Hypertrophic cardiomyopathy is associated with dilated sinus of Valsalva: A case-control study

Ji Ae Yoon, Mirza Mujadil Ahmad, Afshan Husain, Lily Ann Walson, Muhammad Nabeel Syed, A. Jamil Tajik, Khawaja Afzal Ammar [*]

Aurora Cardiovascular and Thoracic Services, Aurora Sinai/Aurora St. Luke's Medical Centers, Advocate Aurora Health, 2801 W. Kinnickinnic River Parkway, Ste. 880, Milwaukee, WI 53215, USA

A R T I C L E I N F O

A B S T R A C T

Background: We aimed to test the hypothesis that there is an association between hypertrophic cardiomyopathy and dilated aorta in a case-control, matched-design fashion.

Methods: Of 65,843 studies done from November 2011 to December 2015, we found, after detailed evaluation by a single author, 153 cases of hypertrophic cardiomyopathy and 3,213 controls who were classified as normal clinically and echocardiographically. Controls were defined as normal patients referred to the echocardiography laboratory with no diagnoses and no known risk factors for dilated aorta (e.g., aortic stenosis, hypertension, aortic regurgitation). Clinical chart review showed none of the risk factors for dilated aorta, and echocardiography did not reveal any abnormalities. Of these 3,213 patients, 153 controls were matched to cases by age and sex by propensity score. Dilated aorta was defined according to clinical, Goldstein, and Lang's criteria.

Results: The prevalence of a dilated sinus of Valsalva was 9 times higher in hypertrophic cardiomyopathy patients than controls (OR = 9.4, $P = 0.003$). The 9-fold higher prevalence in hypertrophic cardiomyopathy patients persisted after adjusting for height, weight, and aortic pathology. Association of dilated mid-ascending aorta with hypertrophic cardiomyopathy was significant after adjustment for height and body surface area but became borderline insignificant after adjusting for weight and aortic valve pathology.

Conclusion: Hypertrophic cardiomyopathy appears to be associated with a dilated sinus of Valsalva, even after adjusting for height, weight, and aortic valve pathology.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent heritable cardiovascular disease, affecting 1 in 500 individuals [1]. It is associated with significantly increased cardiovascular morbidity and mortality, mainly via myopathic processes resulting in sudden cardiac death from arrhythmias or dynamic left ventricular outflow tract obstruction.

A recent study described an increased prevalence of dilated aorta (DA) in HCM [2], but another study failed to demonstrate the association [3]. Both of these studies were limited by small sample size as well as weak epidemiological study designs, i.e., both were case series (Table 1) [2–6]. Neither of them had a well-constructed case-control design. Hence, we designed this study to compare patients with HCM with age- and sex-matched normal controls to see whether HCM is associated with DA.

The interest in the association lies in the significance of both disease processes: aortic dilation can lead to an aortic aneurysm that can rupture or dissect and result in the demise of the patient, and HCM can, by itself, create a jet from the left ventricular outflow obstruction that pressurizes the aorta with each heartbeat, which can either cause dilation or make a pre-existing dilation worse over time.

2. Methods

2.1. Study population

We identified 153 patients with HCM at a hypertrophic cardiomyopathy clinic attached to our tertiary care medical center. This database was developed over a 5-year period. The local institutional review board approved this study and waived the need for informed consent.

Diagnosis was made by a single expert in HCM (A.J.T.). This diagnosis included a detailed history, physical examination,

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* Corresponding author at: Aurora St. Luke's Medical Center, 2801 W. Kinnickinnic River Parkway, Ste. 880, Milwaukee, WI 53215, USA.
  E-mail address: Wi.publishing28@aah.org (K.A. Ammar).

echocardiography, and genetic studies. The aorta was measured at the level of the sinus of Valsalva (SV) as well as the mid-ascending aorta (mAA) by leading-edge-to-leading-edge technique in end-diastole based on American Society of Echocardiography guidelines [5]. Mid-ascending aorta was arbitrarily defined as the portion of the ascending aorta that was about 2 or more centimeters above the ST junction, roughly at the level of pulmonary artery bifurcation. All echocardiograms were performed by sonographers under the direct supervision of A.J.T. All echocardiograms of HCM patients were personally reviewed by A.J.T.

Controls, defined as those patients who were normal clinically and echocardiographically, were initially identified through a database of 65,843 patients who had undergone echocardiography in our healthcare system (Fig. 1A). We evaluated electronic medical records to exclude any of the 28 risk factors associated with DA or aortic aneurysm according to the 2010 American Heart Association guidelines [7]. These risk factors include hypertrophic obstructive cardiomyopathy, primary and secondary diabetes, hypertension, tobacco use, heart failure, Marfan syndrome, ischemic cardiomyopathy, bicuspid aortic valve, aortic valve stenosis and regurgitation, Turner syndrome, pheochromocytoma, cocaine abuse, coarctation of the aorta, history of valve replacement, Ehlers-Danlos syndrome, syphilis, Takayasu's arteritis, giant cell arteritis, Behcet's syndrome, polycystic kidney disease, and corticosteroid immunosuppression. ICD-9 codes were used to identify the above-mentioned clinical diagnoses. The echocardiographic reports of the remaining 3,213 patients were printed and read by one of the investigators (M.N.S.), and all patients with echocardiographic abnormalities, including systolic dysfunction (left ventricular ejection fraction < 50 %), overt cardiovascular disease from final impressions, overt aortic disease, aortic regurgitation, aortic stenosis, mitral regurgitation, and mitral stenosis, were excluded.

Out of 175 cases of HCM, 153 cases were matched to controls in a 1:1 ratio based on age and sex because these are major factors influencing aortic diameter (Fig. 1B, 1C). The selection of matched controls was based on a propensity-matched analysis of HCM patients.

Dilation of aorta was defined by 3 criteria: clinical, Goldstein criteria, and absolute or indexed Lang's criteria [5,6].

For research purposes, the other criteria (Goldstein and Lang's) are more scientifically rigorous because they adjust the size of the aorta according to age, sex, and body surface area, and, therefore, these criteria should be used. However, a busy clinical echocardiography reader usually does not have time to apply all the criteria to every study; therefore, in daily clinical practice, 4 cm for the sinus and 3.8 cm for the mAA are used as the practical clinical cutoffs for launching a clinical work-up for cause of aortic dilation [8]. These clinical cutoffs were used in multivariate analyses (Table 3) because they are practical and readily applied by clinicians in practice.

2.2. Statistical analysis

Our statistical analysis was carried out by JMP Version 10 (SAS Institute, Inc., Cary, NC). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as n (%). Paired *t*-test was performed to compare the 2 groups (HCM vs non-HCM) for continuous variables, and McNemar test was performed to compare categorical variables. The odds ratio (OR) of DA in patients who had HCM was calculated in comparison to controls. We further adjusted this association by other risk factors such as weight, height, and aortic valve pathologies. A *P* value of < 0.05 was considered statistically significant.

Logistic regression was used to analyze the association between HCM and baseline variables such as age, sex, height, weight, hypertension, aortic stenosis, aortic regurgitation, and aortic valve replacement.

Table 1
Studies reporting increased prevalence of DA in HCM.

Study	Study design	N	Prevalence of DA in HCM group (%)	Prevalence of SV dilatation in control group	Prevalence of SV dilatation (%) in HCM	Criteria used	Prevalence of mAA dilatation in control group	Prevalence of mAA dilatation in HCM group	DA and obstruction
Jain R, et al. [3] (2013)	Case series	223	13 (6)	—	517 (2.2–7.6)*	(1) > 40 mm for men, .>36 mm for women 17 (7.6) (2) Roman MJ, et al. [4] (1989) 10 (4.5) (3) Aortic diameter/ BSA > 2.1 cm/ m² 5 (2.2)	—	10 (4.5)	Obstructive HCM:4 (40) non-obstructive HCM 6, (60) During rest and provocation: obstructive HCM 3 (30) non-obstructive HCM 7 (70)
Yousefzai R, et al. [2] (2017)	Case series	201	18 (9)	—	7 (3.5)	Goldstein SA, et al. [5] (2015)	—	11 (5.5)	Obstructive HCM 13 (72) non-obstructive HCM 5 (28)
Current Study	Matched case-control	306	15–26 (4.9–8.5)	0–10 (0–3.2)	12–34 (3.9–11.1)	(1) > 4 cm for SV and >3.8 cm for mAA (2) Goldstein SA, et al. [5] (2015) (3) Lang RM, et al. [6] (2015)	2–12 (0.65–3.9)	18–30 (5.9–9.8)	Obstructive HCM 13.1 %, 95 % CI: 7.5–21.9 % non-obstructive HCM 9.8 %, 95 % CI: 4.6–19.8 %

Data presented as n (%).
— indicates that data are not available.
*based on 3 criteria.
BSA, body surface area; DA, dilated aorta; HCM, hypertrophic cardiomyopathy; mAA, mid-ascending aorta; SV, sinus of Valsalva.
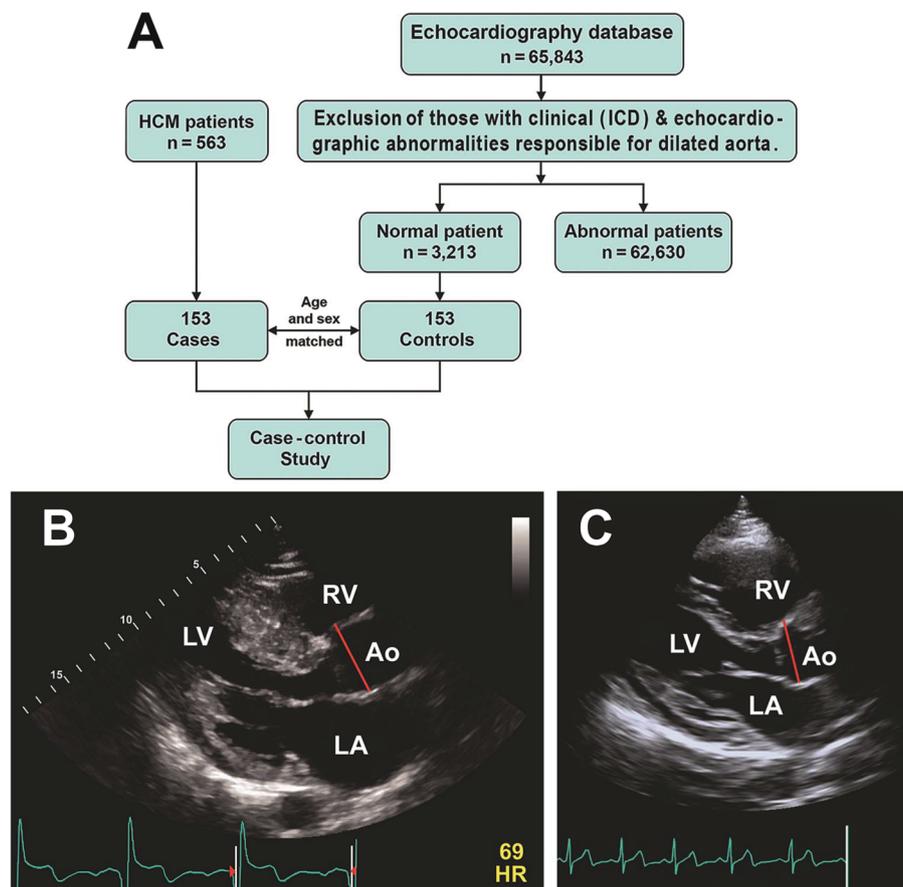
Fig. 1. (A) Flowchart displaying the selection of normal subjects. (B) Dilated aorta (4.4 cm) in a case of HCM. (C) Normal aorta (3.1 cm) in an age- and sex-matched control without HCM. Ao, aorta; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LA, left atrium; LV, left ventricle; RV, right ventricle.

3. Results

We matched 153 cases with 153 controls. Cases were slightly older than controls (53 vs 50 years, respectively; Table 2) and a slightly lower proportion were of male sex (56 % vs 63 %), but these differences failed to reach statistical significance. This indicates that age- and sex-based matching by propensity score matching was successful. Cases were shorter and heavier than controls. Seventy-one percent of cases had hypertension compared with 0 % of controls because hypertension was used in the exclusion criteria for defining normals. Similarly, diabetes and dyslipidemia were more prevalent in the HCM group than the age- and sex-matched controls. Ten patients in the control group developed diabetes after our inclusion and exclusion criteria had been applied to create the study population.

The diameter of the ascending aorta in our controls, men and women combined, was 29.5 ± 4.8 mm (mean ± SD). These findings are similar to those of prior studies [9], in which the ascending aorta dimension (mean diameter ± SD) in women was 29 mm (±2.25 mm) and in men was 32 mm (±2.5 mm) for those with an average age of 50 years (Table 40 in Reference 9)—the average age for our cases and controls. Because our controls included both women and men, we feel that the normal controls in our study are quite similar to the normal controls even if measured by a different technique, i.e., magnetic resonance imaging.

Echocardiographic characteristics of the population were as expected, with HCM patients having smaller cavity size and higher ejection fraction, lower E′ velocity, higher left ventricular filling pressures (E/E′ ratios), and greater wall thickness than controls (Table 2). Right heart pressures were similar in both groups, which is consistent with the fact that these patients were imaged in an outpatient echocardiography laboratory. Cases also had greater mean SV and mAA diameters and much higher prevalence of DA than controls.

The prevalence of a dilated SV was 9.4 times higher in HCM patients than controls. The 9-fold higher prevalence in HCM patients persisted after adjusting for height (OR = 10.6, $P = 0.002$) (Table 3). The prevalence of dilated mAA was 9.5 times higher in HCM patients than controls. This association persisted after adjustment for height (OR 9.64; $P = 0.03$) (Table 3) .

The prevalence of dilated SV in HCM patients compared to normals was as follows: 11.1 % vs 1.3 % by clinical criteria (>4 cm), 8.4 % vs 3.2 % by Goldstein criteria, 9.8 % vs 2.6 % by absolute Lang's criteria, and 3.9 % vs 0 % by indexed Lang's criteria. Similarly, the prevalence of mAA in HCM patients vs normals was 5.9 % vs 0.65 % by clinical criteria (>3.8 cm), 9.8 % vs 3.3 % by Lang's absolute criteria, and 5.9 % vs 3.9 % by indexed Lang's criteria.

The odds of dilated SV were 9 times higher in the HCM group than the control group (OR = 9.4, $P = 0.003$; Table 3). Similarly, the odds of dilated mAA were increased in the HCM group compared with the control group (OR 9.5, $P = 0.03$). The association was further evaluated with adjustment for weight, height, hypertension, and aortic valve pathology and continued to show a statistically significant relationship (Table 3) with both dilated SV and dilated mAA in most, but not all, of the models (aortic valve pathology and weight were exceptions). The odds ratio continued to hover around 10 and the P value was significant in most of the adjusted models, indicating that the association is independent of these important variables.

Out of 153 HCM patients, 84 (55 %) had obstructive physiology. The mean diameter of the SV was similar in obstructive HCM and non-

Table 2
Characteristics of patients with and without hypertrophic cardiomyopathy.

	HCM (n = 153)	Non HCM (n = 153)	Paired *t*-test *P* value
Baseline clinical characteristic			
Age (years)	53.1 ± 16.7	50.1 ± 16.3	0.097
Sex (male)	85 (56)	96 (63)	0.053
Height (cm)	169.5 ± 12.8	173.1 ± 0.7	0.0003
Weight (kg)	90.7 ± 25.5	84 ± 19.9	0.002
BSA (m²)	2.04 ± 0.32	1.99 ± 0.27	0.03
BMI (kg/m²)	27.9 ± 5.9	31.7 ± 9.6	<0.001
Diabetes mellitus	23 (15)	10 (6.5)	<0.001
Hypertension	108 (71)	0	<0.001
Obesity (BMI > 30 kg/m²)	72 (47.06)	43 (28.10)	0.004
Dyslipidemia	105 (68)	38 (25)	0.080
Aortic valve pathology	27 (18)	0 (0)	<0.001
Sinus of Valsalva (cm)	3.23 ± 0.48	3.07 ± 0.41	0.001
Mid-ascending aorta (cm)	3.09 ± 0.50	2.96 ± 0.48	0.01
Echocardiographic characteristic			
Maximum sinus of Valsalva (cm)	3.23 ± 0.49	3.08 ± 0.41	0.001
Maximum mid-ascending aorta (cm)	3.09 ± 0.50	2.95 ± 0.48	0.01
Indexed LA volume (mL/m²)	44.10 ± 16.51	26.50 ± 8.72	<0.001
RA pressure (mmHg)	6.56 ± 2.80	6.76 ± 3.05	0.86
RV systolic pressure (mmHg)	32.36 ± 11.05	27.12 ± 7.48	0.001
IVSd (cm)	2.00 ± 0.59	0.91 ± 0.16	<0.001
LVPWd (cm)	1.30 ± 0.30	0.90 ± 0.15	<0.001
LVEDD (cm)	4.42 ± 0.63	4.73 ± 0.51	<0.001
LVESD (cm)	2.74 ± 0.54	3.06 ± 0.44	<0.001
LVEF (%)	68.74 ± 7.71	62.73 ± 5.26	<0.001
LVOT stroke volume (mL)	114.11 ± 66.65	78.66 ± 24.29	0.001
LVOTd (cm)	2.21 ± 0.24	2.15 ± 0.19	0.22
E′ septal velocity (cm/s)	5.57 ± 2.23	9.45 ± 2.97	<0.001
E′ lateral velocity (cm/s)	7.76 ± 3.43	12.16 ± 4.01	<0.001
MV E velocity (cm/s)	83.90 ± 27.53	75.54 ± 19.23	0.001
MV A velocity (cm/s)	71.02 ± 31.53	65.09 ± 20.55	0.04
Mitral E/A ratio	2.22 ± 10.44	4.29 ± 36.85	0.29
Mitral E/E′ septal ratio	17.25 ± 8.32	8.49 ± 2.72	<0.001
Mitral E/E′ lateral ratio	12.97 ± 7.21	6.68 ± 2.44	<0.001
DT (ms)	223.34 ± 61.88	218.17 ± 52.67	0.30

Continuous variables are expressed in mean ± standard deviation.
Categorical variables are expressed in number (%).
A *P* value of < 0.05 was considered statistically significant.
E′ septal velocity is the velocity of basal septum in early diastole. E′ lateral velocity is the velocity of the basal lateral wall in early diastole. E velocity is the velocity of blood flow in early diastole across the mitral valve, at the level of leaflets. A velocity is the velocity of blood flow in late diastole across the mitral valve.
BMI = body mass index; BSA = body surface area; DT = deceleration time; HCM = hypertrophic cardiomyopathy; IVSd = interventricular septum diameter; LA = left atrial; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; LVOTd = left ventricular outflow tract diameter; LVPWd = left ventricular posterior wall diameter; MV = mitral valve; RA = right atrial; RV = right ventricular.

obstructive HCM (3.23 vs 3.24, respectively; *P* = 0.96). The mean diameter of the mAA was similar in obstructive and non-obstructive HCM (3.14 vs 3.03, respectively; *P* = 0.185). The prevalence of dilated SV (SV > 4 cm) in obstructive HCM was higher than in non-obstructive HCM (13.1 %, 95 % CI: 7.5–21.9 vs 9.8 %, 95 % CI: 4.6–19.8) but failed to reach statistical significance (*P* = 0.54). Similar results were observed with Goldstein criteria for dilated SV (9.52 %, 95 % CI: 4.9–17.7 vs 8.20%, 95 % CI 3.55–17.8; *P* = 0.78). This finding was not different by absolute Lang's criteria (11.90 %, 95 % CI: 7.5–21.9 vs 7.25 %, 95 % CI: 2.6–15.7; *P* = 0.32) and by Lang's indexed criteria (4.76 %, 95 % CI: 2.6–13.2 vs 2.90 %, 95 % CI: 0.3–8.7; *P* = 0.55).

Table 3
Odds of dilated sinus of Valsalva and mid-ascending aorta in hypertrophic cardiomyopathy.

	Odds Ratio	95 % CI	*P* value
Dilated sinus of Valsalva			
Baseline			
HCM	9.44	2.64–60.20	0.003
Adjusted model 1			
HCM	10.60	2.94–67.91	0.002
Height	1.04	1.00–1.08	0.05
Adjusted model 2			
HCM	8.66	2.39–55.48	0.005
Weight	1.01	0.99–1.03	0.19
Adjusted model 3			
HCM	8.77	1.98–38.7	0.001
BSA	3.83	0.84–17.39	0.08
Adjusted model 4			
HCM	8.69	2.34–56.25	0.005
Aortic valve pathology	1.51	0.40–4.7	0.50
Dilated mid-ascending aorta			
Baseline			
HCM	9.5	1.75–176.25	0.03
Adjusted model 1			
HCM	9.64	1.76–179.57	0.03
Height	1.00	0.95–1.05	0.87
Adjusted model 2			
HCM	7.89	1.41–147.64	0.053
Weight	1.022	1.00–1.045	0.06
Adjusted model 3			
HCM	8.44	1.05–68.11	0.01
BSA	6.19	0.81–47.16	0.16
Adjusted model 4			
HCM	7.6	1.27–144.52	0.06
Aortic valve pathology	2.5	0.50–10.19	0.22

The wide confidence intervals suggest the uncertainty due to the small dataset, which can only be resolved by a larger dataset, something that future studies may be able to address.
Sinus of Valsalva enlargement defined as > 4 cm and ascending aorta as > 3.8 cm, as these criteria are in clinical use.
In each of the adjusted models, the first line represents the odds of dilated sinus of Valsalva or of dilated mid ascending aorta in HCM patients as compared to the controls. The second line represents the odds of dilated sinus of Valsalva or dilated mid ascending aorta after adjusting for that new variable like height, weight, and body surface area.
CI, confidence interval; HCM, hypertrophic cardiomyopathy.

The prevalence of dilated mAA (>3.8 cm) was higher in obstructive HCM than non-obstructive HCM (9.5 %, 95 % CI: 4.9–17.7 vs 1.6 %, 95 % CI: 0.3–8.7; *P* = 0.04). The prevalence of dilated mAA was consistently higher in obstructive HCM than non-obstructive HCM by absolute Lang's criteria (11.9 %, 95 % CI: 6.6–20.5 vs 6.6 %, 95 % CI: 2.6–15.7; *P* = 0.13) and by indexed Lang's criteria (7.1 %, 95 % CI: 3.3–14.7 vs 4.9 %, 95 % CI: 1.7–13.5; *P* = 0.46). However, these also failed to reach statistical significance.

4. Discussion

These are the first data systematically evaluating the association between HCM and DA in a matched case-control design. Our data demonstrate the prevalence of SV dilation in HCM was 9 times higher than in those without HCM. The association remained statistically significant after adjusting for multiple variables, including height, weight, and aortic valve disease, with a higher adjusted OR in height.

Prior studies have reported varying prevalence of DA in HCM patients, likely from referral bias and variation in diagnostic criteria (Table 1). These data do show a similarly increased prevalence with the strength of comparison against age- and sex-matched controls. In the current study, the prevalence of dilated SV and prevalence of dilated mAA were consistently increased in HCM patients when compared to normals regardless of the criteria used: clinical, Goldstein criteria, absolute Lang's criteria, or indexed Lang's criteria. A recent study of HCM

patients (n = 1,698 patients) also showed an increased prevalence (13 %) of dilated mAA. However, this study is a case series, whereas ours is a case-control study, a design that is more likely to provide cause-effect associations [10].

In consonance with other studies [2,3], there was no significant difference between obstructive HCM patients and non-obstructive HCM patients in terms of dilated SV. This lack of association was clearly demonstrated in SV dilatation based on Goldstein or Lang's absolute and indexed definitions. Similar results were found for dilated mAA, although there was a trend, not reaching statistical significance, suggesting a slightly larger mAA diameter in obstructive HCM. This observation will be explored in a separate study.

There are many possible mechanistic reasons behind aortic dilatation in HCM. These can vary from genetic to hemodynamic (post-stenotic) reasons.

The hemodynamic mechanism does not seem to be in play in the current study, wherein the statistically significant association with HCM only exists in SV dilatation after adjustment for height, weight, and aortic valve pathologies as shown in multivariate analysis (Table 3). The association between mAA dilatation and HCM did not reach statistical significance. It is known that the stenotic jet of blood exiting the left ventricular outflow tract preferentially strikes the mAA, sparing the SV. Therefore, post-stenotic dilatation is more common in the mAA than the SV. The patients with obstructive HCM (n = 84) had a higher prevalence (11.90 % vs 6.56 %, respectively, $P = 0.282$) of mAA dilatation than those with non-obstructive HCM (n = 61). The association between HCM and DA was stronger in HCM with obstructive physiology but failed to reach statistical significance. We believe that this is likely the result of a small sample size and that, as our database grows, future studies will be able to demonstrate this association with statistical significance.

The genetic reasons are not well studied in our population. There were no data on genes in normals, and data on genes in HCM patients were sparse.

At histopathological levels, there are multiple mechanisms of aortopathy, including increased aortic stiffness, reduced elastic properties, and increased extracellular matrix degradation. The role of increased myocardial and aortic stiffness owing to increased fibrosis in HCM patients has been shown by Boonyasirinant *et al.* [11]. Those HCM patients with altered aortic elastic properties also seem to have increased aortic diameters [12]. The direct link between HCM, fibrosis, and aortic dilatation needs further study at the cellular level. Several studies have reported that HCM cardiomyocytes seem to overexpress transforming growth factor beta and insulin-like growth factor-I. Transforming growth factor beta is known to be associated with thoracic aneurysms via stimulation of extracellular matrix degradation in the vessel wall [13].

The clinical significance of the current study lies in the observation of an increased prevalence of dilated aorta in HCM patients, which if confirmed in other studies, stands to change clinical practice in terms of monitoring the sinus of Valsalva in these patients.

4.1. Strengths and limitations

Chief among the strengths of this study is that this is the first matched case-control study to evaluate the association between SV dilatation and HCM with further multivariate adjustment. It also has the largest sample size to-date. In addition, the normals were rigorously defined after excluding 28 causes of DA, and the abnormals (HCM group) were rigorously defined based on published guidelines [14] by a single expert in an HCM center. This creates a scenario of pure contrast between cases and controls by controlling for confounding variables. The echocardiographic characteristics of the controls clearly demonstrate that they were normal by these multiple strict criteria, down to tissue Doppler velocities, thereby indicating that our process of selection of controls was successful.

The limitations of this study include referral selection bias for both cases and controls. This is unavoidable unless the participants are randomly selected from a community population. However, most other published studies that define normal criteria have recruited normals from similar databases [4], with the exception of a few studies in which the normal group was directly recruited from the general population [15,16]. In addition, the 2 prior studies on HCM and DA [2,3] had the same referral selection bias. Our normals are arguably more normal than those in other studies because we not only used clinical criteria for normalcy, which was utilized in other studies by performing medical record review, we also utilized rigorous echocardiographic criteria to ensure normalcy. This is a rigor not seen in any prior study. This indicates that if the same study is carried out in those other populations, with less rigorous echocardiographic criteria, the odds of DA will be lower in those populations.

We used age- and sex-matched controls because age and sex are two of the most important determinants of the size of the aorta. Adding other variables would be ideal to evaluate the cause-effect relationship but would have reduced the sample size for controls. This is a limitation of the study methodology, owing to the constraints of sample size. Hypertension is a potential contributor to aortic dilatation. Since we defined normal as those without any risk factors for dilated aorta, hypertension was excluded. We intend to pursue future analyses with adjustment for hypertension in HCM patients after our HCM database grows sufficiently. At this time, our sample size of HCM patients is too small to evaluate this effect. We have not used body mass index, but we have presented data adjusted for height, weight, and body surface area, which are the components of the body mass index equation, so we have evaluated the relationship after adjusting for these important contributors.

5. Conclusion

Our data demonstrate the strong association between SV dilatation and HCM adjusting for height, weight, and aortic pathology.

Author statement

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] B.J. Maron, J.M. Gardin, J.M. Flack, S.S. Gidding, T.T. Kurosaki, D.E. Bild, Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study, Coronary Artery Risk Develop. (Young) Adults Circulation 92 (1995) 785–789, https://doi.org/10.1161/01.cir.92.4.785.

[2] R. Yousefzai, A. Agarwal, M.F. Jan, et al., Hypertrophic cardiomyopathy with aortic dilation: a novel observation, Eur. Heart J. Cardiovasc. Imaging 18 (2017) 1398–1403, https://doi.org/10.1093/ehjci/jew292.

[3] R. Jain, A. Helms, S.M. Day, A.M. Booher, Prevalence of aortic dilation in hypertrophic cardiomyopathy, Am. J. Cardiovasc. Dis. 3 (2013) 79–84.

[4] M.J. Roman, R.B. Devereux, R. Kramer-Fox, J. O'Loughlin, Two-dimensional echocardiographic aortic root dimensions in normal children and adults, Am. J. Cardiol. 64 (1989) 507–512, https://doi.org/10.1016/0002-9149(89)90430-x.

[5] S.A. Goldstein, A. Evangelista, S. Abbara, et al., Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging: endorsed by the Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance, J. Am. Soc. Echocardiogr. 28 (2015) 119–182, https://doi.org/10.1016/j.echo.2014.11.015.

[6] R.M. Lang, L.P. Badano, V. Mor-Avi, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Eur. Heart J. Cardiovasc. Imaging 16 (2015) 233–270, https://doi.org/10.1093/ehjci/jev014.

[7] L.F. Hiratzka, G.L. Bakris, J.A. Beckman, et al., 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine, Catheter. Cardiovasc. Interv. 76 (2010) E43-E86. Doi: 10.1002/ccd.22537.

[8] L. Cozijnsen, R.L. Braam, R.A. Waalewijn, et al., What is new in dilatation of the ascending aorta? Review of current literature and practical advice for the cardiologist, Circulation 123 (2011) 924–928, https://doi.org/10.1161/CIRCULATIONAHA.110.949131.

[9] N. Kawel-Boehm, S.J. Hetzel, B. Ambale-Venkatesh, et al., Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update, J. Cardiovasc. Magn. Reson. 22 (2020) 87. Doi: 10.1186/s12968-020-00683-3. Erratum in: J. Cardiovasc. Magn. Reson. 23 (2021) 114. Doi: 10.1186/s12968-021-00815-3.

[10] J.B. Geske, B.D. Nordhues, N.M. Orme, A.J. Tajik, P.C. Spittell, S.R. Ommen, Prevalence and clinical correlates of aortic dilation in hypertrophic cardiomyopathy, J. Am. Soc. Echocardiogr. 34 (2021) 279–285, https://doi.org/10.1016/j.echo.2020.11.003.

[11] T. Boonyasirinant, P. Rajiah, R.M. Setser, et al., Aortic stiffness is increased in hypertrophic cardiomyopathy with myocardial fibrosis: novel insights in vascular function from magnetic resonance imaging, J. Am. Coll. Cardiol. 54 (2009) 255–262, https://doi.org/10.1016/j.jacc.2009.03.060.

[12] E. Vizzardi, E. Sciatti, I. Bonadei, S. Gelsomino, R. Lorusso, M. Metra, Elastic aortic properties in hypertrophic cardiomyopathy: a single center echocardiographic evaluation, Eur. Rev. Med. Pharmacol. Sci. 18 (2014) 3251–3255.

[13] J.A. Jones, F.G. Spinale, J.S. Ikonomidis, Transforming growth factor-beta signaling in thoracic aortic aneurysm development: a paradox in pathogenesis, J. Vasc. Res. 46 (2009) 119–137, https://doi.org/10.1159/000151766.

[14] B.J. Gersh, B.J. Maron, R.O. Bonow, et al., 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, J. Am. Coll. Cardiol. 58 (2011) e212-e260. Doi: 10.1016/j.jacc.2011.06.011.

[15] D.C. Connolly, H.A. Oxman, F.T. Nobrega, L.T. Kurland, M.A. Kennedy, L.R. Elveback, Coronary heart disease in residents of Rochester, Minnesota, 1950-1975. I. Background and study design, Mayo Clin. Proc. 56 (1981) 661-664.

[16] T.R. Dawber, The Framingham Study: The Epidemiology of Atherosclerotic Disease, Harvard University Press, Cambridge, MA, 1980.