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Aortic Stiffness in Youth with Hypertrophic Cardiomyopathy Genotype

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Abstract

Objective—Clinical events in HCM patients are related to the degree of hypertrophy. Aortic stiffness in adult HCM patients has been reported to be higher than control patients. Increased stiffness may cause more LV hypertrophy and thus lead to more clinical events. We sought to a) noninvasively compare aortic structure and function between youth with sarcomeric hypertrophic cardiomyopathy (HCM) genotype versus control youth and b) explore the relation between aortic function and degree of left ventricular (LV) hypertrophy.

Methods—In a prospective study from a single referral center, clinical, anthropometric, and hemodynamic data were acquired on 28 consecutive pathogenic HCM gene mutation carriers and 26 unrelated controls (mean age 16.3, 50% girls). Hemodynamic data included applanation tonometry measured central pulse pressure, carotid-femoral pulse wave velocity (CFPWV), reflected wave augmentation index (AIx). In the HCM gene carriers, LV mass to volume ratio was extracted from clinically indicated echocardiograms as an index of hypertrophy. Associations were assessed using multivariable adjusted linear regression.

Results—The HCM group was comprised of 14 myosin binding protein C3 carriers, 13 myosin heavy chain 7 carriers and 1 child with both. HCM and control groups did not differ by age, sex, height, body mass index, heart rate, or blood pressure. HCM carriers had significantly lower CFPWV than controls (4.46 ± 0.88 m/s vs. 4.97 ± 0.44 m/s, $p=0.01$) and higher AIx magnitude ($27 \pm 19\%$ vs. $18 \pm 7\%$, $p=0.04$). These associations persisted after adjustment for age, sex, height, heart rate, mean pressure, and medication use. Within the HCM group, LV hypertrophy was related to AIx but not CFPWV. CFPWV nor AIx differed by genotype.

Conclusions—Aortic stiffness appears lower but wave reflection appears higher in youth carrying HCM gene mutations. The degree of wave reflection appears correlated to LV

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Author contributions

JPZ conceived the study, designed it, acquired the data, analyzed the data, interpreted the data, and drafted the manuscript. PKJ acquired the data and critically reviewed the manuscript. SDC assisted in the design of the manuscript and critically reviewed the manuscript.

hypertrophy in this high risk cohort, suggesting mitigation of wave reflection may possibly attenuate LV hypertrophy.

Keywords

pediatric; children; hypertrophic cardiomyopathy; vascular; aortic; arterial stiffness

INTRODUCTION

Risk of death from HCM through congestive heart failure or sudden arrhythmic death is related to the degree of hypertrophy. [1, 2] Mutations in sarcomeric genes like myosin heavy chain and myosin binding protein C are causally implicated in HCM generally, but are not directly tied to the degree of hypertrophy. [1, 3] Indeed, the specific determinants of hypertrophy in HCM are not fully described.

From 1st principles, components of ventricular afterload can increase ventricular wall stress and lead to thicker myocardium. [4, 5] A key driver of ventricular afterload is vascular stiffness. Aortic stiffness predicts future hypertension, ventricular hypertrophy, and cardiovascular disease events including congestive heart failure.[6, 7] In adults with hypertrophic cardiomyopathy, higher aortic stiffness has been reported.[8] Increased aortic stiffness could be particularly deleterious in HCM patients as a contributor to ventricular hypertrophy. However adult HCM patient cohorts will often be phenotypically positive and will have other confounding contributors to hypertrophy like hypertension. Youth offer a unique window into the role of arterial stiffness on the development of ventricular hypertrophy in HCM.

Given that previous data does not clarify the temporal relation between phenotypic HCM and higher aortic stiffness, in this cross sectional study, indices of arterial stiffness from youth with pathogenic mutations in sarcomeric genes, with or without phenotypic HCM, were compared to control youth. The relation between arterial stiffness and degree of LV hypertrophy was also explored.

METHODS

Consecutive patients over age 7 seen at a single academic referral pediatric hospital with known definite pathogenic mutations in myosin heavy chain 7 or myosin binding protein C3 (Laboratory for Molecular Medicine, Boston MA) were prospectively enrolled in this study. HCM phenotype was present in some gene carriers but was not required for enrollment. HCM phenotype was defined as by echocardiography as either interventricular septum or left ventricular wall thickness greater than 15mm or greater than 3 z-scores relative to body surface area for children. Control patients were comprised of consecutive patients referred for cardiac evaluation, most commonly for chest pain, who were found to be free of heart disease, family history of sudden death, and family history of HCM on the basis of standardized cardiologist evaluation. Relevant clinical history, anthropometric data, and echocardiography results were extracted from medical records. This study was approved by the Departmental Scientific Review committee and institutional Committee on Clinical Investigation.

Hemodynamic assessment

After 5 minutes of rest in a supine position, recruited youth underwent noninvasive hemodynamic assessment. EKG leads were placed for rhythm strip recording to establish pulse ejection timing. Right arm auscultatory brachial blood pressure (BP) was measured. Arterial applanation tonometry was performed on right-sided carotid, brachial, and femoral pulses (Cardiovascular Engineering, Inc. Norwood MA).[9] To account for parallel transmission, transit distances were measured using external calipers from the suprasternal notch to each pulse measurement site. Arterial waveform signals were digitized (1000Hz) and then analyzed.

As previously described,[⁹⁻¹¹] analysis of arterial waveforms begins by using the ECG-derived R wave as the timing reference point. Tonometry-derived signal averaged brachial waveform was calibrated to the brachial cuff measured systolic and diastolic BP. The calibrated brachial artery waveform was then used to calculate the mean arterial pressure (MAP). The carotid waveform was calibrated to brachial waveform by assuming similar diastolic BP and MAP throughout the body. The carotid waveform was used as a surrogate for central arterial pressure. The transit time to a particular arterial site was recorded in milliseconds by the measuring the time from QRS R wave peak to subsequent tonometry pulse wave onset at that site. Carotid femoral pulse wave velocity (CFPWV) was determined by dividing the transit distance between carotid and femoral sites by the transit time difference between carotid and femoral. The forward pressure wave and reflected wave were noted. Augmentation index (AIx) was calculated at the carotid waveform as the difference between peak systolic BP and peak pressure of the reflected wave, divided by the total pulse pressure (systolic minus diastolic BP) and reported as a percent. Ventricular characteristics were extracted from echocardiograms ordered for clinical purposes in accordance with American Society of Echocardiography pediatric guidelines.[12] Echocardiographic structural measures were converted to age and body size adjusted z -scores. In order to account for the range of concentric LV remodeling associated with HCM gene mutations, LV mass to volume ratio was used as the index of LV hypertrophy. If irregular LV wall thickness was noted, multiple views were assessed and the greatest dimension was used.

Statistical Analysis

The primary analysis used two sided student's t-test for independent samples to determine if the sarcomeric HCM gene mutation carrying individuals had higher CFPWV or secondarily higher AIx. Multivariable adjusted linear regression models were constructed with either CFPWV or AIx as dependent outcomes and gene mutation carriers versus control patients as the independent predictor of interest. Covariates included age, sex, height, heart rate and in addition for CFPWV, MAP given the known relation between CFPWV and arterial distention pressure. Then in exploratory analyses involving only HCM genotype patients, linear regression analyses were used to explore the relations between CFPWV and AIx and LV mass to volume ratio, adjusted for age and sex. To explore the role of hyperdynamic LV function in post hoc analyses, we explored Spearman correlations between left ventricular ejection fraction and vascular indices. Analyses were performed with PASW 17.0 (SPSS Inc; Chicago, IL). Nominal significance level was 0.05. All authors have reviewed and accepted the manuscript.

RESULTS

The control (n=26) and HCM gene positive (n=28) group youth did not differ by age, sex, weight or blood pressure [Table 1]. None of the controls were on blood pressure lowering medications while 43% of HCM gene positive patients were on beta-blockers and/or calcium channel blockers. Similarly, 61% of HCM gene positive youth had phenotypic HCM, 21% had LV Mass z score greater than 5 and these patients with severe phenotypic HCM were older (18 ± 2 vs 14 ± 4 years, $p=0.007$). Implanted cardioverter-defibrillator (ICD) was present in 39% of HCM gene positive patients and none in the controls. HCM mutations in these youth included 46% with mutations in myosin heavy chain 7, 46% with myosin binding protein C3, and 1 person with both mutations.

In univariate comparison, HCM gene positive youth had higher pulse wave reflection (AIx ($27\pm 19\%$ vs. $18\pm 7\%$, $p=0.04$). Directly measured aortic stiffness in HCM gene positive youth was lower (CFPWV 4.46 ± 0.88 m/s vs. 4.97 ± 0.44 m/s, $p=0.01$). These relations persisted after multivariable adjustment [Table 2]. In light of medication treatment status, further adjustment for medication use did not substantially change the associations.

In exploratory analyses within the HCM gene positive group adjusted for age and sex, AIx was associated with LV mass to volume ratio (regression coefficient 0.02[95%CI 0.00–0.04], $p=0.03$, Figure 1), while CFPWV was not ($-0.11[-0.70,0.48]$, $p=0.7$, Figure 2). Ejection fraction was not correlated with AIx ($\rho=0.35$, $p=0.07$) nor CFPWV ($\rho=0.00$, $p=0.99$). HCM phenotype and ICD presence were not associated with significant differences in aortic stiffness or arterial wave reflection (not shown).

DISCUSSION

The role of vascular-ventricular interaction in HCM is of considerable interest. As morbidity and mortality in HCM is substantially tied to pathologic ventricular hypertrophy and afterload is a potent and potentially modifiable contributor of ventricular hypertrophy, vascular properties have been under intense scrutiny in HCM. Youth offer a critical window into the pathophysiologic development of HCM. In this analysis of youth with known pathogenic HCM genes including phenotype positive and negative patients, aortic stiffness was lower but wave reflection was higher compared to controls. Within the HCM gene positive youth, LV hypertrophy was correlated with degree of wave reflection. Therefore, if the present findings are confirmed to have a causal role in future investigations, modulating steady state impedance, i.e. peripheral artery resistance, may have an adjunctive contributory role to the intrinsic genetic myopathy and prove valuable in preventing hypertrophy.^[13, 14]

Previous investigations in adults have demonstrated aortic PWV and AIx are higher in HCM phenotype positive patients.^[8, 15–17] HCM patients with myocardial fibrosis evident on cardiac MRI also have higher PWV.^[8, 17] This myocardial fibrosis may dovetail with other reports noting higher ventricular stiffness in HCM.^[18, 19] Decreased exercise capacity in HCM patients has been linked to both higher aortic stiffness and increased ventricular stiffness, underscoring a plausible ventricular-vascular link over and above intrinsically

dysfunctional sarcomeric programming.[15, 18] Circulating regulators of fibrosis may play a role in stiffening ventricles, large conduit arteries, or both.[20–22]

However, in this group of HCM gene positive youth, aortic stiffness and AIx were discordant. The results herein are an example of the physiologic distinction between AIx and CFPWV. CFPWV is the gold standard measurement of aortic, or at least proximal conduit artery stiffness, and as such predicts ventricular remodeling, future hypertension, and incident atherosclerotic events.[6, 7, 9] The determinants of AIx are more complex. AIx summarizes the interaction of incident pulsatile energy and impedance transition points, i.e. the change from flow impedance of the conduit arteries to the impedance of muscular resistance arteries. As there appeared to be no relation between hyperdynamic function as a driver of excessive pulsatile energy and AIx, the increased AIx are likely related to impedance mismatch. The major determinants of characteristic impedance are aortic dimension and aortic stiffness.[9] Therefore, lower aortic stiffness could widen the mismatch between large artery and resistance artery impedance. It is important to note that while no current therapy is widely accepted to alter aortic stiffness, most antihypertensive agents alter small artery resistance and thereby could match upstream and downstream impedance.

AIx is well documented to be involved in vascular ventricular interactions. [4, 23–26] The reflection of pulsatile energy back to the ventricular outlet effectively increases ventricular afterload. By physiologic principles, the adaptive response to higher afterload and consequent wall tension is increased LV mass and stiffness. In general population and hypertensive patients, the association between higher AIx with LV hypertrophy is well demonstrated. [4, 25, 26]

While this study's strengths include the inclusion of HCM gene positive youth with and without phenotype and adjustment for relevant confounders, there are limitations. The small cohort size limits accounting for more confounders. The cross sectional nature of the study precludes causal inference. The mechanisms in HCM of lower CFPWV and indeed vascular properties overall remained unexplained and deserve further study.

CONCLUSIONS

Youth with pathogenic HCM genes have higher wave reflection compared to control youth, and this wave reflection appears correlated with degree of LV hypertrophy in cross sectional analyses. Longitudinal and mechanistic investigation may elucidate the causal role of vascular function on HCM progression.

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Fig 1.
Left ventricular Mass to Volume Ratio versus Augmentation Index

Fig 2.
Left Ventricular Mass to Volume Ratio versus Carotid Femoral Pulse Wave Velocity in meters per second

TABLE 1

Clinical Characteristics

	HCM gene	Control	P value
N	28	26	
Female	43%	58%	0.4
Age (years)	17 (12,19)	17 (16,18)	0.5
Height (centimeters)	168 (150,178)	166 (160,174)	1.0
Height Z score	0.2 (-0.5,1.0)	-0.1 (-0.5,1.0)	0.9
Body Mass Index (kilograms/meter ²)	22 (19,26)	22 (20,24)	0.9
Body Mass Index Z score	0.4 (0,1.1)	0.7 (0,1.1)	1.0
Systolic Blood Pressure (millimeters mercury)	109 (97,117)	109 (102,116)	0.5
Diastolic Blood Pressure (millimeters mercury)	47 (42,56)	54 (47,59)	0.1
Heart rate	68 (58,75)	64 (61,76)	1.0

All data in median (25%,75% range)or proportions.

Z score indicates age-sex referenced normative value.

TABLE 2

Multivariable adjusted independent variables associated with Vascular Function Outcomes

	Carotid femoral Pulse Wave Velocity		Augmentation Index	
	Regression coefficient (95% confidence interval)	P value	Regression coefficient (95% confidence interval)	P value
HCM gene present	-0.45 (-0.73,-0.17)	0.002	8.57 (0.99,16.14)	0.03
Age	0.07 (0.01,0.13)	0.02	0.68 (-0.93,2.29)	0.4
Sex	-0.43 (-0.74,-0.11)	0.009	-7.01 (-15.34,1.32)	0.1
Height	0.01 (0,0.03)	0.09	0.26 (-0.11,0.62)	0.2
Heart Rate	-0.01 (-0.02,0.01)	0.4	0.26 (-0.13,0.65)	0.2
Mean arterial pressure	0 (-0.02,0.01)	0.9		

Augmentation index model included presence of HCM gene, age, sex, height, and heart rate. Carotid femoral pulse wave velocity model included the same covariates and mean arterial pressure.