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Equilibrium radionuclide angiography compared with tissue doppler imaging for detection of right ventricular dyssynchrony and prediction of acute response to cardiac resynchronization therapy

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Abstract

Objective: The aim of this study was to compare tissue doppler imaging (TDI) and equilibrium radionuclide angiography (ERNA) for detection of right ventricular (RV) dyssynchrony and prediction of the acute response to cardiac resynchronization therapy (CRT).

Methods: This study was approved by the local ethics committee of Huai'an First People's Hospital. Patient consent was not provided due to the use of completely anonymous images from which the individual could not be identified in this study. Thirty-three patients with nonischemic dilated cardiomyopathy underwent both TDI and ERNA before and within 48 hour after CRT implantation. RV dyssynchrony was measured with TDI using the difference in time to peak systolic velocity between the RV free wall and ventricular septum (RV-T). With ERNA, the standard of RV mean phase angle and RV phase standard deviation (RVmPA% and RVPSD%) were assessed.

Results: Moderate positive correlations were observed among baseline RVmPA%, RVPSD% and RV-T ($r = 0.689$ and 0.716, $P < .001$). Twenty patients (61%) with a reduction of at least 15% in LV end-systolic volume were categorized as acute responders after CRT. Responders showed significant reduction in RVmPA% and RVPSD% after CRT ($53.60 \pm 4.15\%$ to $43.95 \pm 6.88\%$ and $14.00 \pm 2.41\%$ to $10.40 \pm 1.67\%$, $P < .05$), whereas RV-T remained unchanged (50.10 ± 10.28 ms to 49.25 ± 13.64 ms, NS). Receiver operating characteristic curve showed that the cut-off value of RV-T was 48.5 ms, yielding 65% sensitivity and 77% specificity to predict acute respond to CRT. The cut-off value of RVmPA% was 49.5%, yielding 85% sensitivity and 85% specificity and the cut-off value of RVPSD% was 11.5%, yielding 85% sensitivity and 92% specificity.

Conclusion: ERNA might be an appropriate alternative to TDI for assessment of RV dyssynchrony. Either RVmPA% or RVPSD% was highly predictive for acute response to CRT.

Abbreviations: CRT = cardiac resynchronization therapy, ERNA = equilibrium radionuclide angiography, IRVD = intra right ventricular dyssynchrony, LV = left ventricular, LVEF = left ventricular ejection fraction, LVESV = LV end-systolic volume, MRI = magnetic resonance imaging, NICM = nonischemic dilated cardiomyopathy, ROC = receiver operating characteristic curve, ROI = region of interest, R–R = R–R cycle, RV = right ventricular, RVEF = RV ejection fraction, RVmPA = RV mean phase angle, RVPSD = RV phase standard deviation, RV-T = time of right ventricular, TAPSE = tricuspid annular plane systolic excursion, TDI = tissue doppler imaging.

Keywords: cardiac resynchronization therapy, equilibrium radionuclide angiography, heart failure, right ventricular dyssynchrony, right ventricular ejection fraction, tissue doppler imaging

1. Introduction

In recent years, the non-drug treatment of chronic heart failure has received more attention and especially cardiac resynchronization therapy (CRT) is an exciting treatment. With the gradual development of CRT research, many clinical studies have shown that the left ventricular (LV) dyssynchrony is 1 of the important predictors of the response to CRT.[1,2] However, the relationship between CRT and right ventricular (RV) dyssynchrony has not

been well described. Recently, several studies showed that the RV function and RV dyssynchrony affected the effects of CRT,[3–6] but there were also some opposite results.[7,8]

Tissue doppler imaging (TDI) is still the standard and reliable technique to evaluate RV dyssynchrony by measuring the free wall.[6] However, the assessment of mechanical dyssynchrony by TDI has many limitations, mainly because of its 2-dimensional nature, the angle dependency of the ultrasound signal, and the resulting signal noise. Magnetic resonance imaging (MRI) may be used for accurately measuring RV ejection fraction (RVEF) and dyssynchrony at baseline, but not after CRT device implantation as MRI-compatible CRT devices are not routinely available.[9]

Equilibrium radionuclide angiography (ERNA) has been used for many years and it is a kind of method to detect ventricular movement.[10,11] In recent years, ERNA technology has become available as a novel promising technique for measuring the RVEF and dyssynchrony.[12–14] But in these studies, ERNA was not compared with other technologies. The aim of this study was to compare between TDI and ERNA for detection of RV dyssynchrony and prediction of acute response to CRT.

2. Materials and methods

2.1. Patients

The study population consisted of thirty-three nonischemic dilated cardiomyopathy (NICM) patients. The selection criteria were sinus rhythm, the left bundle branch block, QRS duration ≥120ms, New York cardiac function class •-• and the left ventricular ejection fraction (LVEF) ≤35%. RV dyssynchrony was measured using ERNA and TDI before and within 48 hour after implantation. LV end-systolic volume (LVESV), LVEF and RVEF were calculated using ERNA before and within 48 hour after implantation. Patients who experienced a reduction in LVESV at least 15% were categorized as acute responders to CRT.[15]

2.2. Pacemaker implantation

CRT implantation was performed through the subclavian vein access and positioned as far as possible in the lateral or posterolateral vein. The right atrial and RV leads were positioned in the right atrial appendage and RV apex, respectively. All patients received a combined CRT defibrillator device, which was programmed in DDD mode. The atrioventricular interval was obtained with TDI to maximize the LV filling and ejection time.

2.3. TDI

The 2-dimensional echocardiography with TDI color imaging was performed by using a broad-band transducer (S5-1, 1-5 MHz, iE33). The images were digitized and transferred to an offline computer (SQ, QLAB, Version 4.2.1, Philips). Myocardial velocity profile signals were reconstituted offline from the TDI color images. Regional myocardial velocity curves were obtained from the apical 4-chamber. A 12 mm by 5 mm region of interest (ROI) was placed in the basal and mid segments of the RV free wall and inter-ventricular septum to obtain Tissue Doppler velocity curves. At the tissue velocity curve of each region, time to peak systolic velocity was measured. For each of the regions, the basal and mid-ventricular measurements were averaged. RV dyssynchrony was by definition the difference in time to peak systolic velocity between the RV free wall and ventricular septum.

2.4. ERNA

All patients underwent ERNA SPECT (GE Infinia Hawkeye-2, GE, Fairfield, Connecticut, USA). The first intravenous injection of 20 ug/kg of pyrophosphate was performed. After about 20 to 25 min, 740–925 MBQ (20–25mCi) ^{99m}Tc-MIBI was injected and then the image was collected after 10 minute. If necessary, the left anterior oblique 45° position of the patient's ventricle was used for imaging to find the optimal position. The acquisition matrix was 64 by 64. 32 frames/cycle was collected within each cardiac cycle and acquisition time was extended for 10 minute.

GE XT-ERNA software (GE, Fairfield, Connecticut) was used to assess RV processing. First, the RV Center was manually chosen on the end-diastolic frame and the software image display showed RV Center images (Fig. 1). Then, the End Diastole ROI and End Systole ROI were drawn interactively (Fig. 1). At last, RVmPA%, RV phase standard deviation (RVPSD)% and time of 1 R–R cycle (ms) (R–R) were shown on the phase image and phase histogram screen (Fig. 2).

By confirming the LV/RV ROI, EF was showed on the LV/RV Ejection Fraction screen. EF was calculated as follows: EF = (end-diastolic ROI counts-background counts)-(end-systolic ROI counts-background counts)/ (end-diastolic ROI counts−background counts) × 100.[13]

GE Xeleris-3 functional imaging workstation (GE, Fairfield, Connecticut) was used to assess the LV volume data. In the first step, we entered the Xeleris-3 functional imaging workstation confirmed the LV ROI. Then the volume curve and the parameter of the LVESV were obtained. LVESV was estimated by the Massardo count-based method.[10]

2.5. Statistical analysis

SPSS16.0 (IBM, Armonk, New York) was used for statistical analysis. The continuous variable was expressed with mean ± standard deviation. t test or χ^2-test was used for number and percentage differences. Pearson's correlation was performed to determine the correlation. The ability of ERNA and TDI to predict acute response to CRT was evaluated by using receiver operating characteristic curve (ROC) and calculating the cut-off value of RVmPA%, RVPSD% and RT-T. For all tests, $P < .05$ was considered statistically significant.

3. Results

3.1. Study population

The study population consisted of 16 males and 17 females, with a mean age of 62.64 ± 9.78 years. The mean QRS interval was 141.61 ± 11.16 ms, 21 cases were NYHA III and 12 cases were NYHA IV. The baseline characteristics of the 33 patients were summarized in Table 1. Before CRT implantation, the patients showed severe LV dilation (mean LVESV 142.58 ± 18.51 mL) and depressed ventricular function (mean LVEF 27.30 ± 3.99% and mean RVEF 31.33 ± 3.93%).

3.2. Comparison of RV dyssynchrony assessed by TDI and ERNA

The baseline RVmPA% and RVPSD% were mean 50.52 ± 5.72% and 12.15 ± 3.15% (Table 3). Moderate positive correlations were observed among RVmPA%, RVPSD% and time of right ventricular (RV-T), respectively (r=0.689 and 0.716, all $P < .001$) (Fig. 3).
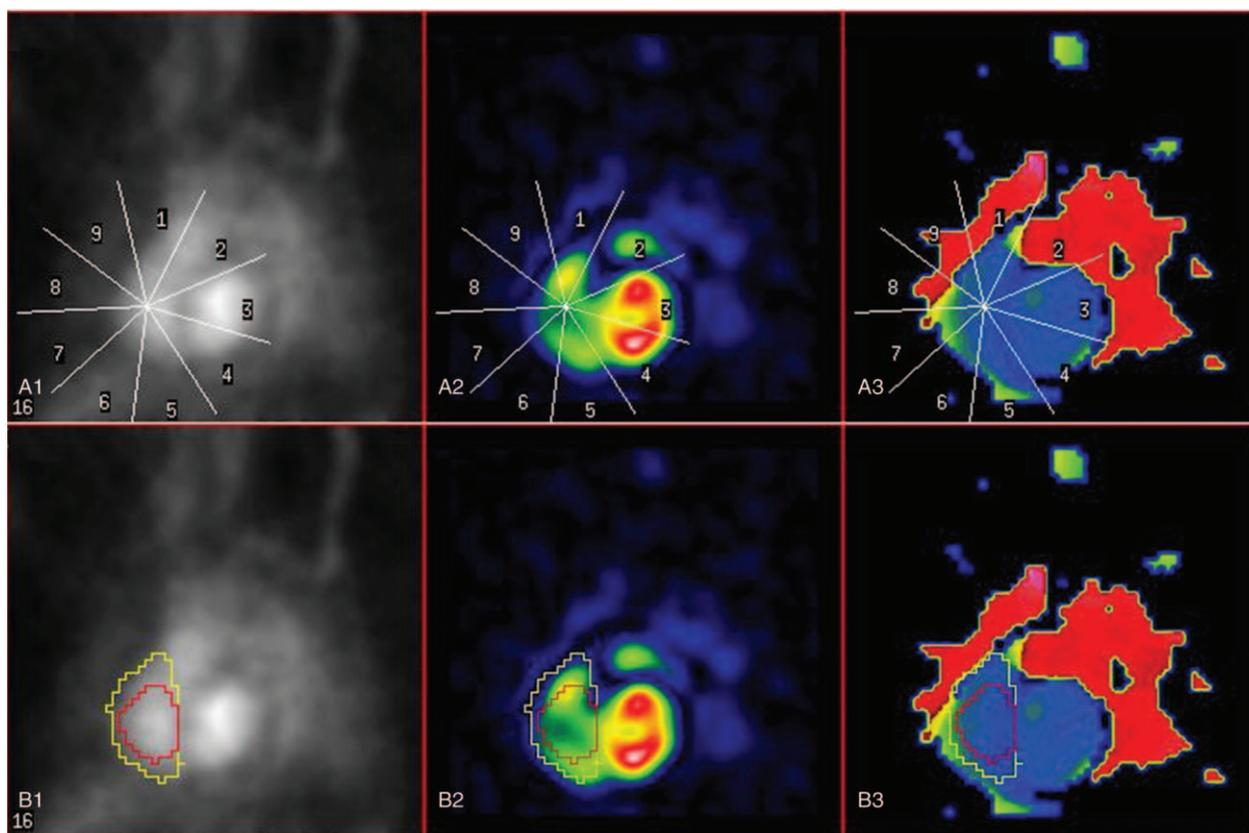
Figure 1. Example of right ventricular (RV) center and RV region of interested (ROI) screen in a 49-yr-old male patient. Panel A: RV center screen. Panel B: RV ROI screen, end diastole ROI (yellow line) and end systole ROI (red line) on all the images. (1) Filtered ED frame. (2) Amplitude image (3) Phases image.

3.3. Acute ERNA and TDI response after CRT

Twenty patients (61%) with a reduction of at least 15% in LVESV were categorized as acute responders after CRT. The responders also showed a significant improvement in LVEF and RVEF (from $27.85 \pm 4.49\%$ to $36.50 \pm 5.79\%$ and from $32.60 \pm 3.80\%$ to $36.35 \pm 2.60\%$, all $P < .001$) (Table 3). All baseline characteristics of the patients were similar between acute responders and nonresponders (Table 2), whereas the baseline RVmPA% and RVPSD% were significantly higher in acute responders compared with nonresponders ($53.60 \pm 4.15\%$ vs $45.77 \pm 4.44\%$, $14.00 \pm 2.41\%$ vs $9.31 \pm 1.70\%$, $P < .05$) (Table 3). Acute responders also showed significant reduction in RVmPA% and RVPSD% after CRT ($53.60 \pm 4.15\%$ to $43.95 \pm 6.88\%$ and $14.00 \pm 2.41\%$ to $10.40 \pm 1.67\%$, $P < .05$), whereas RV-T remained unchanged (50.10 ± 10.28 ms to 49.25 ± 13.64 ms, NS) (Table 3).

3.4. Prediction of acute response after CRT

The ability of 2 techniques to predict acute response to CRT was evaluated by using ROC curve analysis. ROC curve showed that the cut-off value of RV-T was 48.5 ms, yielding 65% sensitivity and 77% specificity to predict acute respond to CRT (area under the curve = 0.706, asymptotic 95% confidence interval = 0.518–0.893, $P < .05$). The cut-off value of RVmPA% was 49.5%, yielding 85% sensitivity and 85% specificity to predict acute response to CRT (area under the curve = 0.885, asymptotic 95% confidence interval = 0.768–1.002, $P < .05$). According to this

cut-off value, 19 patients (58%) had RVmPA% $\geq 49.5\%$ and these patients showed significantly improved in RVEF and LVEF, as compared with patients with RVmPA% $< 49.5\%$ (Fig. 4). The cut-off value of RVPSD% was 11.5%, yielding 85% sensitivity and 92% specificity to predict acute response to CRT (area under the curve = 0.952, asymptotic 95% confidence interval = 0.883–1.021, $P < .05$). According to this cut-off value, 18 patients (55%) had RVPSD% $\geq 11.5\%$ and these patients showed significantly improved in RVEF and LVEF, as compared with patients with RVPSD% $< 11.5\%$ (Fig. 4).

4. Discussion

CRT had been shown to improve clinical symptoms[16,17] and reverse ventricular remodeling.[18,19] However, according to the current guidelines, about 30% of the patients with clinical symptoms did not improve, and about 40% to 50% of patients had no improvement in LV function.[20–23] Since high cost and surgery can lead to serious complications, it is important to determine a target parameter to accurately predict respond to CRT. Currently, the function of RV in CRT is a hot topic of study. TDI, in addition to being useful in the quantification of LV function and dyssynchrony, was also shown to be a reliable method of analyzing RV function and dyssynchrony.[24] Donal et al[25] showed that CRT could improve the tricuspid annular plane systolic excursion (TAPSE) during acute phase. Scuteri et al[26] found that the TAPSE of patients with the unresponsive group was significantly worse than those with the responsive group, and
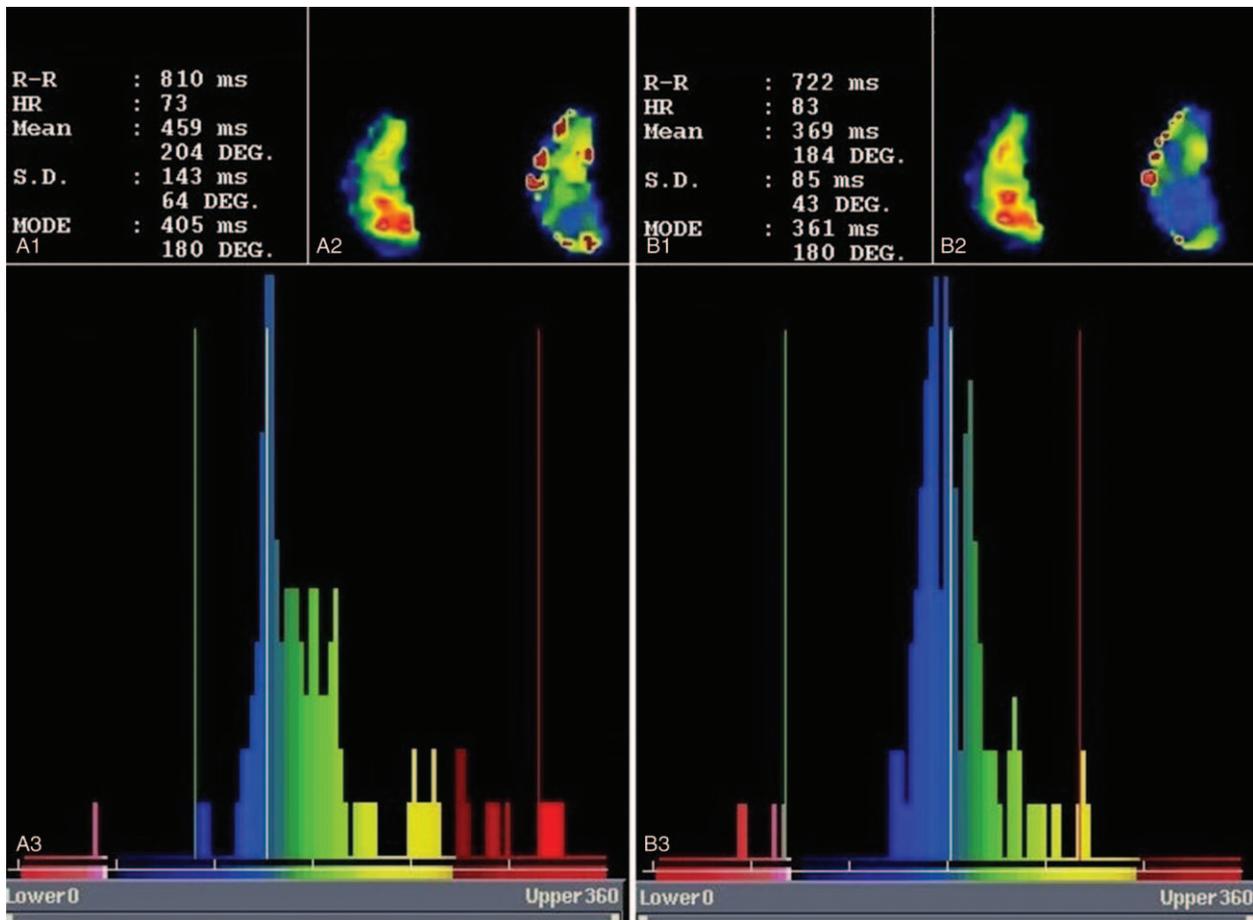
Figure 2. Example of right ventricular (RV) phase histogram and phase analysis screen in a 67-yr-old male patient. Panel A: Pre-CRT, Panel B: Post-CRT. (1) Data statistics: Mean and SD represent RV mean phase angle (RVmPA) and RV phase standard deviation (RVPSD). (2) Phase imaging. (3) Phase histogram. CRT = cardiac resynchronization therapy, RV = right ventricular, RVPSD = the standard of right ventricular phase standard deviation, SD = standard deviation.

that patients with TAPSE ≤14 mm were less likely to respond to CRT. Szulik[6] found that the time delay between the RV free wall and the interventricular septum can predict the CRT clinical effect. However, due to the complex structure of the right

ventricle, it is difficult to measure RV function in normal methods, and the relationship between CRT and RV dyssynchrony has not yet been well studied.

ERNA has been widely used to measure RV function and dyssynchrony.[8,12,13,14,27] The parameter of deviation of RV mean phase angle was frequently used and the results were expressed in terms of phase angle degrees or milliseconds. Singh[13] analyzed the ventricular dyssynchrony of one-hundred eight patients and concluded that the cut-off value of parameter of deviation of right ventricular Mean Phase angle was ≥ 68.7 ms

Table 1

Baseline characteristics of the study population (n=33).

Age, yr	62.64 ± 9.78
Male/Female, n	16/17
NYHAIII/IV, n	21/12
QRS complex, (ms)	141.61 ± 11.16
Medication, n (%)	
ACEI	20 (61)
β-blockers	29 (88)
Diuretics	24 (73)
LVESV, (mL)	142.58 ± 18.51
LVEF, (%)	27.30 ± 3.99
RVEF, (%)	31.33 ± 3.93
RV-T, (ms)	47.06 ± 11.28
RVPSD%, (%)	12.15 ± 3.15
RVmPA%, (%)	50.52 ± 5.72

ACEI = angiotensin-converting enzyme inhibitor, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, NYHA = New York Heart Association functional class, RVEF = right ventricular ejection fraction, RVmPA% = the standard of right ventricular mean phase angles, RVPSD% = the standard of right ventricular phase standard deviation, RV-T = the difference in time to peak systolic velocity between right ventricular free wall and ventricular septum.

Table 2

Baseline clinical characteristics of responders and nonresponders to CRT.

Baseline characteristics	Nonresponders (n=13)	Responders(n=20)	P value
Age, years	63.54 ± 9.79	62.05 ± 9.99	$P=.676$
Male/Female, n	7/6	9/11	$P=.619$
QRS duration, (ms)	140.85 ± 9.48	142.10 ± 12.34	$P=.758$
NYHA, (III/IV)	8/5	13/7	$P=.840$
Medication, n (%)			
ACEI	9 (69)	11(55)	$P=.414$
β-blockers	11(85)	18(90)	$P=.643$
Diuretics	8(62)	16 (80)	$P=.245$

ACEI = angiotensin-converting enzyme inhibitor, CRT = cardiac resynchronization therapy, NYHA = New York Heart Association functional class.

Table 3

Responders versus nonresponders: equilibrium radionuclide angiography and tissue Doppler imaging variables before and after CRT implantation.

	Nonresponders (n = 13)	Responders (n = 20)	P value
RV-T, (ms)			
Baseline	42.38 ± 11.54	50.10 ± 10.28	.053
After implantation	39.23 ± 5.88	49.25 ± 13.64	.018
RVmPA%, (%)			
Baseline	45.77 ± 4.44	53.60 ± 4.15	<.001
After implantation	46.46 ± 6.16	43.95 ± 6.88[*]	.293
RVPSD%, (%)			
Baseline	9.31 ± 1.70	14.00 ± 2.41	<.001
After implantation	9.15 ± 1.57	10.40 ± 1.67[*]	.040
LVESV, (mL)			
Baseline	144.08 ± 19.33	141.60 ± 18.39	.713
After implantation	138.77 ± 16.79	107.10 ± 17.09[*]	<.001
LVEF, (%)			
Baseline	26.46 ± 3.04	27.85 ± 4.49	.336
After implantation	26.92 ± 4.82	36.50 ± 5.79[*]	<.001
RVEF, (%)			
Baseline	29.38 ± 3.40	32.60 ± 3.80	.019
After implantation	28.92 ± 4.09	36.35 ± 2.60[*]	<.001

ACEI = angiotensin-converting enzyme inhibitor, CRT = cardiac resynchronization therapy, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, NYHA = New York Heart Association functional class, RVEF = right ventricular ejection fraction, RVmPA% = the standard of right ventricular mean phase angles, RVPSD% = the standard of right ventricular phase standard deviation, RV-T = the difference in time to peak systolic velocity between right ventricular free wall and ventricular septum.

[*] P < .05, baseline versus follow-up.

or 33.1° to define the RV dyssynchrony. Mancini's study[28] showed that the standard deviation was not accurate in milliseconds because it was associated with a greater heart rate. If the degree of phase angle was used, the effect of the heart rate could be eliminated and the results might be more accurate. But instead, a large sample study[29] showed that the use of milliseconds was better than the degrees. They thought that the milliseconds could be used to show not only the dyssynchrony but also the tachycardia, which might affect the analysis of dyssynchrony. In our study, the RV ROI was more accurately outlined by using XT-ERNA software. RVmPA% and RVPSD%

were standardized with R–R and were more accurate and reliable, which may reflect the tachycardia and eliminate effects of the heart rate.[30]

In this paper, the baseline RVmPA% and RVPSD% were significantly higher in acute responders compared to non-responders. Moreover, acute responders showed a significant reduction in RVmPA% and RVPSD% immediately after CRT. LVEF and RVEF of the acute responders were also increased after CRT. But Mukherjee[8] studied 32 cases of NICM patients and found that the RVEF and intra RV dyssynchrony (IRVD) were no obvious change after 3 months of CRT. However, whether Mukherjee's study could be determined that CRT treatment was ineffective for the right cardiac function was questionable. The treatment of CRT might slow or prevent further deterioration of the patient's cardiac function. But, Mukherjee's study underwent 3 months of follow-up and various factors could accelerate or delay the development of heart failure. In addition, the degree of IRVD was used, which may not reflect the tachycardia.

RV-T, RVmPA% and RVPSD% were moderately correlated in this study, suggesting that ERNA and TDI had good consistency in evaluating RV dyssynchrony. Lack of gold standard, we could only compare these 2 methods by predicting the acute response to CRT to determine who was better. According to the ROC curve, the cut-off value of RVmPA% was 49.5%, with the sensitivity of 85% and the specificity of 85% to predict the acute respond. The cut-off value of RVPSD% was 11.5%, with the sensitivity of 85% and the specificity of 92%. But, the cut-off value of RV-T was 48.5 ms, the sensitivity was only 65% and the specificity was only 77%. Therefore, we believe that RVPS% and RVPSD% are important predictors of the CRT. ERNA might be an appropriate alternative to TDI for the assessment of RV dyssynchrony.

4.1. Study limitations

Our study sample was relatively small, with only 33 patients with CRT, and the follow-up time was shorter, so we needed to increase the sample size and further follow-up study. ERNA usually uses the electrocardiogram R wave as the trigger signal, and if the patient has irregular heart rhythm, the image may not be collected normally. However, we believe that ERNA will be a
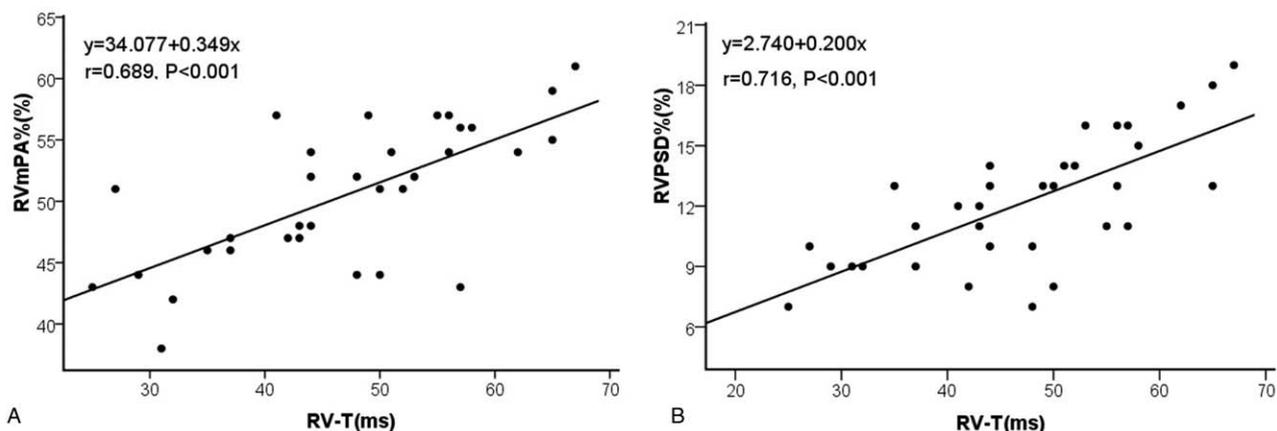
Figure 3. (A) Linear regression plot shows correlation between RVmPA% and RV-T. (B) Linear regression plot shows correlation between RVPSD% and RV-T.
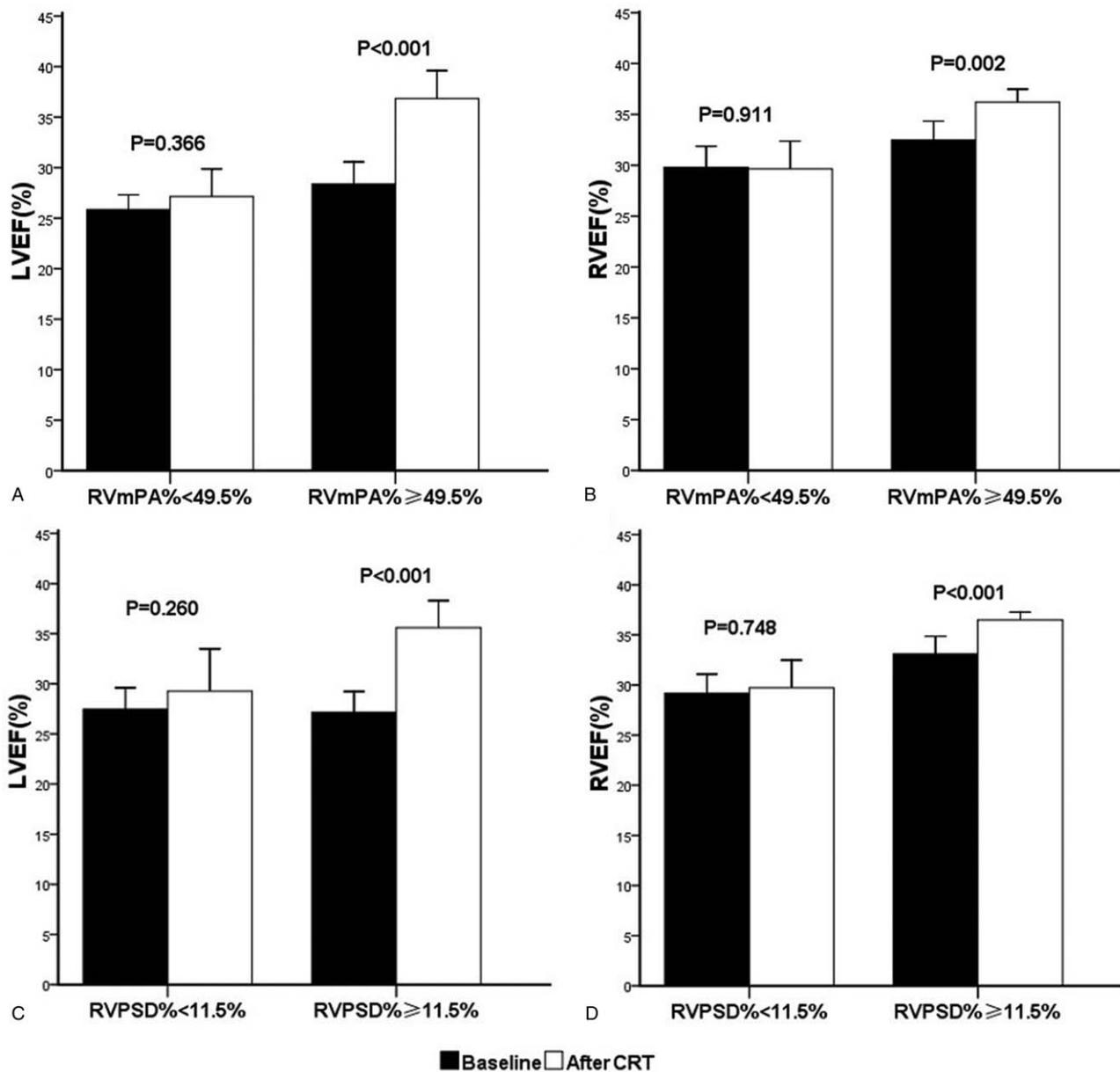
Figure 4. Patients with substantial versus nonsubstantial right ventricular (RV) dyssynchrony (RVmPA%, the cut-off value ≥49.5%; RVPSD%, the cut-off value ≥11.5%). The increase in LVEF (Panel A, C) and RVEF (Panel B, D) is significantly higher in patients with substantial RV dyssynchrony than in patients with nonsubstantial RV dyssynchrony. RVEF = right ventricular ejection fraction, RVPSD = the standard of right ventricular phase standard deviation, RV-T = the difference in time to peak systolic velocity between right ventricular free wall and ventricular septum, LVESV = left ventricular end-systolic volume.

very effective method for evaluating RVEF and RV dyssynchrony in the future.

5. Conclusion

RVmPA% and RVPSD% derived by ERNA correlated significantly with TDI for the assessment of RV dyssynchrony. Either RVmPA% or RVPSD% was highly predictive for acute response to CRT. These findings provide further support for the use of ERNA for assessing RV dyssynchrony. ERNA might be an appropriate alternative to TDI for the assessment of RV dyssynchrony.

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