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Research article

Aortic biomechanics in hypertrophic cardiomyopathy

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ABSTRACT

Background: Ventricular-vascular coupling is an important phenomenon in many cardiovascular diseases. The association between aortic mechanical dysfunction and left ventricular (LV) dysfunction is well characterized in many disease entities, but no data are available on how these changes are related in hypertrophic cardiomyopathy (HCM).

Aim of the work: This study examined whether HCM alone is associated with an impaired aortic mechanical function in patients without cardiovascular risk factors and the relation of these changes, if any, to LV deformation and cardiac phenotype.

Methods: 141 patients with HCM were recruited and compared to 66 age- and sex-matched healthy subjects as control group. Pulse pressure, aortic strain, stiffness and distensibility were calculated from the aortic diameters measured by M-mode echocardiography and blood pressure obtained by sphygmomanometer. Aortic wall systolic and diastolic velocities were measured using pulsed wave Doppler tissue imaging (DTI). Cardiac assessment included geometric parameters and myocardial deformation (strain and strain rate) and mechanical dyssynchrony.

Results: The pulsatile change in the aortic diameter, distensibility and aortic wall systolic velocity (AWS') were significantly decreased and aortic stiffness index was increased in HCM compared to control ($P < .001$) In HCM AWS' was inversely correlated to age($r = -.32$, $P < .0001$), MWT ($r = -.22$, $P < .008$), LVMI ($r = -.20$, $P < .02$), E/Ea ($r = -.16$, $P < .03$) LVOT gradient ($r = -19$, $P < .02$) and severity of mitral regurg ($r = -.18$, $P < .03$) but not to the concealed LV deformation abnormalities or mechanical dyssynchrony. On multivariate analysis, the key determinant of aortic stiffness was LV mass index and LVOT obstruction while the role LV dysfunction in aortic stiffness is not evident in this population.

Conclusion: HCM is associated with abnormal aortic mechanical properties. The severity of cardiac phenotype, not LV deformation, is interrelated to aortic stiffness in patients with HCM. The increased aortic stiffness seems to be promising module that can be added as clinical risk parameter in HCM.

Keywords: Aortic stiffness, Vector velocity imaging, Hypertrophic cardiomyopathy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex genetic cardiac disorder caused by a variety of mutations in genes encoding sarcomeric proteins and defined clinically by the presence of unexplained left ventricular hypertrophy (LVH) with a varied clinical course and outcome.[1] As a result of the clinical and phenotypic heterogeneity of HCM, it is challenging to determine a subset of patients who will have a higher risk of sudden cardiac death and adverse prognosis.[2,3]

Alterations in the mechanical properties of large arteries have a clear pathophysiological link with clinical outcome. In addition to being a measure of the cumulative influence of identified and unidentified cardiovascular risk factors on target organ damage, changes of large artery phenotype may be causative in the pathogenesis of cardiovascular events.[4]

Aortic stiffness has been identified as an important predictor of cardiovascular morbidity and mortality in different patient populations[5], including patients with hypertension[6], diabetes[7], and end-stage renal disease[8], as well as in elderly hospitalized subjects[9] and more recently, in the general population[10]. However, it is uncertain whether these data can be extrapolated to HCM patients without cardiovascular risk factors.

In HCM, vascular alterations may potentially be compromised, and this has been investigated extensively in last few years.[11] Impaired aortic elastic properties are frequently attributed to neurohormonal disturbances, endothelial dysfunction, abnormal baroreceptor reflex in the left ventricle, and intrinsic aortic wall fibrosis.[12] However, there have been few reports so far investigating aortic mechanical function in HCM and its relation to cardiac phenotype and underlying left ventricular (LV) function.

Therefore, the objective of the present study was to explore whether HCM alone, without cardiovascular risk factors, is associated with an impaired aortic mechanical function using conventional echocardiography and tissue Doppler imaging and the relation of these changes, if any, to cardiac phenotype and LV deformation using 2D-strain imaging.

PATIENTS AND METHODS

Study population

HCM group

Between October 2012 and November 2013, we prospectively included 141 HCM patients with age range 5–62 years who were referred to our echocardiographic laboratories for risk stratification. They were examined at a single centre (Yacoub Research Unite, Menoufiya University, Egypt).

The diagnosis of HCM was based on conventional echocardiographic demonstration of a non-dilated, hypertrophic LV ($\geq$15 mm) in the absence of other cardiac or systemic diseases capable of producing the magnitude of hypertrophy evident.[1] Exclusion criteria were obesity (BMI $\geq$ 30 Kg/m^2), diabetes mellitus, arterial hypertension, smoking, dyslipidemia, evidence of coronary artery disease, atrial fibrillation, aortic diseases such as aortic coarctation, marfan syndrome, lung disease, and inadequate echocardiograms.

Control group

We studied 66 age and sex-matched healthy subjects without detectable cardiovascular risk factor or receiving any medication. They were volunteers recruited from among hospital staff, medical and nursing students, and members of the local community.

All of the studied population were enrolled after their informed consent, and the approval of Ethics Committee of Menoufiya University Hospitals.

Procedure

All participants were examined clinically at their initial visit to evaluate their body mass index and cardiovascular status. Patients and control subjects were subjected to conventional echocardiographic examination, pulsed wave aortic Doppler tissue imaging study (PW-DTI) and 2D-strain imaging to examine LV longitudinal deformation.

Conventional echocardiography

Standard Doppler echocardiography and DTI was performed with the subjects in partial left decubitus, variable frequency phased-array transducer (5Hz). 2D- strain tracings were stored for offline analysis.

2D measurements of LV septal and posterior wall thickness was obtained at end-diastole in parasternal long-axis view, and integrated by parasternal short-axis and apical views.[13] LV end systolic (ESD) and end diastolic (EDD) diameter, left atrial (LA) diameter & volume were measured according to recommendations of the American Society for Echocardiography.[12] LV mass was calculated using Devereux's formula and indexed for body surface area. LV ejection fraction was measured using biplane Simpson's method. Mitral regurge severity was assessed using the proximal isovelocity surface area method. Peak systolic (S_m), early diastolic (E_m) and atrial diastolic (A_m) velocity were obtained by placing a tissue Doppler (TDI) sample volume at the septal and lateral mitral annulus in the apical 4-chamber view and the mean value was obtained. The E/E_a ratio was also calculated.

Aortic mechanical function

Aortic root was examined with M-mode echocardiography from parasternal long-axis view. Care was taken to record distinct echoes internally from both the anterior and posterior walls of the aortic root in order to obtain accurate measurement of its internal diameter at a level of 3 cm above the aortic valve. Aortic diameters were measured during systole (ASD) at the time of full opening of the aortic valve (the maximum anterior movement) and during diastole (ADD) at the peak of QRS complex of ECG (the maximum posterior movement). Aortic mechanical function was assessed using the following parameters:

$$\textbf{Pulsatile change} = \textbf{aortic systolic diameter} - \textbf{diastolic diameter};$$

$$\textbf{Aortic strain}\,(\%) = \textbf{pulsatile change} \times 100/\textbf{Diastolic diameter};$$

$$\textbf{Aortic distensibility}\,(\textbf{cm}^2/\textbf{dyne}/10^3) = (2 \times \textbf{aortic strain})/\textbf{PP}.$$

$$\textbf{Aortic stiffness index} = \ln(\textbf{SBP}/\textbf{DBP})/[(\textbf{ASD} - \textbf{ADD})/\textbf{ADD}],$$

ln = natural logarithm. The last formula was validated previously.[14,15]

Aortic Doppler Tissue Imaging study (DTI)

Doppler tissue imaging (DTI) of aortic wall composed of three distinct deflections during each cardiac cycle: the peak aortic wall systolic velocity (AWS'), peak early aortic wall diastolic velocity (AWE'), and late aortic wall diastolic velocity (AWA'). AWA' is a negative wave starting after the ECG P wave. The aortic wall velocities are recorded by placing the sample volume of pulsed-wave DTI on the anterior, and then the posterior aortic wall in the parasternal long-axis view, about 2–3 cm above the aortic valve.[16]

Analysis of LV deformation

2D-strain measurement was based on the vector velocity imaging (VVI). To complete the analysis of the LV systolic function, regional and global longitudinal myocardial deformation was evaluated from standard 2D-images at frame rate (70 ± 20 F/s) and adjusted depending on the heart rate. Tracking and subsequent strain calculations were performed with the software package. Esaote-X-Strain based on a previously validated algorithm[17]. Scanning was performed longitudinally from the apex to acquire best apical 4 chamber view. Peak systolic strain (ε_{sys}), systolic strain rate (SR_{sys}), early and atrial diastolic strain rate (SR_e and SR_a) in the basal, mid and apical segments of septal, and lateral wall were measured and averaged to calculate the global longitudinal deformation. In order to reduce random noise, each sample was obtained by averaging more than one consecutive heart cycle (usually three) (Figure 1).

To estimate LV mechanical dyssynchrony, time to peak strain (TTP) was measured from regional strain curves for each ventricular segment, as time from the beginning of Q wave of ECG to the time to peak systolic strain. Electromechanical delay was measured as the difference of time to peak systolic strain in six LV myocardial segments obtained from apical view (difference between the longest and shortest cycle)[18]. LV dyssynchrony was defined as the standard deviation of the averaged time-to-peak-strain (TTP-SD)[18].

STATISTICAL ANALYSES

Data were presented as numbers and percentages or mean ± SD. Continuous variables were compared using the unpaired or paired Student t test, as indicated. The distributions of qualitative data were

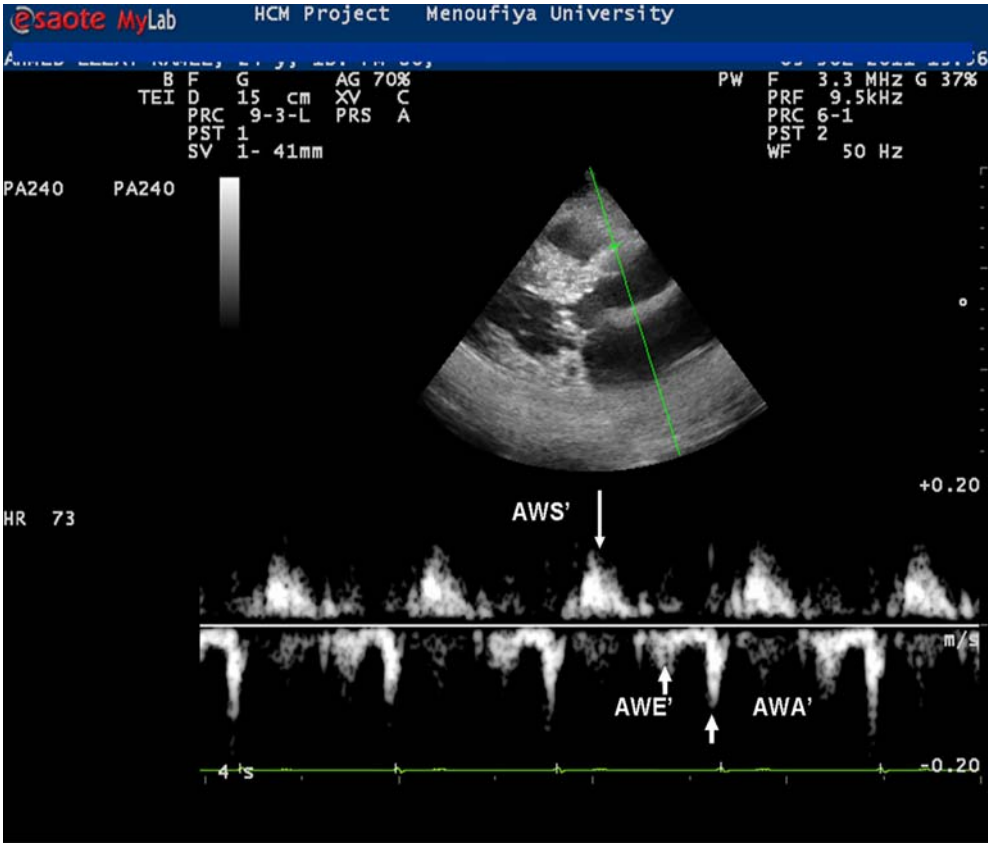

Figure 1. Pulsed wave-DTI of aortic wall showing aortic systolic velocity (AWS'), early (AWE'), and late (AWA') diastolic velocity in HCM patient.

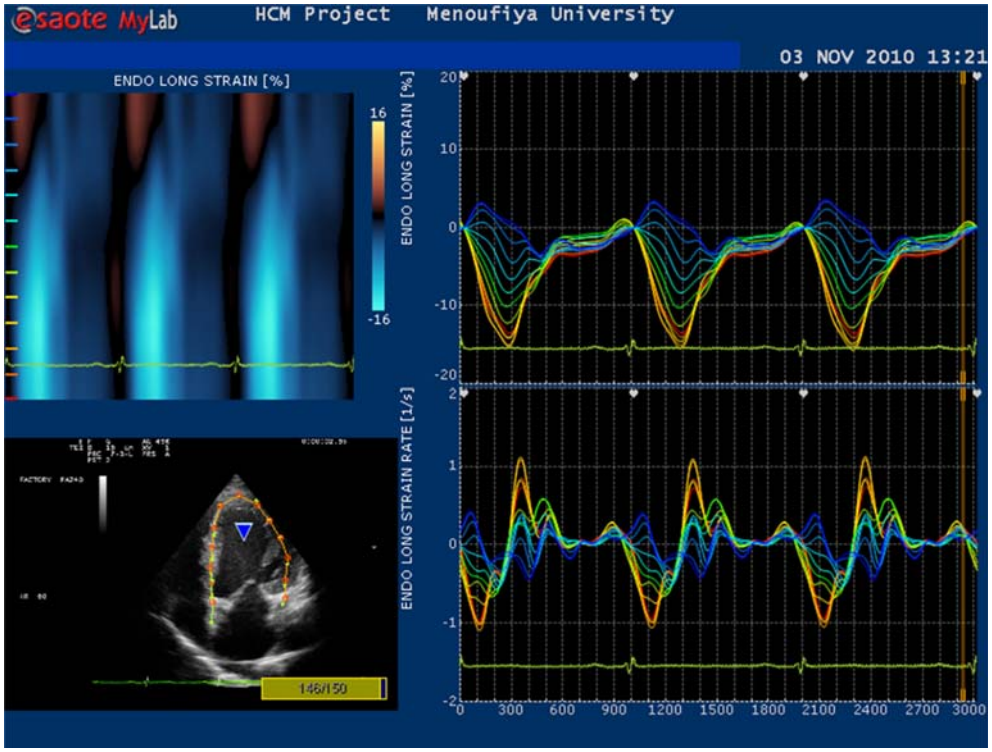

Figure 2. LV strain and strain rate in HCM using VVI.

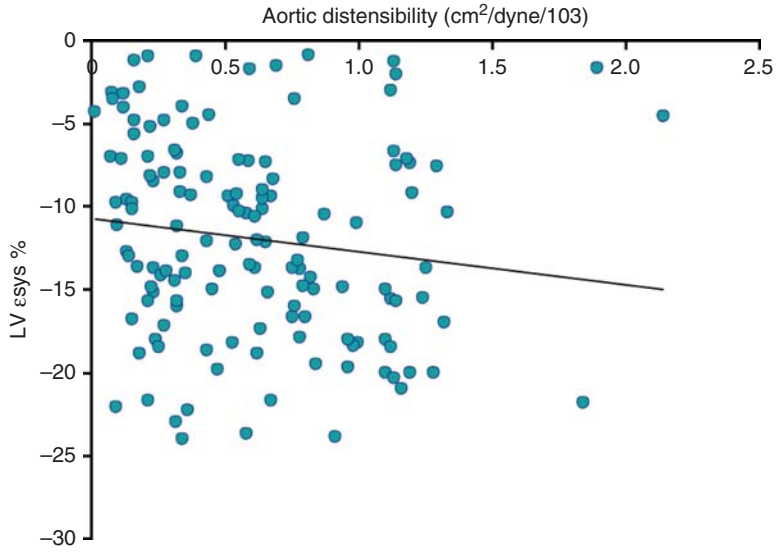

Figure 3. Relation of aortic distensibility to LV ε_{sys} % in all study population ($r = 0.25$ $p < 0.001$).

compared using the Chi-Square or Fisher's exact test, as appropriate. Pearson's correlation coefficient was calculated to express the tightness of the relation between continuous variables. Statistical significance was defined by a p value < 0.05. All tests were bilateral. Variables that were statistically significant in univariate analysis were used in 2 multivariate analysis models. The first was a repeated measures ANOVA used to evaluate the change of pressure gradient from resting values to after 2, 5 and 10 minutes of using nitroglycerine. The second was a forward stepwise logistic regression analysis model used to detect independent predictors of AWS' <6 cm/sec. Statistical analysis was performed using IBM SPSS statistical software for MAC, version 21.

RESULTS

The study population consisted of 141 consecutive patients with HCM with mean age 40 ± 18 year, (62% men), 98 (~70%) were symptomatic of which (30%) were receiving maximally tolerated doses of optimal drugs (including B- blockers and calcium channel blockers). In HCM patients, 30 (21%) had systolic anterior motion (SAM) of the mitral valve, 31 (22%) had >30 mmHg resting LVOT gradient and 3 had ICD. 28 (20%) had concentric LVH, 2 (1.4%) had apical hypertrophy, 111(78.8%) had asymmetric

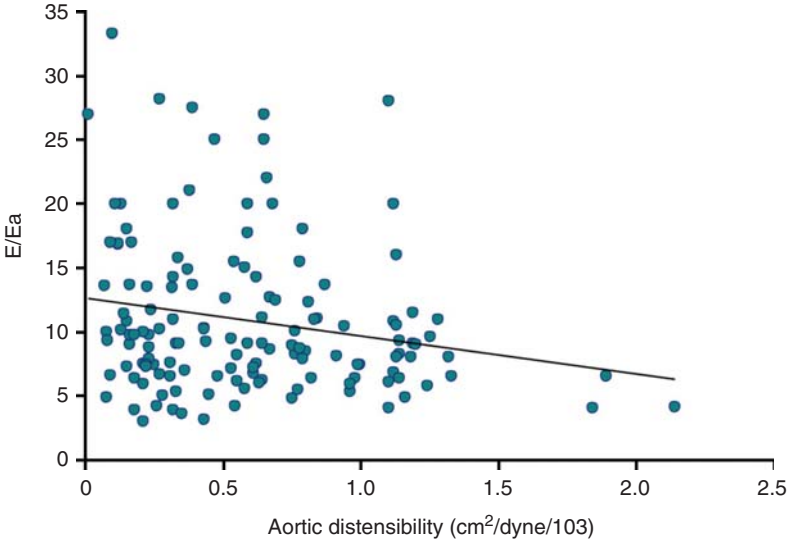

Figure 4. Relationship of aortic distensibility to E/Ea in HCM ($r = -0.23$ $p < 0.001$).

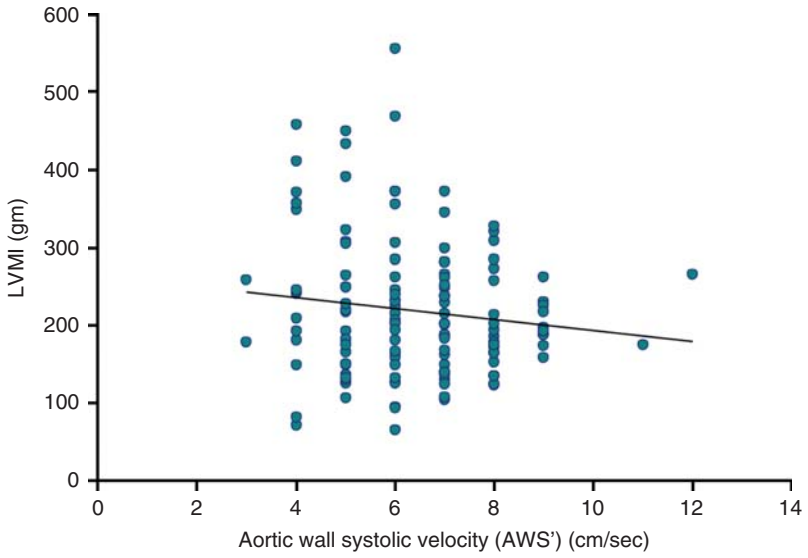

Figure 5. Relationship of AWS' and LVMI in HCM ($r = 0.21$ $p < 0.02$).

LVH. 38(27%) had moderate to severe mitral regurgitation. No differences between HCM and control group in age, gender, BSA or heart rate. (Table 1)

Conventional echocardiographic analysis

LA dimension, volume, and volume index, Septum and LVPW thickness, LVM, LVMI and resting LVOT gradient, EF%, FS and E/Ea were significantly greater, whereas LVESD and LVEDD ($P < .001$) were significantly reduced in HCM group compared to control ($P < .03$). The mean LVOT gradient in this HCM population was 26 ± 38.6 mmHg (Table 1).

Aortic mechanical parameters (Table 2)

The pulse pressure (PP) was significantly increased while ASD and the percent of aortic diameter change (aortic strain) were decreased in HCM group when compared with control group ($p < 0.001$), but there was no significant difference between them in ADD.

Aortic stiffness index was significantly higher (3.3 ± 1.7*vs.* 1.2 ± 0.5; $p < 0.001$) and aortic distensibility was significantly lower (0.59 ± 0.41 *vs.* 1.6 ± 1.1 $cm^2/dyne/10^3$); $p < 0.001$) in patients with HCM compared to control.

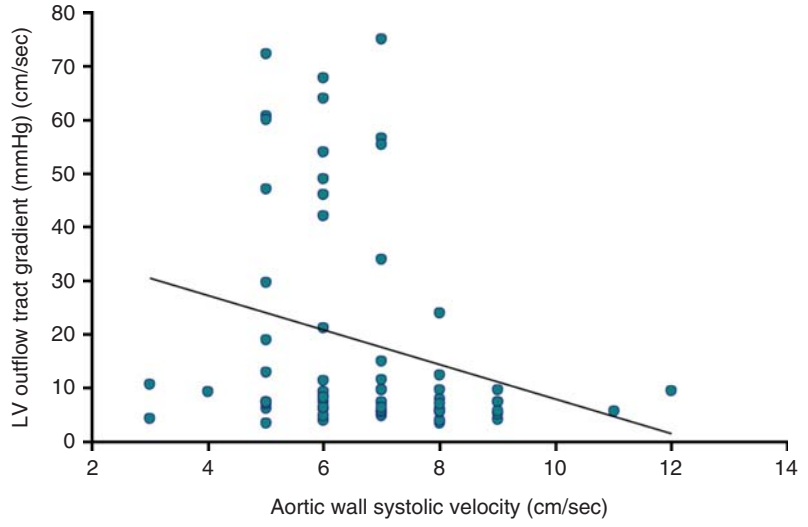

Figure 6. Relationship of AWS' to LV outflow tract gradient in HCM ($r = -19$ $p < 0.02$).

Table 1. Clinical and conventional echocardiographic characteristics.

	HCM (N = 141)	Control (N = 66)
Age	40 ± 9	38 ± 7
Sex (male)	82 (58.6 %)	25 (75.8 %)
BSA	1.81 ± 0.36	1.86 ± 0.15
HR	77 ± 18	76 ± 11
SBP	130 ± 22*	117 ± 11
DBP	83 ± 13	80 ± 7
Septum (mm)	24.5 ± 6.7**	9.7 ± 2.1
LVPW (mm)	14.5 ± 4**	9.66 ± 2.1
MWT (mm)	25.8 ± 7**	9.8 ± 2.1
ESD (mm)	21.9 ± 6.5	32.8 ± 5.6
EDD (mm)	36.2 ± 7.7	45.7 ± 6.7
EF%	70.7 ± 11	62 ± 13
LAD (mm)	37.3 ± 9.1**	30 ± 4
LA volume (ml)	63.6 ± 34**	22 ± 8
FS%	40.4 ± 10.3**	30 ± 8.7
EF%	70.8 ± 11.8**	55.9 ± 13.2
LVMI (gm/m2)	220.0 ± 88.6**	103.4 ± 16.4
LVOT gradient (mmHg)	25.7 ± 38.6	3.9 ± 1.8
mitral E/A	1.44 ± 0.63	1.13 ± 0.11
PAP (mmHg)	29 ± 14	22 ± 3
E/Ea	10.8 ± 6**	4.4 ± 1

LVPW: left ventricular posterior wall, MWT: maximal wall thickness, ESD: left ventricular end-systolic diameter, EDD: left ventricular end-diastolic diameter, EF: ejection fraction, LAD: left atrial diameter; LVMI: left ventricular mass index, LVOT left ventricular outflow tract; E: early mitral inflow velocity; A: atrial mitral inflow velocity; PAP: pulmonary artery pressure; Ea: mitral annulus early diastolic velocity.

Using TDI parameters, both aortic wall systolic expansion velocity (AWS') (6.1 ± 1.6 *vs.* 9.8 ± 1.5) cm/sec; p = 0.003) and aortic wall early diastolic velocity which represent recoil velocity (AWE') (6.4 ± 2 *vs.* 10.5 ± 1.8) cm/sec; p = 0.003) respectively, were significantly lower in patients with HCM than in controls, while late diastolic aortic wall velocity (AWA') velocities did not differ between the two groups. No significant difference in any of aortic mechanical functions between: familial and sporadic HCM, or between asymmetric and concentric LVH (P = NS) (Figure 2–6).

LV deformation in study population

In HCM group, 2D strain analysis detected lower global and regional peak LV ε_{sys} and SR_{sys} ($p < 0.001$) at the level of all analyzed segments in comparison to control. There was lower global early diastolic strain rate (global SR_e). Similarly, intra-V dyssynchrony (TTP-SD) was considerably increased between LV segments compared with its corresponding segments in healthy individuals ($p < 0.001$) (Table 3).

Relation of aortic mechanics to phenotype and LV deformation (Table 4)

We tested the association between various clinical and myocardial parameters and aortic mechanics in the combined study population and in HCM group only. The results are shown in Table 3.

In the combined studied groups, the aortic strain percentage, aortic distensibility and AWS' were negatively correlated to age, functional class, regurgitation, MWT, LVMI and PAP. Additionally aortic

Table 2. Aortic biomechanics in study population.

	HCM (N = 141)	Control (N = 66)
PP (mmHg)	47.3 ± 13.5**	36.3 ± 6.6
ASD (mm)	27.6 ± 5.4**	32.8 ± 3.5
ADD (mm)	24.4 ± 5.3	25.4 ± 4.2
Pulsatile change (mm)	3.22 ± 2.27**	7.63 ± 4.78
Aortic strain (%)	13.8 ± 10.3**	22.2 ± 5.7
Aortic distensibility (cm^2/dyne/10^3)	0.59 ± 0.41**	1.6 ± 1.1
aortic Stiffness index	3.3 ± 1.7*	1.2 ± 0.5
AWS'	6.17 ± 1.6**	9.8 ± 1.5
AWE'	6.4 ± 2.1**	10.5 ± 1.5
AWA'	7.83 ± 2.1	7.36 ± 1.14

*: P < .01, **: P < .001. PP: aortic pulse pressure; ASD: aortic systolic diameter; ADD: aortic diastolic diameter; TDI aortic wall systolic velocity; AWE': aortic wall early diastolic velocity; WAA': aortic late diastolic velocity.

Table 3. LV deformation.

	HCM (N = 141)	Control (N = 66)
ε_{sys} Septum (%)	−11.8 ± 6.5**	−20.4 ± 2.0
ε_{sys} Lateral (%)	−12.4 ± 5.7**	−19.9 ± 2.2
ε_{sys} Anterior (%)	−11.9 ± 8.3**	−19.3 ± 2.9
ε_{sys} Inferior (%)	−11.3 ± 6.9**	−19.8 ± 2.2
ε_{sys} Global (%)	**−11.9 ± 5.9****	**−19.7 ± 1.7**
SR_{sys} Septum (s^{-1})	−0.92 ± 2.1*	−1.21 ± 0.65
SR_{sys} Lateral (s^{-1})	−0.81 ± 0.46	−1.28 ± 0.35
SR_{sys} Anterior (s-1)	−0.76 ± 0.37**	−1.27 ± 0.55
SR_{sys} Inferior (s^{-1})	−0.72 ± 0.57	−1.2 ± 0.32
SR_{sys} Global (s^{-1})	**−0.81 ± 0.66****	**−1.26 ± 0.20**
SR_e Septum (s^{-1})	0.72 ± 0.46**	1.5 ± 0.58
SR_e Lateral (s^{-1})	0.83 ± 0.62*	1.29 ± 0.5
SR_e Anterior (s^{-1})	0.82 ± 0.64**	1.56 ± 0.4
SR_e Inferior (s^{-1})	0.84 ± 0.6**	1.6 ± 0.53
SR_e Global (s^{-1})	**0.81 ± 0.5****	**1.53 ± 0.49**
SR_a Septum (s^{-1})	0.46 ± 0.34**	0.72 ± 0.3
SR_a Lateral (s^{-1})	0.48 ± 0.52	0.58 ± 0.12
SR_a Anterior (s^{-1})	0.44 ± 0.43	0.59 ± 0.27
SR_a Inferior (s^{-1})	0.57 ± 0.39	0.64 ± 0.27
SR_a Global (s^{-1})	**0.49 ± 0.9**	**0.68 ± 0.11**
TTP- SD (ms)	62.5 ± 35.5**	29 ± 16.3

*: P < .001; versus control; **: P < .0001 versus control. ε_{sys}: peak systolic strain; SR_{sys}: peak systolic strain rate; SR_e: early diastolic strain rate; SR_a: atrial diastolic strain rate. TTP: time to peak strain; TTP-SD: standard deviation of time to peak strain.

strain and distensibility were directly correlated to LV deformation ε_{sys}% (r = 0.25 p < 0.001), SR_e (r = 0.25, p < 0.001), and inversely related to mechanical dyssynchrony (r = −0.24, p < 0.001).

AWS' was positively related to LV ε_{sys} % (r = 0.28, p < 0.0001), SR_e (r = 0.24, p < 0.002), SR_{sys} (r = 0.23, p < 0.003) and negatively correlated to TTP-SD (r = −0.27, p < 0.0001).

Of note, in our study population, LV EF% as measured by conventional method was not connected to any aortic functional parameters. However, when patients with HCM were taken separately, the

Table 4. Correlations between aortic mechanics and clinical and echocardiographic parameters.

		AWS'	Aortic stiffness index	Aortic distensibility	Strain	Pulsatile change	PP
Age	r	−.031	.162	−.332	−.306	−.080	.468
	p	.681	.032	.000	.000	.294	.000
Functional class	r	−.146	.172*	−.330	−.253	−.280	.193
	P	.057	.024	.000	.001	.000	.023
LVMI	r	−.325	.070	−.182	−.082	−.166	.039
	P	.000	.356	.016	.281	.028	.649
LA volume index	r	−.266	.029	−.283	−.194	−.213	.045
	P	.000	.701	.000	.011	.005	.598
PAP	r	−.242	.013	−.238	−.157	−.161	.222
	P	.002	.865	.002	.044	.039	.010
MWT	r	−.395	.120	−.356	−.223	−.316	.038
	p	.000	.116	.000	.003	.000	.651
EF%	r	.028	−.142	.030	.153	.083	.093
	p	.657	.071	.601	.070	.300	.223
Global	r	−.282	.102	−.249	−.098	−.243	.050
ϵ_{sys} %	p	.000	.189	.001	.209	.001	.568
TTP- SD	r	−.273	.057	−.239	−.118	−.160	.102
	p	.000	.457	.001	.122	.035	.227
Global SRe	r	.241	−.095	.253	.138	.220	−.065
	p	.002	.220	.001	.074	.004	.453
Global SRa	r	.018	.046	−.029	−.066	−.037	−.066
	p	.814	.553	.704	.395	.630	.441
Global SR_{sys}	r	−.229	.079	−.102	−.017	−.145	.040
	p	.003	.309	.187	.826	.059	.642

LVMI: left ventricular mass index; LA: left atrium; PAP: pulmonary artery pressure; MWT: maximal wall thickness; EF: ejection fraction; ε_{sys}, peak systolic strain; SR_{sys}: peak systolic strain rate; SR_e: early diastolic strain rate; SR_a: atrial diastolic strain rate. TTP: time to peak strain; TTP-SD: standard deviation of time to peak strain.

association between LV deformation and aortic stiffness was no longer statistically significant. Aortic distensibility was directly related to E/Ea ($r = 0.23$, $p < 0.001$). Only AWS' was inversely correlated to age($r = -0.32$, $p < 0.0001$), MWT ($r = -0.22$, $p < 0.008$), LVMI ($r = -0.20$, $p < 0.02$), E/Ea ($r = -0.16$, $p < 0.03$) LVOT gradient ($r = -0.19$, $p < 0.02$) and severity of mitral regurgitation ($r = 0.18$, $p < 0.03$), but not to LV deformation or mechanical dyssynchrony.

For multivariate analysis, a cutoff value equal or less than 6 cm/sec for AWS' was used as an indicator of impaired aortic mechanical function in HCM patients.[10] Variables introduced in the model were those variables that were statistically significant on univariate analysis. The analysis showed that LVMI (Exp B 0.994 {95% IC: 0.989–0.999}; $p = 0.017$) and LVOT gradient (Exp B 0.93 {95% IC: 0.893-0.972}; $p = 0.001$), were the principal independent predictors of aortic stiffness in HCM.

DISCUSSION

Our study confirms recent few reports that HCM is associated with abnormal aortic mechanics as indicated by altered distensibility and reduced aortic wall velocities using TDI. The abnormality is strongly related to cardiac phenotype but not to LV deformation.

In this complex disease, the severity of LV hypertrophy and presence of LVOT obstruction are the principle determinants of aortic stiffness. Abnormal vascular function may be a novel parameter for risk stratification in HCM patients as it reflects a more aggressive phenotype.

AORTIC STIFFNESS AS A CARDIOVASCULAR RISK FACTOR

An expanding body of evidence demonstrates that arterial stiffness is an important, independent predictor of outcome and appears to be associated with different pathologic conditions which make it hard to determine the precise mechanism of increased stiffness.[6–10] Recently, the concept of "continuity disease" has been proposed to describe the relationship between the arteries and the rest of the cardiovascular system.[7–10]

The arterial system has a two-fold role, acting as both a conduit and a cushion. The aorta is a passive organ that does not constrict or dilate by itself; however, it plays a vital role in buffering and smoothing the pulsatile nature of blood flow, due to ventricular contraction, as it travels to the periphery. The proximal ascending aortic segment is the main element as the majority of the buffering capacity of the system resides on it.

During cardiac systole, the ejection of blood from the LV through the aortic valve in the aorta leads to flow, pressure, and diameter pulsations (waves), and these pulsations propagate throughout the arterial tree at a speed determined by the elastic and geometric properties of the arterial wall and the characteristics of the contained blood.[9] The LV stroke volume is temporarily stored in the aorta. After the closure of the aortic valve, the recoil of the large vessels to their diastolic dimensions pushes the blood towards the periphery. Arterial compliance favors LV function as it reduces LV workload, and enhances diastolic perfusion and crucial to the delivery of blood to the myocardium through the coronary vessels.[4]

As the arterial tree becomes stiffer, due to age-related processes or other cardiovascular risk, the pulse wave is transmitted more rapidly and returns to the heart during LV contraction, resulting in a greater augmentation of the central aortic systolic pressure. The late systolic augmentation of the central pressure waveform is associated with an increase in LV mass index independent of age and mean blood pressure.[19] This summation of the reflected waves ensures a progressive increase of afterload in the aortic root, coronary arteries and left atrium. Pulsatile forces contribute substantially to LV diastolic dysfunction.[20]

Aortic mechanics using TDI

In the current study, we defined the elastic properties of the aorta on the basis of distensibility and recoil using M-mode and TDI measurements. Although invasive methods remain the gold standard, several reports have demonstrated that M-mode echocardiography is a reliable alternative to such techniques.[21]

TDI is a practical method for direct and quantitative measurement of changes related to aortic wall movement.[22] It provides further help than other methods like PWV, because it is not affected by hematological and cardiovascular physiology as well as heart rate and blood pressure variations. A number of studies have shown that elastic properties of the ascending aorta could be reproducibly

evaluated by measuring aorta wall velocity in patients with CAD, diabetes, and hypertension.[23,24,15,14] To our knowledge, the present study is the first one assessing elasticity indices of the ascending aorta using TDI in HCM patients.

In the present study reduced distensibility, expansion and recoil velocities, which represent increased stiffness of the aorta, can not be affected by presence of CV risk factor as they are excluded from the study. Arterial stiffness index, using M-mode echocardiography, determines the elastic properties of the arterial wall, in a manner relatively independent of blood pressure, while aortic distensibility evaluates the ability of the arteries to dilate during the cardiac cycle, and measures the function of the artery[25,26,27].

There was significant association between age and aortic stiffness variables and this was probably due to inclusion of wide age range from HCM population. Our data resembles previous reports demonstrating a strong association between the two entities.[7–10]

Relation of aortic mechanics to LV deformation

The cardiovascular system can be thought of as a continuous system consisting of a reservoir, pump and vessels.[28] Therefore, an abnormality in one component might affect the other compartments. A definitive pathophysiological link between LV function and aortic stiffness has not yet been established. In our entire study population, significant relationship was found between aortic mechanical functions and LV deformation (reflect systolic and diastolic functions) and mechanical dyssynchrony. The interaction between vascular changes and LV functions is recently investigated.[29–31]

Koopman et al. examined the interaction between myocardial deformation using TDI, speckle-tracking and vascular structure and function using intima-media thickness, flow-mediated dilatation and aortic pulse-wave velocity, in a subgroup of obese children with lipid abnormalities. Reduced radial and longitudinal myocardial deformations were related to changes in vascular function and suggest abnormal ventricular-arterial interactions in obese children.

In the present study, among the indices of diastolic function, early diastolic strain rate, and E/Ea, which reflect LV end diastolic pressure, were correlated with AWS' and aortic distensibility. In agreement with our findings, a study by Suh et al. examined 126 patients with diastolic dysfunction and normal ejection fraction, they observed decreased aortic wall velocity in patients with diastolic dysfunction and a negative correlation with LV filling pressure.[32,33]

However, the most important and consistent finding in this study is loss of the strong relation between vascular function and subtle changes in LV deformation when HCM group was taken separately. Meanwhile, there was important inverse relationship between aortic distensibility and aortic wall velocity and LVMI, severity of LVOT obstruction, severity of mitral regurgitation, left atrial volume and functional class. The most plausible explanation for this association is that severity of disease and cardiac phenotype may have a direct effect on the aortic wall.

Aortic stiffness and cardiac phenotype in HCM:

With more aggressive phenotype, a significant proportion of HCM patients demonstrate reduced functional capacity. This is traditionally thought to be at least partially due to diastolic abnormalities, LV stiffening and dynamic LVOT obstruction.[3] However, patients with HCM with similar degrees of LV hypertrophy, diastolic dysfunction or LVOT obstruction often have significant variation in their exercise capacity.[4–6] Hence, it is apparent that there are additional, under-appreciated factors influencing exercise capacity in such patients, which is probably attributed to impaired aortic elastic properties and limited vascular function. Recently Austin et al.[34] investigated the relation between exercise capacity and aortic stiffness using PWV in HCM and demonstrated a strong inverse relation between the two; besides aortic stiffness was independent predictor of PVO2 in this population.

In accordance with a recently published study[35], aortic stiffness was directly correlated to the severity of mitral regurgitation in our HCM cohort. Rossi et al.[4] investigated the relation between aortic stiffness using PWV, and functional mitral regurgitation in 175 patients with LV systolic dysfunction. They observed association of PWV with each variable of mitral regurgitation, which was independent of LV volume, cardiac output, and systemic vascular resistance. They concluded that aortic stiffness is an important determinant of the severity of functional MR. We should therefore consider aortic stiffness as an important factor in both LV systolic and diastolic function and mitral regurgitation.

Boonyasirinant et al. investigated aortic stiffness in 100 HCM and 35 normal control subjects. MRI-derived PWV was determined between the mid-ascending and -descending thoracic aorta. Delayed-enhancement MRI was acquired for identification of myocardial fibrosis. They demonstrated increased aortic stiffness as PWV was significantly higher in HCM patients compared with control subjects and was more pronounced in those with myocardial fibrosis.[11] However, in contrast to our study, they did not examine the relation of vascular changes to echocardiographic-derived variables.

Furthermore, Gavallér et al.[36] examined aortic distensibility in 38 patients with typical features of HCM using arteriograph-derived PWV, and compared it to 20 hypertensive patients. Unlike our study they did not exclude patients with cardiovascular risk factors. They demonstrated abnormal aortic elastic properties and hypertensive patients with LVH showed similar alterations to HCM patients.

ETIOLOGY OF ABNORMAL AORTIC STIFFNESS IN HCM

The precise etiology for this vascular dysfunction in HCM is uncertain; increased aortic stiffness has been linked to structural alterations (including increased collagen content[36] of the arterial wall and rearrangement of its three-dimensional structure.[5] HCM is characterised by myocardial fibre disarray, which raises the speculation of a common pathway reflecting the phenotypic characteristics of the same disease process taking part in the arterial wall. Moreover, vascular dysfunction may precede the progression of excessive fibrosis and development of evident LV systolic dysfunction. In our HCM population, lacking of significant relation between aortic stiffness and LV mechanics is suggesting that it is not exclusively a complication of LV dysfunction, but rather a coexisting condition. The development of aortic mechanical dysfunction is likely multifactorial. Recent reports have implicated neurohumoral pathways result from elevated LV pressure, such as the renine angiotensin system or plasma norepinephrine, contribute to vasoconstriction and sodium retention in the vessel wall, resulting in increased stiffness.[25] Endothelial dysfunction and abnormal LV baroreceptor response affects pulsatile pressure buffering and vasodilation of the arterial system through the elaboration of vasoactive substances, such as endothelial-derived relaxing factor[25,37].

OUTCOME OF IMPAIRED AORTIC STIFFNESS IN HCM

The presence of arterial stiffness in large arteries has been reported to be the best predictor of cardiovascular morbidity and mortality.[4] Increased aortic stiffness leads to augmented systolic pressure and attenuated diastolic pressure, resulting in elevated pulse pressure[38] Higher pulse pressure provokes medial damage, pressure overload, and LV hypertrophy[39]. In HCM stiffening of the aorta may impose burden on an already stiff ventricle, increase wall tension, which adversely alters ventriculo-vascular coupling and detrimentally impacts on ventricular performance and diastolic relaxation[39]. Additionally, attenuated diastolic pressure induces a reduction of the coronary perfusion, which is commonly altered by endothelial dysfunction.

Clinically, stiffening of the aorta may contribute to limited exercise capacity via increased stroke work, reduced energy efficiency, inability to generate adequate cardiac output and reduction in skeletal muscle perfusion during exercise.[39] Abnormal vascular function may be part of hypotensive response during exercise, one of the risk factors for sudden cardiac death.

Formerly, it had been assumed that exercise-induced hypotension was related to the inability to maintain stroke volume during tachycardia. However, an invasive hemodynamic study demonstrated that hypotension was related to a fall in vascular resistance from an abnormal vascular response, and occurred despite an appropriate rise in cardiac index[38,39]. Impaired vascular function can be added as clinical risk parameter in HCM; however, this hypothesis requires a further comprehensive study.

STUDY LIMITATIONS

One limitation to the present study is its cross-sectional design, and further longitudinal studies are desirable to confirm the clinical outcome in patients with abnormal aortic mechanics. Second this study included only the proximal segment of ascending aorta while descending thoracic and abdominal segments were not investigated to define which region truly stiffens most. However, the proximal ascending aortic segment is the most important as the majority of the buffering capacity of the system resides on it. Third, the blood pressure measured in the brachial artery (for estimation of aortic distensibility) may be different from the pressures in the ascending aorta, due to pulse pressure amplification towards the periphery. However, the results obtained by this method correlate well with

those from invasive methods and TDI was used for more comprehensive assessment of arterial mechanics.

CONCLUSION

To the best of our knowledge, this study is one of the first to demonstrate abnormal aortic mechanics in HCM patients without cardiovascular risk factors. The severity of cardiac phenotype is interrelated to aortic stiffness in patients with HCM. LV mass index and LVOT obstruction were the key determinant of aortic stiffness. LV strain (measured by VVI) demonstrated concealed LV dysfunction however its role in aortic stiffness is not evident in this population. This study support earlier findings that HCM not only a primary myocardial disease defined by the presence of unexplained LVH with variable LV dysfunction but also a complex cardiac disorder coupled with vascular alteration. The increased aortic stiffness in HCM seems to be promising module that can be added as clinical risk factor in HCM. The standing basis of aortic stiffness and the impact on clinical outcomes warrant further investigation.

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