Equilibrium Radionuclide Angiography in Evaluation of Left Ventricular Mechanical Dyssynchrony in Patients with Dilated Cardiomyopathy: Comparison with Electrocardiographic Parameters and Speckle-Tracking Echocardiography

Abstract

Purpose of the Study: The purpose of this study was to study the role of equilibrium radionuclide angiography (ERNA) in the assessment of left ventricular (LV) mechanical dyssynchrony in patients with dilated cardiomyopathy (DCM), by correlating the findings with electrocardiographic parameters and speckle-tracking echocardiography (STE). **Methods:** This was a prospective observational study. A total of 55 patients with a mean age 42.5 ± 11 years (range: 19–61 years) diagnosed with DCM underwent ERNA and echocardiography sequentially. On ERNA, phase images of LV were obtained, and standard deviation of LV mean phase angle (SD LVmPA) was derived to quantify intra-LV mechanical dyssynchrony (ILVD). Similarly, on STE, "dyssynchrony index" was calculated as the standard deviation of time-to-peak systolic circumferential strain (SDCS) of the six mid-LV segments. The cutoff values used to define mechanical dyssynchrony were SD LVmPA >13.2° (or >27.1 ms) and SDCS >74 ms on ERNA and STE, respectively. The results obtained from the two modalities were then compared. **Results:** Speckle-tracking analysis could be done on the echocardiographic data of only 42 patients. Paired data from ERNA and STE studies of these 42 patients (26 males and 16 females) were compared, which showed no significant difference in the detection of ILVD ($P = 0.125$). The two modalities showed good agreement with Cohen's kappa value of 0.78 ($P < 0.0001$). SD LVmPA and SDCS values showed moderately strong linear correlation ($\rho = 0.69$; $P < 0.0001$). No significant association of mechanical dyssynchrony on ERNA or STE was found with QRS duration and with the presence or absence of left bundle branch block. ILVD was also found to be negatively correlated with LV ejection fraction. **Conclusion:** ERNA is comparable to STE for the assessment of LV mechanical dyssynchrony.

Keywords: *Dilated cardiomyopathy, equilibrium radionuclide angiography, mechanical dyssynchrony, speckle-tracking echocardiography*

Abhinav Singhal[1,2], Bangkim Chandra Khangembam[1,2], Sandeep Seth[3], Chetan Patel[2]

[1]Department of Nuclear Medicine, Institute of Liver and Biliary Sciences, Departments of [2]Nuclear Medicine and [3]Cardiology, Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi, India

Introduction

Cardiac resynchronization therapy (CRT) has now become the standard of care for drug refractory heart failure patients.[1,2] The current clinical guidelines mainly rely on QRS duration derived from electrocardiogram (ECG) for the selection of patients for CRT, with wide QRS morphology (>120 ms) being regarded as an essential criterion.[3] However, even after following the guidelines, 20%–30% of patients fail to respond to CRT.[4-6] Owing to the high cost of CRT implantation and possible procedural complications, it is imperative to search for parameters which can predict response to CRT with better accuracy.

The presence of ventricular contractile dyssynchrony is theoretically considered an essential substrate, which could be corrected by CRT, leading to clinical improvement. Conventionally, wide QRS duration has been presumed to be a surrogate for mechanical dyssynchrony of contractile function. However, subsequent research has pointed that a wide QRS complex may just be a marker of electrical dyssynchrony and may not accurately reflect the mechanical dyssynchrony.[7] Emphasis has been given to indentify the cardiac mechanical dyssynchrony, which may be a better predictor of response to device therapy.[8-10] Various imaging techniques have been used to measure mechanical dyssynchrony

Address for correspondence:
Prof. Chetan Patel,
Department of Nuclear Medicine, Cardiothoracic Centre, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 049, India.
E-mail: cdpatel09@gmail.com

and response to CRT. These include echocardiography, cardiac magnetic resonance, equilibrium radionuclide angiography (ERNA), and gated myocardial perfusion single-photon emission computed tomography.[8-16]

Echocardiography has been used most commonly for this purpose as cardiologists are most familiar with this method. Different echocardiography-derived dyssynchrony parameters have evolved over time, with the tissue Doppler imaging (TDI) being the most widely used technique. However, echocardiography is largely operator dependent, so reproducibility is limited. Moreover, data from PROSPECT trial do not support the use of echocardiography-derived dyssynchrony parameters (including TDI) to be used in routine clinical practice.[15] Speckle-tracking echocardiography (STE) is another novel technique which has shown promise in the post-PROSPECT era; however, the search for a more reproducible method of measuring left ventricular (LV) mechanical dyssynchrony continues.

ERNA is a well-established imaging modality to assess ventricular function and wall motion.[17] Using phase analysis, ERNA has also been investigated for the assessment of dyssynchronous cardiac contraction, and it is proven to be highly reproducible.[18-21] Being noninvasive, highly reproducible, and relatively easy to perform, it may be one of the most promising techniques to quantify dyssynchrony.

The primary objective of our study was to evaluate ERNA in the assessment of mechanical cardiac dyssynchrony in patients of dilated cardiomyopathy (DCM) and compare its results with STE. The secondary objectives were to test the association of mechanical synchrony parameters derived on ERNA and STE with ECG parameters of QRS duration and morphology.

Methods

Fifty-five patients with DCM with low ejection fraction (≤40%) were recruited in the study. Inclusion criteria were (1) clinical heart failure with LV ejection fraction (LVEF) ≤40%, (2) duration of symptoms >1 year, (3) age >12 years, and (4) sinus rhythm. Patients with a history of valvular heart disease and arrhythmias were excluded. ERNA study was successfully performed in all 55 patients. However, satisfactory echocardiographic images required for speckle-tracking analysis could not be obtained in 13 patients, due to lack of proper acoustic window for imaging. Thus, 42 STE studies were available for comparison with ERNA.

Equilibrium radionuclide angiography acquisition and processing

ERNA studies were done at rest with *in vivo* red blood cell labeling with intravenous administration of 0.5–0.9 mg (15 μg/kg of body weight) of stannous chloride,

followed 10–15 min later by 15–20 mCi (550–740 MBq) of technetium-99m pertechnetate. Acquisition was started 10–15 min later with a dual-head gamma camera (Infinia Hawkeye 4; GE Medical Systems, Waukesha, WI, USA) fitted with a low-energy general purpose collimator. Images were acquired in left anterior oblique view (best septal view). The projection was gated with the ECG to get 32 frames spanning the cardiac cycle. Images were acquired in 64 × 64 matrix, with a zoom factor of 1.6; each view acquired for approximately 500–600 kilo counts. The ECG was monitored continuously to ensure R-wave gating of the QRS complex. Elimination of ventricular premature beats was obtained with a window threshold of 20% around the mean R–R interval during acquisition of projections.

Images were analyzed using commercial software (XT-ERNA; GE Medical Systems, Waukesha, WI, USA). Count-based LVEF was then computed using semiautomatic regions of interest (ROI) on two separate regions (end diastolic and end systolic). ROI were drawn automatically by the computer with adjustments of border definition performed by the observer blinded to the state of conduction. Phase images are computed using the first harmonic Fourier transform to display the mechanical contraction time for all the ventricular pixels of the image during one composite cardiac cycle.

Phase image shows the areas of the heart whose change in activity, on a pixel-by-pixel basis, occurs at the same time. This, in effect, shows the progression of mechanical systole through the heart over the R–R interval giving information about the relative timing of contraction of cardiac pixels, that is, the synchronicity. Phase images were generated for cardiac regions using a continuous color scale, corresponding to phase angles from 0° to 360°. From these histograms representing the distribution of the pixels for each ventricle according to their phases, the mean phase and its standard deviation were calculated [Figure 1]. Mean phase angle (mPA) was computed for LV blood pool as the arithmetic mean of the phase angle for all pixels in the corresponding ventricular ROI. The standard deviation of the mPA of LV blood pool (SD LVmPA) represents synchronicity of ventricular motion. SD LVmPA can be expressed in units of degree/angle (°) or time, that is, milliseconds (ms). Expressing SD of mPA in degrees is considered more accurate for comparison across different populations since it negates the effect of different heart rates (and thus R–R interval) among individuals. However, both units are analogous to each other and either can be used for statistical analysis within a sample.

To define intra-LV mechanical dyssynchrony (ILVD), we used cutoff values (mean + 2SD of SD LVmPA) of ERNA which are already established in normal Indian controls.[22] ILVD was thus diagnosed when SD LVmPA value was >13.2° (or >27.1 ms), in the study population.[22] Apart from quantitative analysis, qualitative

visual assessment of the phase images was also done to determine LV regional dyssynchrony.

Speckle-tracking echocardiography acquisition and processing

Echocardiography was performed by an experienced cardiologist in the left lateral decubitus position using the commercially available equipment (Philips Inc.). Data acquisition was performed with a 3-MHz transducer at a depth of 15 cm in the parasternal and apical views (standard 2- and 4-chamber images). For speckle-tracking analysis, standard grayscale two-dimensional (2D) images were acquired in the parasternal short-axis views at the level of the papillary muscles. All of the images were recorded with a frame rate of at least 50 fps to allow for reliable operation of the software (QLab; Koninklijke Philips N.V.). Sector width was also adjusted to ensure that the whole of the LV wall was included in the acquisition, while at the same time, recording as narrow a sector as possible to optimize temporal resolution.

Offline analysis was done on all the recordings, using the vendor provided customized software package (QLab; Koninklijke Philips N.V.). From an end-systolic single frame, ROI were traced on the endocardial cavity interface by a point-and-click approach. Then, an automated tracking algorithm followed the endocardium from this single frame throughout the cardiac cycle. Further, adjustment of the ROI was performed to ensure that all of the myocardial regions were included. Next, acoustic markers, the so-called speckles, equally distributed in the ROI, were followed throughout the entire cardiac cycle. The distance between the speckles was measured as a function of time, and parameters of myocardial deformation were calculated. Circumferential strain (CS) was calculated by dividing the myocardium into six segments, namely, the mid-anterior, mid-anterolateral, mid-inferolateral, mid-inferior, mid-inferoseptal, and mid-anteroseptal. The different segments were color coded, and CS curves were reconstituted in each of the six mid-LV segments [Figure 2].

Parameters derived from speckle-tracking echocardiography

Using peak of the R wave as a reference, time to attain the peak systolic CS was calculated for each segment. To identify dyssynchrony, the "dyssynchrony index" of the LV was calculated as the standard deviation of time-to-peak systolic CS (SDCS) of the six segments.

To calculate the upper limit of the normal value of SDCS, STE was preperformed on 10 apparently healthy volunteers with no history of cardiovascular symptoms and normal ECG and routine echocardiographic parameters. The cutoff limit (mean + 2SD) thus derived to define ILVD from STE was SDCS >74 ms.

Each of the 55 patients first underwent routine 2D echocardiographic examination. However, 2D speckle-tracking acquisition was only possible in 42 patients, in whom satisfactory and low-noise LV short-axis images could be obtained in the parasternal view.

Statistical analyses

Data are presented as mean with standard deviations or median with ranges where appropriate. The Chi-square test/Fisher's exact test was used for the comparison of categorical (qualitative) data between groups. For
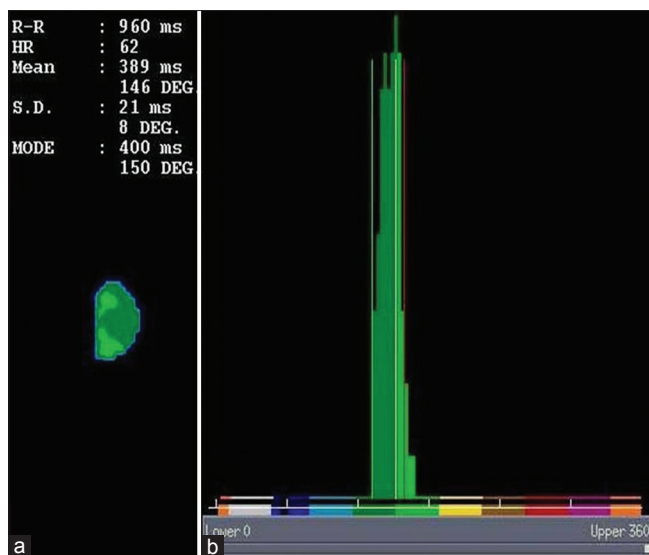

Figure 1: Results of Fourier phase analysis on equilibrium radionuclide angiography study of a control participant showing synchronous contraction. The phase image (a) and the phase histogram (b) are color coded based on the phase angle of each pixel. R–R: R–R interval on electrocardiogram, HR: Heart rate, SD: Standard deviation
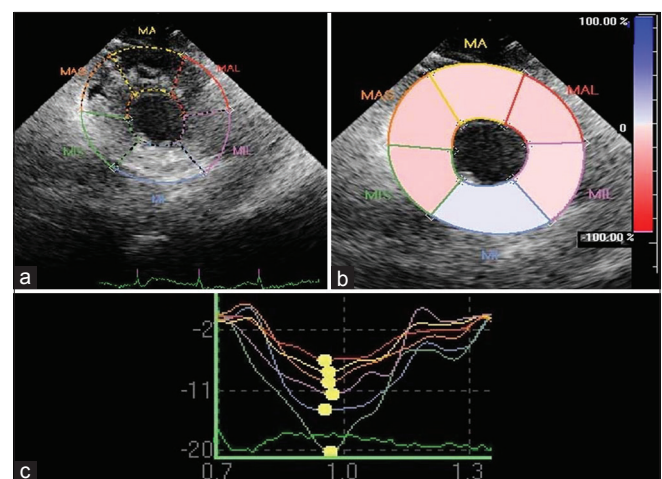

Figure 2: (a) Grayscale short-axis image of the mid-left ventricle at the level of papillary muscles in a healthy control participant. Division of myocardium into six segments is shown. (b) Software-based strain measurement by tracking of speckles. Amplitude of the strain is color coded. (c) Circumferential strain curves of the six segments traced over the cardiac cycle with the yellow dot placed at the nadir, that is, peak strain. Standard deviation of the six time-to-peak strain curves is below 74 ms, thus showing synchronous contraction. MA: Mid-anterior, MAL: Mid-anterolateral, MIL: Mid-inferolateral, MI: Mid-inferior, MIS: Mid-inferoseptal, MAS: Mid-anteroseptal

continuous variables, the Student's *t*-test/Mann–Whitney U-test was applied for comparison between the means of two groups. Kappa analysis and McNemar's test were used to assess intermodality agreement. Pearson's "r"/ Spearman's ρ was used to assess the correlation between quantitative variables where appropriate. Agreement between representative quantitative measures of the two imaging modalities was further tested by calculating Cohen's kappa value and Bland–Altman analysis. *P < 0.05* was considered statistically significant. All the data analyses were performed using the statistical software packages SPSS 17 (SPSS Inc., Chicago, Illinois, USA) and MedCalc 11.3 (MedCalc Software, Mariakerke, Belgium).

Results

The baseline characteristics of the original sample of 55 patients who underwent ERNA and those of the subset of 42 patients in whom STE acquisition could be done for the comparison are summarized in Table 1. The subset of 42 patients (26 males and 16 females) had a mean age of 41.2 ± 10.5 years (range: 19–59 years). The mean LVEF for the entire sample (*n* = 55) was 28% ± 8% (range: 15%–40%) and that of the subset (*n* = 42) was 26% ± 7.7% (range: 15%–40%). The clinical characteristics of this subset (*n* = 42) were compared with the remaining 13 patients in whom STE could not be performed, and no significant differences were observed in age and sex distribution, etiology of DCM, New York Heart Association class, and presence of left bundle branch block (LBBB) (*P > 0.05* for all comparisons). However, QRS duration was significantly shorter (*P = 0.01*) and LVEF relatively better (*P = 0.02*) in patients in whom STE could not be performed.

Intermodality agreement

Since the reference upper limits to label dyssynchrony for both modalities, that is, STE and ERNA were derived from two separate control groups, their demographic profile was compared to the respective patient populations. No significant difference was found in age distributions between patients and STE controls (41.2 ± 10.5 vs. 41 ± 9 years, *P = 0.595*) or patients and ERNA controls (42.5 ± 11 vs. 46.2 ± 14.5 years, *P = 0.109*).

Using the above-described cutoffs, out of 42 patients, ILVD was found in 27 (64%) patients on speckle-tracking analysis and 31 (74%) patients on ERNA. ERNA identified LV mechanical dyssynchrony in all 27 patients classified as having dyssynchronous contraction on STE. The former additionally detected dyssynchrony in four patients in whom results of STE were normal. McNemar's analysis revealed no statistically significant difference between the mechanical dyssynchrony detection by STE and ERNA (*P = 0.125*) [Table 2 and Figures 3, and 4]. The results from the two modalities were further tested by Cohen's Kappa test for intermodality agreement. Kappa

Table 1: Patient characteristics

Clinical characteristics	Value (*n*=55)	Value (*n*=42)
Age (years)	42.5±11 (range: 19-61)	41.2±10.5 (range: 19-59)
Sex		
Male	36 (65.5)	26 (61.9)
Female	19 (34.5)	16 (38.1)
LVEF (%)	28±8 (range: 15-40)	26±7.7 (range: 15-40)
NYHA class		
II	50 (91)	38 (90.4)
III	5 (9)	4 (9.6)
QRS duration (ms)	115±28.5 (range: 72-189)	121.4±30.0 (range: 72-189)
Wide QRS (>120)	21 (38)	20 (47.6)
Narrow QRS (≤120)	34 (62)	22 (52.4)
LBBB		
Present	11 (20)	10 (23.8)
Absent	44 (80)	32 (76.2)
DCM		
Nonischemic (idiopathic)	43 (78)	35 (83.4)
Ischemic	12 (22)	7 (16.6)

Data are presented as mean±SD (median, range), *n* (%). LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, LBBB: Left bundle branch block, DCM: Dilated cardiomyopathy, SD: Standard deviation

Table 2: Contingency table for comparison between equilibrium radionuclide angiography and speckle-tracking echocardiography

	ILVD on ERNA absent	ILVD on ERNA present	Total
ILVD on STE absent	11	4	15
ILVD on STE present	0	27	27
Total	11	31	42

ERNA: Equilibrium radionuclide angiography, STE: Speckle-tracking echocardiography, ILVD: Intra-LV mechanical dyssynchrony, LV: Left ventricle

value of 0.780 was derived (*P < 0.0001*), which indicated good agreement.

A Shapiro–Wilk test showed that the quantitative parameters of dyssynchrony derived from ERNA (i.e., SD LVmPA) and STE (i.e., SDCS) were not normally distributed in the sample (test statistic 0.91; *P < 0.05* and test statistic 0.94; *P < 0.05*, respectively). The association between the two parameters was therefore tested by Spearman's rank correlation test. On analysis, the Spearman's rho (ρ) value was derived to be 0.690 (*P < 0.0001*), indicating a moderately strong linear correlation [Figure 5]. Bland–Altman plot was also constructed to further test the agreement between the above parameters, and the results are summarized in Figure 6. The analysis revealed that differences between almost all the paired measurements were contained within two standard deviations of difference, indicating acceptable agreement. Furthermore, a trend was observed that as the
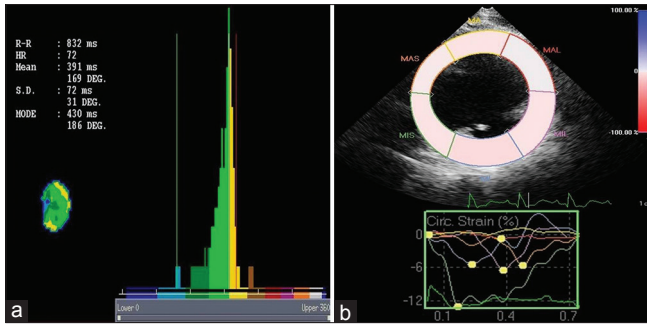
Figure 3: (a) A 25-year-old patient with left bundle branch block (QRS = 189 ms) and left ventricular ejection fraction = 20%. Equilibrium radionuclide angiography based phase image shows significant dyssynchrony (wide variation in timing of contraction among pixels on color scale). Phase histogram is wide, and standard deviation of left ventricular mean phase angle value is 31°. (b) Speckle-tracking echocardiography analysis of the same patient. Standard deviation of time-to-peak strain is 166 ms, that is, higher than the upper limit of normal (see wide scattering of yellow dots) consistent with intraleft ventricular dyssynchrony. R–R: R–R interval on electrocardiogram, HR: Heart rate, SD: Standard deviation
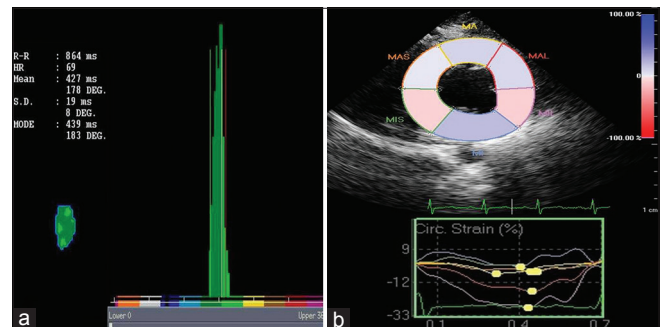

Figure 4: (a) A 38-year-old patient with QRS = 149 ms (intraventricular conduction defect) and left ventricular ejection fraction = 38%. In spite of wide QRS, equilibrium radionuclide angiography shows the absence of dyssynchrony. Value of standard deviation of left ventricular mean phase angle is 8°. (b) Speckle-tracking echocardiography too, done for the same patient, showing absence of intraleft ventricular dyssynchrony with standard deviation of time-to-peak systolic circumferential strain value of 63 ms. R–R: R–R interval on electrocardiogram, HR: Heart rate, SD: Standard deviation
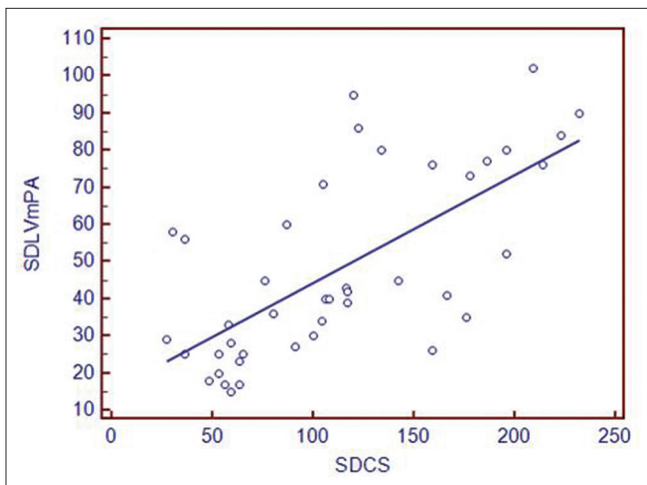

Figure 5: Scatter plot showing linear correlation between standard deviation of left ventricular mean phase angle (ms) and standard deviation of time-to-peak systolic circumferential strain (ms). SD LVmPA: Standard deviation of left ventricular mean phase angle, SDCS: Standard deviation of time-to-peak systolic circumferential strain
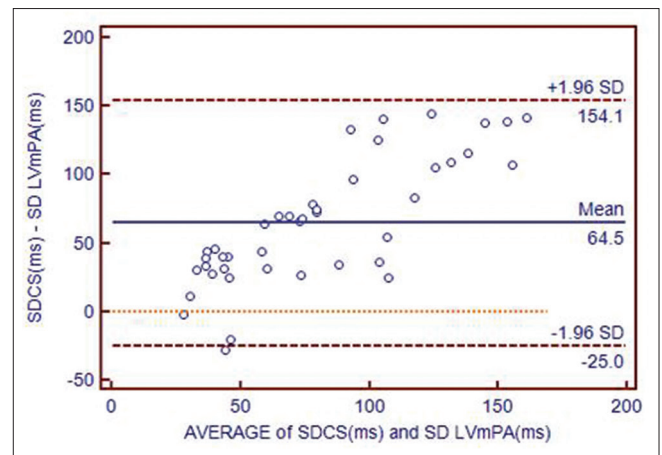

Figure 6: Bland and Altman plot for standard deviation of time-to-peak systolic circumferential strain (ms) and standard deviation of left ventricular mean phase angle (ms). SD LVmPA: Standard deviation of left ventricular mean phase angle, SDCS: Standard deviation of time-to-peak systolic circumferential strain

absolute magnitude of dyssynchrony increases, the difference between STE and ERNA measurements increases, indicating that in highly dyssynchronous LV contractions, either ERNA underestimates or STE overestimates the dyssynchrony. The validation and explanation of this later finding however require further research in future studies with larger sample sizes.

Electrocardiogram versus imaging for mechanical dyssynchrony

Among the study population ($n = 55$), 21 patients (38%) had wide QRS (duration >120 ms). Eleven out of these (20% of total) had LBBB, and two had right bundle branch block pattern. The remaining eight patients (14% of total) were classified as having nonspecific intraventricular conduction defects. In patients with wide QRS, the mean QRS duration was 148 ± 18 ms (range: 122–189 ms). The relationship of electrical with mechanical dyssynchrony was compared between wide QRS and narrow QRS group using both ERNA ($n = 55$) and STE ($n = 42$). While assessed by ERNA, 5 out of 21 patients (20%) with wide QRS duration on ECG did not show mechanical intra-LV dyssynchrony. On the other hand, 21 out of 34 patients (62%) with otherwise narrow QRS showed intra-LV mechanical dyssynchrony. The Chi-square test did not show a significant association of QRS duration and ILVD ($P = 0.268$). When assessed with STE, again no significant association of QRS duration was noted with ILVD ($P = 0.167$).

Effect of LBBB on mechanical dyssynchrony was also assessed using ERNA and STE. Nine out of 11 (82%) patients with LBBB showed ILVD on ERNA; however, 28 out of 44 (64%) patients without LBBB also showed ILVD.

Overall, no significant association was found between the presence or absence of LBBB and ILVD ($P = 0.429$; Chi-square test with continuity correction). Similar results are found with STE ($P = 0.117$; Chi-square test with continuity correction).

We also found that patients with ILVD on ERNA had lower LVEF (24.3% ±6%; median 23%, range 15%–36%) compared to patients without ILVD (34.2% ± 7%; median 37.5%, range 16%–40%) and the difference was statistically significant ($P < 0.001$). A moderately negative Spearman's correlation ($\rho = -0.672$) was observed between SD LVmPA and LVEF ($P < 0.01$) [Figure 7].

Discussion

ERNA is a well-established modality for evaluating both global and regional cardiac functions. It is accurate, reproducible, and simple to perform. Various studies have assessed the feasibility of ERNA in assessing mechanical synchrony and have also validated the accuracy of the method.[19-22] However, to make this technique proceed from the bench to the bedside, we compared and correlated ERNA with the modality, the cardiologist is most familiar with, that is, the echocardiography. To the best of our knowledge, this is the first study comparing ERNA and STE for the assessment of LV mechanical dyssynchrony.

Out of 55 patients with normal sinus rhythm in whom ERNA was successfully performed, adequate parasternal view echocardiographic recording for offline speckle-tracking analysis was possible in only 42 (76%) patients. This was attributed to poor acoustic window in the remaining patients owing to thick chest wall (obesity), rib crowding artifacts, obstructive airway disease, etc., Offline speckle tracking on the images of these patients was visually found to be inconsistent, with poor reproducibility. This is consistent with several previous studies that have reported that lack of adequate imaging window is a limitation of echocardiography in general, even more relevant when
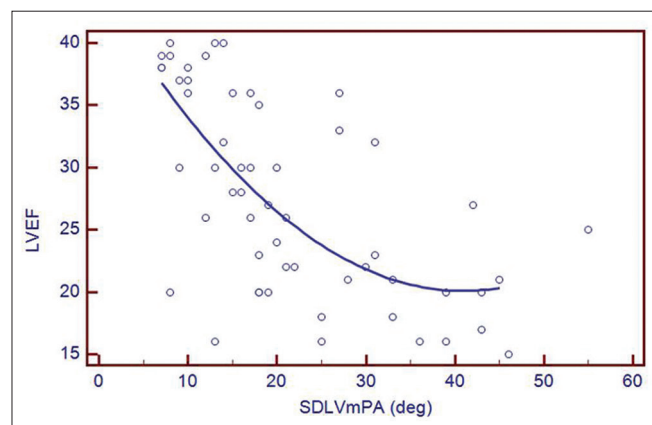
Figure 7: Scatter diagram showing negative correlation between intraleft ventricular mechanical dyssynchrony and left ventricular ejection fraction. SD LVmPA: Standard deviation of left ventricular mean phase angle, LVEF: Left ventricular ejection fraction

performing STE which requires images with high spatial resolution.[23-25] In comparison, image degradation due to overlying soft-tissue attenuation is unlikely during ERNA acquisition. In a subgroup analysis, we found that among the clinical characteristics, QRS duration was significantly shorter and LVEF relatively better in patients in whom STE could not be performed. This may occur because patients with coexisting obesity or obstructive airway disease are more likely to be symptomatic and seek consultation in heart failure clinic at earlier stages with relatively preserved cardiac function. ILVD was thus serially assessed by both modalities in the subsample of 42 patients and the agreement analysis for the detection of mechanical dyssynchrony showed strong agreement between the two modalities.

Compared to STE, ERNA identified ILVD in four additional patients. Visual analysis of the phase images of these patients revealed that the region of dyssynchrony was confined to the apical/inferoapical region. The significance of this finding remains uncertain but may reflect the inherent limitation of 2D nature of speckle tracking which may not provide coverage of adequate longitudinal length of the LV, while dyssynchrony in itself is a 3D phenomenon.[26,27] 3D speckle-tracking technology can overcome the limitations of 2D sampling.[27]

In this study, the QRS duration and LBBB status were not found to have strong correlation with ILVD. Literature review shows conflicting data on the exact relationship of QRS duration with ILVD. Fauchier *et al*.[16] reported higher values of SD LVmPA in DCM patients with QRS >120 ms, while Marcassa *et al*.[28] reported only a weak correlation between QRS duration and SD LVmPA ($r = 0.51$). However, in the studies by Ghio *et al*.[29] and Hara *et al*.,[30] no significant relation was found between ILVD and wide QRS. Our study supports the later studies. Although 76% of our patients with wide QRS had ILVD, 62% of patients with narrow QRS also have ILVD. Other authors have reported the presence of ILVD in up to 50% of patients with normal QRS duration.[28,31]

Interestingly, not all patients with wide QRS show ILVD. Previous studies[28-30] have reported that up to 42% of patients with wide QRS may not have ILVD. In this study, 24% of the patients did not show ILVD despite having QRS width >120 ms. This percentage is very similar to the proportion of nonresponders in the various CRT trials, giving impetus to the hypothesis that the presence of ILVD may be a necessary factor behind the response to CRT.

Ventricular synchrony and function are closely related. Dyssynchronous contraction may have a significant detrimental effect on mechanical pumping efficiency of the ventricles. This is reflected as reduced global ventricular systolic function. Studies by several workers in the past have supported this theory. Fauchier *et al*.[16] reported in 103 patients with idiopathic DCM that a degradation of

the hemodynamic status was associated with an increase in ILVD. Among 13 univariate predictors of cardiac events, the only independent predictors were an increased SD LVmPA ($P = 0.0004$) and an increased pulmonary capillary wedge pressure ($P = 0.009$). Marcassa *et al*.[28] reported in 130 DCM patients, a significant nonlinear inverse relation of LVEF with ILVD ($r = -0.68$, $P < 0.0001$) concordant with our study.

CRT, by means of correcting dyssynchrony, may help in the improvement of LVEF which may be linked with the overall clinical response. It is pertinent thus to investigate the parameter of ventricular synchrony which has the greatest impact on ventricular function measured as LVEF.

The above findings suggest that ILVD might be more important than QRS duration in determining LV function and the subsequent prognosis and should, therefore, be the target of resynchronization therapy. The fact that ERNA has high accuracy and reproducibility in the assessment of ILVD underlines its potential applicability in the assessment of patients with heart failure who are potential candidates for resynchronization therapy.

Conclusion

ERNA as a modality for the assessment of cardiac mechanical dyssynchrony compares favorably with the current standard of care echocardiographic technique for this purpose, that is, STE. The former also overcomes the inherent limitations of the latter in being operator independent and thus being more reproducible and also in being applicable to a wider subset of patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al*. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, *et al*. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr. Drazner MH, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2013;62:e147-239.
4. Fox DJ, Fitzpatrick AP, Davidson NC. Optimisation of cardiac resynchronisation therapy: Addressing the problem of "non-responders". Heart 2005;91:1000-2.
5. Reuter S, Garrigue S, Barold SS, Jais P, Hocini M, Haissaguerre M, *et al*. Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure. Am J Cardiol 2002;89:346-50.
6. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, *et al*. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology/American Heart Association Task force on practice guidelines (Writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices): Developed in collaboration with the American Association for Thoracic Surgery and society of thoracic surgeons. Circulation 2008;117:e350-408.
7. Auricchio A, Yu CM. Beyond the measurement of QRS complex toward mechanical dyssynchrony: Cardiac resynchronisation therapy in heart failure patients with a normal QRS duration. Heart 2004;90:479-81.
8. Pitzalis MV, Iacoviello M, Romito R, Massari F, Rizzon B, Luzzi G, *et al*. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002;40:1615-22.
9. Mukherjee A, Patel CD, Naik N, Sharma G, Roy A. Quantitative assessment of cardiac mechanical dyssynchrony and prediction of response to cardiac resynchronization therapy in patients with non-ischaemic dilated cardiomyopathy using equilibrium radionuclide angiography. Europace 2016;18:851-7.
10. Mukherjee A, Patel CD, Naik N, Sharma G, Roy A. Quantitative assessment of cardiac mechanical dyssynchrony and prediction of response to cardiac resynchronization therapy in patients with nonischaemic dilated cardiomyopathy using gated myocardial perfusion SPECT. Nucl Med Commun 2015;36:494-501.
11. Yu CM, Fung JW, Zhang Q, Chan CK, Chan YS, Lin H, *et al*. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. Circulation 2004;110:66-73.
12. Koos R, Neizel M, Schummers G, Krombach GA, Stanzel S, Günther RW, *et al*. Feasibility and initial experience of assessment of mechanical dyssynchrony using cardiovascular magnetic resonance and semi-automatic border detection. J Cardiovasc Magn Reson 2008;10:49.
13. Chen J, Garcia EV, Folks RD, Cooke CD, Faber TL, Tauxe EL, *et al*. Onset of left ventricular mechanical contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: Development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. J Nucl Cardiol 2005;12:687-95.
14. Chen J, Henneman MM, Trimble MA, Bax JJ, Borges-Neto S, Iskandrian AE, *et al*. Assessment of left ventricular mechanical dyssynchrony by phase analysis of ECG-gated SPECT myocardial perfusion imaging. J Nucl Cardiol 2008;15:127-36.
15. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, *et al*. Results of the predictors of response to CRT (PROSPECT) trial. Circulation 2008;117:2608-16.
16. Fauchier L, Marie O, Casset-Senon D, Babuty D, Cosnay P, Fauchier JP, *et al*. Interventricular and intraventricular dyssynchrony in idiopathic dilated cardiomyopathy: A prognostic study with Fourier phase analysis of radionuclide angioscintigraphy. J Am Coll Cardiol 2002;40:2022-30.
17. Strauss HW, Zaret BL, Hurley PJ, Natarajan TK, Pitt B. A scintiphotographic method for measuring left ventricular ejection fraction in man without cardiac catheterization. Am J Cardiol 1971;28:575-80.
18. Frais M, Botvinick E, Shosa D, O'Connell W, Pacheco Alvarez J, Dae M, *et al*. Phase image characterization of localized and generalized left ventricular contraction abnormalities. J Am Coll

Cardiol 1984;4:987-98.

19. Vallejo E, Jiménez L, Rodríguez G, Roffe F, Bialostozky D. Evaluation of ventricular synchrony with equilibrium radionuclide angiography: Assessment of variability and accuracy. Arch Med Res 2010;41:83-91.

20. Dormehl I, Burow R, Hugo N, Maree M, Van Zandwijk C, Van Vuuren C, *et al*. Phase mapping from left ventricular radionuclide ventriculograms: Interobserver reliability and accuracy of the programme. Nucl Med Commun 1987;8:805-13.

21. Toussaint JF, Peix A, Lavergne T, Vicente FP, Froissart M, Alonso C, *et al*. Reproducibility of the ventricular synchronization parameters assessed by multiharmonic phase analysis of radionuclide angiography in the normal heart. Int J Cardiovasc Imaging 2002;18:187-94.

22. Singh H, Singhal A, Sharma P, Patel CD, Seth S, Malhotra A, *et al*. Quantitative assessment of cardiac mechanical synchrony using equilibrium radionuclide angiography. J Nucl Cardiol 2013;20:415-25.

23. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960-8.

24. Gorcsan J 3rd, Tanabe M, Bleeker GB, Suffoletto MS, Thomas NC, Saba S, *et al*. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. J Am Coll Cardiol 2007;50:1476-83.

25. Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, *et al*. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. J Am Coll Cardiol 2008;51:1944-52.

26. Tanaka H, Hara H, Adelstein EC, Schwartzman D, Saba S, Gorcsan J 3rd, *et al*. Comparative mechanical activation mapping of RV pacing to LBBB by 2D and 3D speckle tracking and association with response to resynchronization therapy. JACC Cardiovasc Imaging 2010;3:461-71.

27. Tanaka H, Hara H, Saba S, Gorcsan J 3rd. Usefulness of three-dimensional speckle tracking strain to quantify dyssynchrony and the site of latest mechanical activation. Am J Cardiol 2010;105:235-42.

28. Marcassa C, Campini R, Verna E, Ceriani L, Giannuzzi P. Assessment of cardiac asynchrony by radionuclide phase analysis: Correlation with ventricular function in patients with narrow or prolonged QRS interval. Eur J Heart Fail 2007;9:484-90.

29. 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;25:571-8.

30. Hara H, Oyenuga OA, Tanaka H, Adelstein EC, Onishi T, McNamara DM, *et al*. The relationship of QRS morphology and mechanical dyssynchrony to long-term outcome following cardiac resynchronization therapy. Eur Heart J 2012;33:2680-91.

31. Bader H, Garrigue S, Lafitte S, Reuter S, Jaïs P, Haïssaguerre M, *et al*. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. J Am Coll Cardiol 2004;43:248-56.