 2500 device (Hewlett-Packard, Palo Alto, USA) using a 2.5 MHz transducer. All examinations were performed using a similar

technique. Two-dimensional M-mode guided measurements were performed according to the recommendations of the American Society of Echocardiography (15). Data collected included diastolic and systolic left ventricular (LV) diameter, posterior wall (PW) and interventricular septum (IVS) thickness, and left atrial (LA) diameter. The intra- and inter-observer variations in these measurements were less than 10%. LA diameter was taken from the leading edge of the posterior aortic wall to the leading edge of the posterior left atrial wall as described by the American Society of Echocardiography (15). LVM was determined by the cube formula, using the Penn convention, as suggested by Devereux and Reichek (16). Left ventricular mass index (LVMI) was calculated by dividing the LVM by the body surface area (BSA). LVH was defined if either the PW or IVS thickness was greater than 11 mm as measured by M-mode echocardiography, or if the LVMI was at least 134 g/m². Relative wall thickness (RWT) was calculated by dividing the sum of the IVS and PW thicknesses by the diastolic dimension. The LV ejection fraction was calculated from end diastolic and end-systolic LV volumes derived by the method of Teichholz *et al.* (17).

In all subjects, weight, height, and body mass index (BMI) were determined. Additional information obtained from the patients' medical records included smoking habits, a family history of premature atherosclerosis, and lipid profile (total cholesterol, low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, and triglycerides).

Table 2. Change in Parameters during Follow-Up

Variable	Baseline	Follow-up	<i>p</i> value
Systolic blood pressure (mmHg)	125±13	120±8	<0.001
Diastolic blood pressure (mmHg)	74±8	73±4	<0.001
Heart rate (beats/min)	68±13	62±7	<0.001
Body mass index (kg/m ²)	21.3±2.1	22.5±1.8	<0.001

Table 3. Comparison between Those Who Were Pre-Hypertensives and Those Who Were Normotensives during Follow-Up

	Normotensives	Pre-hypertensives	<i>p</i> value
Number	305	195*	
Age (years)	21±1	20±3	<0.05
Systolic BP (mmHg)	115±4	127±7	<0.001
Diastolic BP (mmHg)	71±4	75±4	<0.001
Heart rate (beats/min)	61±7	64±8	<0.001
BMI (kg/m ²)	22.3±1.7	22.8±2.0	<0.005
Positive family history (%)	5.9	7.2	n.s.
Smokers (%)	12.1	6.7	<0.05
Serum total cholesterol (mg/dL)	165±34	164±31	n.s.
Serum triglycerides (mg/dL)	79±39	85±48	n.s.
Interventricular septum thickness(cm)	0.89±0.12	0.93±0.11	<0.01
Posterior wall thickness (cm)	0.86±0.11	0.88±0.12	<0.01
End-diastolic dimension (cm)	5.1±0.4	5.1±0.4	n.s.
End-systolic dimension (cm)	3.1±0.3	3.1±0.4	n.s.
Left atrium (cm)	3.3±0.4	3.4±0.4	<0.01
Left ventricular mass (g)	184±39	197±42	<0.001
Left ventricular mass index (g/m ²)	101±19	105±19	<0.05
Relative wall thickness	0.35±0.05	0.35±0.05	n.s.
Concentric pattern (%)	2.3	2.6	n.s.

*Including 12 patients with mild hypertension. BP, blood pressure; BMI, body mass index.

Statistical Analysis

Data are expressed as mean±SD and by median and range. Follow-up values for the subjects were calculated by averaging the measurements obtained during follow-up measurements. The paired *t*-test was used to compare baseline and follow-up measurements. The study population was divided into two groups based on BP measurements found during follow-up. In one group, BP values were lower than 120/80 mmHg, while in the other, BP was in the pre-hypertensive range (systolic values of 120–139 mmHg or diastolic values of 80–89 mmHg). The χ^2 test and independent *t*-test were used to evaluate differences between subgroups. The correlation coefficients between echocardiographic variables and BP levels at baseline and during follow-up were measured by nonparametric Spearman correlations. Multiple logistic regression analyses were conducted to estimate the risk of being above the median BP level by independent variables, including echocardiographic variables, at baseline. The results are presented as odds ratios (OR) and 95% confidence intervals.

To test the hypothesis that IVS thickness at baseline is a predictor of hypertension, receiver-operating characteristic (ROC) analysis was performed. An area under the curve above 0.5 shows the ability of the IVS to predict hypertension.

Results

Baseline Characteristics

Five-hundred aviators, all male, with a mean age of 20.5±3.3 (range, 17–40) years were included in the study (Table 1). Most subjects (87%) were younger than 25 years, and 231 subjects (46%) had BP above 120/80 mmHg at the initial evaluation. Only 6.4% of the subjects had a positive family history for cardiovascular disease, and 10% of the subjects were smokers.

The mean LVMI was 103±20 g/m² (Table 1) and 236 subjects had a LVMI equal to or greater than 100 g/m². Forty subjects (8%) had LVH, and 12 subjects (2.4%) had a concentric pattern (RWT >0.45).

Table 4. Predictors of Blood Pressure Levels during Follow-Up

Variable	Odds ratio	95% confidence interval
SBP (below/above median) during follow-up		
Baseline SBP	5.40	3.62–8.15
IVS	1.99	1.31–3.02
EF	1.89	1.27–2.82
Baseline BMI	1.44	0.97–2.16
DBP (below/above median) during follow-up		
Baseline DBP	4.17	2.82–6.15
BMI	1.59	1.03–2.44
Baseline BMI	1.23	0.80–1.89

SBP, systolic blood pressure; IVS, interventricular septum thickness; EF, ejection fraction; BMI, body mass index; DBP, diastolic blood pressure.

Follow-Up

Subjects were followed annually for 7.5 ± 3.0 (range, 1–12) years. During the follow-up period, systolic BP decreased by 4%, diastolic BP decreased by 1.5%, and heart rate (HR) decreased by 8.5%, whereas BMI increased by 5.5% (Table 2). The decrease in systolic BP during follow-up was less pronounced in subjects with LVH (-2.4 ± 8.8 mmHg) than in those without LVH at baseline (-5.3 ± 9.4 mmHg) ($p=0.07$ between groups). Upon follow-up, diastolic BP decreased by 1.4 ± 6.8 mmHg in those without LVH but increased by 2.4 ± 4.9 mmHg in those with LVH at baseline ($p<0.001$ between groups).

During the follow-up period, 12 (2.4%) subjects had mild hypertension (systolic BP ≥ 140 and <160 mmHg and/or diastolic BP ≥ 90 and <100 mmHg), and 183 (36.6%) subjects had average BP measurements in the pre-hypertensive range. Both subgroups had systolic BP levels that were above the median value (120 mmHg) of our entire study group. These subjects were younger, smoked less, and had greater BMI and HR than their normotensive counterparts (Table 3). Subjects with hypertension or pre-hypertension during follow-up had thicker IVS and PW, as well as larger LVM and left atrium, at baseline than those who were normotensives during follow-up.

Correlation between Echocardiographic Parameters and BP Levels

Baseline BP levels did not correlate with LV parameters. The only correlation was found between baseline systolic BP and left atrial diameter ($r=0.099$; $p=0.029$). However, BP levels during follow-up were correlated with IVS ($r=0.152$; $p=0.001$ for systolic BP and $r=0.118$; $p=0.008$ for diastolic BP) and PW thickness ($r=0.152$; $p=0.001$ for systolic BP and $r=0.119$; $p=0.008$ for diastolic BP). Moreover, baseline IVS was correlated with the change in systolic BP during follow-up ($r=0.092$; $p=0.043$). The ROC analysis showed that IVS predicted future BP (area

under the curve 0.584; $p=0.002$).

Multivariate Analysis

Multivariate analysis revealed that baseline systolic BP, IVS thickness, and ejection fraction determined whether or not a subject was below or above the median systolic BP during follow-up (Table 4). The risk of systolic BP being greater than the median was twice as high in subjects with above-median IVS thickness. Baseline diastolic BP and baseline BMI determined whether or not a subject was below or above the median diastolic BP during follow-up (Table 4). Echocardiographic variables did not predict diastolic BP levels during follow-up.

Discussion

Several studies have shown an association between LVM and BP levels, but these mainly involved hypertensive subjects (6, 7, 18–24). There is little information about the association between LVM and BP in normotensive subjects. Fagard *et al.* found no association between LVM and BP values in 92 healthy subjects (20), whereas Lorber *et al.* did find an association (24). Both studies evaluated relatively small samples. Our study evaluated a large sample of healthy subjects and followed them for a long period. The relatively low BMI and lipid values, along with the low rates of smokers and positive family history of premature atherosclerosis, indicate that our study population represents subjects with low risk profiles.

No association was found between baseline BP values and wall thickness or LVM. This may suggest that BP values in normotensive healthy subjects have no significant effect on the heart's structure or function. However, we should be careful with this conclusion, since we have only a single BP value based on two measurements taken during the baseline evaluation. We cannot exclude the possibility that our study overlooked masked hypertension, since 24 h ambulatory BP monitoring was not done in most of our subjects. It seems more likely, however, that the baseline measurements in our

subjects overestimated the real BP values, as the subjects were under significant stress during the physical examination because of their desire to be accepted into the prestigious air force. This is evident from the fact that, during follow-up, both diastolic and systolic BP and HR decreased, whereas BMI increased.

BP values during follow-up were associated with LVM and wall thickness. The subjects who were found to be pre-hypertensive or hypertensive upon follow-up had thicker LV walls, larger LA, and larger LVM on baseline echocardiography than those who were normotensive. A clear association was found between IVS thickness and systolic BP during follow-up. Surprisingly, subjects with LVH had lower baseline diastolic BP values compared with subjects with no LVH, but during follow-up, diastolic BP increased and systolic BP decreased less than in those with LVH. These findings suggest that LVH may precede the development of hypertension, and that subjects who are normotensive but have echocardiographic evidence of LVH may be at a greater risk of developing hypertension. Our findings raise the question of whether LVH precedes hypertension or is a result of it. Some studies have shown that LVH can precede hypertension (10–14). However, most of those studies included children or middle-aged subjects, whereas our study included a healthy population of young adults with normal BP values and a very low rate of hypertension during follow-up. One study in which LVH was found to precede hypertension was performed by de Simone *et al.*, who followed 132 healthy subjects for a mean of 4.7 years after echocardiography (11). They found that LVM was greater in the 11% of subjects who developed hypertension during the follow-up period than in those who remained normotensive, although the sample size was small. The clear association in our study between IVS thickness and systolic BP during follow-up further substantiates the association between heart muscle structure and the development of hypertension. The reason for this association is unclear. One possible explanation is that the LVH is an early marker of hypertension and is caused by mechanisms that are also responsible for hypertension, such as overactivity of the sympathetic nervous system or the renin-angiotensin system. Heart muscle may be more sensitive than BP to the activation of these systems, and heart muscle changes appear earlier than BP elevation. The fact that IVS, but not PW thickness, was predictive of follow-up systolic BP may be related to the higher sensitivity of the IVS to overactivity of the sympathetic nervous system or the renin-angiotensin system. Harpaz *et al.* also showed that, even in the presence of normal LV mass, only IVS thickness was associated with hypertension (8). Another possible explanation is that the increase in LVM leads to an increase in cardiac output, thereby leading to the development of hypertension.

Risk factors for the development of hypertension are numerous. It is often crucial to estimate the risk of future hypertension, especially in normotensive or pre-hypertensive subjects. Our findings are important, as echocardiographic

examination may become an additional tool to predict hypertension in subjects with pre-hypertension. Subjects with borderline BP values may be at a greater risk for hypertension if they have evidence of IVS thickening on echocardiography, compared with those with normal echocardiographic results. Such subjects should be followed more closely than their counterparts who are pre-hypertensive but have no evidence of LVH. This may prove particularly useful in circumstances where it is crucial to estimate the risk of future hypertension, such as in air crew candidates.

Conclusions

Our work found an association between heart muscle thickness, particularly IVS thickness, and long-term systolic BP. It seems that LVH is not merely a result of long-term hypertension, but is also a predictor of the development of hypertension.

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