Reproducibility of global LV function and dyssynchrony parameters derived from phase analysis of gated myocardial perfusion SPECT: A multicenter comparison with core laboratory setting

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Background. **Gated myocardial perfusion scintigraphy (GMPS) phase analysis is an important tool to investigate the physiology of left ventricular (LV) dyssynchrony. We aimed to test the performance of GMPS LV function and phase analysis in different clinical settings and on a diverse population.**

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Methods. **This is a post hoc analysis of a prospective, non-randomized, multinational, multicenter cohort study. Clinical evaluation and GMPS prior to cardiac resynchronization therapy (CRT)(baseline) and 6-month post CRT (follow-up) were done. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), LV ejection fraction (LVEF), LV phase standard deviation (LVPSD), and percentage of left ventricle non-viable (PLVNV) were obtained by 10 centers and compared to the core lab.**

Results. **276 GMPS studies had all data available from individual sites and from core lab. There were no statistically significant differences between all variables except for LVPSD. When subjects with no mechanical dyssynchrony were excluded, LVPSD difference became non-significant. LVESV, LVEF, LVPSD and PLVNV had strong correlation in site against core lab comparison. Bland–Altman plots demonstrated good agreement.**

Conclusions. **The presented correlation and agreement of LV function and dyssynchrony analysis over different sites with a diverse sample corroborate the strength of GMPS in the management of heart failure in clinical practice. (J Nucl Cardiol 2022;29:952–61.)**

Key Words: MPI • Gated SPECT • Phase analysis • Dyssynchrony • Heart failure

Abbreviations

CRT	Cardiac resynchronization therapy
ECTb4	Emory cardiac toolbox version 4.0
GMPS	Gated myocardial perfusion SPECT
LBBB	Left bundle branch block
LVEDV	Left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end systolic volume
LVPBW	Left ventricular phase histogram bandwidth
LVPSD	Left ventricular phase histogram standard deviation
PLVNV	Percentage of left ventricle non-viable (< 50%)

See related editorial, pp. 962–964

INTRODUCTION

Cardiovascular diseases (CVD) are the most important cause of deaths in the world.[1] In the US population 36,6% of adults have been diagnosed with CVD and it is expected that more than 130 million adults will have some form of cardiovascular complication in 2035 with the total estimated cost of $1,1 trilion.[2] In particular heart failure (HF) was the responsible for 9% of the 836546 CVD deaths in 2015 and an increasing prevalence of 6,5 million was estimated. HF had a total cost of $30,7 billion in 2012 and an increase of 127% is projected for 2030.[2]

Multisite ventricular pacing, also called biventricular pacing or most commonly cardiac resynchronization therapy (CRT), helps to restore atrioventricular interval, inter- and intra-ventricular synchrony, improving left ventricle (LV) function and perfusion.[3,4] As stated by American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) in the 2012 update report,[5] CRT has impact on hospitalizations (30% decrease) and on mortality rate (24% to 36% reduction).[6–8] Unfortunately, no single measure is capable to accurately predict the response to CRT [9,10] and various parameters have been tested for CRT evaluation.[4,6,11–13] In effect, even with strong recommendation by international guidelines together with an established selection criteria, a significant percentage of patients (20% to 40%) did not benefit from CRT.[14–16]

In this sense, Myocardial Perfusion Imaging (MPI) has presented a role for CRT because of its ability to assess scar burden and location, LV function, LV site of the latest contraction, and mechanical dyssynchrony from a single scan.[17,18] Gated myocardial perfusion SPECT (GMPS) left ventricular phase histogram bandwidth (LVPBW) and left ventricular phase standard deviation (LVPSD) were shown to be accurate predictors of CRT response.[19] Single center studies have also demonstrated that positioning the LV CRT lead in the last viable segment to contract yields optimal resynchronization results.[20] Similarly, the international multicenter study VISION-CRT demonstrated that LV dyssynchrony improvement when obtained by GMPS had predicted clinical outcomes in patients undergoing CRT.[21] Moreover systolic LV function measured by LVEF is stated as linearly correlated with dyssynchrony.[22]

It is clear now that GMPS phase analysis is an important tool to investigate the physiology of LV dyssynchrony. However, the feasibility of the method for the clinical practice requires further studies. Some methods are vulnerable to subjective assessment of the myocardial function that is associated with the potential for differences in interpretation by different readers influencing its generalizability.[23] Any technology can be hampered in the process of translating to a generalized setting and for its widespread use by needs such as special expertise, high level training, interobserver and

intraobserver variability, and cost. GMPS studies need to be of high-quality with good myocardial counts to reduce inaccuracies for the evaluation of mechanical dyssynchrony.[24]

In order to investigate this specific topic, we aimed to test the performance of GMPS LV function and phase analysis parameters in different clinical settings and on a diverse population of patients evaluating the differences, correlation, and concordance between site and nuclear core laboratory interpretation.

METHODS

This is a post hoc analysis of a prospective, non-randomized, multinational, multicenter cohort study ''Value of intraventricular synchronism assessment by gated-SPECT myocardial perfusion imaging in the management of HF patients submitted to CRT'' (IAEA VISION-CRT) funded by the International Atomic Energy Agency (IAEA). The methods used in VISION-CRT have been extensively described before.[4,21] The trial involved ten centers from eight countries (Brazil, Chile, Colombia, Cuba, India, Mexico, Pakistan, and Spain). Clinical evaluation and Tc99m-MIBI GMPS prior to CRT (baseline) and 6-month post CRT (follow-up) were done. The demographic and clinical data were collected independently and submitted by each center to the core clinical management center in IAEA headquarters, Vienna. As reported by Peix et al, 198 patients underwent CRT in the IAEA VISION-CRT trial, 195 patients had clinical 6-month follow-up assessed and 179 were included in the final analysis. Sixteen patients died between the baseline and follow-up period.

The standard indication according to the guidelines for CRT implantation was evaluated at the time of implantation. Patients with LVEF $\leq$ 35% and QRS duration $>$ 120 ms in sinus rhythm were included. Exclusion criteria were as follows: arrhythmias that prevented optimal gated acquisition; major coexisting illness affecting survival less than one year; right bundle branch block (RBBB); pregnancy or breast-feeding; acute coronary syndromes, coronary artery bypass grafting or percutaneous coronary intervention in the last three months before enrolment and within six months of CRT implantation.

According to Henneman et al and as described in the IAEA guidance for heart failure a LVPSD cut-off value of 43^{o} as measured by ECTb4 was used for the prediction of response to CRT.[18,25] Minnesota Living with Heart Failure questionnaire (MLHFQ®) and New York Heart Association Class (NYHA class) were also used to evaluate CRT response.

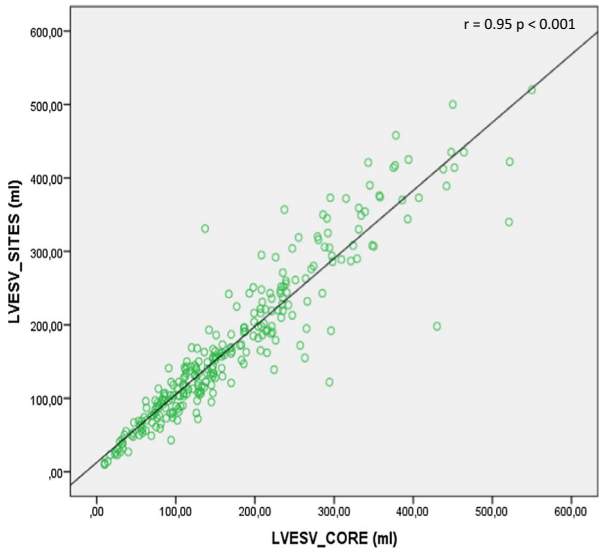

Figure 1. Scatter plot showing correlation between LVESV from sites vs LVESV from core lab. *LVESV* Left ventricular end systolic volume.

SPECT Acquisition and Data Analysis

VISION-CRT methods for standardizing acquisition and Data Analysis have been described in detail elsewhere,[21] briefly, GMPS scans were acquired 30 minutes post rest injection using 740 to 1110 MBq (20 to 30 mCi) of 99mTc-sestamibi. The images were reconstructed using the same iterative method and standardized settings (Ordered subset expectation maximization—OSEM, 3 iterations, 10 subsets, Butterworth filter, power 10, cut-off frequency of 0.3 cycles/mm). All reconstructed transaxial slices were reoriented to short axis slices and sent to ECTb4 (Emory Cardiac Toolbox, Atlanta, GA) where they underwent perfusion, function and phase dyssynchrony analysis[21] by experts at the individual centers without any specific training for this study. The raw planar projections were also sent to the Emory core lab where the same procedure as the sites was done independently blinded to the results for all patients from the ten centers and from clinical data. All the clinical sites and the core lab evaluated the quality of each study. The two main acquisition parameters were the accuracy of the ECG gating and the counts per voxel in the LV myocardial short axis slices as described in Jimenez-Heffernan et al[26] The usual processing parameters extracted from the automatic processing were confirmed or manually edited, particularly the orientation angle of the LV and the base detection. The parameters obtained by the 10 centers and then compared to the core lab were left ventricular end

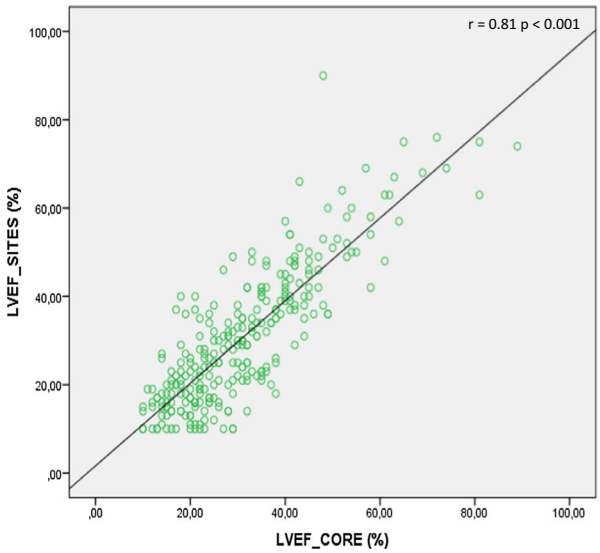

Figure 2. Scatter plot showing correlation between LVEF from sites vs LVEF from core lab. *LVEF* Left ventricular ejection fraction.

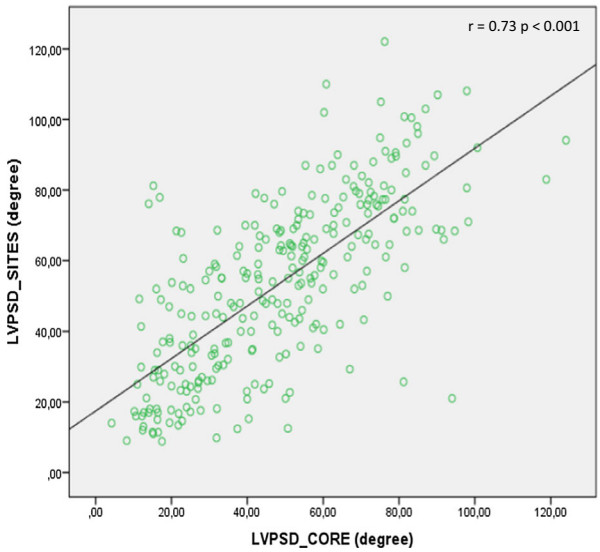

Figure 3. Scatter plot showing correlation between LVPSD from sites vs LVPSD from core lab. *LVPSD* Left ventricular phase histogram standard deviation.

systolic volume (LVESV), left ventricular end diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), left ventricular phase histogram standard deviation (LVPSD) and percentage of left ventricle non-viable (PLVNV). In addition, LVPSD and their difference between baseline and follow-up was compared selecting those with dyssynchrony criteria (LVPSD $\geq 43^{o}$) at baseline.[18] PLVNV was determined as the percent of LV myocardial voxels that were determined to be non-viable. Non-viable voxels were determined to

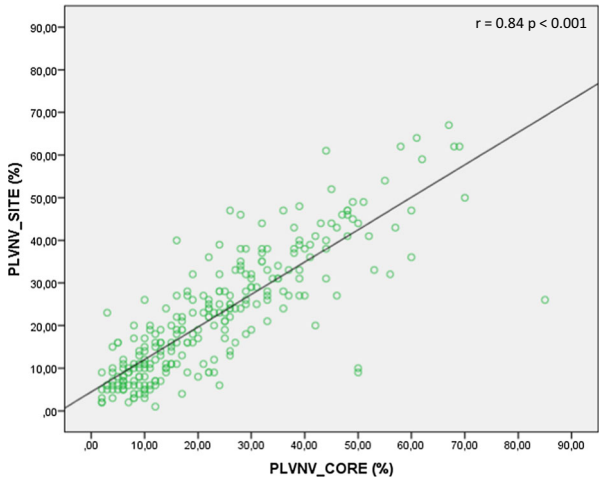

Figure 4. Scatter plot showing correlation between PLVNV from sites vs PLVNV from core lab. *PLVNV* Percentage of left ventricle non-viable (< 50%).

be those with normalized uptake less than 50% of the maximal LV normalized uptake (most-normal voxel).

Statistical Analysis

Statistical analysis was carried out using SPSS 21 (IBM). Data were presented as number, percentage (%), and mean ± SD/median (min–max) as appropriate. The differences between parameters from the 10 centers and from the core lab were obtained using paired samples Wilcoxon signed rank test. Linear regression was done to demonstrate the correlations and Spearman rank correlation coefficient were calculated. Bland–Altman analysis was done for concordance evaluation with 95% limits of agreement for each comparison (average difference ± 1.96 standard deviation of the difference). $P < .05$ was considered to be statistically significant.

RESULTS

A total of 195 patients were enrolled in the trial. The baseline clinical characteristics are presented in Table 1. From this sample, for the post hoc analysis, 276 GMPS studies had all data available from individual sites and from core lab, of which 147 were baseline data and 129 were follow-up data.

The adequacy of the technical quality of the SPECT studies as independently determined by the core lab and the individual sites is shown on Table 2. The criteria for adequacy used were primarily LV count density and ECG gating accuracy as described in detail elsewhere.[26] These results demonstrate that only a small number of studies were considered to be of inadequate quality. A total of 21 patients' scans were considered inadequate

Table 1. Baseline clinical characteristics of patients

Variable	N = 195
Age, years	60 (11)
Females, N (%)	74 (38)
Height, cm	164 (11)
Weight, kg	71 (15)
Ethnicity	
Hispanic	101 (52)
Asian	12 (6)
Indian	38 (19)
Caucasian	26 (13)
African	18 (9)
History of CAD	60 (31)
Previous myocardial infarction	42 (22)
Previous revascularization	9 (5%)
Hypertension	111 (57)
Diabetes	50 (26)
Dyslipidemia	56 (29)
Smoking	38 (19)
Medical treatment	
Aspirin	96 (49)
Beta blockers	167 (85)
ACE inhibitors	118 (61)
ARBs	51 (26)
Diuretics	160 (82)
Statins	74 (38)
Aspirin	96 (49)

Age, height, and weight are expressed as mean ± SD. The rest of variables are presented as the number (%)
ACE angiotensin-converting-enzyme, *ARB* angiotensin II receptor blocker, *CAD* coronary artery disease

because of issues like gating errors, patient movement, low counts, or extracardiac uptake. However even these data were not excluded from the analysis in order to better represent clinical practice issues.

Reproducibility of Parameters of LV Function

There were no statistically significant differences between the parameters obtained by sites and by core lab for all variables except for LVPSD (Table 3). However, when subjects with no mechanical dyssynchrony were excluded (cutoff value of $< 43°$), the LVPSD difference became non-significant. According to the core lab analysis 157 of 276 (56.9%) of the patients had mechanical dyssynchrony while for sites analysis it was present in 179 of 276 (64.8%).

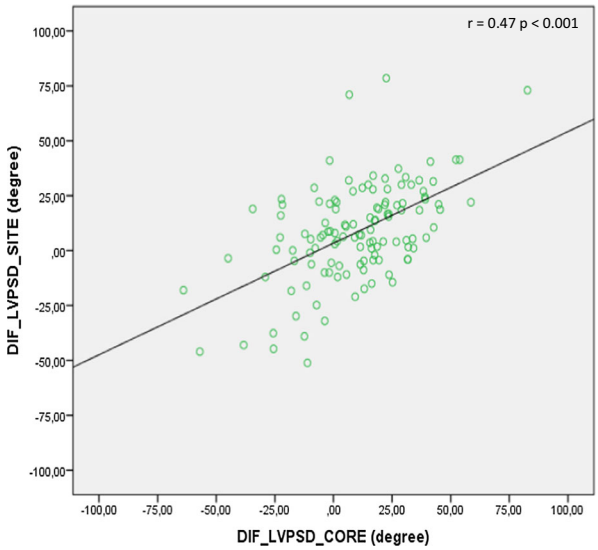

Figure 5. Scatter plot showing correlation between LVPSD changes from basal to follow up phase analysis from sites vs LVPSD changes from core lab. *LVPSD* Left ventricular phase histogram standard deviation.

As demonstrated in Figs. 1, 2, 3 and 4, the LVESV, LVEF, LVPSD and PLVNV obtained by the individual sites had a strong correlation with the same parameters when obtained by the core lab.

An additional analysis was done taking under consideration the change in LVPSD before (basal) and 6 months after (follow-up) CRT. The correlation between sites and core lab was 0.47 ($P < .001$) and it is shown in Fig. 5.

The Bland–Altman plots (Figs. 6, 7 and 8) also demonstrate good agreement between sites and core lab. Only LVESV tended to have an increase in the variability related to ventricle volume.

DISCUSSION

In this study we demonstrate the robustness of gated myocardial perfusion SPECT for quantification of LV function and phase analysis in a multicenter comparison. To our knowledge, this is the first study to compare GMPS performance for dyssynchrony. A total of ten nuclear medicine departments from eight different countries and with diverse population were compared to a reference lab showing the feasibility of the method in a generalized clinical practice. Many studies have looked for markers of CRT response analyzing different methods and promising results were obtained from single center studies.[12,19,27–32] In contrast, no multicenter trial was able to replicate those outcomes. The Predictors of Response to CRT (PROSPECT) trial enrolled 498 patients from fifty-three centers in Europe,

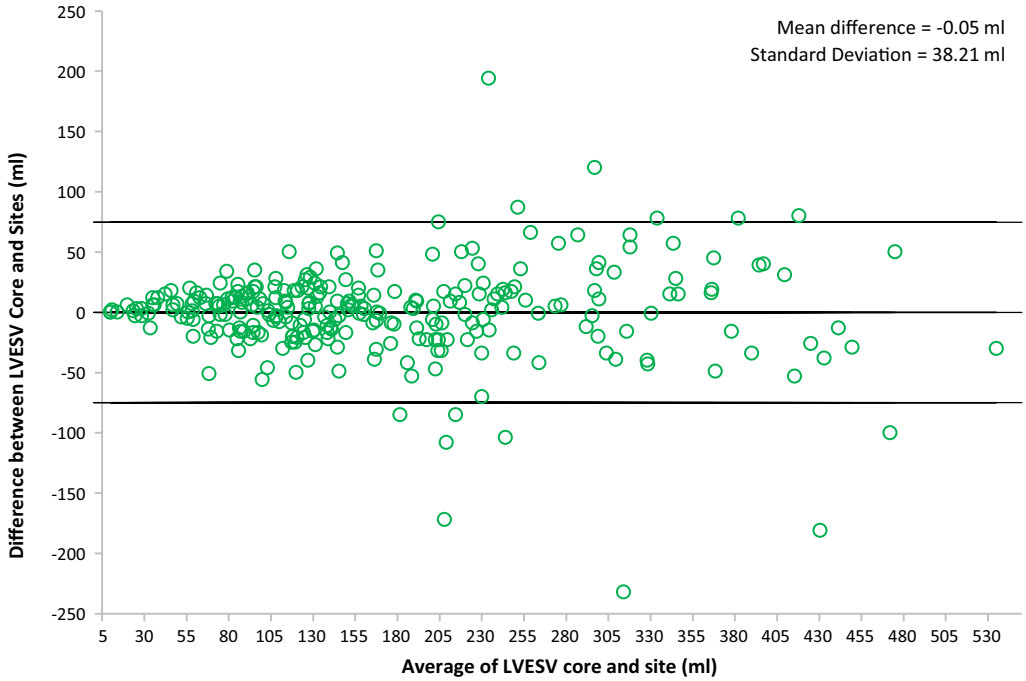

Figure 6. Agreement between core and sites for LVESV (Bland–Altman plot). *LVESV* Left ventricular end systolic volume.

Table 2. Adequacy comparison

Quality evaluation	Core	Sites
Excellent	84	72
Good	92	131
Adequate	91	67
Inadequate	9	6

Hong Kong, and the United States and succeed to predict response applying twelve echocardiographic parameters, however the large variability in the results prevented any recommendation.[27] The authors showed that the sensitivity ranged from 9% to 77% and specificity from 31% to 93% for the ESV response criteria.[27]

In our post hoc analysis there was no statistical difference between individual sites and core lab when comparing quantitative GMPS parameters for LV function as left ventricular ejection fraction, percentage of left ventricle non-viable, end-systolic and end-diastolic volumes. Equally, regarding to dyssynchrony phase analysis, phase standard deviation were not different between centers when those below the 43° dyssynchrony criteria were excluded.[18] Other important result was that strong correlations between sites and core lab were shown for all parameters as well as for the change in LVPSD at baseline, before CRT, and at follow-up, 6 months after the therapeutic procedure. The agreement between departments was also demonstrated to be acceptable independent of parameter magnitude.

The good reproducibility of GMPS quantification reported here can be partially explained by the standardization of the acquisition procedure. No modification or specific training were made in relation to GMPS acquisition protocol long ago used for coronary artery disease,[33] except for an established minimum quality criteria. The simplicity and high level of standardization of this technique is in contrast to other imaging modalities more prone to user interactions and cultural differences.[27]

The semi-automatic characteristic of the software applied to reorient the LV axis and to calculate the LV function and dyssynchrony parameters can also help to elucidate the smaller variance of GMPS quantification in comparison to other techniques. It requires minimum or no user intervention, nevertheless the phase analysis is more susceptible to variations as demonstrated by Folks et al[34] Technical aspects of acquiring and processing these studies are described in detail by Heffernan et al.[26]

The significant differences found in measuring LVPSD between the sites and the core laboratory is a finding that points to the need for improving the measurement. The main

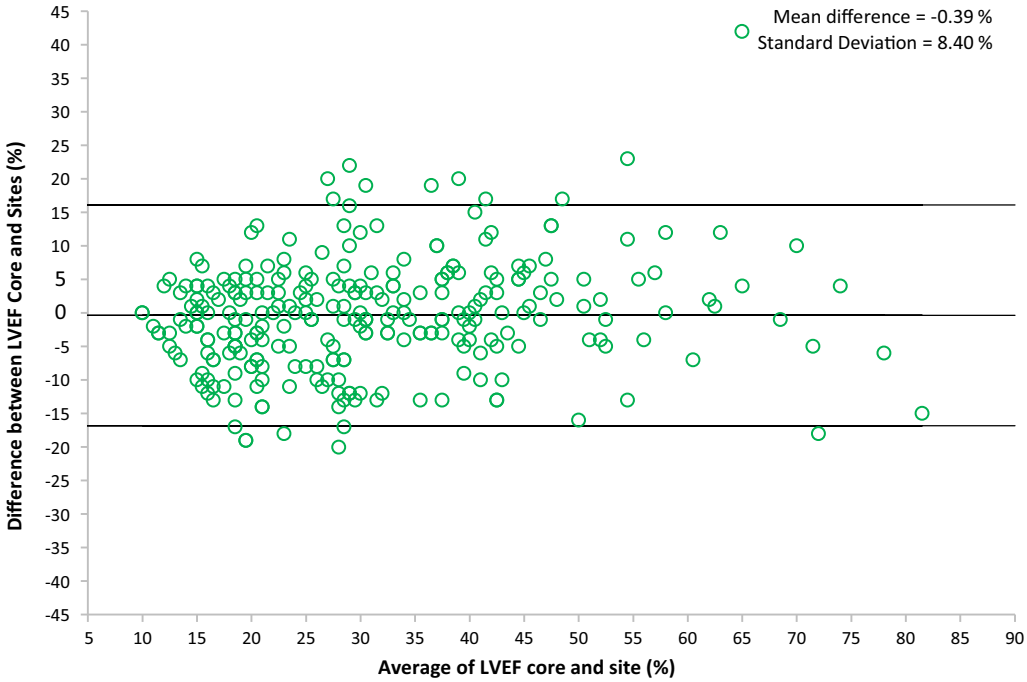

Figure 7. Agreement between core and sites for LVEF (Bland–Altman plot). *LVEF* Left ventricular ejection fraction.

variables that caused this difference were as follows: (1) although the acquisition projections used were the same for the site and core lab, each study was reconstructed from the beginning by a different operator for each site and for the core lab, (2) each study was also reoriented manually by a different operator, (3) the base selection, when deemed to need manual repositioning was done by different operators, and (4) it is known that base selection and thus LVPSD measurement is less reliable in patients with severe LV dysfunction due to shape remodeling.[35] Although we are working in improving the LVPSD reproducibility, the excellent agreements between core and sites in LVESV, LVEDV and LVEF is a positive trend that indicate we are close to target. Moreover, the excellent repeatability and reproducibility reported by Trimble et al[35] in measuring LVPSD in one laboratory indicate that perhaps site training in reconstruction and reorientation would have been beneficial to our study.

This study has several limitations. First of all, it was a post hoc analysis of a prospective non-randomized trial, so the sample size was too small for intra and inter individual sites comparison. Another limitation was that all centers used the same software (ECTb) for cardiac orientation and parameters estimation. Because the approaches of other software providers to quantify LV function and dyssynchrony are different, the results from one cannot be directly translated to other.[36,37] Further studies are required to address these issues. Additionally, as presented in Table 1, the BMI range reported in our population from developing countries is lower than those reported for the USA populations. Since BMI is known to be associated with image quality, the generalizability of our results should be applied with caution. LVPBW reproducibility was not assessed in this study because it is known that it is associated with a larger degree of variability compared to LVPSD, particularly in patients with LV dysfunction.[35] Finally, another limitation is that repeatability of the results could not be tested as the two studies in each patient were acquired six months apart with the CRT treatment in between.

NEW KNOWLEDGE GAINED

GMPS has presented a role for CRT because of its ability to assess scar burden and location, LV function, LV site of the latest contraction, and mechanical dyssynchrony from a single scan. In this sense, our work demonstrates that GMPS is reproducible and correlates not only for synchronicity results but for most of the LV functional parameters. The procedure robustness was shown from image reconstruction to the quantification. It is important for the translation of GMPS phase analysis for clinical practice and for its applicability on international multicenter trials.

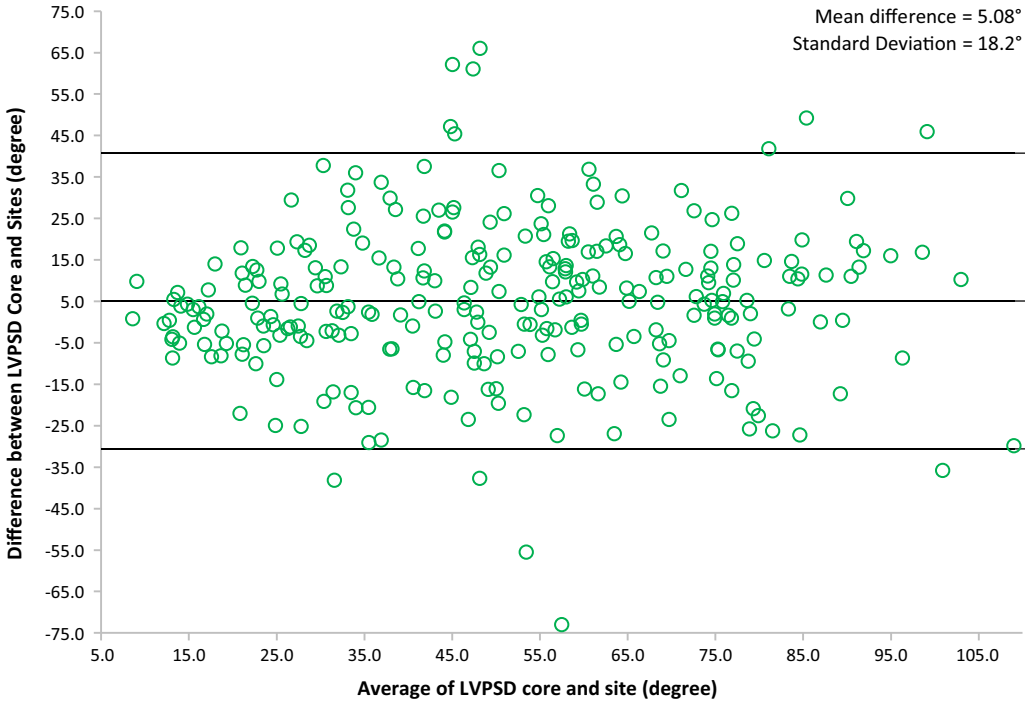

Figure 8. Agreement between core and sites for LVPSD (Bland–Altman plot). *LVPSD* Left ventricular phase histogram standard deviation.

Table 3. Parameters of LV Function

Variable	Sites		Core		*P*
LVESV	143.0	(96.0, 230.2)	147.0	(94.0, 232.0)	.44
LVEDV	206.5	(151.2, 293.2)	204.0	(152.0, 299.7)	.57
LVEF	28.5	(18.0, 40.0)	29.0	(21.0, 39.7)	.28
PLVNV	19.0	(10.0, 31.0)	20.0	(10.0, 32.0)	.16
LVPSD	55.0	(33.3, 71.5)	48.5	(27.3, 66.8)	< .001
LVPSD[a] (n = 96)	68.9	(57.0, 79.9)	63.9	(54.1, 75.9)	.02
Δ LVPSD[b] (n = 122)	7.4	(− 4.3, 22.0)	9.5	(− 4.0, 24.1)	.18

Sites against core lab comparison (*n* = 276)
Values are in median (quartile)
[a]LVPSD at baseline and cutoff value of < 43°
[b]LVPSD difference with cutoff value of < 43°

CONCLUSIONS

The absence of statistical differences, the good correlation, and the agreement of LV function and dyssynchrony analysis over different sites and with a diverse sample of individuals presented in this study corroborate the role of GMPS in the clinical practice for heart failure. In particular, LVPSD seems to be more prone to variations requiring more attention by the experts during processing.

Author contributions

FAF, AP, CTM, EVG: Conception and design or analysis and interpretation of data, or both; drafting of the manuscript or revising it critically for important intellectual content; and

final approval of the manuscript submitted. RG, GK, TM, CP, LMP, AJH, EA, SB, AK, VM, OM, DP: Conception and design or analysis and interpretation of data, or both.

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Disclosure

Dr. Ernest Garcia receives royalties from the sale of the Emory Cardiac Toolbox and has equity positions with Syntermed, Inc. The terms of these arrangements have been reviewed and approved by Emory University in accordance with its conflict of interest policies. Fernando Fernandes, Amalia Peix, Raffaele Giubbini, Ganesan Karthikeyan, Teresa Massardo, Chetan Patel, Luz Pabon, Amelia Heffernan, Erick Alexanderson, Sadaf Butt, Alka Kumar, Victor Marin, Olga Morozova, Diana Paez, and Claudio Mesquita have no conflicts of interest to disclose.

Ethical approval

The study was approved by the participant countries' scientific councils and complies with the Declaration of Helsinki.

Informed consent

Written informed consent was obtained from all participants and patient anonymity was maintained during data analysis

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