Effects of increasing afterload on early diastolic dysfunction in hypertrophic non-obstructive cardiomyopathy

GERD HAUSDORF,† VOLKER SIGLOW,* CHRISTOPH ANIENABER*

From the Departments of *Cardiology and †Pediatric Cardiology, University of Hamburg, Hamburg, West Germany

SUMMARY The effects of increasing afterload on early diastolic dysfunction in 10 patients with hypertrophic non-obstructive cardiomyopathy were studied by computer assisted analyses of digitised M mode echocardiograms. Infusion of angiotensin II increased the end systolic pressure by a mean (SD) of 36.2 (10.3) mm Hg. As the afterload increased early diastolic dysfunction tended to become more normal: the interval and the change in dimension between minimal cavity dimension and mitral valve opening decreased and the duration of rapid diastolic filling and the accompanying change in dimension increased. None the less, the end diastolic dimension and thus the overall diastolic filling remained unchanged.

Impaired early diastolic function in hypertrophic cardiomyopathy is at least partly caused by altered loading conditions.

In hypertrophic cardiomyopathy diastolic function is impaired especially in early diastole.¹⁻³ Dysfunction in early diastole is probably caused by prolonged or incomplete relaxation and reduced distensibility of the left ventricle.⁴⁻⁶ Recently, Brutsaert *et al* showed that relaxation was significantly dependent on loading conditions,^{7,8} which suggested that impaired relaxation in hypertrophic cardiomyopathy could be to some extent the result of reduced wall stress.⁸

We have used non-invasive techniques to analyse the effects of increasing afterload on early diastolic dysfunction in patients with hypertrophic non-obstructive cardiomyopathy without mitral regurgitation.

Patients and methods

PATIENTS

We studied 10 patients (aged 21-61) with hypertrophic non-obstructive cardiomyopathy. All of them had had diagnostic cardiac catheterisation. Patients with left ventricular outflow tract obstruction and mitral valve regurgitation were excluded. Table 1 shows the patient data. All medications were stopped

at least 12 hours before the examination. Six patients had been taking oral verapamil (240-320 mg) and four patients were not on medication.

CONTROLS

We also studied 30 healthy volunteers (aged 18 to 30). None had a history of cardiovascular disease. Physical examination, electrocardiography, M mode and cross sectional echocardiography showed no abnormalities. None of them was taking medications.

ECHOCARDIOGRAMS

Echocardiograms were performed with a Hewlett Packard 77020A ultrasound imaging device with a 2.5 MHz transducer. M mode echocardiograms were recorded while the left ventricular short axis was continuously visualised by cross sectional echocardiography. We took care to record the M mode echocardiogram through the centre of the left ventricular short axis with the ultrasound beam perpendicular to the posterior wall. The M mode echocardiogram and cross sectional echocardiogram were recorded at the tip of the mitral valve leaflets in standard position with a paper speed of 100 mm/s. The transducer was held in position for all measurements and all echocardiograms were recorded by one echocardiographer. Intraobserver and interobserver variability was below 7% for all measurements. A carotid pulse tracing was recorded

Requests for reprints to Dr Gerd Hausdorf, Universitätsklinik Hamburg, Kinderkardiologie, Martinistrasse 52, D-2000 Hamburg 20, Federal Republic of Germany.

Table 1 Patient data and baseline values

Case	Age (yr)	Sex	D_{ed} (cm)	PW_{ed} (cm)	SW_{ed} (cm)	Verapamil (oral)
1	47	M	3.75	1.2	2.7	320 mg
2	50	M	4.1	1.6	2.8	240 mg
3	56	M	5.2	1.3	3.2	—
4	42	M	4.9	1.5	2.5	—
5	41	M	5.0	1.2	3.1	—
6	53	F	5.1	1.2	1.6	—
7	61	F	4.3	1.2	2.2	240 mg
8	36	M	4.0	1.3	2.7	—
9	38	M	3.65	1.5	2.9	240 mg
10	21	F	3.3	3.0	3.1	240 mg

D_{ed} , end diastolic left ventricular dimension; PW_{ed} , end diastolic posterior wall thickness; SW_{ed} , end diastolic septal wall thickness.

simultaneously with the M mode echocardiogram. This was corrected for pulse transmission delay by aligning it with the aortic valve echocardiogram.

MEASUREMENT OF END SYSTOLIC PRESSURE

Systolic and diastolic blood pressures were measured by a Dinamap 845 Vital Signs Monitor (Criticon Inc). This device estimates central aortic pressure accurately over a wide range of pressures, independently of cardiac index, systemic vascular resistance, heart rate, and body surface area.¹⁰ The end systolic pressure was estimated by the method of Stefadourous *et al*¹¹ by linear interpolation of the height of the dicrotic notch of the indirect carotid pulse tracing.^{10 11}

STUDY PROTOCOL

All examinations were performed with the patient at rest and semi-supine. The patients relaxed for at least 15 min before the examination. Intravenous atropine (0.01 mg/kg) was given before the examination to reduce reflex cardiac slowing caused by baroreceptor stimulation.¹²⁻¹⁴ After baseline recordings the blood pressure was slowly increased by the infusion of angiotensin II (0.5–3.5 µg/min). We attempted to increase the systolic blood pressure to 30 mm Hg above baseline values. We obtained simultaneous recordings of the M mode echocardiogram, carotid pulse tracing, and arterial blood pressure when pressure was highest. We also recorded the cross sectional echocardiogram on a video tape recorder.

Informed consent was obtained from all patients and the study protocol was approved by the local committee for human research.

COMPUTER ASSISTED ANALYSES

We accepted only high quality echocardiograms for analysis. The M mode echocardiograms were digitised with a Cardio 200 computer (Kontron Image Analysis). Three consecutive cardiac cycles were analysed and the mean was used for further calculations. We made the following time and dimensional measurements.

MEASUREMENT OF TIME INTERVALS

We used the start of the Q wave of the electrocardiogram as the zero reference point. The interval between the point where the fibre shortening velocity curve crossed zero and mitral leaflet separation was regarded as the interval between minimum cavity dimension and opening of the mitral valve (fig 1).¹⁵⁻¹⁷

MEASUREMENT OF DIMENSIONS AND DIMENSIONAL CHANGES

The end diastolic left ventricular dimension (DD) was measured at the start of the first Q wave of the cardiac cycle being analysed. The left ventricular dimension at aortic valve closure was taken as the end systolic dimension (DS). Fractional shortening (FS) was calculated as a parameter of systolic ejection:

$$FS = \frac{(DD - DS)}{DD} \times 100\%$$

The maximal rate of fibre lengthening was measured as the maximum of the first derivative of the instantaneous left ventricular internal dimension curve¹⁵ (fig 1).

The change of dimension between minimal cavity dimension and mitral valve opening was defined as^{16 17}

$$dDS - MO = \frac{DMO - DS}{DD2 - DS} \times 100\%$$

where DS is the minimal cavity dimension; DMO the dimension at mitral valve opening; and DD2, the end diastolic dimension at the end of the cardiac cycle.

The end of rapid diastolic filling was defined as the point at which the velocity of fibre shortening had decreased to 50% of its peak value³ (fig 1). The change of dimension with rapid diastolic filling (dRF) was calculated as:

$$dRF = \frac{DRF - DMO}{DD2 - DMO} \times 100\%$$

where DRF is the dimension at the end of rapid diastolic filling; DMO, the dimension at mitral valve opening; and DD2, the end diastolic dimension at the end of the cardiac cycle.

Fig 1 (a) Change in instantaneous left ventricular dimension and its first derivative (b) at baseline conditions (black line) and with increased afterload (broken line). When the afterload was increased early diastolic filling tended to become more normal—the interval and change of dimension between minimal cavity dimension (DF) and mitral valve opening (MVO) decreased and the duration and change of dimension with rapid diastolic filling (RF) increased. End diastolic dimension remained unchanged, while minimum cavity dimension and maximal fibre lengthening rate decreased.

Septal and posterior wall thickness were measured at end diastole as defined above.

STATISTICAL ANALYSIS

We used a paired t test to compare changes with increasing afterload in individuals. A p value of less than 0.05 was regarded as statistically significant.

Results

END DIASTOLIC PRESSURE AND SYSTOLIC EJECTION

The average (SD) increase of the end systolic pres-

sure was 36.2 (10.3) mm Hg ($p < 0.0001$) and the baseline end systolic pressure was 107 (15.6) mm Hg (table 2, fig 2). This increase of the end systolic pressure was accompanied by an average reduction in fractional shortening of 13.2 (3.97)% (absolute change) ($p < 0.0001$); the baseline fractional shortening was 49.4 (9.2)% (fig 2, tables 2 and 3). The heart rate showed no significant change during the increase in afterload (table 2).

DIMENSIONAL CHANGES IN EARLY DIASTOLE
During baseline conditions the average change of dimension between the minimum dimension and

Table 2 Echocardiographic and pressure data at baseline conditions and after afterload increment

Case	Baseline conditions									
	HR (beats/min)	P_{es} (mm Hg)	D_{ed} (cm)	D_{es} (cm)	FS (%)	tDS-MO (ms)	dDS-MO (%)	tRF (ms)	dRF (%)	VLR _{max} (cm/s)
1	56	111	3.75	2.0	47	150	20	75	26	7.3
2	59	120	4.1	2.15	48	125	49	20	20	10.0
3	63	113	5.3	2.5	53	150	55	40	13	13.1
4	76	93	4.9	2.6	47	169	43	80	30	13.3
5	59	116	5.0	2.6	48	150	71	45	8	6.4
6	74	117	4.9	2.6	55	105	21	120	43	13.0
7	65	126	4.3	3.05	29	155	40	60	8	7.1
8	93	99	4.0	1.6	60	140	38	40	0	13.8
9	72	106	3.65	1.4	62	155	64	60	32	10.5
10	67	73	3.3	1.8	55	120	20	120	40	11.3

HR, heart rate; P_{es} , end systolic pressure; D_{ed} , end diastolic left ventricular dimension; D_{es} , end systolic left ventricular dimension; FS, fractional shortening; tDS-MO, time between minimal cavity dimension and mitral valve opening; dDS-MO, change of dimension between minimal cavity dimension and mitral valve opening; tRF, time of rapid filling; dRF, change of dimension with rapid diastolic filling; VLR_{max}, maximal fibre lengthening rate.

Fig 2 (a) Individual data for fractional shortening (FS) during baseline conditions and during increased afterload. Fractional shortening decreased by $13.2 (4.0)^{\circ}_{\circ}$ (absolute change) during the increase in afterload, from a mean value of $49.4 (9.2)^{\circ}_{\circ}$ at baseline ($p < 0.0001$). (b) Individual data for the maximum rate of fibre lengthening (VLR_{max}) at baseline conditions and during increased afterload. The maximum rate of fibre lengthening decreased by $25 (13.1)^{\circ}_{\circ}$ when the afterload was increased ($p < 0.001$).

mitral valve opening was $42 (18.2)^{\circ}_{\circ}$, and the change of dimension during rapid diastolic filling was $22 (14.6)^{\circ}_{\circ}$ (table 2). At peak pressure the change in dimension between minimal dimension and mitral valve opening decreased by $26 (16.0)^{\circ}_{\circ}$ (absolute change) ($p < 0.001$) (fig 3, tables 2 and 3) and the change of dimension with rapid diastolic filling was reduced by $19 (15.7)^{\circ}_{\circ}$ (absolute change) ($p < 0.01$) (fig 3, tables 2 and 3). The maximal fibre lengthening rate showed a relative decrease of $25 (13.1)^{\circ}_{\circ}$ from the baseline value ($p < 0.001$) (fig 3, tables 2 and 3).

END DIASTOLIC DIMENSION

The end diastolic left ventricular dimension showed no significant change when the afterload was increased (average increase $0.14 (0.22)$ cm; NS) (table 2).

Fig 3 Individual data points for the variables of early diastolic function for baseline conditions and during increased afterload. The change of dimension between minimal cavity dimension and mitral valve opening ($dDS-MO$) tended to decrease to normal values with increasing afterload (a). The absolute change was $26 (16)^{\circ}_{\circ}$ ($p < 0.001$). The change of dimension with rapid diastolic filling (dRF) (b) decreased by $19 (16)^{\circ}_{\circ}$ (absolute change) ($p < 0.01$). The interval between minimal cavity dimension and mitral valve opening ($tDS-MO$) (c) panel decreased by $70 (28)$ ms ($p < 0.0001$) and the duration of rapid diastolic filling (tRF) (d) by $33 (25)$ ms ($p < 0.01$).

Increased afterload

HR (beats min)	P_e (mm Hg)	D_{ed} (cm)	D_{es} (cm)	FS ($^{\circ}_{\circ}$)	$tDS-MO$ (ms)	$dDS-MO$ ($^{\circ}_{\circ}$)	tRF (ms)	dRF ($^{\circ}_{\circ}$)	VLR_{max} (cm/s)
58	143	3.75	2.45	35	50	8	90	42	7.3
60	153	4.1	2.6	36	85	20	50	25	8.7
63	148	5.4	3.5	35	60	26	50	21	10.0
78	123	5.5	3.95	28	65	3	155	84	12.1
56	162	5.3	3.4	36	115	32	80	21	6.4
81	163	5.1	3.0	41	80	14	130	52	12.1
65	140	4.2	3.2	24	70	20	40	15	4.9
86	122	4.3	2.4	44	70	21	40	15	8.2
72	132	3.7	1.9	49	60	6	120	62	9.3
68	120	3.2	2.1	34	60	9	60	73	7.8

Table 3 Intraindividual changes during increased afterload in hypertrophic non-obstructive cardiomyopathy

Case	P_n (mm Hg)	FS (%)	VLR_{max} (cm/s)	$tDS-MO$ (ms)	$dDS-MO$ (%)	tRF (ms)	dRF (%)
1	32	-12	-16	-100	-12	15	16
2	33	-12	-13	-40	-29	30	5
3	35	-18	-24	-90	-29	10	8
4	50	-19	-9	-95	-40	75	54
5	46	-12	-42	-35	-39	35	13
6	46	-14	-7	-25	-7	10	9
7	24	-5	-30	-85	-20	30	7
8	23	-16	-41	-70	-17	0	11
9	26	-13	-12	-95	-58	60	30
10	47	-11	-31	-60	-11	60	33
Mean	36	-13	-25	-70	-26	33	19
SD	10.3	4.0	13.1	27.9	16.0	25.2	15.7
p	< 0.0001	< 0.0001	< 0.001	< 0.0001	< 0.001	< 0.01	< 0.01

All changes are given as absolute values except the change of the maximal fibre lengthening rate (VLR_{max}) which is given as percentage change of the baseline value.

See table 2 for abbreviations.

CHANGES OF TIME INTERVALS IN EARLY DIASTOLE

The mean interval between minimal dimension and mitral valve opening was 141 (17) ms at baseline conditions and the duration of rapid diastolic filling was 66 (33.5) ms (table 2). At maximum pressure the time between minimal dimension and mitral valve opening decreased by 70 (28) ms ($p < 0.0001$) (fig 3, tables 2 and 3), and the time of rapid diastolic filling by 33 (25) ms ($p < 0.01$) (fig 3, tables 2 and 3).

Discussion

In severe hypertrophy the afterload has to be analysed in terms of wall stress.^{18,19} But in hypertrophic cardiomyopathy calculation of wall stress is difficult.²⁰ The myocardial fibre disarray, asymmetric hypertrophy, and irregular shape of the left ventricle (in particular at end systole) may lead to major errors if the current formulae for calculation of circumferential or meridional wall stress are used. This is because in all models for calculation of wall stress the shape of the left ventricle is assumed to be ellipsoid, a sphere, or a cylinder.²¹⁻²³ These simplifications do not reflect the altered shape of the left ventricle in hypertrophic cardiomyopathy, particularly at end systole, when deformation is greatest. Because of these difficulties we did not attempt to measure wall stress. Instead we measured the increase in end systolic pressure as an index of individual increases in afterload.²⁴ The pressure at end ejection rather than at end systole is used for the non-invasive assessment of pressure at end systole.^{12,14,25} Because both can differ considerably when there is mitral regurgitation,²⁶ and because the non-invasive measurement of the end systolic left ventricular pressure depends on the absence of an outflow tract obstruction, we studied only patients with hypertrophic non-obstructive cardiomyopathy without mitral

regurgitation. Also it has been shown that use of angiotensin II to increase the afterload abolishes both outflow tract obstruction and mitral regurgitation in hypertrophic cardiomyopathy,²⁷ thus it seems unlikely that outflow tract obstruction or mitral regurgitation developed during the increase in afterload.

In most patients with hypertrophic cardiomyopathy diastolic function is significantly impaired.¹⁻³ Early diastolic dysfunction has been extensively evaluated by digitised echocardiography.²³ Our data confirm these findings, because in our patients we found that the time between minimal cavity dimension and mitral valve opening was prolonged at baseline conditions (figs 1 and 2), indicating delayed mitral valve opening.^{2,3,16} The change of dimension between minimal dimension and mitral valve opening was increased, indicating incoordinate relaxation.^{2,16,17} Peak filling rate, time of rapid diastolic filling, and the contribution of rapid diastolic filling to total diastolic filling were reduced at baseline conditions in our patients (figs 1-3, table 2). This impairment of early diastolic function is probably caused by prolonged or incomplete relaxation and the reduced distensibility of the hypertrophied left ventricle.

Recently, Brutsaert *et al*^{7,8} showed that relaxation was significantly dependent on afterload. Based on this concept of "triple control of relaxation"⁸ impaired early diastolic function in hypertrophic cardiomyopathy could be partly the result of altered systolic and diastolic loading conditions. Various loading conditions, such as end systolic wall stress, wall stress after mitral valve opening, and coronary filling during isovolumic relaxation, may be altered in hypertrophic cardiomyopathy.⁸ To evaluate the load dependence of early diastolic function in hypertrophic cardiomyopathy we measured the effects of increasing afterload on early diastolic function.

We found that the indices of early diastolic function tended to become more normal when afterload was increased in patients with hypertrophic non-obstructive cardiomyopathy (tables 2 and 3, figs 1 and 3)—the time interval between minimal cavity dimension and mitral valve opening shortened, the change of dimension during this period decreased, and the time of rapid diastolic filling and the change of dimension during rapid filling increased. This improvement of early diastolic function may result in part from an increase in filling pressures during the infusion of angiotensin II. In controls we found that end diastolic dimension, and hence end diastolic fibre stretch, did not increase when afterload was increased by the infusion of angiotensin II.²⁸ This result contrasts with other agents (such as methoxamine) that are used to produce diagnostic increases in afterload.¹²⁻¹⁴

Despite improved early diastolic function the end diastolic dimension and thus overall diastolic filling did not increase with increasing afterload in patients with hypertrophic cardiomyopathy. Although the underlying mechanism(s) cannot be assessed precisely by non-invasive techniques, this effect might to some extent be the result of reduced elastic recoil, since systolic emptying deteriorated significantly with increasing afterload (figs 1 and 2).

We conclude that impaired early diastolic function in hypertrophic cardiomyopathy is at least to some extent the result of reduced afterload and that an increase in afterload does not result in normal diastolic function.

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