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Prevalence, Clinical Correlates and Functional Impact of Subaortic Ventricular Septal Bulge (From the Baltimore Longitudinal Study of Aging)

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Abstract

A localized hypertrophy of the subaortic segment of the ventricular septum - ventricular septal bulge (VSB) - has been frequently described in series of elderly persons, but its prevalence with age, clinical correlates and impact on cardiac function and exercise capacity remain uncertain. We explored these associations in a cross-sectional sample without known cardiac disease from the Baltimore Longitudinal Study of Aging. We randomly selected 700 participants (50% men, mean age 64±15, range 26–95 years) and reviewed their echocardiograms. We identified 28 men and 21 women with VSB (7% overall prevalence). The prevalence of VSB significantly increased with age in both genders ($p<.0001$). In multivariate logistic regression including hypertension and other cardiovascular risk factors, only age displayed a significant independent association with VSB (OR 1.06 per year, 95% CI 1.03–1.10, $p=0.0001$). After multiple adjustments, participants with VSB as compared to those without had enhanced global left ventricular contractility (fractional shortening 41±1.3 vs. 38±0.3%, $p=0.04$; ejection fraction 71±1.6 vs. 67±0.4%, $p=0.06$; systolic velocity of the mitral annulus 8.4±0.1 vs. 8.9±0.3, $p=0.06$), and larger aortic root diameters (3.3±0.06 vs. 3.1±0.02 cm, $p=0.02$). In subgroup of participants who completed a maximal treadmill test (177 women and 196 men), those with VSB (19, 5.1%) had significantly lower peak oxygen consumption than their counterparts (19.6±3.8 vs. 22.9±6.6 mL/kg per minute, $p=0.03$). However this association was no longer significant after multiple adjustments. In conclusion, the

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presence of VSB is independently associated with older age, determines enhanced left ventricular contractility, without any evident impact on exercise capacity.

Keywords

septal bulge; septal hypertrophy; hypertrophic cardiomyopathy; elderly

INTRODUCTION

A localized hypertrophy of the subaortic segment of the ventricular septum has been frequently described in elderly persons, and variously termed subaortic ventricular septal bulge (VSB) ^{1,2}, sigmoid-shaped septum ³, localized ^{4–6} or discrete upper septal hypertrophy ^{7,8}. It has been considered mainly as an incidental finding associated with older age and hypertension ^{6,8}, although some authors have suggested that it may be part of the spectrum of hypertrophic cardiomyopathy ^{9,10}, may determine some degree of left ventricular (LV) obstruction ^{1,3,5,11}, which in turn may potentially cause symptoms such as syncope and dyspnea on effort ³. However, the prevalence with age and clinical correlates of this particular feature of the LV septum have been little explored in populations free from cardiac disease, as well as its potential impact on LV function and structure after accounting for all potential age-related comorbidities. Furthermore, because of few previous reports showing increased LV outflow tract (LVOT) gradients with VSB under stress conditions ^{1,11}, as it is generally described in patients with labile hypertrophic cardiomyopathy ¹², it is reasonable to hypothesize that the VSB may impair peak exercise capacity. We therefore assessed the prevalence of VSB in a large sample of healthy-aging women and men dispersed over a wide age range enrolled in the Baltimore Longitudinal Study of Aging (BLSA), explored clinical correlates beyond age and hypertension and examined the potential impact of VSB on maximal exercise capacity.

METHODS

The study sample was drawn from a population of healthy adults participating in the BLSA, an ongoing prospective study of normative aging ¹³. Participants are enrolled in the study if they are healthy at baseline, and undergo 3 days of medical examinations approximately every two years ¹³. Seven hundred BLSA participants without a history of coronary artery disease and/or heart failure and without valvular disease greater than mild in severity and/or LV systolic dysfunction (defined as LV ejection fraction <40%) at the index visit were randomly selected from the BLSA echocardiography database, in order to cover a wide age distribution, according to the first aim of the study. An equal number of women and men was selected, with comparable age distribution (men: mean age=64±15, range 27–94 years; women: mean age=63±15, range 26–95 years; p=0.20). The study protocol was approved by the National Institute on Aging and the MedStar Health Research Institute (Baltimore, MD). All participants provided informed participation consent.

All transthoracic echocardiograms were performed at rest with the same echocardiographic instrument (HP Sonos-5500, Philips, Andover, MA). Echocardiographic images were retrieved from the BLSA digital archive (which started in 2004) and reviewed independently

by one trained reader (O.M.) and one experienced echocardiographer (M.D.). Measurements to characterize the presence of a subaortic VSB were made in all 700 selected participants from the two-dimensional parasternal long-axis view at end-diastole. According to a combination of criteria applied in previous studies ^{1,4,8}, the presence of subaortic VSB was defined as a proximal focal area (within the first third of total septal length) of localized septal hypertrophy with a dune-like structure protruding in the LVOT, a thickness 13 mm in men and 12 mm in women, and more than 50% greater than the thickness of the septum at its mid-distal-point (Figure 1). Systolic anterior movement of the mitral valve was evaluated in the same image, but never observed. The aortic root and the LVOT diameters were measured from the same view ¹⁴. LV posterior wall thickness, dimensions, mass, volumes, ejection fraction and fractional shortening were calculated as previously reported ¹⁵. Left atrial volume was measured by planimetry in the apical four-chamber view. The latter, the LV mass and volumes were indexed to body surface area. Prevalence of LV concentric remodeling and hypertrophy (combining concentric and eccentric) were estimated using gender-specific cutoffs for LV mass index ¹⁴. Tissue Doppler diastolic (Em) and systolic (Sm) velocities of the septal and lateral mitral annulus were also measured and averaged ¹⁶. The ratio between the mitral flow E and A wave velocities (E/A ratio) was considered as an index of LV relaxation, while the ratio between E and mean Em (E/Em ratio) as an index of LV filling pressures ¹⁶. LVOT velocities and velocity-time integral were studied at rest by pulsed wave Doppler from the apical window. Three cardiac cycles were averaged for each one of these functional measurements.

Hypertension was defined as mean systolic blood pressure 140 mm Hg and/or mean diastolic blood pressure 90 mm Hg on three consecutive measurements at the brachial artery right before the echocardiography, or as use of antihypertensive medications. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria ¹⁷ or use of diabetes medications. Participants were classified as physically active if reporting 1,000 kcal/week of exercise activity at medical interview ¹⁸. Waist circumference was defined as the minimal abdominal circumference between the lower edge of the rib cage and the iliac crests and it was measured with a flexible tape measure while maintaining close contact with skin, without compressing the underlying tissues and with participants in a standing position and breathing normally. Body mass index was calculated as weight divided by height-squared (kg/m²). Participants were identified obese if their body mass index was 30 kg/m². The glomerular filtration rate (GFR), calculated by the simplified modification of diet in renal disease (MDRD) formula, was used to determine renal function, and renal failure was defined as GFR <60 ml/min/1.73 m² at the index visit. Fasting, 2-h postchallenge plasma glucose, plasma triglyceride and total cholesterol concentrations were measured as previously reported ¹⁹.

Oxygen consumption was measured continuously during a modified Balke protocol, and the highest value was termed peak VO₂, expressed in milliliters per kilogram per minute, as previously reported ²⁰. Participants with a respiratory exchange ratio <1.1, a marker of a maximal treadmill effort, were excluded from the analysis. We also estimated the change per year in peak VO₂ for those participants who had one or more additional peak VO₂ evaluation available after the index visit.

Data were analyzed using the SAS package (version 9.3, SAS Institute Inc., Cary, NC), and are presented as percentages and means $\pm$ standard deviation (or standard error of the adjusted means). A Student t test or chi-squared test was used as appropriate to assess statistical difference between participants with and without VSB. Adjusted means of echocardiographic measures were compared between the two groups by analysis of covariance before and after controlling for significant potential confounders. Univariate and multivariate logistic regressions were used to examine the association of clinical variables selected from previous significant comparisons with the presence of VSB. Univariate and multivariate linear regressions were used to evaluate the impact of the presence of VSB on exercise capacity estimated by peak VO₂ (or the change in peak VO₂ per year), accounting for variables already known to have a significant impact on oxygen consumption. Collinearity was assessed calculating the variance inflation factor which was found acceptable (below 1.5) in all models. Statistical significance was set at $p < 0.05$.

RESULTS

According to our diagnostic criteria, participants with VSB (28 men and 21 women, 7% overall prevalence) had higher proximal septum thickness and proximal to mid septum thickness ratio than those without VSB, while there was no difference in mid septum thickness. (Table 1) When comparing men and women within a group, women had significantly smaller wall thicknesses than men, except for proximal septum thickness in those with VSB (Table 1).

Clinical characteristics of the study population by the presence of VSB are shown in Table 1. The prevalence of VSB significantly increased with age in both genders (Figure 2), from 1.7% in those younger than 57 years to 16.7% in those older than 78 years. There was no significant difference in the prevalence of VSB between gender in each age quartile and in the overall population (Figure 2). Nineteen out of the 49 subjects with VSB (mean age 73 years, range 60–87) underwent one or more echocardiography examinations (total 63, mean per subject 3, range 2–6) before the index visit (mean time before index visit 5.1 years, range 2–7). Eleven of them (58%) had one or more previous echocardiograms meeting criteria for the diagnosis of VSB, while the remaining 8 subjects did not meet these criteria before the index visit.

Significant determinants of VSB in univariate analysis are shown in Table 2. In multivariate logistic regression the presence of VSB was significantly associated only with older age, and this result remained substantially unchanged after performing stepwise backward elimination (Table 2). No significant difference was found if waist circumference or obesity was substituted for body mass index, or renal failure for glomerular filtration rate, or use of antihypertensive medications for hypertension (data not shown).

Table 3 shows the difference in echocardiographic structural and functional parameters by the presence of VSB after accounting for confounders. Participants with VSB were found to have increased systolic function parameters (such as fractional shortening, LV ejection fraction, and systolic velocity of the mitral annulus) and they also had larger aortic root diameters as compared to those without VSB, even after adjusting for body surface area.

Two hundred and fifty seven participants did not have treadmill data available at the same study visits, and other 70 were excluded because were not able to perform a maximal exercise test (i.e. had a respiratory exchange ratio <1.1). Thus, the final sample for this analysis included 373 individual (177 women, 196 men) of whom 19 with VSB (5.1%). Peak VO₂ was significantly lower in participants with VSB (22.9±6.6 vs. 19.6±3.8 mL/kg per minute, p=0.03), and the presence of VSB was significantly associated with reduced peak VO₂ in univariate analysis (Table 4). However, after multiple adjustments, this association became not significant, and in the reduced model significant determinants of reduced exercise capacity remained older age, female gender, higher body mass index (or obesity), diabetes and reduced physical activity (Table 4). Out of these original 373 participants, 127 (115 without bulge, 12 with bulge, 9.5%) had one or more (range 1–4) additional prospective evaluations of peak VO₂ (mean follow up 3.7 years, range 1–7 years). The decrease per year in peak VO₂ in the two groups (i.e. without VSB vs. with VSB, whose mean age at baseline was 67±12 vs. 72±12 years, p=0.17) was respectively 0.54 vs. 0.35 mL/kg per minute (p=0.53), and similar results were found after adjusting for significant covariates in Table 4. Using the same previous multivariate model in Table 4, the presence of a septal bulge was not predictive of a future decline in peak VO₂, while female gender, obesity and diabetes were (data not shown).

DISCUSSION

Herein we confirmed an increased prevalence of subaortic VSB with age, while we did not find any significant independent association of VSB with hypertension and other cardiovascular risk factors. After multivariate adjustments, the presence of VSB was associated with enhanced global LV systolic function, and some dilation of the aortic root. No significant impact on exercise capacity was noticed after accounting for potential confounders.

Our findings are consistent with previous reports showing that the presence of VSB increases with age^{2,7,8}. The BLSA represented the ideal population for confirming this association, since we were able to select an equal number of men and women with a wide and comparable age distribution and free from cardiac diseases and LV systolic dysfunction, which were likely important confounders in several previous studies^{4,6,7}. A previous manuscript published by our group on this topic included only 56 healthy BLSA volunteers, and demonstrated a significant decrease in the angulation of the aorta on the interventricular septum in the 6 subjects diagnosed with VSB². This parameter, however, is highly dependent on the position of the transducer, little reproducible and better estimated by cardiac magnetic resonance²¹, therefore it was not evaluated at present time. Instead, and in comparison with previous population studies where a visual screening was initially used^{6,7}, our study protocol required the thickness of the proximal and mid interventricular septum to be measured in all the 700 participants included in the analysis. Using comprehensive numeric criteria for the diagnosis of VSB and after multivariate adjustments, we failed to demonstrate the association between the VSB and systolic blood pressure or hypertension reported in previous studies^{7,8}. Methodological issues and differences in study populations may explain part of these discrepancies. Notably, a more symmetric rather than asymmetric distribution of LV hypertrophy would be expected in the presence of hypertension²², as the

cardiomyocytes usually respond to pressure overload with the parallel addition of sarcomeres, resulting in concentric ventricular wall thickness²³. However, some authors suggest that hypertension might be responsible for uncovering a genetic predisposition to develop an HCM-like cardiomyopathy in some individuals⁸, conveniently called VSB but that in reality represents a less invasive form of HCM of aging. Very recent data from Mayo Clinic seem to support this hypothesis, suggesting that the majority of patients with clinically diagnosed HCM after the age of 65 have a sigmoidal pattern very similar to that of patients classified as VSB and that they more frequently present with concomitant hypertension²⁴. However, the yield of genetic testing in these patients appeared very low (11% as compared to 38% in the overall population, $p < 0.001$), which prompted the authors of the study to suggest that HCM diagnosed in elderly patients is likely an acquired/non-genetic subtype of HCM rather than a heritable condition²⁴. This localized hypertrophy of the interventricular septum may otherwise represents a silent form of senile infiltrative cardiomyopathy, such as cardiac amyloidosis²⁵, though there was no evidence of plasma cell dyscrasia in any of our participants. This form of cardiomyopathy was unexpectedly reported in up to 7 of 98 non-HCM patients who underwent septal myectomy at Mayo Clinic Rochester from 1996 to 2000²⁶, and may remain undiagnosed despite a seemingly appropriate work-up.

After accounting for several potential confounders, participants with VSB appeared to have a tendency for enhanced LV systolic function, as previously reported^{1,7}. On the contrary, after adjusting for appropriate confounders, we could not find any significant impact of the VSB on LV diastolic parameters, as it was previously reported⁸. The finding that individuals with VSB had significantly enlarged aortic root diameter is intriguing, and adds to the current debate on aortic dilation in patients with similar conditions such as asymmetric septal hypertrophy²⁷ and HCM²⁸. In addition, data from the Framingham study have recently shown an increased prevalence of aortic regurgitation in participants with VSB⁷. While this association may simply be due to some measurement artifacts (i.e., the sigmoidal shape of the septum determines an overestimation of the aortic root diameter in those with VSB), further studies are needed to understand if these patients are at increased risk for aortic related complications, such as dissection and rupture, which are associated with increased aortic size.

Finally, conflicting reports suggest that the VSB might be responsible for some increase in LV outflow tract velocities both at rest^{1,3,5} and during provoked stress^{1,11}. The contribution of systolic anterior movement of the mitral valve to this phenomenon in previous reports appeared negligible^{1,3}, contrary to that in patients with HCM, for whom it represents the major responsible of obstructive physiology¹². We were not able to detect any significant increase in LVOT velocities at rest in participants with VSB. Unfortunately stress echocardiography is currently not part of the BLSA protocol, and whether provocative tests should be performed and dynamic LVOT gradients assessed in the presence of VSB remains debatable. In the present study, we used maximal exercise capacity estimated by means of peak VO₂ as a proxy to investigate the potential impact of VSB on cardiac output and physical performance at maximal stress condition. We could not find any significant effect of the VSB on this outcome. While our analysis may be limited and underpowered to test this hypothesis, our results are comforting and in line with previous data from

Framingham, showing no association between VSB and the occurrence of cardiovascular disease and mortality at a mean follow-up of 15 years ⁷.

Our study represents the first study evaluating the VSB in a healthy population of community-dwelling individuals free from coronary disease, valve disease, and LV systolic dysfunction, all of which may be independently responsible for the presence of the VSB ²⁷. As for the limitations, first, the cross-sectional design does not allow causal inference. Second, a certain degree of observer bias cannot be excluded, since the 700 echocardiograms were specifically reviewed for the presence of VSB. Nevertheless, the two readers were blind to all demographic and clinical data, and were only asked to measure the thickness of the interventricular septum at all segments according to the study protocol (not to specifically make a diagnosis of VSB, as in previous studies ^{6,7}). Prevalence of VSB was then calculated based on numeric criteria detailed before. With this regard, we choose to use different wall thickness cutoffs for men and women, according to what is recommended by the guidelines ¹⁴. This was not done in previous studies ^{1,4,8}, and for this reason it is likely that those studies underestimated the prevalence of VSB in women.

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Figure 1. Example of measurement of a subaortic ventricular septal bulge

From the two-dimensional image acquired in the parasternal long-axis view at end-diastole, the presence of subaortic septal bulge was defined as i) a proximal focal area (within the first third of total septal length) of localized septal hypertrophy with a dune-like structure protruding in the left ventricular outflow tract, ii) a thickness 13 mm in men and 12 mm in women, and iii) more than 50% greater than the thickness of the septum at its mid-distal-point (at the second third of the septum). In the example, a male participants who met the criteria for a diagnosis of septal bulge (i.e. proximal focal hypertrophy with a thickness of 18 mm and 63% greater than the thickness of the mid septum).

Figure 2.
Prevalence of subaortic septal bulge by gender, age quartiles and overall.

Table 1

Clinical characteristics of the study population.

Variable	Ventricular Septal Bulge		P value
	No (n=651)	Yes (n=49)	
Proximal septum thickness (overall, men/women, cm)	1.06 1.15/0.97 [†]	1.64 1.7/1.6	<.0001*
Mid septum thickness (overall, men/women, cm)	0.91 0.99/0.83 [†]	0.93 1/0.84 [†]	>0.46*
Ratio proximal to mid (overall, men/women)	1.20 1.19/1.21	1.80 1.69/1.95 [†]	<.0001*
Age (years)	65±14	76±11	<.0001
Men	50%	57%	0.30
Heart rate (beats/min)	67±10	70±13	0.10
Systolic blood pressure (mmHg)	117±15	122±18	0.02
Diastolic blood pressure (mmHg)	66±9	65±10	0.26
Hypertension	37%	55%	0.01
On antihypertensive medications	35%	51%	0.02
Body mass index (kg/m ²)	27±5	27±4	0.62
Waist circumference (cm)	90±13	91±14	0.42
Obesity	23%	20%	0.63
Fasting plasma glucose (mg/dL)	91±18	97±21	0.01
2-h postchallenge plasma glucose (mg/dL)	124±52	137±54	0.11
Diabetes mellitus	10%	20%	0.03
Glomerular filtration rate (ml/min/1.73 m ²)	78±18	70±20	0.003
Renal failure	15%	25%	0.06
Triglyceride (mg/dL)	103±62	119±64	0.10
Total cholesterol (mg/dL)	192±36	192±37	0.89

* p value also for comparison of participants with and without ventricular septal bulge of the same gender.

[†] p value for comparison between men and women within the group <0.003

Table 2

Univariate and multivariate logistic models predicting the presence of ventricular septal bulge.

	Univariate Analysis			Multivariate Analysis			Reduced Analysis		
	OR	(95% CI)	P value	OR	(95% CI)	P value	OR	(95% CI)	P value
Age (year)	1.07	(1.04–1.10)	<.0001	1.06	(1.03–1.10)	0.0001	1.07	(1.04–1.10)	<.0001
Male gender	1.36	(0.76–2.45)	0.30	1.33	(0.71–2.51)	0.38			
Hypertension	2.07	(1.16–3.72)	0.015	1.02	(0.51–2.05)	0.95			
Systolic blood pressure (mmHg)	1.02	(1.00–1.04)	0.016	1.01	(0.99–1.03)	0.37			
Glomerular filtration rate (ml/min/1.73 m ²)	0.98	(0.96–0.99)	0.003	0.99	(0.97–1.01)	0.23			
Body mass index (kg/m ²)	1.02	(0.96–1.08)	0.62	1.03	(0.96–1.11)	0.39			
Diabetes Mellitus	2.24	(1.07–4.68)	0.03	1.10	(0.42–2.87)	0.85			
Fasting plasma glucose (mg/dL)	1.01	(1.00–1.02)	0.02	1.01	(0.99–1.03)	0.28			

OR=odds ratio. CI=confidence intervals. Reduced analysis was obtained performing stepwise backward elimination of the non-significant variables ($p>0.05$).

Table 3

Adjusted mean and percentages $\pm$ standard error of echocardiographic structural and functional measures by the presence of subaortic septal bulge.

Variable	Ventricular Septal Bulge		P value	P value (unadjusted)
	No (n=651)	Yes (n=49)		
E/A ratio*	1.04 $\pm$ 0.01	0.97 $\pm$ 0.05	0.23	<0.001
Em (cm/s)*	9.4 $\pm$ 0.1	9.3 $\pm$ 0.3	0.71	<0.0001
E/Em ratio*	8.3 $\pm$ 0.1	8.6 $\pm$ 0.4	0.59	0.007
Left atrial volume index (mL/m ²)	16.3 $\pm$ 0.3	15.7 $\pm$ 1.1	0.61	0.40
LVOT velocity at rest (m/sec)*	1.11 $\pm$ 0.01	1.13 $\pm$ 0.03	0.53	0.46
LVOT velocity time integral at rest*	23.7 $\pm$ 0.19	24.3 $\pm$ 0.73	0.39	0.22
LVOT diameter (cm) [†]	2.05 $\pm$ 0.01	2.09 $\pm$ 0.03	0.19	0.55
Aortic root diameter (cm) [†]	3.1 $\pm$ 0.02	3.3 $\pm$ 0.06	0.02	0.003
LV posterior wall (cm) [†]	0.95 $\pm$ 0.01	0.94 $\pm$ 0.02	0.80	0.06
LV mass index (g/m ²)	74.3 $\pm$ 0.84	73.4 $\pm$ 3.28	0.79	0.27
LV remodeling categories				
No LV remodeling	43%	45%	0.78	0.06
Concentric LV remodeling	46%	48%	0.77	0.06
LV hypertrophy	11%	7%	0.40	0.96
End-diastolic volume index (mL/m ²)	40.7 $\pm$ 0.6	41.8 $\pm$ 2.2	0.63	0.87
End-systolic volume index (mL/m ²)	14.4 $\pm$ 0.3	15.6 $\pm$ 1.1	0.28	0.72
LV ejection fraction (%)*	67 $\pm$ 0.4	71 $\pm$ 1.6	0.06	0.004
Fractional shortening (%)*	38 $\pm$ 0.3	41 $\pm$ 1.3	0.04	0.003
Sm (cm/s)*	8.4 $\pm$ 0.1	8.9 $\pm$ 0.3	0.06	0.97

Means and percentages are adjusted for age, gender, hypertension, systolic blood pressure, diabetes and body mass index. Heart rate was an additional covariate for functional parameters*, and body surface area for structural parameters that are generally not indexed[†]. LV=left ventricular, LVOT= left ventricular outflow tract.

Table 4

Univariate and multivariate linear models predicting peak oxygen consumption.

	Univariate Analysis			Multivariate Analysis			Reduced Analysis		
	B	β	P value	B	β	P value	B	β	P value
Ventricular Septal Bulge	-3.35	-0.11	0.03	-0.99	-0.03	0.35			
Age (year)	-0.29	-0.61	<.0001	-0.29	-0.63	<.0001	-0.30	-0.65	<.0001
Male gender	4.33	0.33	<.0001	5.01	0.40	<.0001	4.96	0.40	<.0001
Hypertension	-3.61	-0.26	<.0001	-0.66	-0.05	0.17			
Body mass index (kg/m ²)	-0.46	-0.32	<.0001	-0.48	-0.36	<.0001	-0.49	-0.36	<.0001
Diabetes	-2.91	-0.17	0.001	-1.85	-0.12	0.001	-1.95	-0.12	<.001
Regular exercise activity (1,000 kcal/week)	2.55	0.20	0.001	1.43	0.11	0.001	1.46	0.11	0.001

B= beta estimate; β =standardized beta estimate. Reduced analysis was obtained performing stepwise backward elimination of the non-significant variables ($p>0.05$).