

Effect of hypertrophy on left ventricular diastolic function in patients with hypertrophic cardiomyopathy

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ABSTRACT: Background. Hypertrophic cardiomyopathy (HCM) is characterized by asymmetric LV hypertrophy (LVH) and impairment in diastolic function. We assess the relationship between LVH and invasive indexes of diastolic function.

Methods. 21 HCM patients underwent cardiac catheterization to assess pulmonary capillary wedge pressure, LV end-diastolic pressure (measured by microtip catheters), and LV volumes (calculated by simultaneous radionuclide angiography). We calculated from LV pressure the time constant of isovolumetric relaxation (τ , variable asymptote method, ms), and from LV pressure and volume the constant of chamber stiffness (k , ml^{-1}). LVH was assessed by different indexes: maximal wall thickness, number of hypertrophied LV segments, LVH index, and Wigle's score.

Results. Wigle's score was directly related to pulmonary capillary Wedge pressure ($r=0.436$, $p=0.048$), peak V wave of pulmonary capillary wedge pressure ($r=0.503$, $p=0.024$), LV end-diastolic pressure ($r=0.643$, $p=0.002$) and k ($r=0.564$, $p=0.015$). HCM patients were divided into 2 groups according to Wigle's score: 10 with mild or moderate LVH (< 8), and 11 with severe LVH (≥ 8). HCM patients with severe LVH showed a higher pulmonary capillary Wedge pressure (15.1 ± 7.2 vs 9.5 ± 2.4 , $p=0.033$), peak V wave of pulmonary capillary wedge pressure (20.7 ± 4.6 vs 14.6 ± 4.9 , $p=0.011$), LV end-diastolic pressure (23.9 ± 10.9 vs 10.6 ± 2.5 , $p=0.002$), k (0.0465 ± 0.032 vs 0.015 ± 0.007 , $p=0.022$) and LV outflow tract gradient (72 ± 36 mmHg vs 29 ± 30 mmHg, $p=0.01$). τ was similar in the two groups. Other indexes of LVH were not related to diastolic function.

Conclusions. Wigle's score is the only index of LVH that relates to invasive indices of diastolic function. (Heart International 2006; 2: 106-14)

KEY WORDS: Cardiomyopathy, Diastole, Hypertrophy

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease, characterized by left ventricular hypertrophy (LVH), normal or supernormal systolic function and impaired diastolic function, including chamber stiffness and impaired relaxation (1, 2).

Active relaxation is an energy-consuming process, and its impairment in HCM may be related to abnormal calcium kinetics (3), subendocardial ischemia (4), non-uniform temporal and regional distribution of load and inactivation (5).

An increase in chamber stiffness reflects abnormalities in the intrinsic elastic properties of the myocardi-

um. One possible cause is increased interstitial fibrosis, often associated with the high degree of hypertrophy and myocyte disorganization (6). This increase in chamber stiffness results in an increased diastolic pressure with respect to volume, hence, the diastolic pressure volume curve is shifted upward and/or to the left (7).

Although hypertrophy is the synonym of HCM, the relationship between LVH and impaired diastolic function has not been clearly demonstrated in patients with HCM. This is mostly due to the inherent difficulty in measuring LVH in HCM: the classical echocardiographic formula for mass measurement (8) implies an ellipsoidal LV cavity with constant wall thicknesses which does not hold true HCM.

Spirito et al (9) reported that impaired LV relaxation, determined by means of Doppler mitral inflow velocities, is not related to the magnitude of LV hypertrophy, assessed as a sum of maximal wall thickness in four ventricular segments. However, in a previous study (10), using M-mode echocardiography techniques, the same authors found a relation between the extent of LVH and impaired relaxation. Moreover, Wigle and co-workers (11) demonstrated a direct relationship between LV end-diastolic pressure and the extent of LVH, and our group showed that diastolic filling varies in different regions of the LV and is influenced by regional septal thickness (12).

The aim of our study was to assess if a relationship exists between magnitude and distribution of LVH and invasive indexes of LV diastolic function in HCM.

METHODS

Patient population. Twenty one consecutive patients with HCM, aged 37 ± 14 years (12 males) from the cardiomyopathy outpatient clinic at Federico II University School of Medicine were enrolled. The diagnosis of HCM was based on the echocardiographic evidence of hypertrophic, nondilated left ventricles without apparent cause, such as systemic hypertension, aortic stenosis etc. (13). All patients were in normal sinus rhythm, and had no atrioventricular conduction abnormalities or left or right bundle branch block. All cardioactive medications were withdrawn for at least five half-lives before the study.

Echocardiography. Each patient underwent standard

M-mode, 2-dimensional and color Doppler echocardiography. Echocardiograms were performed using a Hewlett-Packard ultrasonic scanner (Sonos 1000, Hannover, MA) equipped with 2.5 MHz and 1.9 MHz transducers. M-mode echocardiograms were obtained from the 2-dimensional images under direct anatomic visualization. Left atrial, LV end-diastolic and end-systolic diameters were measured according to the guidelines of the American Society of Echocardiography (14). LV hypertrophy was evaluated by different indexes:

- a) a point score system, the Wigle's score, which takes into account the thickness of the ventricular septum, the presence of septal hypertrophy at papillary or apical levels, and the presence of anterolateral wall extension of hypertrophy; the score is the sum of these factors, spanning from 0 to 10 (Fig. 1) (11).
- b) Sum of the maximal wall thickness measured in the short axis view at either mitral valve or papillary muscle level in each of the 4 ventricular segments (anterior and posterior septum, posterior and lateral walls) (hypertrophy index) (9)
- c) number of hypertrophied LV segments (10)
- d) maximal wall thickness (15).

Color Doppler flow imaging was used for identifying and semiquantitatively estimating mitral regurgitation (16). Peak LV outflow tract gradient was recorded, both at rest and during provocation by amyl nitrite inhalation, by a 1.9 MHz non-imaging transducer, using the simplified Bernoulli equation ($P=4V^2$, where P is pressure and V is flow velocity). Care was taken to distinguish ejection velocity from the mitral regurgitation jet (17).

Cardiac catheterization and hemodynamic measurement. All patients underwent cardiac catheterization for diagnostic purposes (exercise-induced chest pain or assessment of LV outflow tract gradient). A 7Fr Swan-Ganz thermodilution catheter (Edwards Laboratories Inc., Santa Ana, California) was introduced into the pulmonary artery to measure pulmonary artery and wedge pressures, and cardiac output (average of 3 determinations).

A 7Fr pigtail high-fidelity transducer-tipped catheter (Sentron v.g.f., Roden, The Netherlands) was introduced through a 9Fr arterial sheath into the left ventricle. Systemic arterial pressure was monitored through the side port of the 9Fr arterial sheath: this size, 2Fr bigger than that of the catheter, was selected to allow reliable recording of the arterial pressure. The LV outflow

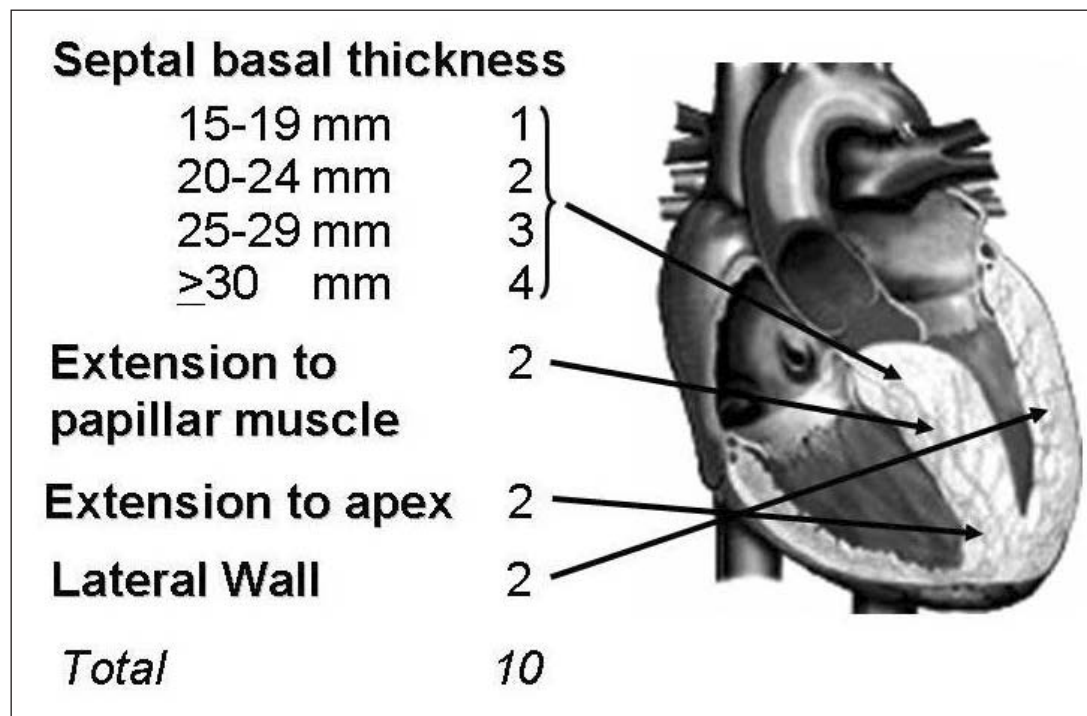


Fig. 1 - Scheme to assess the Wigle's score, a point score system which takes into account the thickness of the ventricular septum (1= between 15 and 19 mm, 2= between 20 and 24 mm, 3= between 25 and 29 mm, and 4= \geq 30 mm), the presence of septal hypertrophy at papillary (scored as 2) and/or apical (scored as 2) levels, and the presence of anterolateral wall extension of the hypertrophy (scored as 2). The total score is the sum of these individual factors and spans from 0 to 10.

tract gradient was defined as peak-to-peak difference between the LV and arterial pressures (18, 19). It was measured at rest in all patients and during amyl nitrite inhalation in those with resting gradients <30 mmHg.

LV pressure and its first derivative (dP/dt) were recorded at a paper speed of $250 \text{ mm} \cdot \text{s}^{-1}$, and sent to the gamma camera-computer system to build pressure-volume curves.

High-speed LV pressure was digitized at high temporal resolution ($\leq 4 \text{ ms}$) for calculation of the time-constant of isovolumetric relaxation τ using the shifting asymptote technique (20). Digitization started from minimal dP/dt and ended when LV pressure was 5 mmHg above the following end-diastolic pressure. From the equation $P = P_a + P_0 e^{-t/\tau}$ (where P is pressure, τ is time, P_a is the pressure asymptote, and P_0 is LV pressure at the beginning of isovolumetric relaxation), the time-constant of isovolumetric relaxation τ was calculated, as $\tau = -1/\alpha$ by nonlinear curve fitting (SPSS for Windows, version 10.0).

Left ventriculography was performed in the 30° right anterior oblique position. The end-diastolic volume was measured (21) on the first well-opacified sinus beat not following an ectopic beat by a graphic tablet interface

with a computer; the volume was used to convert the radionuclide angiographic counts into milliliters, as described below. To minimize the differences in body size between patients, cardiac output, systemic vascular resistances, and LV volumes were normalized to the patient's body surface area. For diagnostic purposes, coronary arteriography in multiple views was performed in patients aged ≥ 40 years.

Radionuclide angiography. Equilibrium radionuclide angiography was done with patients lying on the cardiac catheterization cradle in the supine position by a small field-of-view gamma camera (LEM ZLC Siemens Gammasonics, Des Plaines, Illinois) in a 45° left anterior oblique view with a 15° caudal tilt. Red blood cells were labeled *in vivo* with 740 to 945 MBq of Technetium^{99m}. Electrocardiographic-gated images were acquired with a 2X digital zoom, at $50 \text{ frames} \cdot \text{s}^{-1}$. At least 150,000 counts/frame were collected in the baseline study. Time-activity curves represent the average of many cardiac cycles (as many as needed to acquire a sufficient counts statistic); they were corrected for isotope decay at baseline and expressed in milliliters by normalizing their end-diastolic counts to end-diastolic volume measured by contrast angiography.

Ejection fraction was calculated on unfiltered time-activity curve. Peak filling rate was calculated after filtering by a Fourier expansion with 5 harmonics. It was measured in $\text{ml} \cdot \text{s}^{-1}$ and further normalized by end-diastolic and stroke volumes.

Left ventricular pressure-volume analysis. LV pressure was sent to a custom-designed interface (Medie s.r.l., Milan, Italy) connected to the gamma camera-computer system, as previously described (18, 19); this device writes pressure data into the counts matrix: in this way, the obtained pressure points correspond to the volume points. By plotting pressure as a function of volume we built pressure-volume curves. The LV constant of chamber stiffness (k) was measured by using the elastic model with shifting asymptote method (20). Calculation was made from minimum pressure to end-diastole, by the formula $P = B + Ae^{kV}$, where P is pressure, V is volume, A and k are fitting constants, and B the pressure asymptote. Fitting was achieved by a computer program that allows nonlinear fitting (SPSS for Windows, version 10.0).

Statistics. Data was expressed as mean \pm 1 standard deviation. Univariate and multivariable logistic regression analyses were performed. Unpaired Student's t -test was done to determine differences for continuous variables between the 2 HCM groups: mild or moderate LVH (Wigle's score < 8) and severe LVH (Wigle's score ≥ 8). When appropriate, chi-square test with Yate's correction for continuity was used to analyze categorical variables. A probability value of < 0.05 was considered statistically significant. All statistical calculations were performed by SPSS for Windows, release 10.0 (Chicago, Illinois).

RESULTS

Patient characteristics. The clinical, echocardiographic and invasive baseline characteristics of the 21 HCM patients are shown in Table I. Atrial enlargement was evident in 11 patients (52%). Mitral regurgitation was found in 11 patients, and was semiquantitatively ranked mild in 8 patients, moderate in 1 patient, and severe in 2 patients. By both catheterization and Doppler echocardiography, 14 patients (67%) showed a significant LV outflow tract gradient at rest (≥ 30 mmHg), whereas 3 of the remaining 7 patients developed a sig-

nificant (≥ 50 mmHg) gradient during provocation by amyl nitrate inhalation. Patients who underwent coronary angiography had normal coronary arteries.

LV hypertrophy and diastolic function

Wigle's score was directly related to pulmonary capillary Wedge pressure ($r=0.436$, $p=0.048$, Fig. 2-A), peak V wave of pulmonary capillary wedge pressure ($r=0.503$, $p=0.024$), LV end-diastolic pressure ($r=0.643$, $p=0.002$, Fig. 3-A) and k ($r=0.564$, $p=0.015$ Fig. 4-A). LV end-diastolic volume was inversely related to Wigle's score ($r=-0.503$, $p=0.024$).

The HCM patients were also divided into 2 groups according to Wigle's score: 10 HCM patients with mild or moderate LVH (< 8), and 11 HCM patients with severe LVH (≥ 8). The clinical, echocardiographic and invasive baseline characteristics of the 2 HCM patients groups are shown in Table II. HCM patients with severe LVH, compared to patients with mild or moderate LVH, showed a higher pulmonary capillary Wedge pressure ($p=0.033$, Fig. 2-B), higher peak V wave of pulmonary artery wedge pressure (21 ± 5 vs 14 ± 5 , $p=0.011$), higher LV end-diastolic pressure ($p=0.002$, Fig. 3-B), and higher constant of chamber stiffness (k , $p=0.022$, Fig. 4-B).

TABLE I - THE CLINICAL, ECHOCARDIOGRAPHIC AND INVASIVE BASELINE CHARACTERISTICS OF THE HCM PATIENTS

Age (years)	37 \pm 14
Males (%)	11 (52)
Heart rate (beats/min)	80 \pm 10
Maximal wall thickness (mm)	27 \pm 6
LV outflow tract gradient (mmHg)	52 \pm 40
Cardiac index ($\text{Lmin}^{-1}/\text{m}^2$)	3.1 \pm 0.9
Pulmonary capillary wedge pressure (mmHg)	12 \pm 6
Peak V wave of pulmonary artery wedge pressure (mmHg)	18 \pm 6
LV pressure (mmHg)	
Systolic	167 \pm 41
End-diastolic	18 \pm 10
LV volumes (ml/m^2)	
End-diastolic	79 \pm 28
End-systolic	15 \pm 14
Ejection fraction (%)	83 \pm 12

LV: left ventricular

TABLE II - THE CLINICAL, ECHOCARDIOGRAPHIC AND INVASIVE BASELINE CHARACTERISTICS OF THE HCM PATIENTS WITH WIGLE'S SCORE <8 AND ≥8

	Wigle's score <8	Wigle's score ≥8	p
Number	10	11	
Age (years)	36±13	39±14	N.S.
Males (%)	5 (50)	6 (54)	N.S.
Heart rate (beats/min)	79±11	82±8	N.S.
Maximal wall thickness (mm)	25±6	28±7	N.S.
Maximal wall thickness ≥30 mm	3 (30%)	4 (36%)	N.S.
LV outflow tract gradient (mmHg)	29±30	72±30	0.01
Significant LV outflow tract gradient	6 (60%)	10 (91%)	N.S.
Cardiac index (Lmin-1/m ²)	3.2±1.1	3.1±0.8	N.S.
Pulmonary capillary wedge pressure (mmHg)	9±2	15±7	0.033
Peak V wave of pulmonary artery wedge pressure (mmHg)	14±5	21±5	0.011
LV pressure (mmHg)			
Systolic	149±38	183±39	0.05
End-diastolic	11±2	24±11	0.002
LV volumes (ml/m ²)			
End-diastolic	89±33	67±15	0.077
End-systolic	19±16	10±7	N.S.
Ejection fraction (%)	81±14	85±10	N.S.

LV: left ventricular

HCM patients with severe LVH showed higher degree of LV outflow tract gradient (72±36 mmHg vs 29±30 mmHg, p=0.01). Time-constant of isovolumetric relaxation τ was not different in the two groups.

There was no relationship determined between the other indexes of LV hypertrophy and diastolic function assessed.

In multiple regression analysis, Wigle's score was the only index of LV hypertrophy predictor of higher pulmonary capillary Wedge pressure (F=4.455, p=0.048), higher LV end-diastolic pressure (F=13.347, p=0.002) and higher constant of chamber stiffness (F=7.465, p=0.015).

DISCUSSION

In this paper, we demonstrated that the magnitude and distribution of LV hypertrophy, assessed by Wigle's score, were related to invasive indexes of passive diastolic dysfunction. In fact, we demonstrated that HCM patients with severe LV hypertrophy (Wigle's score ≥8) showed higher pulmonary capillary wedge pressure (Fig. 1), LV end-diastolic pressure (Fig. 2), and constant of chamber stiffness (Fig. 3).

LV hypertrophy, fibrosis and diastolic function

LV chamber stiffness is increased by virtue of the increase in muscle mass, decrease in ventricular volume, and increase in muscle stiffness, caused by myocardial fibrosis (6). The association of hypertrophy, disarray, and increased interstitial fibrosis leads to a stiffer LV wall: this implies that the diastolic pressure-volume relationship moves leftward and slightly upward as compared to the normal (7).

Diastolic dysfunction is primarily due to myocardial hypertrophy and fibrosis (22). Our group demonstrated a remodeling in the extracellular matrix composition in HCM: as collagen synthesis prevails over degradation, passive diastolic dysfunction occurs (23). Varnava et al showed that the magnitude of hypertrophy correlated with the severity of fibrosis and disarray (24). Furthermore, they found that interstitial fibrosis increased with age and was directly related to maximal wall thickness, while disarray was present at an early age and diminished with time. For this reason, these authors suggested that myocyte disarray is a direct response to functional or structural abnormalities of the mutated sarcomeric protein, while fibrosis and hypertrophy are later, secondary responses.

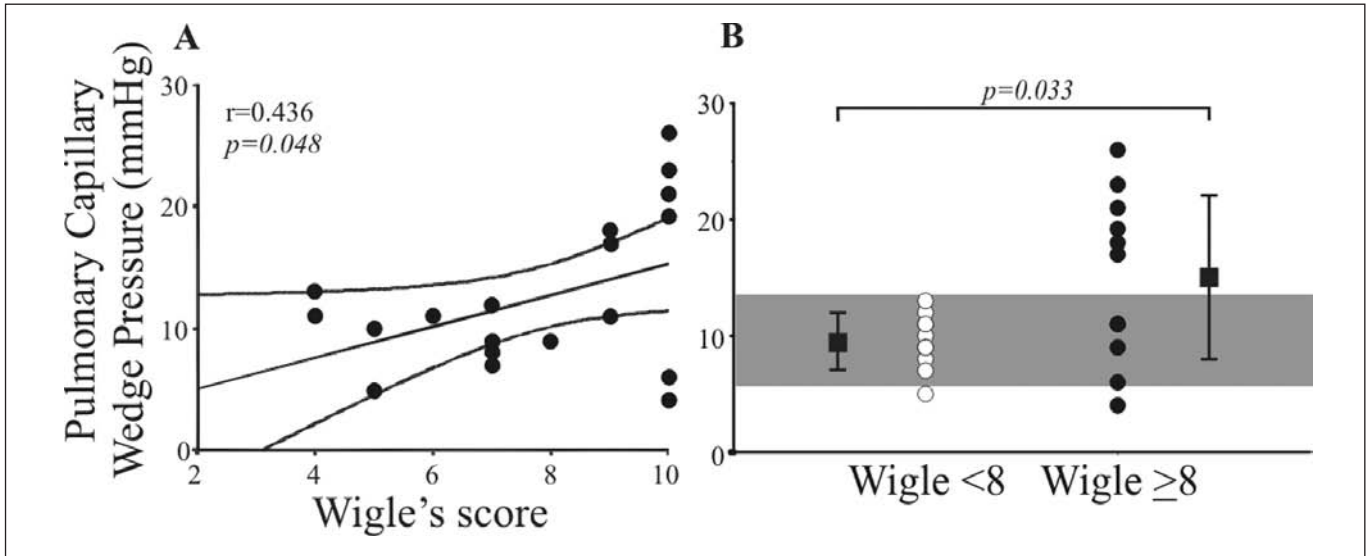


Fig. 2 - A) Pulmonary capillary wedge pressure plotted as a function of the Wigle's score. Curved lines show 95% confidence limits for the fitted line. **B)** Individual values of pulmonary capillary wedge pressure in patients with Wigle's score <8 (open circle) and ≥8 (closed circle). Closed squares with vertical bars represent mean value ± 1 SD. The grey box indicates the mean value ± 2 SD of the patients with Wigle's score <8.

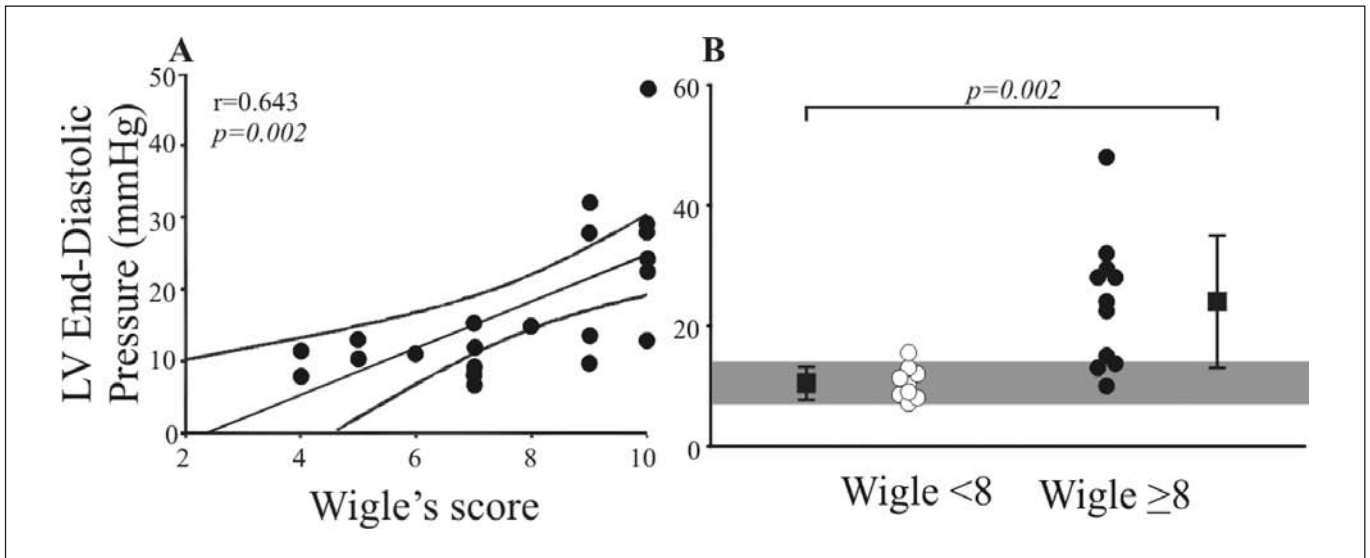


Fig. 3 - A) LV end-diastolic pressure plotted as a function of the Wigle's score. Curved lines show 95% confidence limits for the fitted line. **B)** Individual values of LV end-diastolic pressure in patients with Wigle's score <8 (open circle) and ≥8 (closed circle). Closed squares with vertical bars represent mean value ± 1 SD. The grey box indicates the mean value ± 2 SD of the patients with Wigle's score <8.

Spirito and Maron (9) reported that impaired LV relaxation is not necessarily related to magnitude of LV hypertrophy. They assessed LV relaxation by means of Doppler mitral inflow velocities, but if internal or exter-

nal restoring forces, or both, are excessive (11) or if left atrial pressure is markedly elevated in cases of extensive hypertrophy, indexes that reflect LV relaxation could fall within the normal range (pseudonormalization)

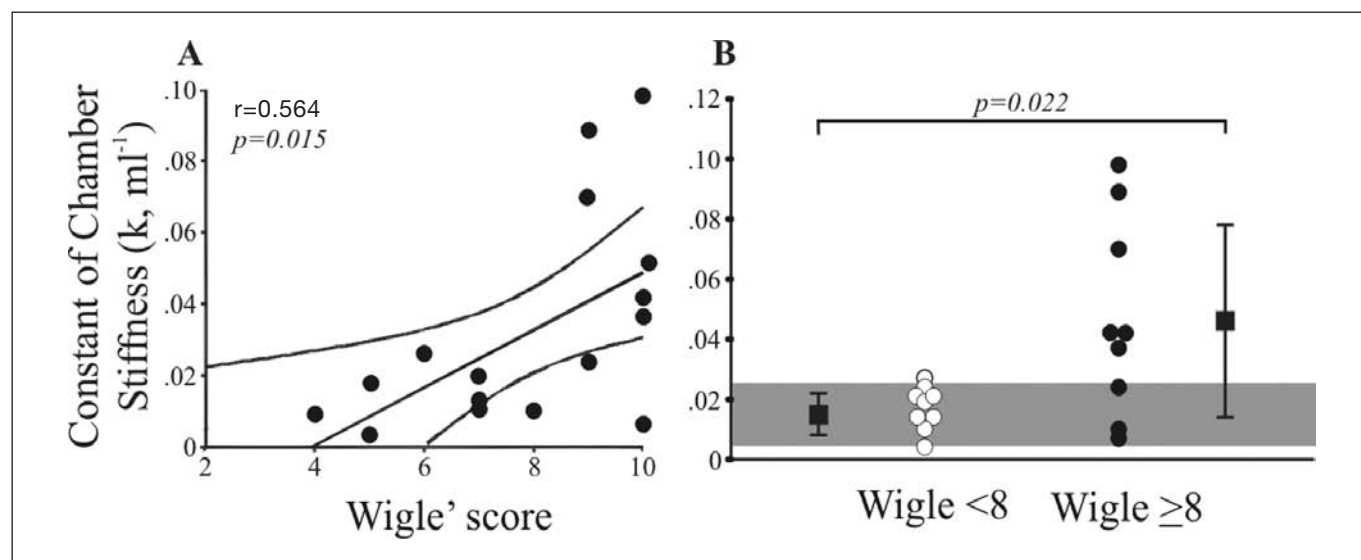


Fig. 4 - A) Constant of chamber stiffness (k) plotted as a function of the Wigle's score. Curved lines show 95% confidence limits for the fitted line. B) Individual values of LV constant of chamber stiffness (k) in patients with Wigle's score <8 (open circles) and ≥ 8 (closed circles). Closed squares with vertical bars represent mean value ± 1 SD. The grey box indicates the mean value ± 2 SD of the patients with Wigle's score <8.

(25). Besides, they did not explore Doppler pulmonary vein flow velocities that complement transmitral Doppler flow velocity in the assessment of increased chamber stiffness (26). Moreover, in a previous study (10), using M-mode echocardiography techniques, they found a relation between the extent of LVH and impaired relaxation.

Wigle's score and other indexes of LV hypertrophy

We evaluated LV hypertrophy by different indexes. Such indices try to overcome the heterogeneity of LVH in HCM by adding wall thickness in different regions (9), or consider only maximal wall thickness (15), or even count the number of hypertrophied segments (10). This approach is empirical and reflects the inadequacy of LV mass measurement in HCM. The traditional and validated formula by Devereaux and Reichek (8) cannot be used: in HCM, the catenoidal shape of the septum and of the heterogeneity in wall thickness imply that LV cavity is not an ellipsoid; hence, the conceptual assumption Devereaux and Reichek's formula is based on is not correct. In principle, the only way to assess LV mass in HCM should be magnetic resonance imaging; magnetic

resonance imaging is capable of identifying regions of LV hypertrophy not readily recognized by echocardiography (27). Wigle's score is not a measure of LV mass, however, it takes into consideration the distribution and the extent of LVH in a semiquantitative way. Wigle's score was related to invasive indexes of passive diastolic dysfunction, namely filling pressure (peak V wave of pulmonary artery wedge pressure), end-diastolic pressure, and the constant of chamber stiffness. The relationship of passive diastolic dysfunction to Wigle's score (and the lack thereof of other indices of LVH) does not imply itself that Wigle's score better describes LVH in HCM; this is also shown by the overlap in parameters of diastolic function in the 2 hypertrophy subgroups. It is to be noted, however, that patients with less hypertrophy (i.e. a Wigle's score < 8) are very likely to have normal diastolic function. In contrast, the subgroup of patients with higher degrees of hypertrophy include subjects with depressed or still normal diastolic function.

HCM patients with severe LVH showed higher degree of LV outflow tract gradient and a higher (albeit not significant) incidence of significant (≥ 30 mm Hg) obstruction, which may influence the difference in diastolic function in the 2 HCM patients group. However, we

analyzed the HCM patients according to the presence of LV outflow tract obstruction and we did not find any differences in the invasive indexes of diastolic function in HCM patients, with and without LV outflow tract obstruction.

In conclusion, Wigle's score is the only index of LVH that relates to invasive indices of diastolic function and it helps categorize patients with HCM in terms of diastolic dysfunction.

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