

Right ventricular myocardial involvement in either physiological or pathological left ventricular hypertrophy: an ultrasound speckle-tracking two-dimensional strain analysis

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Aims

To analyse right ventricular (RV) myocardial deformation in patients with left ventricular (LV) hypertrophy secondary to either hypertrophic cardiomyopathy (HCM) or athlete's competitive endurance training.

Methods and results

Standard Doppler echo, exercise stress echo, and 2D speckle-tracking strain echocardiography (2DSE) of RV longitudinal deformation in RV septal and lateral walls were performed in 50 top-level endurance athletes and in 35 patients with HCM, all men, having evidence of LV hypertrophy. Right ventricular global longitudinal strain (GLS) was calculated by averaging local strains along the entire right ventricle. The two groups were comparable for age and blood pressure, whereas athletes showed lower heart rate and increased body surface area than HCM. Interventricular septal thickness was higher in HCM, whereas both LV and RV end-diastolic diameters (LVEDD and RVEDD) and LV stroke volume were increased in athletes. Right ventricular tricuspid annulus systolic excursion was comparable between the two groups. Conversely, RV GLS and regional peaks of RV myocardial strain were significantly impaired in patients with HCM (all $P < 0.001$). Multiple linear regression models detected an independent association between RV GLS and LVEDD (β -coefficient = -0.68 , $P < 0.0001$) in athletes, as well as an independent correlation of the same RV GLS with septal thickness ($\beta = 0.63$, $P < 0.0001$) in HCM. An RV GLS cut-off value of -0.16% differentiated athletes and HCM with an 86% sensitivity and a 92% specificity. Furthermore, in the overall population, RV GLS ($\beta = 0.51$, $P < 0.0001$) was a powerful independent predictor of maximal workload during exercise stress echo.

Conclusion

Right ventricular myocardial systolic deformation is positively influenced by preload increase in athletes and negatively associated with increased septal thickness in HCM. Therefore, 2DSE may represent a useful tool in the differential diagnosis between athlete's heart and HCM, underlining the different involvement of RV myocardial function in either physiological or pathological LV hypertrophy.

Keywords

Two-dimensional strain • Hypertrophic cardiomyopathy • Athlete's heart • Right ventricle • Diastole • Left ventricular hypertrophy

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Right ventricular (RV) chamber is often involved in left ventricular (LV) pathologies as a consequence of a direct injury extension, afterload changes, or ventricular inter-dependence which is mainly due to the close anatomic association between the two ventricles.^{1–3}

Hypertrophic cardiomyopathy (HCM) is a primary heart disease usually characterized by increased LV wall thickness and normal or decreased internal cavity dimension.^{3–6} It is reasonable that the right ventricle may participate to the disease because of an extension of myopathic process and/or because right and left ventricles share anatomically hypertrophied interventricular septum. Previous studies showed increased RV wall thickness and RV diastolic dysfunction in a large proportion of patients affected by HCM by using magnetic resonance imaging, two-dimensional (2D) echocardiography, and biplane RV angiography.^{7–11} However, few data are presently available about RV myocardial modifications in this pathology.^{12–15}

Haemodynamic overload due to long-term endurance training typically involves both left and right ventricles, inducing changes in cardiac structure globally described as ‘athletes heart’.^{16–20} Although standard Doppler echocardiography has been widely used to distinct athlete’s heart from pathological LV hypertrophy, few reports have described the RV myocardial adaptation to extensive physical exercise.^{21–23}

On this ground, the aim of the present study was to analyse the different involvement of RV myocardial function in LV hypertrophy secondary to either HCM or athlete’s competitive endurance training by the use of 2D speckle-tracking strain echocardiography (2DSE). This technique provides accurate information about segmental myocardial deformation during the cardiac cycle and offers the advantage, with respect to conventional tissue Doppler and 1D Doppler strain, to assess systolic function of both the ventricles independent of Doppler interrogation angle.^{24–26}

Methods

Study population

From an initial cohort of 55 patients with HCM and 105 top-level athletes, 35 untrained young patients with HCM and 50 age- and sex-comparable endurance athletes (long-distance swimmers), all with echocardiographic evidence of LV hypertrophy (LV mass index $>50 \text{ g/m}^2$), were enrolled into the study after their informed consent, and the approval of the Ethics Committee of Monaldi Hospital was obtained. Exclusion criteria were diabetes mellitus, arterial hypertension, coronary artery disease (angina and/or ECG signs of myocardial ischaemia), valvular heart disease, more than second grade of mitral regurgitation, patients in New York Heart Association (NYHA) functional classes II–IV, sinus tachycardia, atrial fibrillation, lung disease and pulmonary hypertension, and inadequate echocardiograms.

Hypertrophic cardiomyopathy group

Diagnosis of HCM was confirmed by echocardiographic evidence of asymmetric hypertrophy of interventricular septum ($>15 \text{ mm}$) without any other cardiac or systemic disease capable of producing the magnitude of hypertrophy evident.⁶ Right ventricular diameters were evaluated by 2D measurement of RV free wall at two different

levels (base and mid-RV segments). Extent and distribution of hypertrophy were measured in parasternal short-axis view. Patients taking cardiac drugs (primarily beta-blockers and calcium channel blockers) were excluded from therapy at least 72 h before the echocardiogram, according to the rules of our Institutional Committees. Eight patients (22%) were defined to have obstructive HCM on the basis of the evidence of LV outflow tract gradient $\geq 30 \text{ mmHg}$.

Athlete’s group

All the athletes had been trained intensively for 15–20 h/week for >5 years, undergoing intensive aerobic isotonic dynamic exercise at incremental workloads of 70–90% of maximal heart rate (HR). In particular, they performed 3 h/day of incremental long-distance swimming (7000 m/day divided into series of 400–800 m), 3 h/week of long-distance running, and only 2 h/week of weight lifting at low workload.

Standard and tissue Doppler echocardiography

Standard Doppler echocardiography and tissue Doppler were performed with the subjects in partial left decubitus by Vivid 7 ultrasound system (GE Vingmed Ultrasound).

Left ventricular mass was calculated according to the Penn convention²⁷ by the following formula:

$$\text{LV mass (g)} = 1.04[(\text{LVEDD} + \text{IVST} + \text{PWT})^3 - (\text{LVEDD})^3] - 13.6,$$

where IVST is the interventricular septal thickness, PWT is the posterior wall thickness, and LVEDD is left ventricular end-diastolic diameter. Left ventricular mass was indexed for height^{2,7} (Cornell adjustment).²⁸ Stroke volume was obtained by LV outflow Doppler method as the product between outflow tract area and LV output time–velocity integral.²⁹ Left ventricular ejection fraction was measured using a commercially available software program that applied modified Simpson’s rule on the two-chamber and four-chamber views. Pulsed Doppler assessment of LV inflow was performed in apical four-chamber view, with the sample volume placed at the level of valve tips. The following measurements of global LV diastolic function were determined: peak velocities of E- and A-wave (m/s) and their ratio, deceleration time of E-wave (ms), isovolumic relaxation time (ms). Transmitral inflow was analysed also by Valsalva manoeuvre to detect pseudonormal patterns. By pulsed tissue Doppler, the early (E_m) and late (A_m) diastolic annular velocities were measured at the lateral corner of the mitral and tricuspid annulus, in accordance with the method proposed by Nagueh *et al.*³⁰ Mitral E velocity, corrected for the influence of relaxation (i.e. the E/E_m ratio), was calculated to estimate LV filling pressures.³⁰

Right ventricular end-diastolic chamber size was accurately assessed using three parameters according to American Society of Echocardiography guidelines for chamber quantification, integrating apical four-chamber and short-axis views.^{31–32} Care must be taken to obtain a true non-foreshortened apical four-chamber view, oriented to obtain the maximum RV dimension, before making these measurements. Two of the three parameters were the measurements of the mid-cavity and basal RV diameter in the apical four-chamber view at the end diastole. The third one was the measurements of RV outflow tract at subpulmonary region from parasternal short-axis view. Pulsed Doppler RV diastolic indexes were determined in apical four-chamber view, placing the sample volume at the tips of tricuspid valve: E and A peak velocities (m/s) and their ratio were calculated.

The following measurements of global RV filling were determined: *E* and *A* peak velocities (m/s), *E/A* ratio and *E*-wave deceleration time.

Tricuspid annular plane systolic excursion (TAPSE) was calculated as an index of the RV global systolic function by the difference between end-diastolic and end-systolic measurement (in mm).³³ The Tei index (RV myocardial performance index) was calculated as described previously.³⁴ In order to obtain a measure of global myocardial RV function, peak systolic velocity (S_m) obtained at the tricuspid annulus and base and mid-RV segments were averaged, as reported by others.^{35–36}

Two-dimensional echocardiographic right ventricular strain

Two-dimensional strain uses grey-scale (B-mode) sector image and is based on frame-by-frame tracking of small rectangular image blocks with stable speckle pattern. A minimum frame rate of 30 Hz was required for reliable operation of this program, and frame rates of 60–90 Hz were used for routine grey-scale imaging. Apical four-chamber view (the same of the RV diameter measurement) was obtained using the same ultrasound system and the probe used for standard echocardiography; end-systole was chosen as the single frame for the endocardial-to-epicardial region of interest to include maximal wall thickness for strain calculation. The 'Zoom/RES' feature on the echocardiographic machine was used to improve the accuracy of right ventricle measurements. A region of interest was traced on the endocardial cavity interface of the apical four-chamber view at RV systole (minimum cavity area) by a point-and-click approach. Then a second larger region was automatically generated, which was near the epicardium with a width of 10 mm. The region of interest then included the entire RV myocardial wall, and a click feature increased or decreased the width of the two circles for thicker or thinner walls, respectively. The tracking algorithm followed the endocardium from this frame throughout the cardiac cycle. Accordingly, for RV longitudinal strain, myocardial thickening was represented with a negative value, colour-coded as red; myocardial thinning was represented with a positive value, colour-coded as blue; and then these were superimposed to conventional 2D images. The software then automatically divided the image into six standard segments and provided an automated tracking score, similar to statistical standard deviation, as feedback of the stability of the regional speckle tracking, ranging from 1.0 to 3.0 arbitrary units. A tracking score value of <2.5 was determined as acceptable as described previously, and slight adjustments were made to the placement of the region of interest in regions with greater SDs to attempt to improve tracking stability. The tracking process and conversion to Lagrangian strains were performed offline using a dedicated software (EchoPAQ PC 2D strain, GE Healthcare, Milwaukee, WI, USA). Longitudinal strains for each individual segment were measured and averaged for RV septal and lateral walls. In addition, the software calculated RV global longitudinal strain (GLS) by averaging local strains along the entire right ventricle.^{24–26}

Exercise stress echocardiography

All patients enrolled in the study underwent a supine bicycle exercise stress echocardiography test after the resting echocardiogram. The test was analysed by cardiologists blinded to the study. Participants were included into the study if they demonstrated negative results for myocardial ischaemia. Two-dimensional images were obtained in four standard views (parasternal long-axis, parasternal short-axis, apical four- and two-chamber views) using Vivid 7 ultrasound systems at baseline, at each exercise step, and during recovery, and recorded using a quad-screen cine-loop system. The following functional indexes were assessed at peak effort: maximal HR, maximal

systolic blood pressure (SBP), maximal workload (number of Watts achieved by supine bicycle test), and rate–pressure product (maximal HR × maximal SBP).

Statistical methods

All the analyses were performed using a commercially available package (SPSS, Rel. 11.0, 2002, SPSS Inc., Chicago, IL, USA). Variables are presented as mean ± SD. Two-tailed *t*-test for paired and unpaired data was used to assess changes between groups. Linear regression analyses and partial correlation test by Pearson's method were done to assess univariate relations.

To identify significant independent determinants of RV myocardial strain in patients with left ventricular hypertrophy (LVH), their individual association with relevant clinical and echocardiographic variables was assessed by multivariable Cox regression analysis. The following variables were included into the analysis: clinical data (age, BSA, mean blood pressure), standard echocardiographic indexes (LV diameters, LV septal thickness, RV diameters, Doppler mitral and tricuspid inflow measurements, TAPSE, RV Tei index, pulmonary artery pressure). These variables were selected according to their clinical relevance and potential impact on RV function, as shown by earlier studies.⁶ Variable selection was performed in the multivariable linear regression analysis as an interactive stepwise backward elimination method, each time excluding the one variable with the highest *P*-value according to Wald statistics. The assumption of linearity was checked graphically by studying the smoothed martingale residuals from the null model plotted against the covariate variables. The linearity assumptions were satisfied. The Hosmer–Lemeshow goodness-of-fit test was used to check that the model adequately fit the data. The model also underwent bootstrap validation (200 runs).³⁴ In order to decrease the inflation of the type 1 error rate due to multiple testing, the statistical significance was defined as two-sided *P*-value <0.01.

Receiver operating characteristic (ROC) curve analysis was performed to select optimal cut-off values of echocardiographic measurements.

Reproducibility of 2DSE measurements was determined in all the subjects. Inter-observer variability and intra-observer variability were examined using both Pearson's bivariate two-tailed correlations and the Bland–Altman analysis. Relation coefficients, 95% confidence limits, and per cent errors were reported.

Results

Clinical characteristics of the study population

The two groups were comparable for age (34.4 ± 9.9 years in HCM vs. 35.9 ± 7.5 years in athletes) and mean blood pressure (84.5 ± 4.5 mmHg in HCM vs. 82.2 ± 3.3 mmHg in athletes), whereas athletes showed lower HR (58.1 ± 6.6 bpm in athletes vs. 75.9 ± 10.2 bpm in HCM, $P < 0.0001$) and increased body surface area (1.89 ± 0.11 m² in athletes vs. 1.8 ± 0.08 m² in HCM, $P < 0.01$).

Left ventricular standard Doppler echocardiographic analysis

Left ventricular mass index was mildly increased in HCM. In particular, septal thickness was higher in HCM, whereas both LVEDD and LV stroke volume were increased in athletes

Table 1 Left ventricular standard Doppler echocardiographic comparison between the two groups

Variable	HCM (n = 35)	Athletes (n = 50)	P-value
Septal wall thickness (mm)	21.8 ± 4.2	11.5 ± 0.8	<0.0001
LV posterior wall thickness (mm)	8.4 ± 1.1	10.8 ± 1	<0.01
LV end-diastolic diameter (mm)	47.4 ± 3.7	53.4 ± 3.2	<0.001
LV end-systolic diameter (mm)	27.0 ± 4.7	30.8 ± 1.9	NS
LV ejection fraction (%)	58.7 ± 3.7	58.2 ± 5.2	NS
LV stroke volume (mL)	65.7 ± 12.5	91.6 ± 6.9	<0.0001
LV mass index (g/m ^{2.7})	64.5 ± 9.7	58.6 ± 5.5	<0.01
Mitral peak E velocity (m/s)	0.68 ± 0.09	0.87 ± 0.2	<0.0001
Mitral peak A velocity (m/s)	0.66 ± 0.06	0.36 ± 0.1	<0.0005
Mitral peak E/A ratio	1.04 ± 0.4	2.44 ± 0.8	<0.0001
Mitral deceleration time (ms)	215.4 ± 30.9	165.1 ± 14.8	<0.0001
Mitral IVRT (ms)	89.0 ± 10.5	76.5 ± 9.7	<0.0001
Mitral E/E _m ratio	4.3 ± 2.1	8.3 ± 3.1	<0.001
LA diameter (mm)	43.2 ± 9.1	38.2 ± 3.5	<0.01

IVRT, isovolumic relaxation time; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; LA, left atrial.

(Table 1). Left ventricular ejection fraction was comparable between the two groups. Conversely, all transmitral Doppler indexes were higher in athletes, with increased both E/A and E/E_m ratios, whereas left atrial diameter was increased in HCM.

Right ventricular standard echocardiographic and two-dimensional strain analysis

Right ventricular diameters were mildly increased in patients with athletes, whereas TAPSE and RV fractional area change were comparable between the two groups (Table 2). In addition, RV Tei index, tricuspid E/A ratio, and RV tissue Doppler S_m peak were mildly impaired in HCM.

Overall, RV speckle tracking was possible in 480 (94.5%) of 510 attempted segments from the 85 subjects with technically adequate images, with only 5.5% of segments eliminated with tracking variation scores >2.5. Overall tracking variation scores were <2.0 in 82%. Right ventricular GLS and regional peak myocardial RV strain were significantly impaired in patients with HCM (all *P* < 0.001) at the level of all the analysed myocardial segments. Figure 1 shows 2DSE patterns in a patient with HCM and in an athlete. Of note, no difference of 2DSE RV measurements was found between patients with HCM having or not LV obstruction.

Table 2 Right ventricular standard echo and two-dimensional strain measurements at the baseline in the overall study population

Variable	HCM (n = 35)	Athletes (n = 50)	P-value
RV wall thickness (mm)	4.3 ± 0.4	4.1 ± 0.7	NS
RV diameter (four-chamber annulus) (cm)	2.9 ± 0.5	3.4 ± 0.6	<0.01
RV diameter (four-chamber middle ventricle) (cm)	2.8 ± 0.6	3.1 ± 0.3	<0.05
RVOT diameter (short-axis) (cm)	2.6 ± 0.5	2.7 ± 0.8	NS
RV fractional area change (%)	33.2 ± 2.4	34.2 ± 1.4	NS
TAPSE (cm)	1.87 ± 0.33	1.91 ± 0.35	NS
RV Tei index	0.47 ± 0.04	0.39 ± 0.06	<0.01
Tissue Doppler RV S _m peak velocity (m/s)	9.4 ± 2.1	12.3 ± 3.1	<0.01
Tricuspid peak E velocity (m/s)	0.57 ± 0.2	0.64 ± 0.1	<0.05
Tricuspid peak A velocity (m/s)	0.45 ± 0.09	0.46 ± 0.2	NS
Peak E/A ratio	1.21 ± 0.09	1.49 ± 0.56	<0.01
Tricuspid deceleration time (ms)	118.2 ± 39.2	130.8 ± 8.5	NS
Tricuspid IVRT (ms)	79.8 ± 11.2	66.8 ± 9.2	<0.05
Tricuspid E/E _m ratio	5.1 ± 2.3	4.6 ± 2.4	<0.05
RV lateral wall mean 2DSE (%)	14.3 ± 4.1	22.4 ± 3.8	<0.001
RV septal wall mean 2DSE (%)	14.2 ± 4.5	21.4 ± 3.4	<0.001
RV GLS (%)	14.2 ± 4.4	21.7 ± 3.6	<0.001

RV, right ventricle; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion; GLS, global longitudinal strain.

Supine bicycle stress test

During physical effort, as expected, athletes showed a better functional capacity, with greater maximal workload achieved with lower maximal HR and comparable maximal SBP (Table 3).

Univariate relations of two-dimensional speckle-tracking strain echocardiography indexes

Right ventricular GLS was inversely related to LVEDD in athletes group (*r* = -0.76, *P* < 0.0001) (Figure 2) and directly associated with IVST in HCM patients (*r* = 0.68, *P* < 0.0001) (Figure 3).

Multivariate analysis

Stepwise forward, multiple linear regression analyses were performed in the overall population to weigh the independent associations between RV myocardial parameters and LV measurements. By this model, after adjusting for potential determinants, the

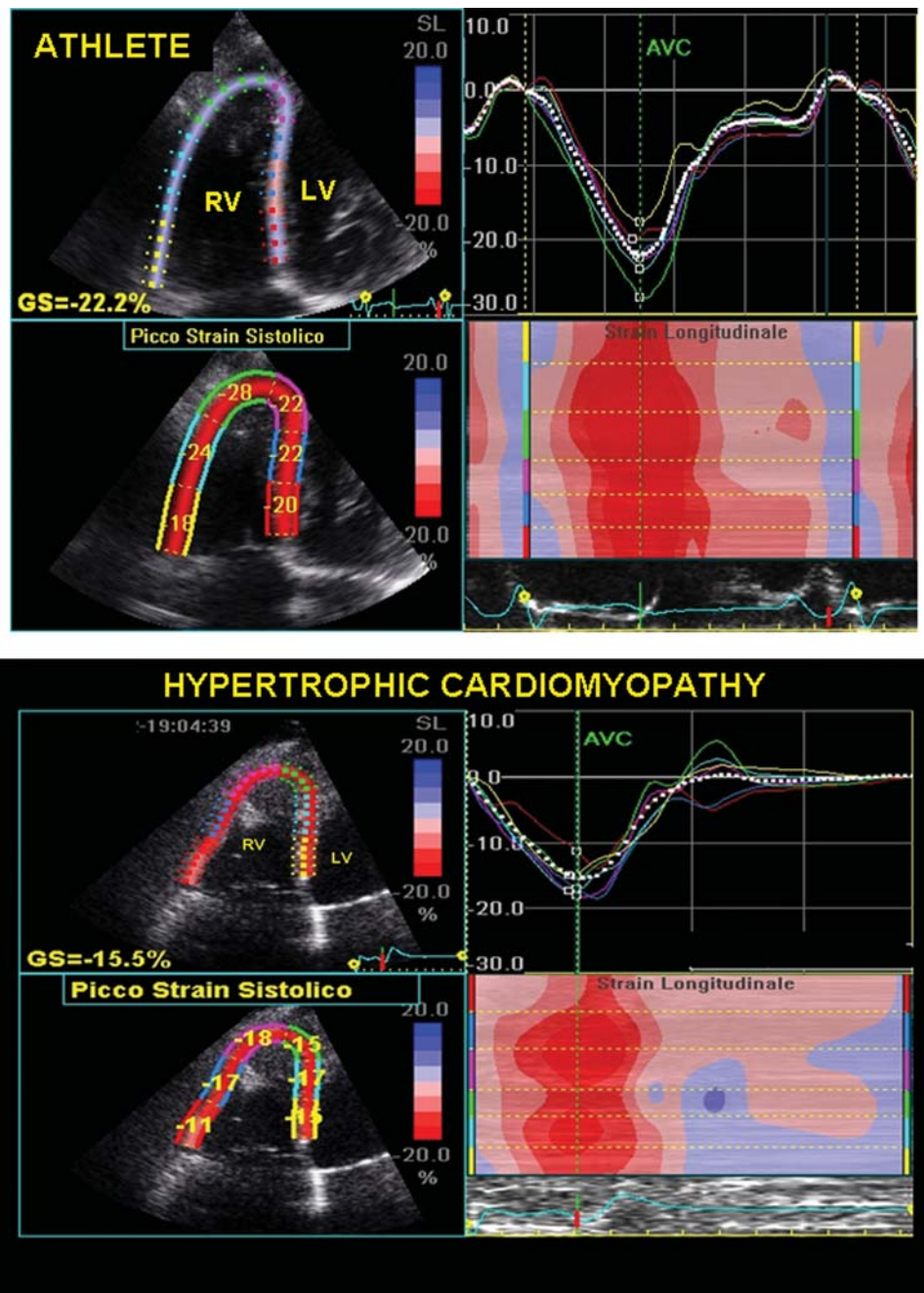


Figure 1 Right ventricular two-dimensional speckle-tracking strain echocardiography pattern in an athlete and in a patient with hypertrophic cardiomyopathy (upper and lower panels, respectively).

independent association between RV GLS and LVEDD (β -coefficient in the final model -0.68 , $P < 0.0001$; β -coefficient estimate averaged across bootstrap samples -0.67 , $P < 0.0001$) in athletes and the independent correlation of the same RV GLS and IVST (β -coefficient in the final model 0.63 , $P < 0.0001$; β -coefficient estimate averaged across bootstrap samples 0.62 , $P < 0.0001$) in HCM were confirmed. Furthermore, in the overall population, RV GLS (β -coefficient in the final model 0.51 , $P < 0.0001$; β -coefficient estimate averaged across bootstrap

samples 0.50 , $P < 0.0001$) was a powerful independent predictor of maximal workload during exercise stress echo.

Sensitivity and specificity of standard Doppler and two-dimensional speckle-tracking strain echocardiography

The sensitivity and specificity of standard Doppler-derived tricuspid peak velocity E and of 2DSE measured RV GLS were

Table 3 Functional parameters during physical effort in patients with either physiological or pathological left ventricular hypertrophy, using supine bicycle ergometer

Variable	HCM (n = 35)	Athletes (n = 50)	P-value
Maximal HR	181.9 ± 11.3	167.9 ± 14.3	<0.01
Maximal SBP	178.15 ± 24.2	173.44 ± 21.2	NS
Rate–pressure product (bpm mmHg × 10 ⁻³)	32.5 ± 9.3	27.8 ± 6.3	<0.01
Watts achieved	142.11 ± 21.5	194.21 ± 34.7	<0.0001

L VH, left ventricular hypertrophy; SBP, systolic blood pressure; HR, heart rate.

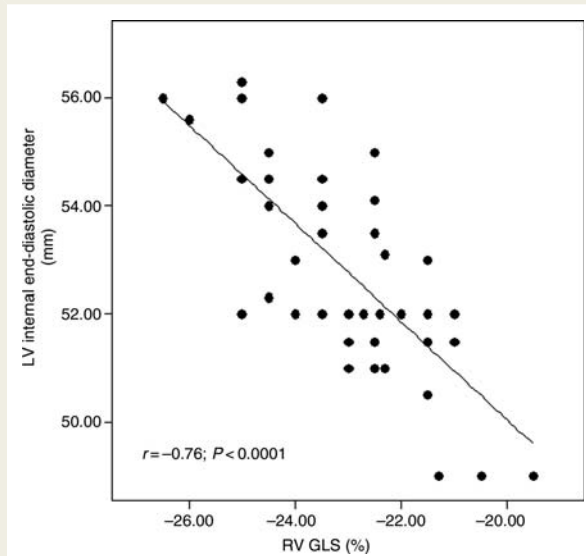


Figure 2 Inverse relation between left ventricular end-diastolic diameter and right ventricular global longitudinal strain in the athletes' group.

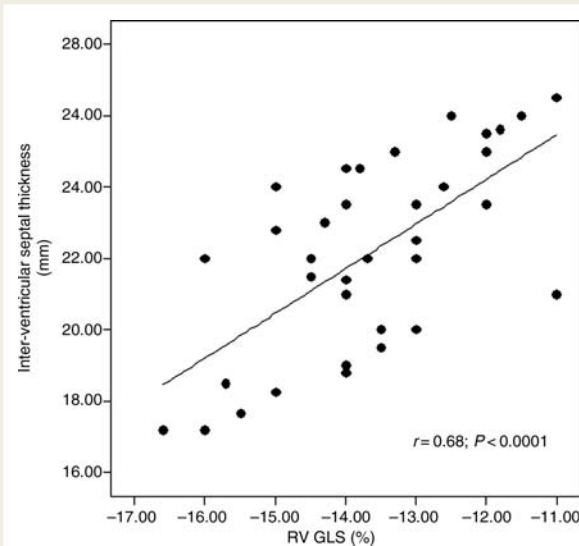


Figure 3 Direct relation between interventricular septal wall thickness and right ventricular global longitudinal strain in the hypertrophic cardiomyopathy group.

determined to compare athlete's heart and HCM. By ROC curve analysis, a cut-off point of tricuspid *E* peak velocity <0.60 m/s had a sensitivity of 73% and a specificity of 80%. Conversely, a 2DSE RV GLS cut-off point of -16% differentiated better athletes and HCM (sensitivity 86%, specificity 92%).

For the model of RV GLS, each of the variables in the final models appeared in the bootstrap models over 90% of the time. According to model validation statistics, discrimination of the model was adequate—RV GLS: c-statistic 0.772; calibration, shrinkage coefficient 0.78; Hosmer–Lemeshow *P*-value = 0.81.

Reproducibility of two-dimensional speckle-tracking strain echocardiography right ventricular strain

Intra-observer variability

Pearson's correlations: RV lateral wall: $r = 0.87$, $P < 0.00001$; RV septal wall: $r = 0.87$, $P < 0.00001$; RV GLS: $r = 0.85$, $P < 0.00001$.

Bland–Altman analysis: RV lateral wall (95% CI ± 1.8; per cent error 3.2); RV septal wall (95% CI ± 1.2; per cent error 3.3); RV GLS (95% CI ± 1.5; per cent error 3.4).

Inter-observer variability

Pearson's correlations: RV lateral wall: $r = 0.86$, $P < 0.00001$; RV septal wall: $r = 0.86$, $P < 0.00001$; RV GLS: $r = 0.84$, $P < 0.00001$.

Bland–Altman analysis: RV lateral wall (95% CI ± 1.9; per cent error 3.3); RV septal wall: (95% CI ± 1.5; per cent error 3.5); RV GLS (95% CI ± 1.7; per cent error 3.6).

Discussion

At times, termed 'the forgotten ventricle', the right ventricle can prove difficult to accurately and reproducibly assess, as a result of its shape and volume dependency.^{3,37} Various techniques for RV assessment have been employed, including invasive ventriculography, conventional echocardiography, gated nuclear imaging, and magnetic resonance imaging. Transthoracic echocardiography is, generally speaking, the most commonly used technique for routine clinical assessment of the right ventricle. However, various limitations exist which impair the accuracy of transthoracic echocardiographic assessment of the RV, including inadequate visualization of the RV free wall which can limit

visual assessment, RV fractional area change, and ejection fraction measurements.

The present study demonstrates the usefulness of pulsed 2DSE to analyse myocardial pattern of right ventricle in either physiological or pathological LV hypertrophy. To the best of our knowledge, this is the first study to compare RV regional deformation by the use of 2DSE between patients affected by HCM and competitive endurance athletes. The main findings are that: (i) despite the absence of manifest RV global systolic dysfunction athletes by standard echocardiography, RV global and regional 2DSE measurements were largely impaired in HCM compared with athletes; (ii) even after correction for potential confounders, an index of global RV myocardial longitudinal deformation was inversely related to LVEDD in athletes, and directly associated with septal thickness in HCM; (iii) in the overall population of patients with LV hypertrophy, RV GLS was a powerful independent predictor of maximal workload during physical effort.

The advantages of two-dimensional speckle-tracking strain echocardiography in the study of right ventricular function in left ventricular hypertrophy

Previous reports have documented that echocardiography with its newer applications such as tissue Doppler may represent useful additional modalities in the comprehensive echo-Doppler assessment of RV function in different clinical scenarios.³⁵ In particular, Miller *et al.*³⁴ compared RV tissue Doppler indices with Simpson's biplane RV ejection fraction, finding that RV ejection fraction had a significant, yet weak, correlation with RV myocardial systolic peak.³⁴ In our previous reports, we found that both tissue Doppler RV systolic (S_m) and early-diastolic (E_m) myocardial peaks were significantly lower in patients with HCM compared with either sedentary controls¹² or endurance top-level athletes,¹³ even if tricuspid annular systolic excursion by M-mode did not differ. Finally, in a very recent report by Morner *et al.*,¹⁴ patients with HCM showed impaired global and regional RV tissue Doppler-derived myocardial performance index with respect to healthy controls.

However, tissue Doppler and 1D Doppler strain estimation, with their angle dependency, present important limitations due to a poor alignment between Doppler beam and myocardial wall. Conversely, in the present study, we used 2DSE, a novel approach to quantify RV myocardial deformation within a scan plane that is inherently 2D and independent of interrogation angle as it tracks speckle patterns (acoustic markers) within serial B-mode sector scans.^{24–26}

Right ventricular myocardial function in hypertrophic cardiomyopathy

The current American Heart Association classification of the cardiomyopathies defines HCM as a disease with left and/or RV hypertrophy, which is usually asymmetric and involves the interventricular septum.^{6,15} Using cardiovascular magnetic resonance imaging, Maron *et al.*³⁸ demonstrated that morphological RV abnormalities are present in a substantial proportion of the patients with HCM. In addition, RV diastolic dysfunction was

observed by Maeda *et al.*,¹⁰ who described impaired RV isovolumic relaxation by biplane RV angiography, and by Suzuki *et al.*,¹¹ who found lower early peak filling rate by magnetic resonance. Furthermore, in previous reports analysing the inflow of patients with HCM by standard echocardiography Doppler RV, Okamoto *et al.*³⁹ and Larrazet *et al.*⁴⁰ described slow deceleration of rapid filling wave, increase in the lengthening of atrial contraction, and reduction of tricuspid *E/A* ratio. Similar findings were observed also in our study where patients with HCM presented lower tricuspid peak *E* and *E/A* ratio in comparison with the athletes' group, confirming a pattern of RV impaired filling in HCM.

On the other hand, the present study highlights also an RV myocardial systolic dysfunction in young male patients with HCM, since RV GLS and regional 2DSE peaks were significantly impaired, despite comparable TAPSE measurements and slightly impaired RV Tei index and tissue Doppler measurements. Of note, the degree of septal hypertrophy was an independent determinant of RV early-diastolic peak velocity, explaining >60% of its variability. In addition, an RV GLS of –16% differentiated better than echo Doppler athletes and HCM.

Such impairment of RV myocardial deformation in our patients with HCM might be explained on the grounds of a direct involvement of RV wall by myopathic process, as suggested by the impairment of 2DSE peaks measured in different RV myocardial segments. On the other hand, the lower RV myocardial indexes found in HCM than in the athletes' group suggest ventricular interaction as further explanation of impairment in RV myocardial function. Ventricular interaction is an expression of close anatomic association between the two ventricles, which are encircled by common muscle fibres, share a septal wall, and are enclosed within the pericardium, and is underscored in our study by the close relation between the degree of septal thickness and RV myocardial deformation.

Right ventricular myocardial function in athletes

Although few recent reports described LV and left atrial tissue Doppler and 2DSE patterns in different subsets of athletes undergoing different training protocols,^{41–45} little is known about RV 2DSE changes in endurance training by this technique. In agreement with our previous reports showing higher RV myocardial velocities analysed by tissue Doppler in competitive athletes,^{21–23} RV myocardial GLS and regional 2DSE peaks were significantly increased, indicating a training-induced improvement of RV myocardial deformation. Multivariate analysis provided further information about this association by adjusting for several confounders, chosen according to the heart physiology. By this analysis, LVEDD was an independent determinant of RV GLS, explaining >65% of its variability. This independent association confirms a reciprocal optimal cooperation between the two ventricles in the athlete's heart. An RV GLS increase might be partially the final result of a better RV diastolic filling, due to the venous overload secondary to endurance training and to lower early diastolic pressure. This better RV chamber relaxation might determine a progressive improvement of RV myocardial deformation, an increase in RV stroke volume, with a consequent LV preload

increase, corresponding to a greater LVEDD. Increased preload is the basis to explain the enhancement of LV stroke volume in trained hearts by a better utilization of the Frank–Starling mechanism,⁴⁶ and the consequent increased cardiac performance during maximal physical effort. On the other hand, LV stroke volume increase might induce in its turn the venous overload.

These data highlight the influence exerted by preload on 2DSE measurements.⁴⁷ It has, however, to be considered how athletes represent an extreme model where loading changes are markedly evident.²⁴

Study limitations

Our study has several limitations. The first one is the lack of a gold standard for assessing baseline RV function. Although previous studies used TAPSE, RV Tei index, and tissue Doppler to assess RV function, more data are needed, particularly in correlating echocardiographic data with invasive measures of RV function.³⁵

Another study limitation is the lack of haemodynamic data. An assessment by RV heart catheterization might have provided more accurate information about RV and right atrial pressures. Furthermore, the data of the present study may not be extrapolated to the overall population of HCM because of the exclusion of severe heart failure classes which may have eliminated patients with advanced systolic impairment from statistical analyses. However, we intentionally selected relatively asymptomatic patients to examine early changes of 2DSE regional properties in HCM.

As specified previously, this is the first report analysing RV function in patients with LVH by the use of speckle-tracking 2DSE. In particular, we used EchoPAC PC program from GE HealthCare for 2D strain analysis. Since a definite 2DSE software for RV 2D strain has not yet been provided, we applied a 2DSE program for LV strain to analyse RV strain also. The feasibility and the reproducibility of RV strain patterns and measurements were good. However, in future studies, changes in the software may be needed in order to improve the tracking ability of the speckle-tracking system for RV functional study.

A technical limitation is that speckle-tracking echocardiography is dependent on frame rate as well as on image resolution. Low frame rate results in the speckle pattern changing too much from frame to frame, which prevents the precise characterization of regional myocardial motion and impacts the overall temporal resolution of the regional strain map. In contrast, increasing the frame rate reduces scan line density, which reduces image resolution. Frame rate in our setting ranged from 60 to 90 frame/s; this value is lower than the frame rate available with Doppler strain; however, indexes of RV function used in this study did not rely on the difference in the timing of contraction.

Our analysis was limited by data collection from the apical four-chamber view, as this was the only image plane that provided reliable information on longitudinal RV deformation in a sufficient number of patients. It would be desirable to obtain information on RV deformation from the complete RV cavity. However, in the present study, RV radial strain was not calculated from the parasternal short- and long-axis views because the RV wall is probably too thin to be properly analysed in these views.

As for the analysis of global RV deformation, 2DSE software cannot accurately separate LV components from RV components of septum and thus half the global indexes may be determined by septal function. However, in our study and also in a previous report,⁴⁸ we performed RV free-wall assessment of myocardial deformation, and the results of RV global and regional involvement in HCM were comparable.

Finally, sample size limited our ability to draw definitive conclusions regarding RV myocardial deformation in selected patient subsets.

Conclusions

This study demonstrates for the first time that a novel speckle-tracking algorithm applied to routine grey-scale 2D images represents a promising and feasible non-invasive technique to assess RV myocardial function in patients with physiological or pathological LVH.

Right ventricular myocardial deformation is positively influenced by preload increase in athletes and negatively associated with increased septal thickness in HCM. Therefore, 2DSE may represent a useful tool in the differential diagnosis between athlete's heart and HCM, underlining the different involvement of RV myocardial function in either physiological or pathological LV hypertrophy.

Additional longitudinal studies by 2DSE analyses are warranted to further our understanding of the natural history of RV myocardial deformation in LVH, the extent of reversibility of RV dysfunction with medical therapy, and the possible long-term impact of such changes on outcomes in patients with HCM.

Conflict of interest: none declared.

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