

Two-Dimensional Longitudinal Strain in Hypertrophic Cardiomyopathy with Preserved Ejection Fraction

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RESUMO

Introduction: The new technology of two-dimensional strain (st2D) allows a more accurate analysis of global and segmental function of the left ventricle (LV), including its apical portion as it is angle-independent. **Objective:** To assess global LV systolic function with st2D in patients (pts) with hypertrophic cardiomyopathy (HCM). **Methods:** We included 21 pts with HCM and preserved LV ejection fraction (G-HCM) and 21 pts without HCM comprising the control group (G-nl). The global endocardiological longitudinal st2D (st2D-L) of 18 LV segments were measured, by using the opticalflow technique, from 3 apical views. We used the Student's t-test for analysis of continuous variables and chi-square (Pearson) for non-continuous variables, considering a significance level of 0.05. **Results:** No difference was observed between the groups regarding age, sex, systolic and diastolic blood pressure, and heart rate. Sixteen pts of G-HCM presented with asymmetric septal form of hypertrophy, with or without additional involvement of adjacent walls (G-HCMs), and five presented with apical form of HCM (G-HCMap). Despite the LV ejection fraction was preserved in the 2 groups, st2D-L was globally reduced in G-HCM (14.6 ± 4.3 versus $18.6 \pm 2.6\%$ in G-C, $p = 0.009$). In G-HCMs it was noted significant lower values of st2D-L compared to G-nl (13.6 ± 3.9 versus $18.5 \pm 2.5\%$, $p < 0.0002$), with no significant difference between G-nl and G-HCMap. **Conclusion:** The st2D-L was significantly reduced in HCM compared to G-nl, indicating early change of LV systolic function in HCM despite a preserved ejection fraction.

Descriptors: Hypertrophic Cardiomyopathy, Left Ventricular Function; two-dimensional strain.

RESUMEN

Introducción: La nueva tecnología de *strain* bidimensional (st2d) permite un análisis más preciso de la función global y segmentar del ventrículo izquierdo (VI), incluyendo su porción apical, por ser ángulo-independiente. **Objetivo:** Evaluar la función sistólica global del VI con el st-2d en pacientes (pcs) con Cardiomiopatía Hipertrofica (CMH). **Métodos:** Fueron incluidos 21 pcs con CMH y fracción de eyección del VI preservada (G-CMH), y 21 pcs sin CMH, componiendo el grupo control (G-nl). Fue mensurado el st-2d longitudinal endocárdico global (st2D-L), por la técnica *opticalflow*, de los 18 segmentos del VI, a partir de 3 cortes apicales. Se empleó la prueba *t* de Student para análisis de variables continuas, y el *Qui-cuadrado* (Pearson) para variables no continuas, considerándose un nivel de significancia de 0,05. **Resultados:** No fue observada diferencia entre los grupos cuanto a la edad, sexo y presión arterial sistólica y diastólica, y frecuencia cardíaca. Dieciséis pcs del G-CMH presentaban la forma asimétrica septal de la hipertrofia, con involucramiento adicional o no de paredes adyacentes (G-CMHs), y cinco presentaban la forma apical de la CMH (G-CMHap). A pesar de la fracción de eyección del VI ser preservada en



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los 2 grupos, el st2D-L se mostró globalmente reducido en el G-CMH ($14,6 \pm 4,3$ vs $18,6 \pm 2,6\%$ en el G-C; $p=0,009$). En el G-CMHs, se notó valor significativamente menor de st2D-L con relación al G-nl ($13,6 \pm 3,9$ versus $18,5 \pm 2,5\%$; $p<0,0002$), no habiendo diferencia significativa entre el G-nl y el G-CMHap. **Conclusión:** El st2D-L se mostró significativamente reducido en la CMH con relación al G-nl, indicando alteración precoz de la función sistólica del VI en la CMH, a pesar de una fracción de eyección preservada.

Descriptores: Cardiomiopatía Hipertrófica; Función Ventricular Izquierda; Strain bidimensional.

INTRODUCTION

The Hypertrophic Cardiomyopathy (HCM) is one phenotypic manifestation of a process which includes inadequate myocyte hypertrophy associated with disarray of the same, and irregular fibrosis of the left ventricular (LV)^{1,2}. Some studies on HCM have demonstrated reduced left ventricular function analyzed by measuring the heart strain, despite a preserved ejection fraction (EF)³. Although both the longitudinal and transverse strain may be compromised in HCM, longitudinal functional parameters are the most significantly affected³⁻⁵, possibly because the circumferential shortening may be preserved in that pathology.

In the last decade and a half, the strain has been measured by magnetic resonance imaging (MRI), but such technology demands too much time for execution, besides its low temporal resolution, and allows analyzing only the systolic period of the cardiac cycle. With the advent of speckle tracking by echocardiography, it was possible to quantify the strain in a fast, simple, and accurate way, allowing the analysis of the entire cardiac cycle, making it more accessible and useful in practical application.

In this study, we evaluated the two-dimensional strain by speckle tracking in patients with HCM and preserved LV ejection fraction.

MATERIALS AND METHODS

This is an observational, prospective, consecutive study with patients diagnosed with HCM based on clinical history, physical examination, electrocardiogram, and echocardiogram. The diagnosis was made due to the presence of ventricular hypertrophy without cavity dilatation, and absence of conditions that could induce hypertrophy.

The asymmetric form of HCM was defined as the presence of septal thickness greater than 15 mm and a thickness ratio between the septum and the posterior wall greater than 1.3. The characterization of the apical form of HCM was based on the increased apical thickness with a thickness ratio between the apex and the posterior wall greater than 1.5.⁶

21 patients with HCM and preserved LV ejection fraction (L-HCM), and 21 patients in the control group (G-nl) were included. Five patients presented the predominant apical form

of HCM (G-HCMap) and the remaining 16 patients presented a predominant involvement of the interventricular septum (G-HCMs). The global endocardial longitudinal two-dimensional strain (st2D-L) was measured by opticalflow technique for the 18 LV segments, from 3 apical views (Figure 1). For better understanding, the absolute value of st2D-L was considered.

We used the Student's t-test for analysis of continuous variables and chi-square (Pearson) for non-continuous variables. The comparison between the means of the variables was performed by analysis of variance (ANOVA), and correlation between variables by linear regression analysis, considering a significance level of 0.05.

RESULTS

The groups were homogeneous with respect to age, gender, systolic and diastolic blood pressure, and heart rate (Table 1), with a higher frequency of patients with functional class II-III (NYHA) in G-HCM.

Echocardiographic data showed an ejection fraction and cavity diameters similar in both groups (Table 2), with significant differences with respect to thickness of the septum and LV posterior wall and left atrial diameter. Four patients presented with obstructive form, being subaortic in three patients (maximum gradient of 64.3 ± 8.3 mmHg) and mid-ventricular in one case (maximum gradient = 40 mmHg), which showed apical asynergy.

Analysis between groups

The global st2D-L was significantly reduced in the G-HCM compared to G-nl (14.6 ± 4.3 versus $18.6 \pm 2.6\%$, $p = 0.009$) (Figure 2A). In the regional analysis, we observed also a significant reduction of st2D-G in G-HCM compared to G-nl at the basal (15.7 ± 6.9 versus $18.9 \pm 5.0\%$, $p < 0.0001$), middle (14.3 ± 5.7 versus $18.8 \pm 4\%$, $p < 0.0001$) and apical regions (16.9 ± 6.7 versus $19.1 \pm 4.6\%$, $p = 0.003$) of the LV (Figure 2B).

Analysis between subgroups of HCM and G-nl

When analyzed the subgroups of HCM, those with the apical form (G-HCMap), showed no significant difference

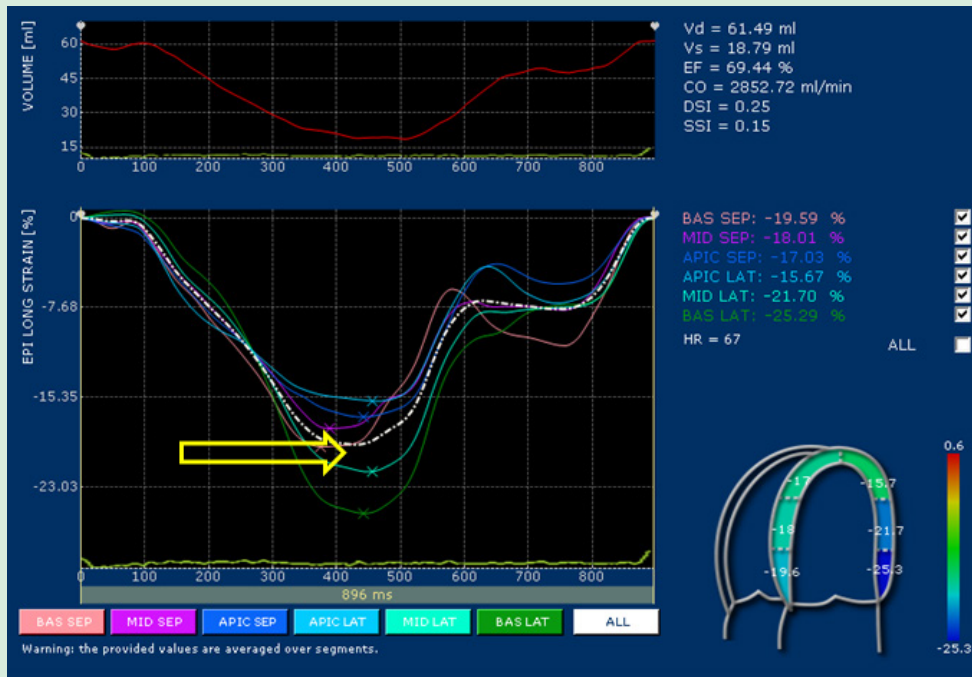


Figure 1: Processed image of two-dimensional strain showing strain curves derived from each segment in apical four-chamber view; the dashed white line shows the average global strain of this view, being highlighted the strain peak (arrow); the same procedure was repeated in apical two- and three-chamber view and derived the average of global strain of the three apical views.

Table 1: Clinical data and group background

	G-nl (n = 21)	G-HCM (n = 21)	P
Age (years)	45.3 + 19.4	54.1 + 16.61	ns
Gender M (%)	57.1	80.9	ns
HR (bpm)	66.4 + 7	62.7+6.1	0.07
SBP (mmHg)	130.5+19.3	132.5 + 15.2	ns
DBP (mmHg)	81.5 + 11.8	82.5+12.9	ns
FC I (%)	100	76.2	0.02
Pathologies			
AH (%)	28.5	66.7	0.01
DM (%)	0	28.5	0.008
Chagas (%)	0	0	ns
CAD (%)	0	23.8	0.02
Medicines			
Diuretics (%)	4.7		ns
B-Blockers (%)	0	76.2	<0.0001
ACE inhibitor (%)	28.5	42.8	Ns
Calc. Bloc. (%)	0	23.8	0.002

HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, FC: NYHA functional class; AH: Arterial hypertension, DM: diabetes mellitus, CAD: coronary artery disease, B-Blocker: Beta blocker, ACE inhibitors: angiotensin converting enzyme inhibitor; Calc. Bloc.: calcium channel blocker.



Table 2: Echocardiographic data of both groups

	G-C (n = 21)	G-HCM (n = 21)	P
DD (mm)	49,0 + 4	47,8 + 4,3	ns
SD (mm)	30,0 + 3,2	28,5 + 5,2	ns
EF (%)	68,7 + 4,2	68,6 + 5,3	ns
LA (mm)	36,9 + 4,9	46,2 + 4,0	<0,0001
IVS (mm)	8,6 + 0,9	16,2 + 6,2	<0,0001
PW (mm)	7,9 + 0,76	9,76 + 1,54	<0,0001

DD: diastolic diameter of the left ventricle, SD: systolic diameter of the left ventricular, EF: ejection fraction, LA: Left atrium; IVS: interventricular septum diastolic thickness; PW: posterior wall diastolic thickness.

of st2D-L compared to G-nl or to G-HCMs. However, the significant difference remained between G-nl and G-HCMs, with even smaller values of st2D in G-HCMs (13.6 ± 3.9 versus $18.5 \pm 2.5\%$; $p = 0.0002$) as shown in Figure 3A.

Regional analysis of subgroups of HCM and G-nl

The st2D-L of basal and middle regions of G-HCMs was significantly lower compared to the corresponding segments of G-nl (basal: 14.2 ± 6.6 versus $18.9 \pm 5.0\%$ - $p < 0, 0001$, middle: 12.9 ± 5.1 versus $18.9 \pm 4.1\%$ - $p < 0.0001$) and G-HCMap (basal: 14.2 ± 6.6 versus 20.6 ± 5.7 - $p < 0.0001$, middle: 12.9 ± 5.1 versus 18.5 ± 5.0 - $p < 0.0001$). However, the apical region showed a significant reduction of st2D-L only in G-HCMs compared to G-nl (16.6 ± 6.8 versus $19.1 \pm 4.6\%$, $p = 0.006$), as shown in Figure 3B.

Analysis between regions of each subgroup of HCM

Regarding the comparative analysis between the regions of the LV in each group individually, no difference was found between them in G-nl.

In G-HCM a significant difference of st2D-L was observed only between middle ($14.3 \pm 5.6\%$) and apical regions ($17.0 \pm 6.7\%$, $p < 0.003$), with no difference between the other regions of this group (Figure 2B).

In the analysis of G-HCMs, significant reduction of strain was observed in the middle region compared to apical region (12.9 ± 5.2 versus $16.6 \pm 6.8\%$, $p < 0.0003$), and in basal region compared to apical region (14.2 ± 6.6 versus $16.6 \pm 6.8\%$, $p < 0.03$), with no significant difference between the middle and basal regions (Figure 3B).

With respect to G-HCMap, there was slight significant reduction from basal to apical region (Figure 3B).

Analysis between the segments of each group

In the comparison between each segment of G-HCM and the corresponding segment of G-nl, the st2D-L was significantly lower in G-HCM in mid-basal regions of the anterior septal wall, inferior septum wall, and anterior wall, and in the middle region of the inferior and posterior walls of the LV (Figure 4), with no significant difference in this parameter between the remaining corresponding segments of the two groups. A significant correlation was observed between the thickness of the anterior basal septum and the st2D-L of that segment, by linear regression analysis, including patients from both groups ($r = 0.52$, $p < 0.0004$), as shown in Figure 5.

DISCUSSION

This study evaluated the role of recent technology of 2D strain in estimating the global and regional function of HCM. It was observed that global st2D-L was significantly lower in patients with HCM compared to G-nl, although in those with apical form of st2D-L no difference was observed compared to normal individuals. Additionally, st2D-L of some hypertrophic segments of G-HCM was significantly lower compared to the corresponding segments of G-nl.

In the literature, 2D strain has shown to be efficient and accurate in the evaluation of ventricular function and^{7,8}, in normal individuals, showed values similar to those obtained in G-nl of this study. Additionally, a lower interobserver variability is reported for this technique compared to tissue Doppler derived strain^{8,9}.

Comparison with other studies

Some previous studies have demonstrated reduction of longitudinal and circumferential strain by techniques derived from tissue Doppler and MRI¹⁰ and¹¹ in patients with HCM. Additionally,

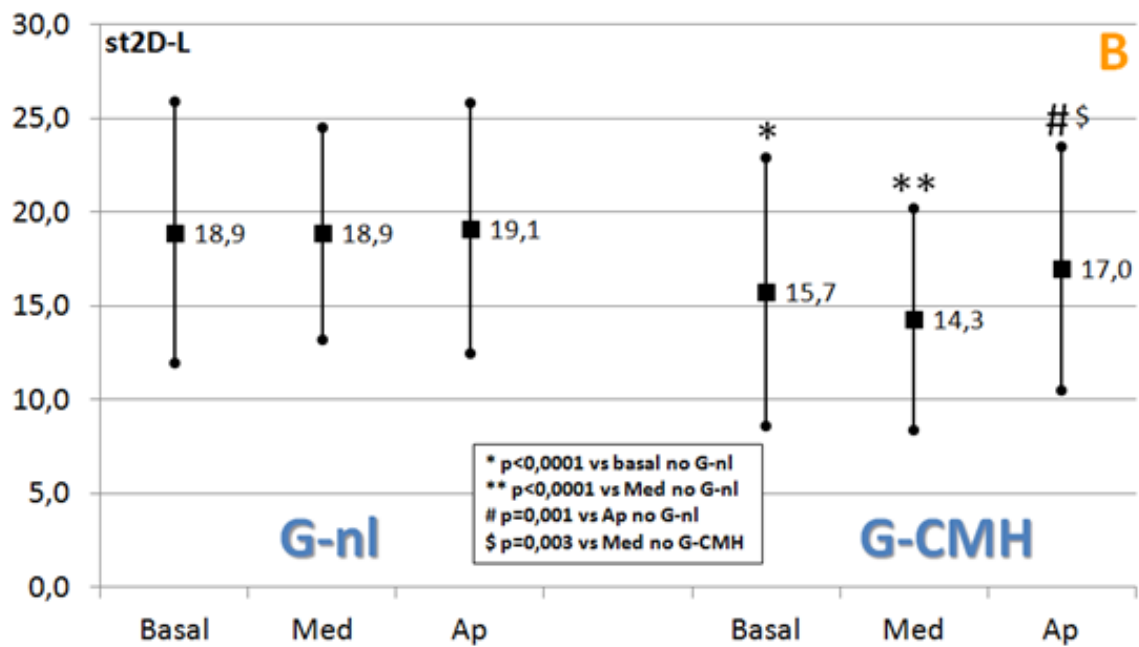
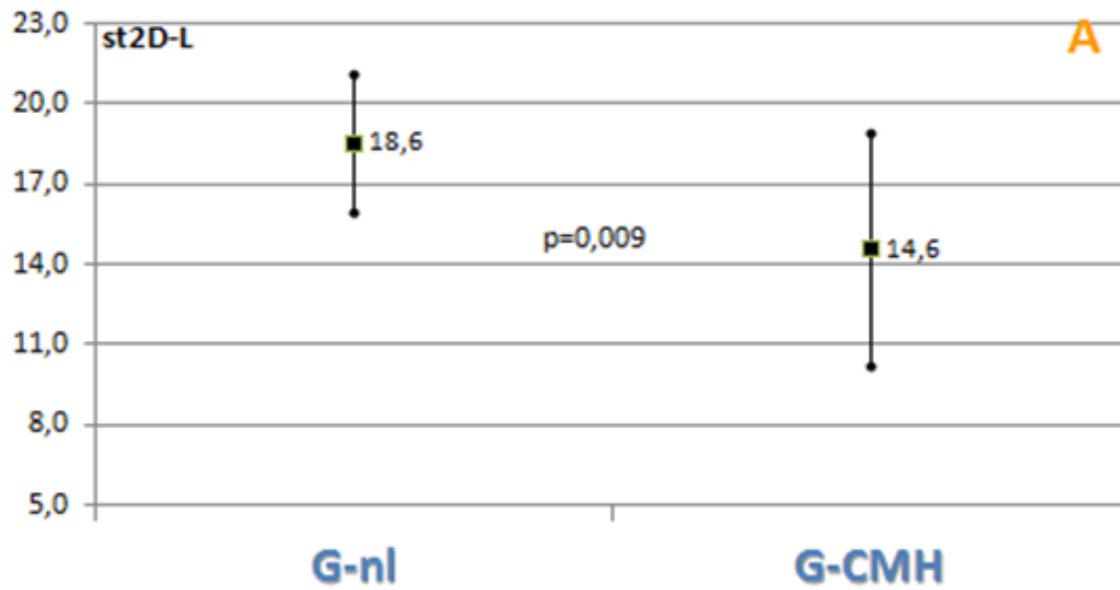


Figure 2: (A) Graph showing the mean and standard deviation of the longitudinal strain in each group, with significant difference between them; (B) Analysis between the corresponding regions of each group.

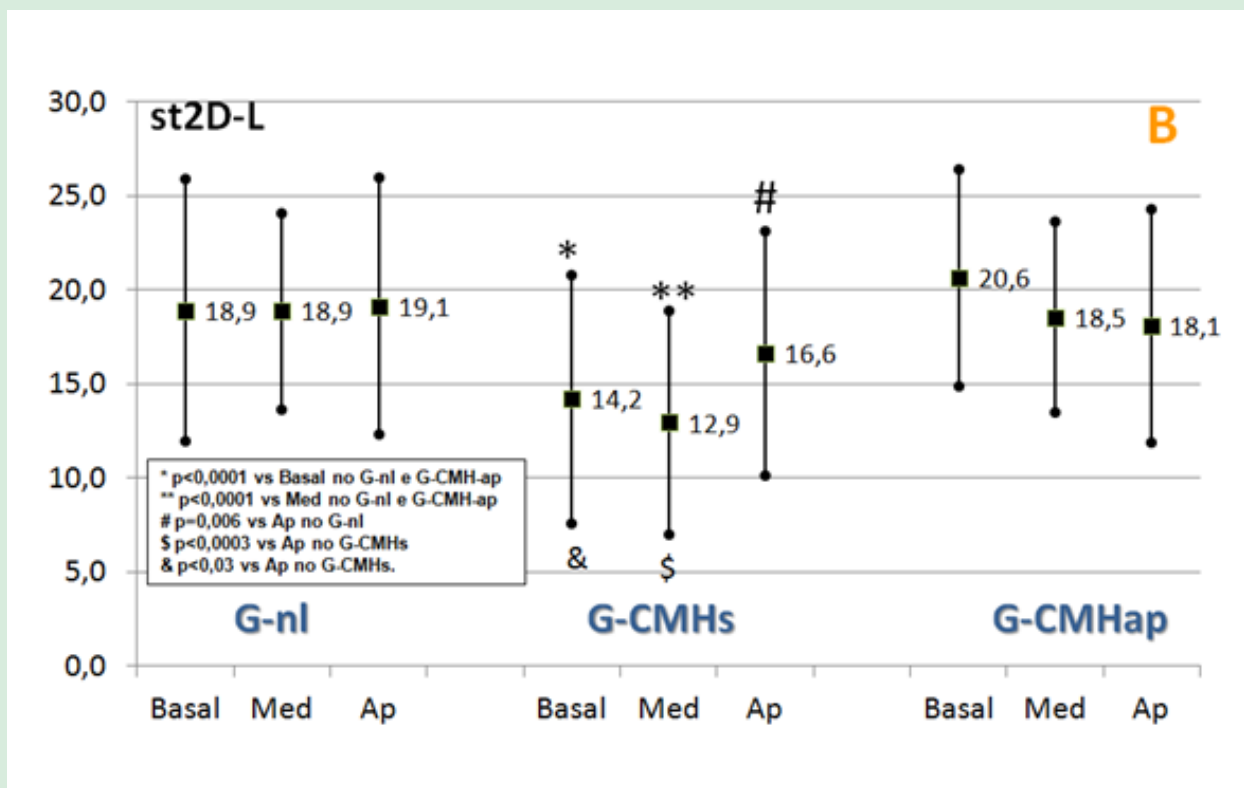
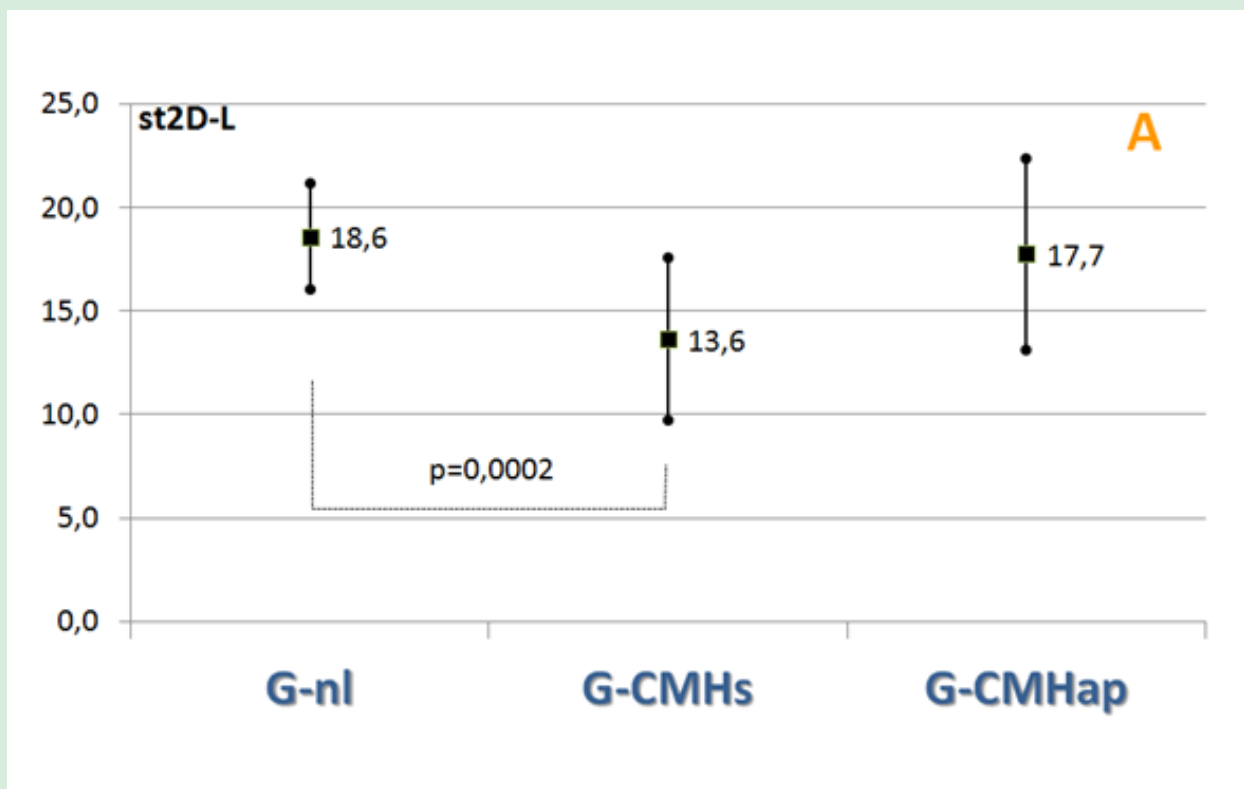


Figure 3: (A) Graph showing the mean and standard deviation of the longitudinal strain regarding the subgroups with apical form (G-HCM_{ap}) and asymmetric septal form (G-HCM_s), (B) Analysis between the corresponding regions of each subgroup.

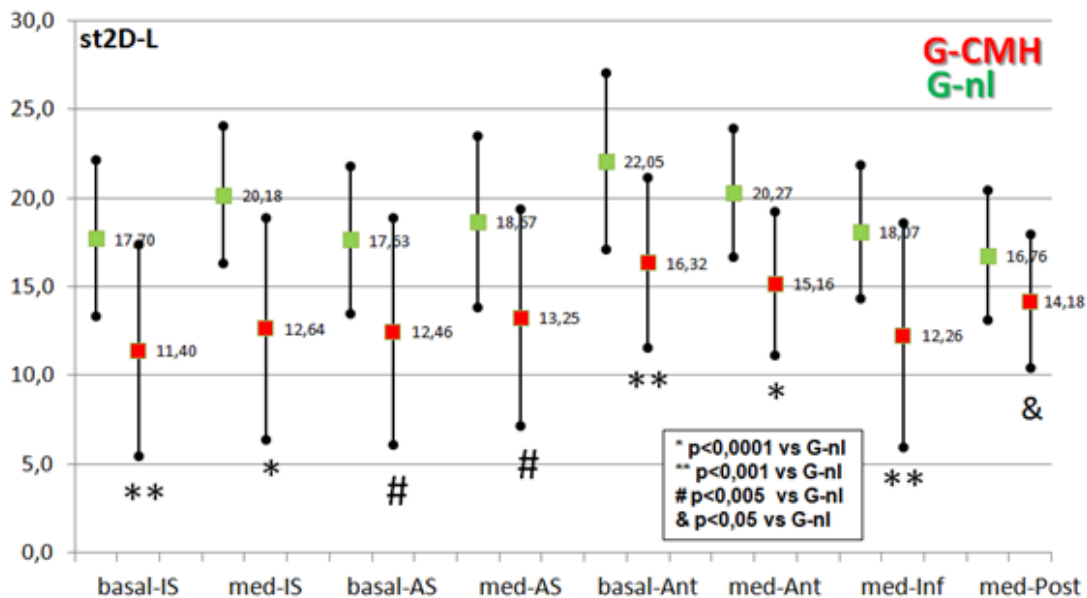


Figure 4: Graph comparing the mean and standard deviation of the longitudinal strain of the corresponding segments of each group, including only those significantly different from each other.

Mid: Middle region; AS: anterior septal wall, IS: inferior septal wall; Ant: Anterior wall; Inf: inferior wall; Post: Posterior wall.

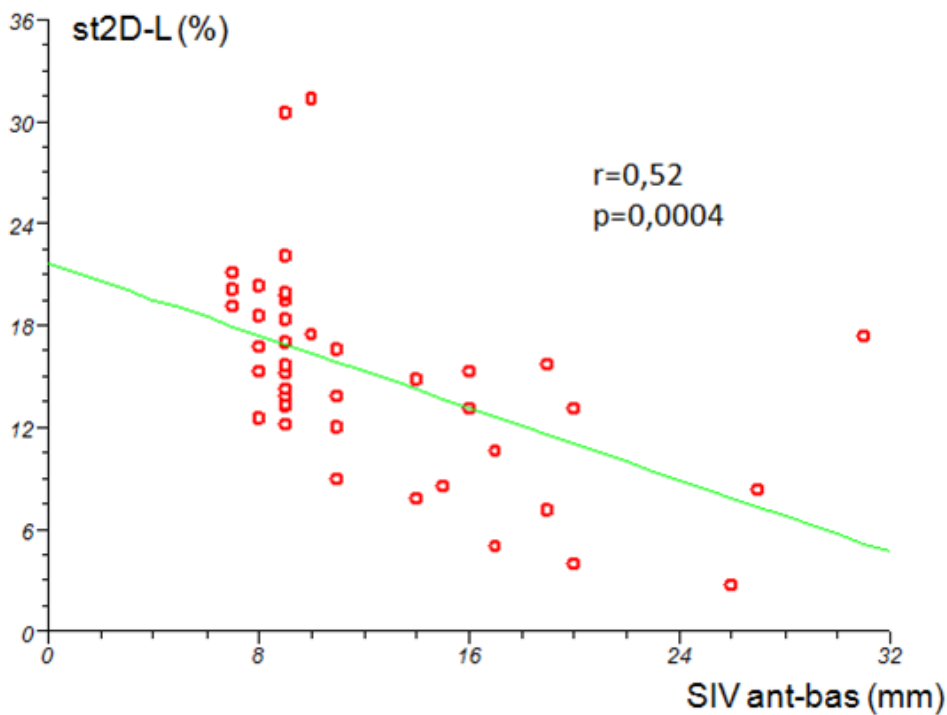


Figure 5: Graph showing the correlation between st2D-L of the basal anterior septal wall (IVS ant-bas) and the thickness (in mm) of the same segment.

other authors have reported reduced strain in hypertrophic and non-hypertrophic segments¹². By employing the speckle tracking technique derived from two-dimensional echocardiography, the literature also confirmed such findings, demonstrating reduced value of longitudinal strain compared to reference control groups^{9,13,14}. In the current study, this observation was confirmed by a significantly reduced longitudinal strain in HCM cases compared to control group (Figures 2A e6), indicating that this technique is more sensitive in identifying global myocardial dysfunction compared to standard methodology, reinforcing the diffuse nature of the HCM.

Additionally, studies employing speckle tracking demonstrated that in those patients with asymmetric form, the longitudinal septal strain was significantly lower compared to other segments not hypertrophic⁹, similarly to other reports using tissue Doppler imaging, in which septal strain was lower compared to control group¹⁵. In the same way, the present study also showed a significantly reduced value of st2D-L for some myocardial segments, with increased thickness compared to the corresponding segments in G-nl, except for apical region. The significant correlation between the anterior basal septum thickness and the st2D-L of this segment, observed in this study, demonstrates that reduced strain may be related to increased myocardial thickness.

Reports on the strain behavior in the apical form are inconsistent. Some studies including patients with the apical

form demonstrated reduction of longitudinal strain of LV apex compared to control group^{13,16}. Additionally, in a report of two cases with apical HCM, Reddy et al.¹⁷ found reversion of apical longitudinal strain (paradoxical systolic lengthening) in the absence of apical dyskinesia by conventional echocardiography. In contrast, in this study there was no significant difference of st2D-L in the apical region of the G-HCM compared to G-nl. Although the number of patients with the apical form is reduced in this study, hampering a conclusion regarding this data, a possible explanation for this disparity of results may be the technology used to obtain the strain. The block matching technique calculates the strain, covering a significant portion of the myocardial thickness, while the opticalflow mode used in this study analyzes the strain located in the subendocardial region. The arrangement of myocardial fibers varies along the myocardial thickness, with a more longitudinal direction in the subendocardial region and a more circumferential direction in mesocardial region¹⁸. Thus, a reduced longitudinal strain in the apical region, detected by block matching technique could reflect the behavior of the mesocardial contraction, while the opticalflow mode would reflect the behavior of subendocardial contraction, responding, in part, by the differences found. Additionally, the segmental hypertrophy degree and the intramyocardial fibrosis degree in different studies could affect differently the strain of this apical region.

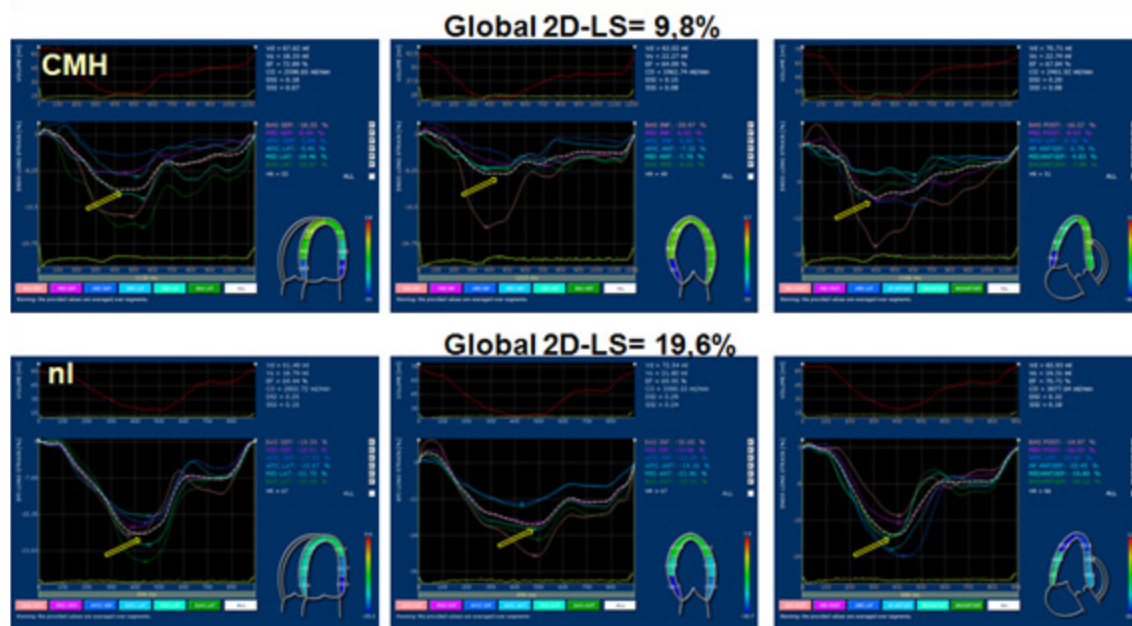


Figure 6: Processed image of longitudinal strain curves in 3 apical pathways, showing reduced value of st2D-L in G-HCM compared to G-nl.

Regarding the regional behavior of the longitudinal strain in basal, middle, and apical region of the LV, the literature also showed some slightly conflicting results. In normal subjects, an increased longitudinal strain from base to apex of the heart is reported^{19,20}, justifying this finding, possibly, the predominance of fibers longitudinally arranged in the apical region and predominantly circumferential fibers in the basal and middle regions²¹. However, other studies including normal subjects did not reproduce the same result²²⁻²⁴ as in the present work, showing no progressive increase of st2D-L from base to apex in G-nl.

In HCM, the behavior of the gradient from the base to the apex of LV may also vary, depending in part on the type of HCM. Some authors have shown an increasing st2D-L from base to apex in HCM^{9,13,25} while, in contrast, the apical HCM showed reduced st2D-L from base to apex¹³ and even reversal (systolic lengthening)¹⁷ in the apical region. In the current study, no progressive increase of st2D-L from base to apex in G-HCM was observed, demonstrating a significant reduction of st2D-L only in the middle region compared to the apical region. When groups were analyzed separately, we have found in the G-HCMs a significant reduction of st2D-L, only in middle region compared to the apical region, probably, in part, due to a more pronounced involvement of those regions by myocardial hypertrophy. With respect to G-HCMa patients, we observed a slight reduction of st2D-L from the base to apex, although not statistically significant, maybe due to the small number of patients. Additionally, in this subgroup, as previously mentioned, the arrangement of myocardial fibers and the technology used could explain this difference regarding findings from the literature.

CLINICAL IMPLICATIONS

Although some studies have reported reduced strain on hypertrophic walls^{9,15}, other authors reported reduced strain even on walls not affected by hypertrophy¹³, due to the participation of other structural changes present in HCM, such as intramyocardial fibrosis. The reduction of the longitudinal strain happened in HCM patients, regardless of myocardial hypertrophy degree¹³, and those with fibrosis showed even more reduced values.

The intramyocardial fibrosis degree appears to be related to a higher frequency of cardiac arrhythmias²⁶ with prognostic implications. Thus, patients with very low value of st2D-L could represent groups with the highest intramyocardial fibrosis degree, indicating poor prognosis and requiring rigorous follow-up. Correia et al. have found higher frequency of²⁷ ventricular arrhythmias in patients with reduced st2D-L, and the st2D-L lower than 10.5% in the middle septal region was an independent predictor of non-sustained ventricular arrhythmias in patients with HCM.

LIMITATIONS

One limitation of this study was the evaluation only of longitudinal strain by speckle tracking. The myocardial strain can also be measured in the circumferential, radial, and more recently, tangential direction, the last called shear strain^{28,29}. However obtaining the longitudinal strain, primarily via apical 4-chamber view was more feasible than other forms by speckle tracking²⁰. Additionally, the longitudinal strain was effective in discerning secondary hypertrophy to the other etiologies and was significantly different²⁵ in normal individuals, even in the presence of preserved ejection fraction^{9,13,14}, showing changes in contractility which was not revealed by conventional methods.

Another contrast was the small number of patients with the apical form of HCM in this study, hindering solid conclusions regarding the findings, but it may guide future studies.

As already mentioned, the methodology used to calculate the st2D-L was the opticalflow, which more accurately reflects the contraction of the subendocardial region, and may derive results differing from this variable in relation to block matching technique, although the literature shows a good correlation between both methodologies for longitudinal strain³⁰.

CONCLUSION

The st2D-L was significantly reduced in patients with hypertrophic cardiomyopathy compared to control group, indicating early change of left ventricular systolic function, despite of preserved ejection fraction.

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