Am J Cardiovasc Dis 2013;3(2):79-84
www.AJCD.us /ISSN:2160-200X/AJCD1305001

Original Article

Prevalence of aortic dilation in hypertrophic cardiomyopathy

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Received May 7, 2013; Accepted May 22, 2013; Epub June 10, 2013; Published June 15, 2013

Abstract: Recent studies have suggested that hypertrophic cardiomyopathy (HCM) is associated with increased stiffness of the aorta. However, a potential relationship between HCM and aortic dilation has not been established. Aorta size was characterized in 223 consecutive patients diagnosed with HCM. Aorta size was measured at the level of the sinuses (n = 223) and ascending aorta (n = 115) using the parasternal long-axis echocardiographic view. Hypertrophy pattern, maximum wall thickness, and left ventricular outflow tract gradient were measured. Aortic dilation was defined using previously published criteria that control for body surface area, age, and gender. Mean aorta size among the HCM cohort was 33.0 ± 5.0 mm at the sinuses and 34.0 ± 5.0 at the tubular aorta. Using the age-based nomogram controlling for body surface area, 10 (4.5%) of the study population had dilated aortas at the sinuses of Valsalva. Only gender (10/10 male in dilated group, 127/213 in non-dilated group, p = 0.008) was associated with dilation, while characteristics of HCM (LVOT obstruction, maximum wall thickness, hypertrophy pattern) were not. Use of other criteria for dilation did not result in an association with HCM characteristics. Aortic dilation in HCM does not seem to occur more frequently than in the general population and is not related to the extent of hypertrophy or LVOT obstruction.

Keywords: Aorta, dilation, hypertrophic cardiomyopathy

Introduction

Hypertrophic cardiomyopathy (HCM) is a common cardiac genetic disorder, affecting 1 out of 500 in the population [1]. Familial HCM is inherited in an autosomal dominant fashion, and the majority of mutations described are in proteins of the cardiac sarcomere [2]. Aortic pathology has recently been described in patients with HCM; furthermore, there may be common signaling pathways that mediate dilated aorta and HCM [3-5]. Therefore, we identified patients with HCM and dilated ascending aorta, and investigated whether characteristics of HCM are associated with dilation in this population.

Methods

The study included all adult patients diagnosed with hypertrophic cardiomyopathy who had previously agreed to participate in the hypertrophic cardiomyopathy registry at the University of Michigan from July 24, 2007 to September 1, 2010. Patients were included in the registry if hypertrophic cardiomyopathy was diagnosed in accordance with published clinical guidelines [6]. Clinical data was collected, including age, gender, weight, height, presence of hypertension, systolic and diastolic blood pressure, left ventricular outflow tract (LVOT) obstruction, related medications, myectomy status, and results of genetic testing. LVOT obstruction was considered significant if ≥ 30 mm Hg at rest or with provocation (either exercise or valsalva).

Echocardiography examinations were reviewed and measurements of aortic size was repeated in blinded fashion by the study team Measurements were obtained at the level of the sinus of Valsalva, the sinotubular junction, and, when views were available, at the tubular ascending aorta (n =). Measurements were performed using 2-D echocardiography as recommended in the American Society of

Table 1. Characteristics of Study Population

Variable N=223	Number (%) or Mean ± SD
Gender (male)	137 (63%)
Age (years)	49.1 ± 15.6
Height (cm)	173.0 ± 23.6
Weight (kg)	90.8 ± 21.4
BSA (m^2)	2.04 ± 0.29
Hypertension	79 (35%)
SBP (mm Hg)	127 ± 17
Presence of Resting LVOT obstruction	72 (30%)
Resting Peak LVOT gradient (mm Hg)	26.0 ± 33.2 (range, 2 – 174)
Presence of Provocable LVOT obstruction	58 (26%)
Prior Myomectomy	42 (19%)
Maximal LV wall thickness (mm)	16.4 ± 5.9 (range, 12 – 38)
Sarcomere mutation positive (testing in n=87)	55 (58%)
Aorta measurement at sinus of Valsalva (mm)	33.0 ± 5.0
Aorta measurement at Tubular aorta* (mm)	34.0 ± 5.0
Aorta sinus measurement/BSA (mm/m^2)	16.3 ± 2.6

*Aorta measurements at the tubular aorta were only available in 115/223 patients.

Echocardiography Chamber Quantification Guidelines [7]. The inner edge to inner edge technique was used to measure the maximum diameter seen on all views at end-diastole. Additional echocardiographic measurements included the LVOT gradient, maximal left ventricular wall thickness, hypertrophy pattern (asymmetric septal, concentric, or apical), presence of systolic anterior motion of the mitral valve, presence and severity of valvular stenosis and regurgitation, and left ventricular dimensions.

Aortic size measurements were then corrected for body surface area (BSA) as calculated by the modified Dubois method [8]. Our primary definition of aortic enlargement was an aorta diameter at the sinus of Valsalva > 95% upper confidence limit for the regression line of aorta size to BSA as characterized by Roman *et al.* and supported by the ACC/AHA thoracic aortic disease guidelines published in 2010 [9, 10]. Separate regression limits were used for adults > 40 years of age and adults < 40 years of age. For comparison, secondary definitions, also as characterized by Roman *et al.,* were used and included; 1) diameter/BSA > 2.1 cm/m^2, and 2) diameter > 36 mm for women or > 40 mm for men [9]. Enlargement of the tubular ascending aorta was defined using the age-based nomogram characterized from CT imaging by Hannuksela *et al.* and supported by the current ACC guidelines [10, 11]. Patients with a dilated aorta by any of these criteria were included in the study group, and compared to patients with hypertrophic cardiomyopathy and a normal size aorta.

Continuous data is presented as mean ± standard deviation. Student's t-test or analysis of variance (ANOVA) was performed to compare continuous variables between populations. Rank sum method and Kolmogorov-Smirnov Z-test were performed to validate the unpaired t-test and ANOVA for non-parametric factors, respectively. Two-tailed Fisher's exact test or chi-squared test was used to compare categorical variables. Statistical significance was defined as a two-sided *P*-value < 0.05.

This study was approved by the University of Michigan Hospital Institutional Review Board.

Results

A total of 223 patients with a clinical diagnosis of HCM meeting the study inclusion criteria were identified from the HCM registry. Clinical characteristics of the overall study population are shown in **Table 1**. Of note, none of the patients had an echocardiographic diagnosis of either a bicuspid aortic valve or severe aortic valve stenosis or regurgitation.

Aortic dilation at the level of the sinus of valsalva

Dilation of the aortic root and ascending aorta has multiple definitions in the literature. When an absolute cut off diameter for the aortic sinuses of > 40 mm for men or > 36 mm for women was employed, 17 patients (7.6%), of whom 15 (88%) were male, were defined as having aortic dilation. When the definition of aortic dilation at the sinus of Valsalva proposed by Roman et al [9]. was used (> 95% upper confidence limit from the age-adjusted regression

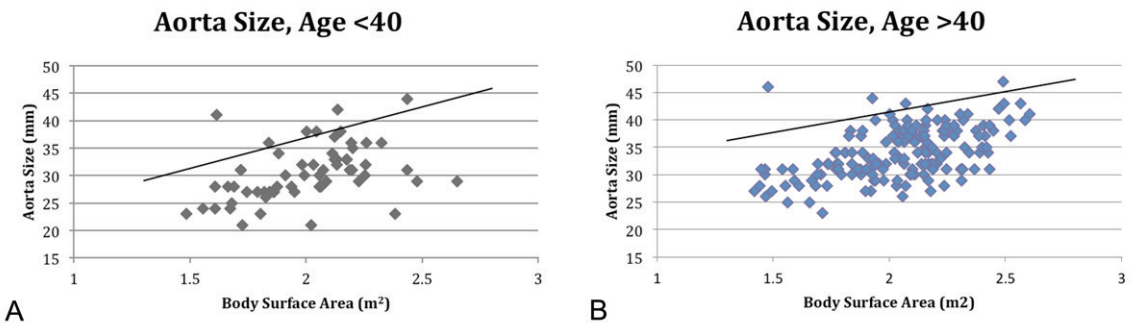

Figure 1. Aorta size at the sinuses of Valsalva plotted against the 95% upper confidence limit regression line derived from Roman et al. 9 for age less than 40 (A) and greater than 40 (B).

Table 2. Characteristics of Patients with Dilated vs Non-dilated Aortas at the Sinuses of Valsalva (using dilated as > 95% upper confidence limit from the Roman regression line for BSA to aorta size)

Variable	Dilated Aortas (n = 10)	Non-Dilated Aortas (n = 213)	*P* value
Gender (Male)	10 (100%)	127 (60%)	0.008
Age	44 + 17	49 + 16	0.32
Height (cm)	165 + 34	173 + 23	0.95
Weight (kg)	87.3 + 24.5	91.0 + 21.3	0.59
BSA (m^2)	2.00 + 0.32	2.04 + 0.29	0.70
Hypertension	2 (20%)	77 (36%)	0.34
SBP (mm Hg)	130 + 19	127 + 17	0.65
LVOT obstruction (rest only)	4 (40%)	68 (32%)	0.60
LVOT obstruction (rest or provocable)	3 (30%)	89 (42%)	0.53
LVOT rest gradient (mm Hg)	25.7 + 25.7 (range, 3 – 86)	28.7 + 33.5 (range, 2 – 174)	0.83
History of Myectomy	2 (20%)	40 (19%)	0.93
Mutation Positive (testing in n = 55)	2/4 (50%)	53/83 (64%)	0.62
Intraventricular septal thickness (mm)	22 ± 7 (range, 15 – 37)	19 ± 6 (range, 12 – 38)	0.11

line for BSA), 10 patients (4.5%) met criteria for aortic dilation (**Figure 1A** and **1B**). The only clinical characteristic associated with aortic dilation by this definition was gender (**Table 2**). Notably, patterns of HCM associated hypertrophy, LVOT obstruction, systolic anterior motion of the mitral valve and the presence of hypertension did not correlate with aortic dilation by this definition.

When using a cut-off of aortic diameter/BSA > 2.1 cm/m^2, only 5 (2.2%) patients were defined as having aortic dilation, with only weight (p = 0.0002) and BSA (p = 0.0004) associated with dilation.

Of the 3 parameters above, 22 (9.9%) patients were defined as dilated by one or more criteria, 7 (3.1%) by two or more criteria, and 3 (1.3%) by all three criteria.

Aortic dilation at the level of the tubular ascending aorta

Acceptable echocardiographic views of the ascending aorta were available in 105 of the 223 patients in the cohort. Using the age-based nomogram of Hannuksela and colleagues [11], 10 patients (9.5% of those with adequate imaging; 4.5% of the total cohort) met criteria for ascending aortic dilation as shown in **Table 3**. Men were more likely to have a dilated aorta using these criteria.

Discussion

In this study, we showed that the prevalence of dilation of the aorta at the level of the sinuses (4% in our cohort) is similar to that expected for the general population, based on a definition of dilated as greater than the 95% upper confi-

Table 3. Characteristics of Patients with Dilated vs Non-Dilated Aortas at the Tubular Ascending Aorta (using age nomogram)

Variable	Dilated Aortas (n = 10)	Non-Dilated Aortas (n = 105)	*P* value
Gender (Male)	10 (100%)	72 (69%)	0.04
Age	49 ± 13	52 ± 14	0.39
Height (cm)	180 ± 8	174 ± 12	0.08
Weight (kg)	98 ± 25	93 ± 19	0.40
BSA (m^2)	2.17 ± 0.31	2.07 ± 0.25	0.23
Aortic sinus dilation	4 (40%)	2 (2%)	< 0.001
Hypertension	2 (20%)	38 (36%)	0.30
LVOT obstruction (rest only)	5 (50%)	36 (34%)	0.33
LVOT obstruction (rest or provocable)	6 (60%)	63 (60%)	1.0
LVOT rest gradient (mm Hg)	23 ± 19 (range, 3 – 55)	30 ± 36 (range, 2 – 160)	0.54
History of Myectomy	2 (20%)	20 (19%)	0.94
IVS thickness (mm)	25 ± 6 (range, 12 – 38)	19 ± 5 (range, 19 – 34)	0.002

dence limit from prior normative data [9]. In addition, the mean aortic size measurement at the sinuses (3.3 ± 0.5 cm) was similar to the previously published normative data (3.17 +/- 0.39 cm) [9]. The primary associations with aortic size were age, body size, and gender – similar to the general population. Hypertension was not associated with dilation in our study, likely due to its lesser association with aortic size at the sinuses of Valsalva, as well as generally adequate antihypertensive control in this cohort [12]. Characteristics of HCM, including the presence of prior or current LVOT obstruction, LVOT gradient, maximum wall thickness, and hypertrophy pattern were not associated with aortic dilation. To our knowledge, aortic size at the level of the sinuses has not been previously reported in an HCM population.

While aortic disease has not been previously clinically recognized in HCM, a recent study by Boonyasirinant and colleagues showed that aortic stiffness is increased in patients with HCM compared with controls as measured by magnetic resonance imaging pulse wave velocity [3]. This association was speculated to result from one of a number of mechanisms, including intrinsic aortic fibrosis in HCM, neurohormonal disturbance, endothelial dysfunction, or abnormal left ventricular baroreceptor response. Interestingly, previous studies have shown a role for TGF-beta in the development of fibrosis and hypertrophy in HCM [4, 5, 13]. TGF-beta also has an important association with the development of aortic aneurysm and dissection [14]. However, TGF-beta involvement in HCM may only be related to regional overexpression in the myocardium, in a mechanism independent of its involvement in aortic disease [15, 16]. Our study suggests that any potential increase in aortic stiffness in HCM is not associated with significant concomitant dilation, and therefore, may not put patients at increased risk for aortic related complications, such as dissection and rupture, that are associated with increased aortic size.

The prevalence of aortic dilation was dependent on the criteria used for defining dilation, ranging from 2.2% of the population using an aortic diameter/BSA > 2.1 cm/m^2 to 7.6% using absolute cut-offs of 40mm for men and 36mm for women. In addition, the different parameters did not agree in individual patients (22% of the population would be defined as dilated using any of the 3 criteria, while only 1.3% would be designated as dilated if all 3 criteria were required to be present). Some of these differences are likely due to incomplete correction for clinical variables that affect aorta size in this population. For example, gender was strongly associated with aortic dilation using the age-based BSA nomogram, since gender is not adjusted for in this nomogram. In contrast, body size was not adequately compensated for when using the purely gender-based criteria. These observations highlight the inconsistencies in defining dilation of the ascending aorta by different criteria. Both the criteria for aortic dilation, as well the optimal imaging techniques, remain controversial [17].

The tubular ascending aorta was not well visualized in a substantial portion of the population, limiting definitive conclusions about this segment of the aorta. However, the ascending

aorta in a smaller cohort of HCM patients has previously been shown to be similar in size compared with controls [3]. Furthermore, similar to the aorta at the sinuses of Valsalva, no clinical parameters specific to HCM were associated with dilation of the ascending aorta.

Limitations

The primary limitation of this study was that assessment of aorta size was by echocardiography only, as CT or MRI studies of the aorta were available in too few of the patients to warrant inclusion. Maximal aortic diameter may be over- or under-estimated when the captured echocardiographic view is not aligned correctly with the midline of the aorta. In addition, the ascending aorta was not well visualized in all patients, limiting definitive conclusions about enlargement in that segment. We used the inner-edge to inner-edge technique for size measurement since it has better intrerobservor reliability and possible improved correlation with CT/MRI measurements [7, 18].

Conclusion

Despite potential mechanistic links of HCM and aortic pathology, we found a prevalence of aortic dilation in this cohort of patients with HCM similar to what would be expected in the general population. Clinical characteristics specific to HCM, such as LVOT obstruction, are not associated with the presence of aortic dilation. Current methodology for defining aortic enlargement is not precise in correcting for all clinical variables that affect aortic size.

Conflict of interest

None.

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