Stress Echocardiographic Strain–Dyssynchrony Interactions Identify Prognostic Phenotypes in Chagas Cardiomyopathy: A Pilot Study

Guilherme Augusto Teodoro Athayde,[1] Bruno Campanha Carter Borges,[1] Andreia Oliveira Pinheiro,[1] Aline L. Souza,[1] Camila Parente Oliveira,[1] Sérgio Augusto Mezzalira Martins,[1] Ricardo Alkmim Teixeira,[2] Sérgio F. Siqueira,[1] Wilson Mathias,[1,3] Martino Martinelli Filho[1]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP – Brazil
Universidade do Vale do Sapucaí - UNIVÁS, Pouso Alegre (MG) – Brasil
Fleury Medicina e Saúde – Cardiologia,[3] São Paulo, SP – Brazil

Abstract

Background: **Mechanical heterogeneity is a hallmark of advanced cardiomyopathy, although stress echocardiography traditionally focuses on ischemia or global systolic reserve. Exercise stress echocardiography may identify distinct mechanical phenotypes in chronic Chagas cardiomyopathy (CCC) through integrated assessment of strain and dyssynchrony behavior.**

Objective: **To investigate the interaction between contractile reserve and intraventricular dyssynchrony (IVD) during exercise stress echocardiography and its association with clinical outcomes in patients with CCC.**

Methods: **Forty patients with severe CCC (left ventricular ejection fraction ≤ 35%, non-LBBB QRS morphology) underwent symptom-limited treadmill stress echocardiography. Global longitudinal strain (GLS), IVD, and conventional echocardiographic parameters were assessed at rest and immediately after peak exercise. Patients were stratified into four groups according to GLS and IVD variation. The primary endpoint was a composite of death, heart transplantation, or hospitalization for heart failure over a 2-year follow-up. Statistical significance was defined as $p < 0.05$.**

Results: **After a median follow-up of 729 days, 20 patients (50%) reached the primary endpoint. Patients without contractile reserve and without dyssynchrony improvement during exercise had significantly lower event-free survival compared with the remaining groups ($p < 0.01$). When analyzed separately, both absence of contractile reserve and unfavorable dyssynchrony response were associated with adverse outcomes. In multivariable analysis, only right ventricular function remained independently associated with the primary outcome (hazard ratio 0.83, 95% confidence interval 0.71–0.96; $p = 0.014$).**

Conclusions: **Integration of strain-derived contractile reserve and IVD during physiologic stress may help identify prognostic phenotypes beyond ejection fraction in CCC and supports the concept of dynamic mechanical phenotyping in advanced cardiomyopathy.**

Keywords: **Stress Echocardiography; Chagas Cardiomyopathy; Ventricular Dysfunction.**

Introduction

The presence of contractile reserve is a recognized marker of better prognosis in patients with heart failure (HF) of different etiologies,[1,2] in addition to predicting a better response to cardiac resynchronization therapy (CRT).[3] Likewise, the increase in intraventricular dyssynchrony (IVD) after stress is associated with worsening of mitral regurgitation and changes in cardiac output[4] and is an independent determinant of peak oxygen consumption during cardiopulmonary testing[5] and of a greater number of clinical events.[6]

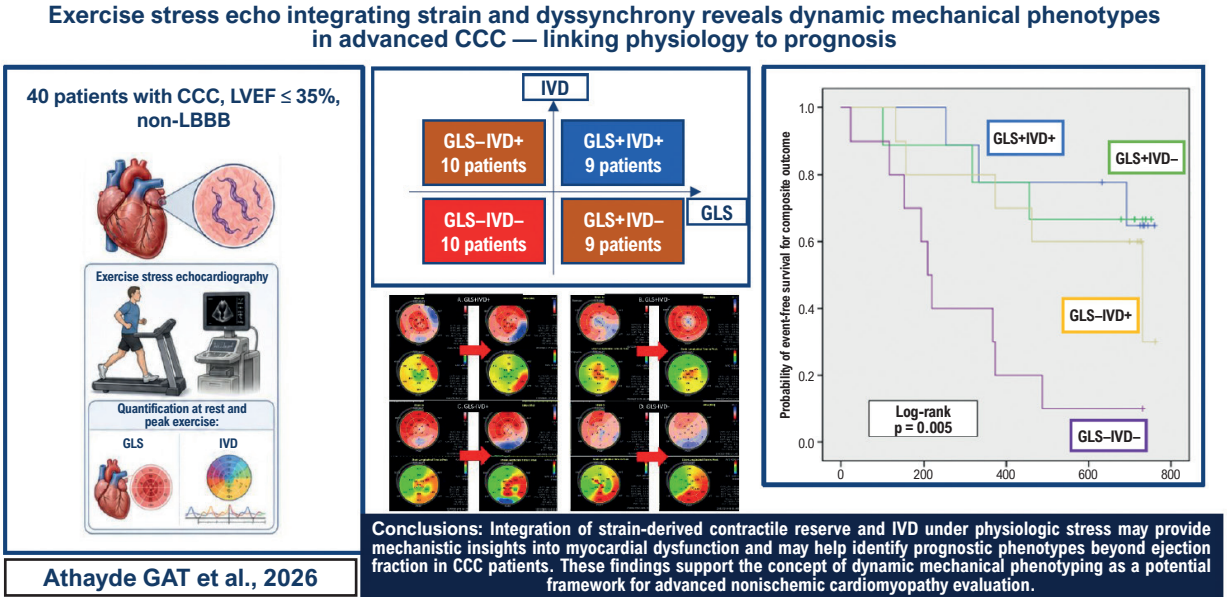
Since right bundle branch block (RBBB) is the most common intraventricular conduction disturbance (IVCD) and left bundle branch block (LBBB) has a low prevalence,[7] the indications for CRT in CCC are often limited. Furthermore, the prognosis of patients with CCC undergoing CRT is worse than that of patients with other heart diseases.[8]

We previously demonstrated that exercise stress echocardiography can identify distinct mechanical phenotypes in chronic Chagas cardiomyopathy (CCC), integrating strain and dyssynchrony behavior during exercise. Patients with CCC and severe myocardial dysfunction present different echocardiographic and exercise patterns when dynamically evaluated, making it possible to identify

Mailing Address: Guilherme Augusto Teodoro Athayde •
Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – Av. Dr. Enéas de Carvalho Aguiar, 44. Postal Code 05403-900, São Paulo, SP – Brazil
E-mail: gtathayde@gmail.com
Manuscript received December 26, 2025, revised manuscript June 22, 2026, accepted July 10, 2026
Editor responsible for the review: Nadine Clausell

DOI: https://doi.org/10.36660/abc.20250890i

Central Illustration: Stress Echocardiographic Strain–Dyssynchrony Interactions Identify Prognostic Phenotypes in Chagas Cardiomyopathy: A Pilot Study



Arq Bras Cardiol. 2026; 123(9):e20250890

Forty patients with nonischemic Chagas cardiomyopathy, LVEF ≤ 35%, and non-LBBB underwent dynamic echocardiographic assessment with GLS and IVD at rest and during exercise. Patient stratification according to GLS and IVD response identified subgroups with different prognoses. The GLS−IVD− group showed the highest risk of adverse outcomes. Dynamic GLS and IVD assessment suggested additional prognostic information beyond LVEF. CCC: chronic Chagas cardiomyopathy; GLS: global longitudinal strain; IVD: intraventricular dyssynchrony; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction.

subgroups with contractile reserve, evaluated by global longitudinal strain (GLS), and greater IVD.[9]

While GLS reflects myocardial deformation and IVD captures temporal dispersion of contraction, their integrated behavior under stress conditions has not been systematically explored. In advanced cardiomyopathy, where electromechanical coupling is profoundly altered, the dynamic interplay between these parameters may reveal latent functional reserve not apparent at rest.

The prognostic and pathophysiologic significance of these dynamic mechanical patterns remain uncertain. Therefore, this study aimed to investigate the interaction between contractile reserve and IVD during exercise stress echocardiography and its association with clinical outcomes in patients with CCC (Central Illustration).

Methods

This is a pilot, prospective, observational, single-center cohort study. Patients with CCC and HF were recruited by convenience sampling from the outpatient clinics of the Instituto do Coração of the Faculdade de Medicina of Universidade de São Paulo (InCor–FMUSP) between August 23, 2018 and April 3, 2019. Eligible patients were consecutively screened during routine clinical care and invited to participate based on availability, without random selection.

Patients

Patients meeting the following criteria were considered eligible: aged ≥ 18 years and ≤ 75 years; positive serology for Chagas disease in at least 2 different tests (indirect hemagglutination, indirect immunofluorescence, or enzyme-linked immunosorbent assay [ELISA]); non-LBBB IVCD on the electrocardiogram (ECG); left ventricular ejection fraction (LVEF) less than or equal to 35%; no cardiac implantable electronic devices (CIED) at the time of inclusion; and informed consent to participate in the study.

Patients were excluded based on the following criteria: an acoustic window considered inadequate by the examiners; physical limitation to perform an exercise stress test; myocardial ischemia induced during the exercise stress test; a life expectancy of less than 1 year due to the disease itself or comorbidities; or previous withdrawal from this study.

All patients signed an informed consent form, according to the guidelines of the Ethics Committee of our institution, which approved the study (CAPPesq: 5556/18 in August 2018).

Clinical evaluation and echocardiographic protocol

All procedures performed in each patient have been previously described.[9] Initially, each participant underwent a standardized clinical evaluation by an experienced investigator, including assessment of demographic characteristics, comorbidities, and current medications. A resting ECG was obtained and interpreted according to current guidelines.

Subsequently, all patients underwent transthoracic echocardiography at rest and immediately after symptom-limited treadmill exercise using the Naughton protocol (Micromed, São Paulo, Brazil). At peak exertion, patients were rapidly positioned in the left lateral decubitus position, and post-exercise images were acquired within the first minute of recovery. High-frame rate acquisitions were obtained for myocardial deformation and tissue Doppler imaging (TDI) analysis of IVD from the apical two-, three-, and four-chamber views. A total of six acquisitions of three cardiac cycles each were recorded for subsequent analysis.

All echocardiograms were performed using a Vivid E95 scanner (GE Healthcare, Milwaukee, Wisconsin, USA). Digital raw data were stored for offline analysis using EchoPAC software (GE Healthcare, Milwaukee, Wisconsin, USA) by two independent investigators blinded to clinical data.

LVEF and left atrial (LA) volume were calculated using the Simpson biplane method. Left ventricular diastolic dimensions were obtained from the parasternal long-axis view at the level of the mitral valve leaflets. Tricuspid annular plane systolic excursion (TAPSE) and systolic (S′) wave velocity were measured according to current echocardiographic standards.

Longitudinal strain analysis was performed from the apical two-, three-, and four-chamber views. The endocardial border was manually traced, ensuring exclusion of the epicardial layer, with a narrow region of interest adjusted to the myocardial wall thickness. GLS was calculated as the average of the three apical projections. A GLS value $< -8\%$ was defined as a marker of very severe left ventricular dysfunction (LVD).[10]

Because no validated exercise-induced GLS threshold for contractile reserve exists in advanced CCC, we intentionally adopted an exploratory cohort-derived definition designed for physiologic stratification rather than clinical classification, defining contractile reserve as a GLS increase greater than the mean variation observed in the study population.

Mechanical dyssynchrony was quantified using tissue synchronization imaging and expressed as the Yu index, defined as the standard deviation of time to peak systolic velocity across 12 left ventricular segments. A Yu index ≥ 33 ms was considered indicative of significant mechanical dyssynchrony.[11]

Patient grouping and follow-up

Patients were categorized into four groups according to the dynamic response pattern of GLS and IVD (Yu index) between rest and peak exercise.

- GLS+IVD+: patients exhibiting contractile reserve and improved intraventricular synchrony after exercise, defined as an increase in GLS and a decrease in the Yu index greater than the mean change observed in the study population;
- GLS+IVD−: patients showing contractile reserve but no meaningful variation in synchrony after exercise;
- GLS−IVD+: patients without contractile reserve but demonstrating improved synchrony (reduction in Yu index) after exercise;
- GLS−IVD−: patients with neither contractile reserve nor improvement in synchrony following exercise.

Clinical follow-up was performed every six months for up to two years, through in-person visits at the Cardiac Stimulation Unit of InCor–HCFMUSP. During each visit, adherence to medical therapy, vital signs, and adverse events were recorded. The study was originally designed with a prespecified 2-year follow-up window to ensure homogeneous follow-up duration across participants and reduce variability introduced by differential long-term surveillance.

From March 2020 onward, due to restrictions imposed by the SARS-CoV-2 pandemic, follow-up assessments were conducted via structured telephone interviews. Throughout the study, all patients received optimized HF therapy according to current guideline-directed medical treatment recommendations.[12]

Outcomes

The primary endpoint was a composite of death, heart transplantation, and hospitalization for HF. The secondary endpoint was death and heart transplantation.

Statistical analysis

Sample size was estimated by convenience in 40 patients, whose data were processed using the software packages Excel 2017 (Microsoft Corp., Redmond, Washington, USA) and SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA).

Continuous variables were tested for normality using the Shapiro–Wilk test. Continuous variables with a normal distribution were described using mean ± standard deviation, and continuous variables without a normal distribution were described using median and interquartile range. Categorical variables were expressed as frequency and percentages. Comparisons between rest and post-exercise values were performed using paired t tests or Wilcoxon signed-rank tests, as appropriate. Comparisons among groups were performed using one-way ANOVA or Kruskal–Wallis tests for continuous variables, and chi-square tests for categorical variables. When overall between-group comparisons were significant, post hoc pairwise comparisons were performed using the Bonferroni test after one-way ANOVA and Dunn's test with Bonferroni adjustment after Kruskal–Wallis tests.

Event-free survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Predictors of the primary outcome were initially explored using

univariate Cox analyses. A multivariate Cox proportional hazards model was performed using a parsimonious approach to reduce the risk of overfitting, considering the relatively small number of events observed in the cohort. Accordingly, the number of covariates included in the final model was deliberately limited. Hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) were estimated for each covariate. Statistical significance was established at $p < 0.05$.

Results

Clinical characteristics of the sample

This study included 40 patients. During the exercise stress test, one patient had well-tolerated sustained ventricular tachycardia and the test was discontinued. Dynamic imaging was feasible in 95% of patients, as Yu index could not be measured in one patient due to intense myocardial trabeculation. The mean GLS response between rest and exercise was an absolute −0.74% increase over resting values, and the mean Yu index response was an absolute decrease of 6.9 ms. Therefore, out of the 38 patients whose exercise parameters could be measured, 9 patients were allocated to the GLS+IVD+ group, 9 to the GLS+IVD− group, 10 patients to the GLS−IVD+ group, and 10 patients to the GLS−IVD− group.

Table 1 summarizes the clinical and echocardiographic data of the population studied. The mean age was 58 years, and the majority of patients were male (62.5%). RBBB on ECG was present in 70% of patients, and mean QRS duration was 140 (120–160) ms. Most patients were in New York Heart Association (NYHA) functional classes I and II (90%), and drug treatment included high rates of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) use (85%), beta-blockers (90%), and spironolactone (77.5%). There were no relevant differences between clinical and electrocardiographic data among groups.

Echocardiographic findings at rest and during exercise

The median LVEF was 28% (22%–33%), and the GLS at rest was −7.1 ± 2.4% with no difference among the groups. The IVD at rest, measured by the Yu index, was 49 ± 18.6 ms; it was different among the groups and more significant in the GLS−IVD+ group. Figure 1 exemplifies the behavior of the IVD and GLS at rest and after exercise in each of the groups.

LA volume and TAPSE also differed among groups, with higher LA volume and lower TAPSE in the GLS−IVD− group. After post hoc pairwise comparisons with Bonferroni correction, only TAPSE remained significantly lower in the GLS−IVD− group compared with the GLS+IVD+ group (adjusted $p = 0.009$); and resting Yu index differed significantly between the GLS+IVD+ and GLS+IVD− groups (adjusted $p = 0.032$), as well as between the GLS+IVD− and GLS−IVD+ groups (adjusted $p = 0.024$). No significant pairwise differences persisted after Bonferroni correction for LA volume or GLS during exercise.

Overall, 87.5% of patients had significant IVD at rest (Yu index ≥ 33 ms) and 67.5% had GLS < −8% at rest. A consistent directional improvement in GLS, from values of −7.1% to −7.9% ($p = 0.018$), and reduction in dyssynchrony parameters, Yu index from 49 ms to 42 ms ($p = 0.03$), were observed during stress (Figure 2). Although absolute changes were modest, relative variations reached approximately 10% for GLS and 14% for dyssynchrony indices, indicating a consistent directional response to stress.

Of the 40 patients evaluated, 27 (67.5%) had very severe LVD (GLS < −8%), while 13 had better global contractility assessed by longitudinal strain (GLS > −8%). In addition, among patients with very severe LVD, 11 patients had contractile reserve after performing the exercise stress test. Interobserver variability analysis had been previously performed in the original methodological study using the same acquisition protocol and software platform. GLS showed low intra- and interobserver variability, with coefficients of variation ~1% and strong correlation ($r > 0.9$; $p < 0.001$).[9]

Analysis of clinical outcomes

After a mean follow-up of 729 (± 33) days, 20 patients (50%) presented the composite primary outcome. Among these, there were 10 (25%) hospitalizations for HF (5 of whom died during follow-up), in addition to 14 deaths and heart transplants (35%) (Table 2).

There was a statistical difference among the groups in relation to the composite primary outcome, with the highest frequency in the GLS−IVD− group (61.9%) ($p = 0.005$). Regarding deaths, there was no statistically significant difference among the groups ($p = 0.15$). When the variables GLS and IVD were analyzed separately, we observed that the patients who showed a favorable behavior for GLS and IVD during exertion in relation to rest showed a lower prevalence of the composite outcome ($p = 0.036$ and $p = 0.011$, respectively), but with no difference in relation to the secondary outcome ($p = 0.084$ and $p = 0.36$, respectively) (Figure 3).

In univariate Cox regression analysis (Table 3), larger LA volume was associated with a higher risk of the primary outcome, whereas higher TAPSE and GLS during exercise were associated with a lower risk of events. In the multivariate model, which included TAPSE, LA volume, and GLS during exercise, only TAPSE remained independently associated with the primary outcome (HR 0.83, 95% CI 0.71–0.96; $p = 0.014$).

Discussion

This study is the first, to our knowledge, to assess the behavior of myocardial function and dyssynchrony and their prognostic impact, through the analysis of the GLS and IVD using stress echocardiography in patients with advanced CCC who were not candidates for CRT. Using these measures, we were able to demonstrate that integrating strain-derived contractile reserve and IVD during exercise stress echocardiography may reflect distinct mechanical response patterns with prognostic implications in patients with CCC, severe LVD, and non-LBBB.

Table 1 – Clinical and echocardiographic characteristics of the studied population

	Total (n=40)	GLS+IVD+ (n=9)	GLS+IVD– (n=9)	GLS–IVD+ (n=10)	GLS–IVD– (n=10)	p
Male	25 (62.5%)	6 (66.7%)	5 (55.6%)	5 (50%)	8 (80%)	0.52
Age	58.8 ± 9.2	61.4 ± 7.8	53.8 ± 11.6	61.2 ± 8.4	58 ± 8.9	0.389
Atrial fibrillation	10 (25%)	2 (22.2%)	1 (11.1%)	4 (40%)	3 (30%)	0.53
QRS interval (ms)	142.9 ± 29.7	137.8 ± 29.9	140.6 ± 22.4	146 ± 33.7	143 ± 37.7	0.983
RBBB	28 (70%)	5 (55.6%)	6 (66.7%)	8 (80%)	7 (70%)	0.72
Dyspnea (NYHA)						
I	15 (37.5%)	5 (55.6%)	3 (33.3%)	4 (40%)	3 (30%)	0.79
II	21 (52.5%)	4 (44.4%)	5 (55.6%)	6 (60%)	4 (40%)	
III	4 (10%)	0	1 (11.1%)	0	3 (30%)	
Beta-blockers	36 (90%)	7 (77.8%)	8 (88.9%)	10 (100%)	9 (90%)	0.81
ACEI/ARB	34 (85%)	8 (88.9%)	8 (88.9%)	9 (90%)	7 (70%)	0.55
Spironolactone	31 (77.5%)	7 (77.8%)	6 (66.7%)	10 (100%)	7 (70%)	0.56
Loop diuretic	28 (70%)	6 (66.7%)	6 (66.7%)	6 (60%)	9 (90%)	0.47
OAC	17 (42.5%)	2 (22.2%)	5 (55.6%)	5 (50%)	5 (50%)	0.47
LA volume (mL)	57.5 [43–71.8]	48.2 ± 15	47.9 ± 16.2	62 ± 14.2	74.5 [57–80.1]	0.027*
LVDD (mm)	68 ± 7.5	62 [60–69]	66.6 ± 7.3	70.1 ± 6.8	68.3 ± 8.6	0.746
LVSD (mm)	58.3 ± 9	56.1 ± 8.2	56.3 ± 11.6	60 ± 5.8	59.5 ± 10.1	0.832
LVEF (%)	28 [22–33]	27.8 ± 3.4	33 [30–35]	26.2 ± 6.6	24.7 ± 7.7	0.327
TAPSE (cm)	16 ± 3.9	18.7 ± 3.2	16.9 ± 3.2	15.6 ± 4.4	13.3 ± 2.8	0.040*
GLS at rest (%)	–7.1 ± 2.4	–7 ± 1.4	–7.8 ± 2.4	–7.3 ± 2.4	–6.8 ± 3.2	0.913
Yu at rest (ms)	49 ± 18.6	55 ± 13.3	37 ± 10.1	59 ± 17.2	41 ± 20.1	0.036*
PSD	86 [70–118.5]	98 ± 33.6	78 [66–92]	85 [78–112]	90 [70.3–118.8]	0.83
GLS during exercise (%)	–7.9 ± 3	–9.1 ± 1.8	–9.9 ± 2.9	–6.8 ± 2.3	–6.1 ± 3.5	0.034
Yu during exercise (ms)	42 ± 17.5	36 ± 21.5	44 ± 13.8	40 ± 16.6	45 ± 19	0.844
VO_2 max (mL/kg/min)	13.8 [10.4–20.6]	18.3 ± 7	17.9 ± 6	15.8 ± 6	7.1 [7.1–13]	0.067
MET	4 [3–5.9]	5.2 ± 2	5.1 ± 1.7	4.5 ± 1.7	2 [2–3.7]	0.067

*Values are presented as mean ± standard deviation, median [interquartile range], or number (%) of patients, as appropriate. Between-group comparisons were performed using one-way ANOVA or Kruskal–Wallis test for continuous variables, according to data distribution, and chi-square test for categorical variables. When overall between-group comparisons were significant, post hoc pairwise comparisons were performed using Bonferroni correction after one-way ANOVA and Dunn's test with Bonferroni adjustment after Kruskal–Wallis tests. *Statistically significant between-group difference. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; GLS: global longitudinal strain; IVD: intraventricular dyssynchrony; LA: left atrium; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; MET: metabolic equivalent; NYHA: New York Heart Association; OAC: oral anticoagulant; PSD: peak systolic displacement; RBBB: right bundle branch block; TAPSE: tricuspid annular plane systolic excursion; VO_2 max: maximal oxygen uptake.*

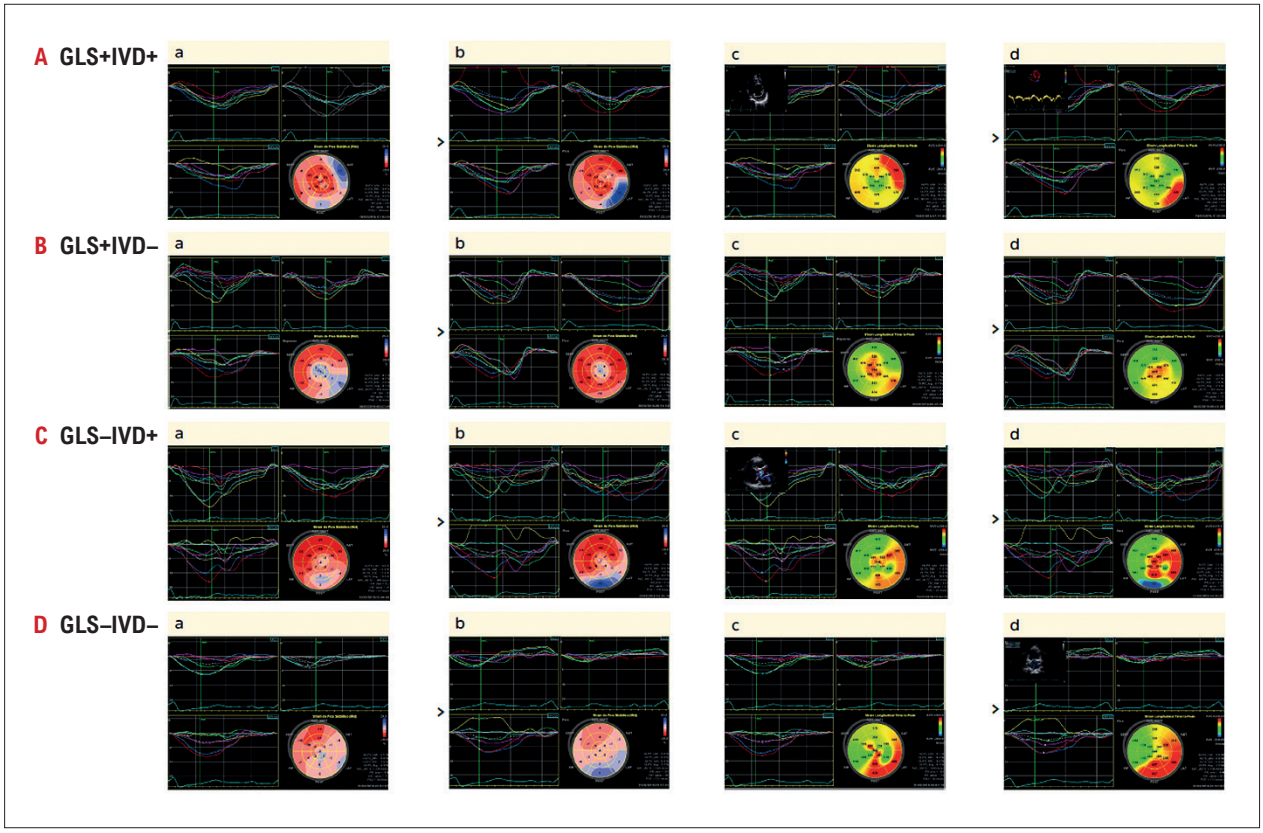


Figure 1 – *Examples illustrating the behavior of myocardial mechanics (global longitudinal strain and intraventricular dyssynchrony) at rest and after exercise in patients with chronic Chagas heart disease among the study groups. GLS: global longitudinal strain; IVD: intraventricular dyssynchrony.*

Previous research by our group established the feasibility of assessing mechanical patterns under exercise in CCC.[9] The present investigation extends those observations by linking dynamic mechanical behavior to clinical outcomes and pathophysiologic mechanisms. Importantly, the variability of GLS and IVD between rest and exercise was documented by dividing patients into four different subgroups, with different echocardiographic and exercise profiles, but with similar resting LVEF and GLS values.

Although the absolute changes in GLS and dyssynchrony parameters were small, the key finding of this study lies not in the magnitude of variation but in the directional and integrative response under stress conditions. In advanced cardiomyopathy, even subtle changes during stress may reflect underlying myocardial reserve and electromechanical adaptability. Thus, the combination of strain and dyssynchrony responses provides a functional phenotype, rather than relying on absolute cutoff values. This concept is aligned with prior observations that dynamic responses to stress may carry incremental prognostic value beyond resting measurements, particularly in advanced disease stages.[13]

In addition, the GLS and IVD dynamic response pattern between rest and exertion was associated with the composite outcome (death, heart transplantation, and hospitalization for HF), insofar as the group with the least favorable GLS and IVD responses on exertion presented more outcomes in relation to the other groups, similarly demonstrated in other populations with HF.[14,15]

In our study, TAPSE was the only resting parameter to significantly predict the primary outcome. However, our cohort already presented baseline right ventricular (RV) dysfunction (median TAPSE 16 mm). While RV failure is a known late-stage predictor in Chagas disease,[16,17] the integration of GLS and IVD identifies the specific mechanical phenotypes that drive progressive left ventricular failure even when the RV is already compromised, offering a more nuanced framework for myocardial exhaustion in advanced CCC.

Our sample differs from other studies with CCC in terms of the severity of the patients included, since it approached a population with lower values of GLS and LVEF.[18,19] In addition to the reduced LVEF, GLS values $< -8\%$ have been considered a marker of very severe LVD[10] and were present in the majority of the sample, which may have intrinsically contributed to the high number of events observed. Furthermore, most of the sample had significant IVD (Yu index ≥ 33 ms) at rest, a more expressive number than that found in other studies that evaluated it in populations of patients with HF with reduced ejection fraction, even with LBBB.[20-22]

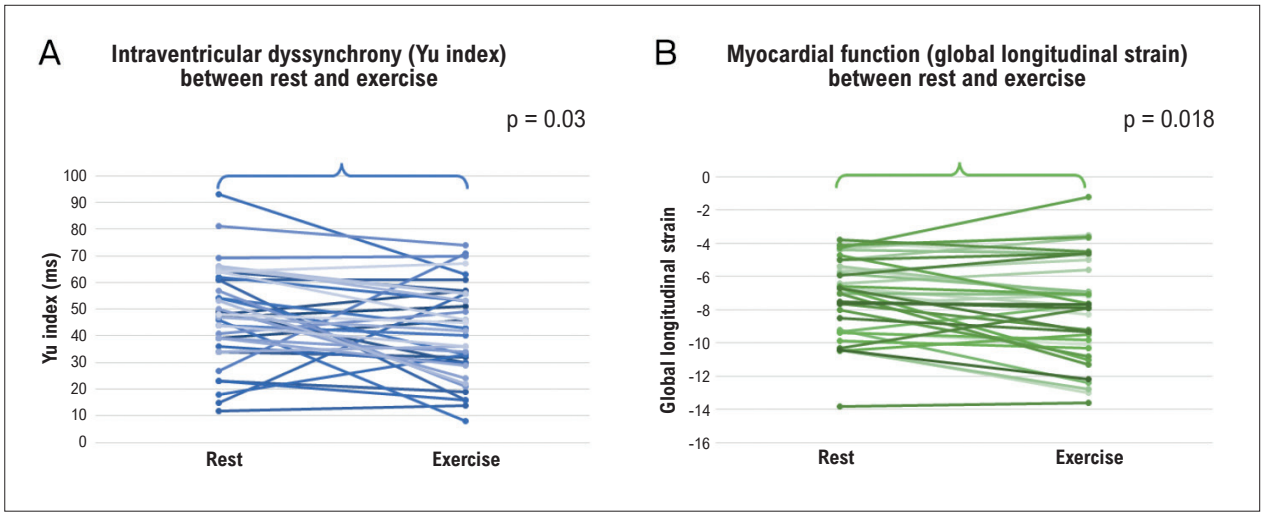


Figure 2 – *Dynamic assessment of intraventricular dyssynchrony (Yu index) between rest and exercise (A) and myocardial function (global longitudinal strain) (B) in the entire sample.*

Table 2 – Primary and secondary outcomes in the total sample and among groups according to changes in GLS and IVD

	Total (n=40)	GLS+IVD+ (n=9)	GLS+IVD– (n=9)	GLS–IVD+ (n=10)	GLS–IVD– (n=10)	p
Death, heart transplantation, and hospitalization due to HF	20 (50%)	3 (15%)	3 (15%)	5 (25%)	9 (45%)	0.005
Death and heart transplant	14 (35%)	2 (14.3%)	2 (14.3%)	4 (28.6%)	6 (42.8%)	0.15

GLS: global longitudinal strain; HF: heart failure; IVD: intraventricular dyssynchrony.

The coexistence of absent contractile reserve and exercise-induced dyssynchrony likely represents a phenotype of mechanical exhaustion, characterized by limited myocardial recruitability and progressive loss of temporal coordination. Although the absolute changes in GLS and IVD from rest to exercise were modest, the direction of these dynamic responses appeared to be clinically relevant.

Patients demonstrating a tendency toward improved contractility and reduced dyssynchrony under physiologic stress likely represent an adaptive mechanical phenotype, characterized by preserved myocardial recruitability and coordinated systolic timing, which translated into better prognosis. Conversely, persistence or worsening of impaired strain and mechanical dispersion during exercise identified a mechanical exhaustion phenotype, suggesting limited contractile reserve and progressive temporal dyssynchronization, a condition associated with poor two-year outcomes, as demonstrated in our cohort.

Patients with CCC have a low prevalence of LBBB,[7] which limits CRT indications in this population due to the lack of evidence for more favorable outcomes in a group that predominantly demonstrates non-LBBB IVCD.[8,23] It therefore remains relevant to determine whether CRT is useful in patients who continue to exhibit dyssynchrony and who obtain better left ventricular function during exercise (GLS+IVD− subgroup), that is, patients with a greater degree of dyssynchrony who still have contractile reserve. Dynamic mechanical phenotyping may help refine patient selection for these advanced strategies.

This study has several limitations. First, the small sample size, male predominance, limited number of events, and relatively short follow-up duration restrict statistical power and limit the robustness of inferential analyses.

Second, the use of convenience sampling may introduce selection bias and limit external validity. Third, the definition of contractile reserve based on a population-derived threshold reflects a data-driven approach and should not be interpreted as a clinically validated cutoff.

Fourth, subgroup stratification resulted in small groups, which may reduce robustness. Finally, the use of conventional parameters for RV assessment may not fully capture the complexity of RV involvement in Chagas cardiomyopathy, as, at the time of study design, RV free-wall strain was not systematically available in our laboratory workflow.

Conclusions

The integration of contractile reserve and intraventricular dyssynchrony under physiologic stress may provide mechanistic insights into myocardial dysfunction and is

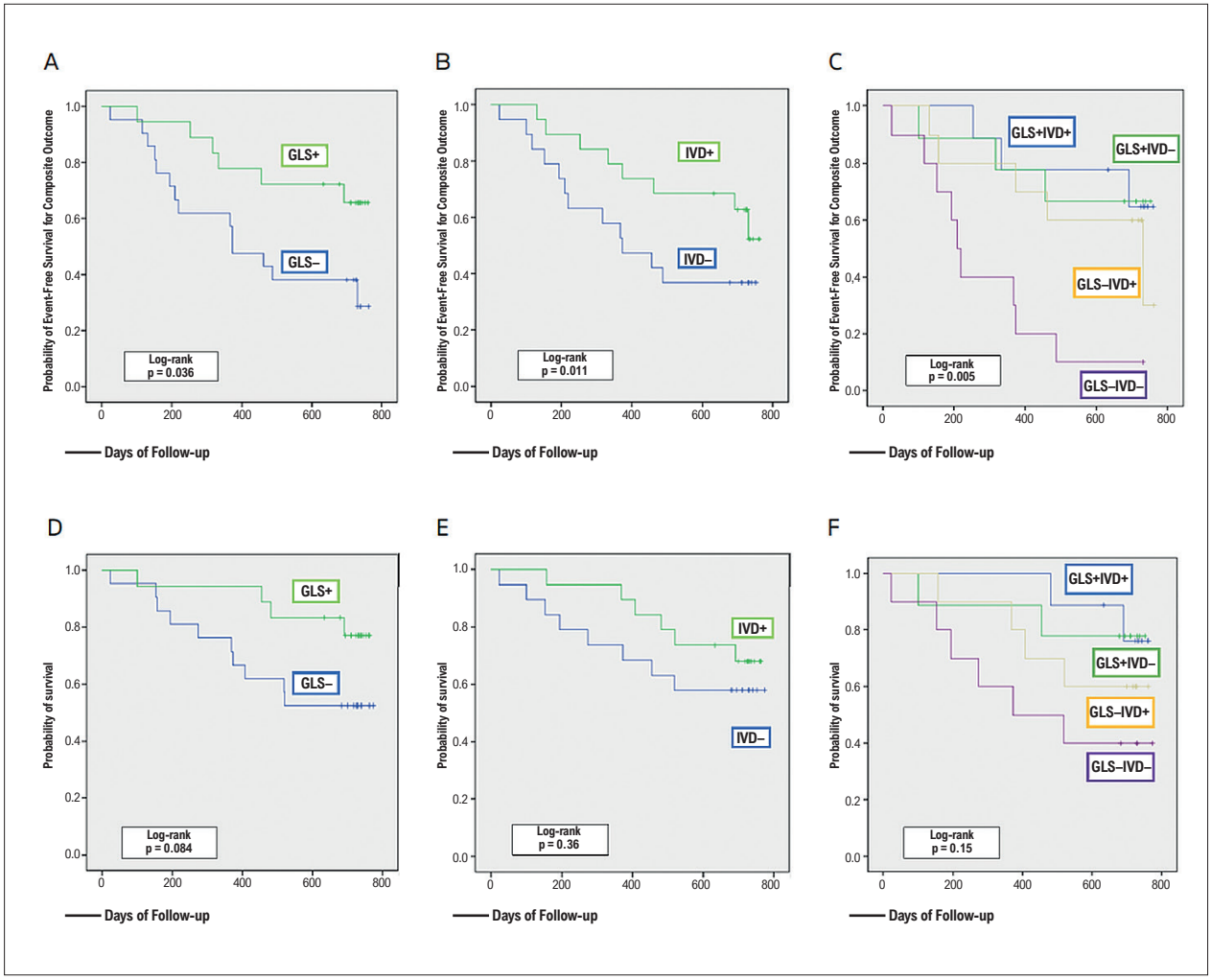


Figure 3 – *Kaplan–Meier probability curves of survival free of the composite primary outcome (A, B, and C) and survival free of death (D, E, and F) according to changes in global longitudinal strain from rest to exercise (A and D), changes in intraventricular dyssynchrony from rest to exercise (B and E), and the groups evaluated in the study (C and F).*

associated with clinical outcomes in patients with CCC.

These findings support the concept of dynamic mechanical phenotyping as a promising framework for functional assessment, although larger studies are needed to validate its prognostic value.

Author Contributions

Conception and design of the research: Athayde GAT, Martins SAM, Siqueira SF, Mathias W, Martinelli Filho M; Acquisition of data: Athayde GAT, Borges BCC, Oliveira CP, Mathias W; Analysis and interpretation of the data: Athayde GAT, Borges BCC, Pinheiro AO, Souza AL, Oliveira CP, Martins SAM, Siqueira SF, Mathias W, Martinelli Filho M; Statistical analysis: Athayde GAT, Pinheiro AO, Souza AL; Writing of the manuscript: Athayde GAT, Teixeira RA; Critical revision of the manuscript for intellectual content: Athayde GAT, Martins SAM, Teixeira RA, Siqueira SF, Mathias W, Martinelli Filho M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of Doctoral submitted by Guilherme Augusto Teodoro Athayde, from Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the CAPPesq under the protocol number 5556/18. All the

Table 3 – Univariate and multivariable predictors of the primary outcome by Cox regression analysis

	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	0.99 (0.95–1.04)	0.742		
QRS (ms)	1.01 (0.99–1.02)	0.451		
LA volume (mL)	1.03 (1.01–1.04)	0.006*	1.02 (1.00–1.04)	0.101
LVDD (mm)	1.02 (0.96–1.08)	0.538		
LVSD (mm)	1.03 (0.98–1.08)	0.319		
LVEF (%)	0.97 (0.90–1.04)	0.365		
TAPSE (cm)	0.83 (0.72–0.94)	0.005*	0.83 (0.71–0.96)	0.014*
GLS at rest (%)	0.89 (0.72–1.10)	0.286		
Yu at rest (ms)	1.00 (0.98–1.03)	0.916		
GLS on exertion (%)	0.83 (0.70–0.99)	0.035*	0.98 (0.81–1.19)	0.845
Yu on exertion (ms)	1.02 (0.99–1.04)	0.232		
Delta-GLS (%)‡	0.80 (0.61–1.05)	0.102		
Delta-Yu (ms)‡	1.01 (0.99–1.03)	0.446		
VO_2 max (mL/kg/min)	0.96 (0.89–1.02)	0.194		
MET	0.85 (0.67–1.08)	0.194		

Values are medians and interquartile ranges or numbers (%) of patients. CI: confidence interval; GLS: global longitudinal strain; HR: hazard ratio; IVD: intraventricular dyssynchrony; LA: left atrium; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; MET: metabolic equivalent; TAPSE: tricuspid annular plane systolic excursion; VO_2 max: maximal oxygen uptake. ‡Delta-GLS and delta-Yu refer to variation between values on exertion and at rest.

procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT for translation, grammatical correction, and the creation of the central illustration. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

References

1. Stipac AV, Otasević P, Popović ZB, Cvorović V, Putniković B, Stanković I, et al. Prognostic Significance of Contractile Reserve Assessed by Dobutamine-Induced Changes of Tei Index in Patients with Idiopathic Dilated Cardiomyopathy. Eur J Echocardiogr. 2010;11(3):264-70. doi: 10.1093/ejechocard/jep208.
2. Matsumoto K, Tanaka H, Onishi A, Motoji Y, Tatsumi K, Sawa T, et al. Bi-Ventricular Contractile Reserve Offers an Incremental Prognostic Value for Patients with Dilated Cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2015;16(11):1213-23. doi: 10.1093/ehjci/jev069.
3. Kloosterman M, Damman K, Van Veldhuisen DJ, Rienstra M, Maass AH. The Importance of Myocardial Contractile Reserve in Predicting Response to Cardiac Resynchronization Therapy. Eur J Heart Fail. 2017;19(7):862-9. doi: 10.1002/ejhf.768.
4. Lafitte S, Bordachar P, Lafitte M, Garrigue S, Reuter S, Reant P, et al. Dynamic Ventricular Dyssynchrony: An Exercise-Echocardiography Study. J Am Coll Cardiol. 2006;47(11):2253-9. doi: 10.1016/j.jacc.2005.11.087.
5. D'Andrea A, Caso P, Cuomo S, Scarafile R, Salerno G, Limongelli G, et al. Effect of Dynamic Myocardial Dyssynchrony on Mitral Regurgitation during Supine Bicycle Exercise Stress Echocardiography in Patients with Idiopathic Dilated Cardiomyopathy and 'Narrow' QRS. Eur Heart J. 2007;28(8):1004-11. doi: 10.1093/eurheartj/ehm021.
6. D'Andrea A, Mele D, Nistri S, Riegler L, Galderisi M, Agricola E, et al. The Prognostic Impact of Dynamic Ventricular Dyssynchrony in Patients with Idiopathic Dilated Cardiomyopathy and Narrow QRS. Eur Heart J Cardiovasc Imaging. 2013;14(2):183-9. doi: 10.1093/ehjci/jes154.

7. Ribeiro AL, Marcolino MS, Prineas RJ, Lima-Costa MF. Electrocardiographic Abnormalities in Elderly Chagas Disease Patients: 10-Year Follow-Up of the Bambui Cohort Study of Aging. J Am Heart Assoc. 2014;3(1):e000632. doi: 10.1161/JAHA.113.000632.

8. Martinelli M Filho, Peixoto GL, Siqueira SF, Martins SAM, Nishioka SAD, Pedrosa AAA, et al. A Cohort Study of Cardiac Resynchronization Therapy in Patients with Chronic Chagas Cardiomyopathy. Europace. 2018;20(11):1813-8. doi: 10.1093/europace/eux375.

9. Athayde GAT, Borges BCC, Pinheiro AO, Souza AL, Oliveira CP, Martins SAM, et al. Myocardial Function Reclassification: Echocardiographic Strain Patterns in Patients with Chronic Chagas Cardiomyopathy and Intraventricular Dyssynchrony. Int J Cardiol. 2022;348:102-7. doi: 10.1016/j.ijcard.2021.12.005.

10. Potter E, Marwick TH. Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. JACC Cardiovasc Imaging. 2018;11(2 Pt 1):260-74. doi: 10.1016/j.jcmg.2017.11.017.

11. Yu CM, Zhang Q, Fung JW, Chan HC, Chan YS, Yip GW, et al. A Novel Tool to Assess Systolic Asynchrony and Identify Responders of Cardiac Resynchronization Therapy by Tissue Synchronization Imaging. J Am Coll Cardiol. 2005;45(5):677-84. doi: 10.1016/j.jacc.2004.12.003.

12. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032. doi: 10.1161/CIR.0000000000001063.

13. Thein PM, Mirzaee S, Cameron JD, Nasis A. Left Ventricular Contractile Reserve as a Determinant of Adverse Clinical Outcomes: A Systematic Review. Intern Med J. 2022;52(2):186-97. doi: 10.1111/imj.14995.

14. Paraskevaidis IA, Adamopoulos S, Kremastinos DT. Dobutamine Echocardiographic Study in Patients with Nonischemic Dilated Cardiomyopathy and Prognostically Borderline Values of Peak Exercise Oxygen Consumption: 18-Month Follow-Up Study. J Am Coll Cardiol. 2001;37(6):1685-91. doi: 10.1016/s0735-1097(01)01194-9.

15. Kang SJ, Lim HS, Choi BJ, Choi SY, Yoon MH, Hwang GS, et al. The Impact of Exercise-Induced Changes in Intraventricular Dyssynchrony on Functional Improvement in Patients with Nonischemic Cardiomyopathy. J Am Soc Echocardiogr. 2008;21(8):948-53. doi: 10.1016/j.echo.2008.01.009.

16. Rassi A Jr, Rassi A, Marin-Neto JA. Chagas Disease. Lancet. 2010;375(9723):1388-402. doi: 10.1016/S0140-6736(10)60061-X.

17. Nunes MC, Rocha MO, Ribeiro AL, Colosimo EA, Rezende RA, Carmo GA, et al. Right Ventricular Dysfunction is an Independent Predictor of Survival in Patients with Dilated Chronic Chagas' Cardiomyopathy. Int J Cardiol. 2008;127(3):372-9. doi: 10.1016/j.ijcard.2007.06.012.

18. García-Álvarez A, Sitges M, Regueiro A, Poyatos S, Pinazo MJ, Posada E, et al. Myocardial Deformation Analysis in Chagas Heart Disease with the Use of Speckle Tracking Echocardiography. J Card Fail. 2011;17(12):1028-34. doi: 10.1016/j.cardfail.2011.08.007.

19. Gomes VA, Alves GF, Hadlich M, Azevedo CF, Pereira IM, Santos CR, et al. Analysis of Regional Left Ventricular Strain in Patients with Chagas Disease and Normal Left Ventricular Systolic Function. J Am Soc Echocardiogr. 2016;29(7):679-88. doi: 10.1016/j.echo.2016.03.007.

20. Haghjoo M, Bagherzadeh A, Fazelifar AF, Haghighi ZO, Esmaielzadeh M, Alizadeh A, et al. Prevalence of Mechanical Dyssynchrony in Heart Failure Patients with Different QRS Durations. Pacing Clin Electrophysiol. 2007;30(5):616-22. doi: 10.1111/j.1540-8159.2007.00722.x.

21. Ghio S, Constantin C, Klersy C, Serio A, Fontana A, Campana C, et al. Interventricular and Intraventricular Dyssynchrony are Common in Heart Failure Patients, Regardless of QRS Duration. Eur Heart J. 2004;25(7):571-8. doi: 10.1016/j.ehj.2003.09.030.

22. Emkanjoo Z, Esmaeilzadeh M, Hadi NM, Alizadeh A, Tayyebi M, Sadr-Ameli MA. Frequency of Inter- and Intraventricular Dyssynchrony in Patients with Heart Failure According to QRS Width. Europace. 2007;9(12):1171-6. doi: 10.1093/europace/eum234.

23. Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A, et al. Surface Electrocardiogram to Predict Outcome in Candidates for Cardiac Resynchronization Therapy: A Sub-Analysis of the CARE-HF Trial. Eur J Heart Fail. 2009;11(7):699-705. doi: 10.1093/eurjhf/hfp074.

This is an open-access article distributed under the terms of the Creative Commons Attribution License