ORIGINAL ARTICLE

Left ventricle radial contraction pattern is altered by right ventricular pacing in patients with heart failure and baseline intraventricular dyssynchrony

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Abstract: Aims – Baseline mechanical intraventricular dyssynchrony showed only a weak correlation with response to CRT in HF patients with wide QRS. We aimed to evaluate the effects of RV pacing on baseline intraventricular dyssynchrony in patients submitted to CRT. **Methods –** In 40 consecutive HF patients (LBBB, sinus rhythm, normal PR interval, 22 ischemic etiology, 65.5±10.7 years, 21 women, NYHA class 3.3 ± 0.5, LV ejection fraction 20.1±4.1%), speckle tracking radial strain was performed during sinus rhythm (ODO mode) and during RV pacing (DDD with optimum AV interval) one week after biventricular device implantation. RV lead was placed on interventricular septum (RVS, n=30) and RV apex (RVA, n=10). Patients had significant baseline intraventricular dyssynchrony, (i.e. ≥130 ms time difference in peak septal wall to infero-lateral wall strain). Maximum LV delay area (MDA) was defined as the segment with the latest systolic peak from the 6 regional color-coded time-strain curves. Midventricular global radial strain (mGRS) was determined averaging the segmental radial strain values. **Results –** Overall, RV pacing did not significantly increased intraventricular dyssynchrony (350±98 ms vs. 322±90 ms during SR, p=0.08). However, RVA pacing significantly increased LV dyssynchrony (367±58 ms vs. 312±60 ms during SR, p<0.001). mGRS was significantly reduced during RV pacing (13.3±8.5% vs. 18.3±7.4% during SR, p<0.001). The location of MDA shifted during RV pacing in 31 out of 40 patients (77%). **Conclusions –** In HF patients with wide QRS submitted to CRT, RV pacing alters the pattern of intraventricular dyssynchrony and impairs LV strain.
Keywords: cardiac resynchronization therapy, LBBB, intraventricular dyssynchrony, RV pacing, LV strain

Rezumat: Obiective – Asincronismul mecanic intraventricular inițial prezintă doar o slabă corelație cu răspunsul la terapia de resincronizare cardiacă la pacienții cu ICC și QRS larg. Obiectivul studiului a fost evaluarea efectelor de stimulare de VD asupra asincronismului intraventricular la pacienții tratați cu terapie de resincronizare cardiacă. **Metoda –** La 40 de pacienți consecutivi cu insuficiență cardiacă (ritm sinusal, BRS, interval PR normal, 21 au fost de sex feminin, 22 ischemici, vârsta 65,5±0,5 ani, FEVS 20,1±4,1%) și terapie de resincronizare cardiacă la o săptămână post-implant a fost efectuată ecocardiografie speckle tracking cu evaluarea deformării radiale în ritm sinusal (mod ODO) vs stimulare VD (mod DDD cu interval AV optim). Poziționarea sondei de VD a fost în 30 din cazuri septală, iar în 10 apicală. Toți pacienții aveau în condiții bazale asincronism intraventricular semnificativ (timpul între vârful de contracție septal și cel al peretelui inferolateral de peste 130ms în incidența parasternal ax scurt la nivelul mușchilor papilari). Aria cu întârziere maximă a ventriculului stâng a fost definită prin identificarea segmentului cu cea mai mare întârziere dintre cele 6 segmente studiate în aceeași incidență. Deformarea radială midventriculară globală a fost determinată făcând o medie a deformării radiale pe fiecare segment studiat. Rezultate: Stimularea septală de VD în modul DDD nu a crescut semnificativ disincronia intraventriculară (350±98 ms vs. 322±90 ms, p= 0,08), spre deosebire de stimularea apicală a VD în modul DDD care s-a dovedit a crește semnificativ disincronia de contracție a VS (367±58 ms vs. 312±60, p=<0,001). Stimularea VD a redus semnificativ deformarea midventriculară radială globală (13,3±8,5% vs 18,3±7,4%, p<0,001). Localizarea ariei de întârziere maximă a contracției de VS s-a schimbat în timpul stimulării VD la 31 din 40 de pacienți (77%). **Concluzii –** La pacienții cu insuficiență cardiacă și QRS larg referiți pentru TRC, stimularea de VD alterează pattern-ul de disincronie intraventriculară și alterează deformarea sistolică a VS.
Cuvinte cheie: terapie de resincronizare cardiacă, BRS, asincronism intraventricular, stimularea de VD, deformarea de VS

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WHATS NEW?

In patients with CHF due to LVD, LBBB and normal PR interval, during CRT with standard "optimized" AVI interval:

- RV pacing changes LV dyssynchrony pattern (shifts the maximum delay area)
- RV pacing augments LV dyssynchrony (significantly at least for RVA leads)
- RV pacing further impairs LV strain (suggesting a deleterious effect on LV systolic function)

INTRODUCTION

Cardiac resynchronization therapy (CRT) improves quality of life (QoL), reduces hospitalizations and total mortality in patients with left ventricle (LV) systolic dysfunction, wide QRS and moderate to severe chronic heart failure (CHF) despite optimal medical therapy[1]. Clinical response to CRT is observed in 60%[1] to 70%[2] of the patients, while structural response (LV reverse remodeling) is present in only 56% of the patients[2]. Noteworthy, CRT improves long-term survival only in patients with significant LV reverse remodeling (a ≥10% reduction in LV end systolic volume)[3]. Patient selection guided by echocardiographic detection of mechanical intraventricular dyssynchrony seemed appealing, with some data showing a superior effect of CRT in patients with a concordance between maximum delay area and LV lead position[4]. However, a prospective trial failed to prove that anyone of the echocardiographic parameters available for identification of baseline intraventricular dyssynchrony has a good correlation with clinical or structural response to CRT[2]. Possible explanations could be the weak reproducibility of these parameters[5] and complex torsion movement of the asynchronous failing LV[6]. An alternative explanation could reside in the biventricular pacing configuration used to deliver CRT in the majority of centers, constantly introducing right ventricle (RV) pacing, an issue that has never been explored.

It is currently not know if RV pacing during CRT does not change the magnitude and the distribution of intraventricular dyssynchrony, an issue that was addressed with the present investigation.

METHODS

Patients: Between January 2010 and February 2012, we selected 40 consecutive patients with CRT and complete echocardiographic windows (including an analyzable mid-ventricular short axis view). Eligibility for CRT was chronic moderate to severe heart failure [New York Heart Association (NYHA) functional class III or IV] on optimal pharmacological therapy, moderate to severe LV systolic dysfunction [LV ejection fraction (LVEF) £ 35%] and left bundle branch block (LBBB) with QRS complex ≥120 ms. Ischemic heart disease was considered the etiology of LV systolic dysfunction in the presence of significant coronary artery stenosis (³50% in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction and/or previous coronary revascularization. The study protocol was approved by the institution ethic committee and written informed consent was obtained in all patients.

Cardiac resynchronization therapy device implantation: The right atrial lead was positioned conventionally into the right atrial appendage (RAA). After coronary sinus (CS) cannulation and occlusive retrograde CS venogram, LV lead (Attain BP 4194, Medtronic Inc., Minneapolis, MN, USA) was inserted in a lateral or postero-lateral vein. Right ventricular lead was placed on the interventricular septum in 30 patients (guided by the earliest detected RV electrogram relative to the beginning of intrinsic QRS and the narrowest paced QRS)[7]. In 10 patients the RV lead was implanted at RV apex (RVA) (one operator implanting exclusively RVA leads). All leads were connected to a dual chamber biventricular implantable pacemaker or cardioverter-defibrillator (Insync III or Insync Maximo, Medtronic Inc.).

ECG measurements: QRS duration was determined during intrinsic rhythm and during DDD RV pacing using 12-leads recordings at a 50 mm/s speed.

Echocardiographic evaluation: All patients underwent standard transthoracic 2D and color Doppler echocardiography one week after implantation of a CRT device with a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Using a 3.5 MHz transducer (16 cm depth), images were obtained in the parasternal (long- and short-axis) and apical (2-, 3-, and 4-chamber) views. LV volumes [end-diastolic volume (LVEDV), end-systolic volume (LVESV)] and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's formula. Digital routine gray-scale 2D cine-loops from 3 consecutive beats (with gain settings adjusted to optimize endocardial definition) were obtained at end-expiratory apnea from mid-LV short-axis view at the papillary muscle level. After a 5 minutes equilibrium

phase, images were acquired during intrinsic rhythm (CRT-off, ODO) or during RV pacing (DDD 30, with the standard optimum AV delay, i.e. the shortest possible AV delay without mitral inflow truncation)[8]. Sector width was optimized to allow for complete myocardial visualization while maximizing frame rate (mean 63±14 Hz). Offline analysis of radial strain was then performed on digitally stored images (EchoPAC 7.0.0 GE Vingmed Ultrasound). Using a point-and-click approach a circular endocardial region of interest was traced counterclockwise beginning at 9 o'clock at end-systole, with special care taken to adjust tracking of all endocardial segments. A second larger concentric circle was then automatically generated and manually adjusted near the epicardium or manually traced. The region of interest was individually fine-tuned using visual assessment during cineloop playback to ensure that segments were tracked appropriately. The mid-LV image was divided into six standard segments and time-strain curves were generated from each segment. LV breakthrough area and LV maximum delay area were defined as the segments with the earliest and respectively latest systolic peak from the 6 regional color-coded time-strain curves, while radial dyssynchrony was determined as the time differences in peak strain between the earliest and latest segment, with a cutoff value of ≥130 ms[4]. Midventricular global radial strain (mGRS) was calculated averaging the 6 segmental peak systolic strain values of the LV mid-ventricular short-axis view[9].

Reproducibility analysis: Intra- and inter-observer variability of echocardiographic measurements were evaluated in 14 randomly selected patients. To test intra-observer variability, the same primary operator analyzed selected data sets twice at least 3 weeks apart. Operator was blinded to the result of the previous measurements during second evaluation. For the inter-observer variability testing, a second experienced observer was given data sets with no access to information regarding all prior measurements. Intra- and inter-observer variability were calculated as an absolute difference between two measurements over the mean of those measurements and presented as the mean percentage error.

Statistical analysis: The measured values are expressed as mean ± SD. Data showing Gaussian distribution were compared using paired and Student's *t*-tests (comparing data in the subgroups). Dichotomous variables were compared using x2 test. Non-parametric data were compared using Wilcoxon test. The level of significance was set at 0.05.

RESULTS

Patients: Baseline characteristics of the 40 patients included in this study are summarized in Table 1. Mean age was 65.5±10.7 years (21 women), with moderate to severe CHF (mean NYHA functional class 3.3 ± 0.5), with severe LV systolic dysfunction (LVD, mean baseline LVEF 20.1±4.1%). The etiology of LVD was ischemic in 22 patients. All patients were in sinus rhythm and QRS morphology was left bundle branch block (LBBB) in all patients. Mean heart rate was 70±14 bpm during intrinsic rhythm and 71±13 bpm during DDD RV pacing (p=NS).

LV dyssynchrony: There was no difference between QRS duration during intrinsic rhythm (180±18 ms) and QRS duration during RV pacing (179±35 ms, p=NS). Radial dyssynchrony assessed by 2D mid-ventricular speckle-tracking radial strain had a inter- and intra-observer variability of 12+8 and respectively 8+5%. Overall RV pacing has not significantly increased the quantity of intraventricular dyssynchrony (350±98 ms vs. 322±90 ms during SR, p=0.08) (Table 2). In the group with RVA lead LV dyssynchrony significantly increased from 312±60 ms in SR to 367±58 ms during RVA pacing (p<0.001).

The LV breakthrough area: The area with the earliest systolic peak during SR was antero-septal in 30 patients, anterior in 6 patients and inferior in 4 pati-

Table 1. Baseline patient characteristics (n=30)

Sex (female/male)	21/19
Age (years)	65.5±10.7
Etiology (ischemic/idiopathic)	22/18
NYHA functional class	3.3±0.5
LV End Diastolic Volume (ml)	235±71
LV End Systolic Volume (ml)	182±63
LV ejection fraction %	20.1±4.1
Sinus rhythm	40 (100%)
PR interval (ms)	171±25
QRS width (ms)	180±18
LBBB morphology n (%)	40 (100%)

NYHA=New York Heart Association, LV=left ventricular, LBBB = left bundle branch block

Table 2. LV dyssynchrony and radial shortening during sinus rhythm and during RV pacing (n=30)

Parameter	Intrinsic	RV pacing	P value
QRS duration (ms)	180±18	179±35	NS
LV dyssynchrony (ms)	322±90	350±98	0.08
Global radial strain (%)	18.3±7.4	13.3±8.5	<0.001

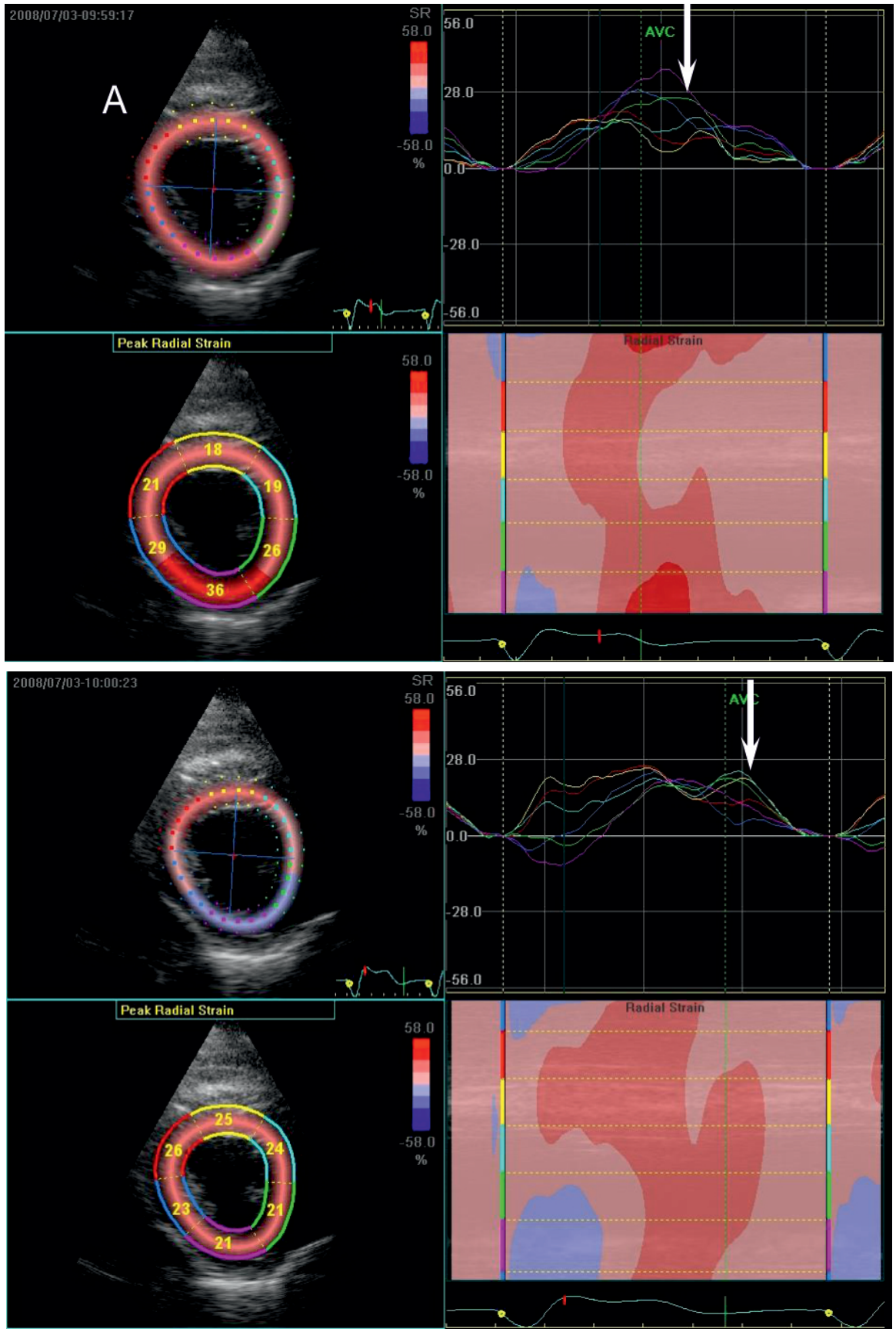

Figure 1. 2D speckle-tracking radial strain at the mid-ventricular level during sinus rhythm (A) and during RV septal pacing (B). The area with the latest peak changes from the infero-lateral wall to the lateral wall. Concomitantly, global radial strain is reduced.

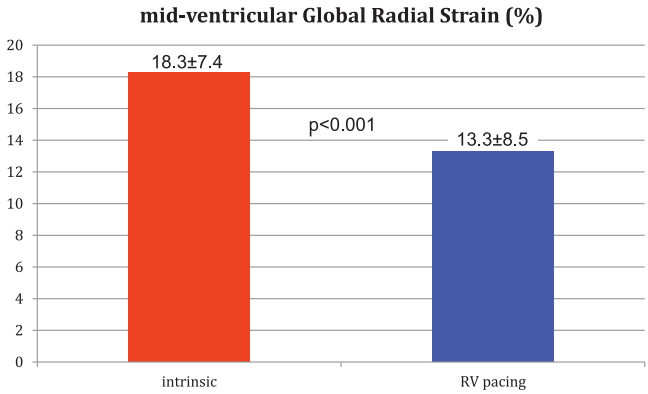

Figure 2. Acute effects of RV pacing on LV mid-ventricular global radial strain.

ents. The location of breakthrough area during DDD RV pacing remained unchanged in 35 out of 40 patients. The mean time interval from beginning of QRS to the earliest systolic peak during SR and during RV pacing was similar (234±75 ms vs. 220±94 ms, p=NS).

Maximum LV delay area: Concomitantly the location of the maximum delay area shifted in 31 out of 40 patients (77%) (Figure 1). Baseline maximum delay area was located on the lateral wall in 9 patients (22.5%), on the infero-lateral wall in 20 patients (50%) and on the inferior wall in 11 patients (27.5%). During RV pacing maximum delay area was located in the inferior wall in 31 patients (77.5%), on the infero-lateral wall in 5 patients (12.5%) and on the lateral wall in 4 patients (10%).

LV radial deformation: The mean midventricular peak systolic global radial strain was significantly reduced during RV pacing (13.3±8.5% vs. 18.3±7.4% during SR, p<0.001) (Figure 2).

DISCUSSIONS

This study shows that in patients with moderate to severe CHF, LV systolic dysfunction, LBBB and normal PR interval, CRT with standard optimized AV delay[8] introduces RV pacing. RV pacing produces an overall a non-significant increase in LV dyssynchrony, changes the dyssynchrony pattern and further impairs LV global radial strain. Specifically, RVA pacing significantly worsened LV dyssynchrony. This change of LV mechanic dyssynchrony pattern induced by RV pacing during CRT may explain why echocardiographic indices of intra-ventricular dyssynchrony as assessed during sinus rhythm are not well correlated with CRT response.

Area of LV breakthrough and area of maximum delay: Changes in the location of the area of maximum delay during RVA pacing in patients with LVD and LBBB have been described during LV endocardial mapping[10,11] as well as at the level of the LV epicardium[12,13]. If this changes in electrical activation are translated into changes in the contraction pattern is currently not known. Present study showed that in patients with LVD and LBBB, although DDD RV pacing with optimum AV delay does not significantly change the area of earliest systolic peak, it does change the location of maximum LV delay at midventricular level in more than 75% of the patients. This might explain the weak correlation between echocardiographic parameters available for identification of baseline intraventricular dyssynchrony and clinical or structural response to CRT[2]. An indirect support for the effects of RV pacing on dyssynchrony pattern comes from studies of epicardial CRT. Placing the LV lead at sites of maximum electrical delay assessed during RVA pacing significantly increased the percentage of responders[15].

Effects of RV pacing on LV dyssynchrony: RV pacing increases the risk of HF and death in patients with systolic LV dysfunction (LVD)[15,16] as well as in patients with normal baseline LV systolic function[17,18]. The risk is higher in patients with baseline wider QRS[19,20] as well as in patients with wider paced QRS[21,22]. The underlying mechanism is induction of intraventricular dyssynchrony, with consecutive impairment of LV systolic function, an effect observed acutely in patients with normal baseline systolic function[23-25] as well as in patients with systolic LVD[26,27], In patients with systolic LVD, intraventricular dyssynchrony induced by RV pacing is further augmented in the presence of a wide QRS[27-29], especially in the presence of LBBB[29]. In the present study RV pacing overall did not significantly increase intraventricular dyssynchrony in patients with systolic LVD and LBBB. However, in the small subgroup of patients with RVA pacing there was a significant increase in LV dyssynchrony. This can be explained by the fact that the vast majority of patients in the present study had RVS pacing, which is probably less dyssynchronous than RVA pacing[8,30] or in some patients is able to partially capture distal part of the His fascicle and/or LBB[31]. Another possible explanation is that the DDD pacing with optimized AV interval used in this study may still allow some degree of fusion with intrinsic activation in patients with normal AV conduction, therefore blurring the deleterious effects of RV pacing[32].

LV radial deformation: Intraventricular dyssynchrony induced and/or augmented by RV pacing alters LV systolic function acutely[24,25,28,29] as well as chronically[18,26], and this effect is largest in patients with systolic LVD and LBBB[29]. Present investigation showed that midventricular GRS was significantly reduced during RV pacing, suggesting an acute reduction in LV systolic function since GRS has been reported to be correlated with LVEF[9,33]. This also might explain the superior response in HF patients with limited RV pacing during CRT[10,34,35].

LIMITATIONS

This is an acute study and present findings may not apply to a chronic RV pacing. However, current data showed that baseline dyssynchrony induced by RV pacing significantly impacts LV function on long term[21,23], suggesting that the effect is persistent. The results may be limited as well by the relatively small number of patients in this study as well as intra- and interobserved variability in measuring radial strain. Although the latter is in range with other studies (or even smaller)[36], these could explain the lack of statistical significance for the difference in the magnitude of intraventricular dyssynchrony. Moreover, the protocol used for RVA pacing (DDD with optimized AVI i.e. shortest AVI without mitral inflow truncation), may allow fusion with intrinsic rhythm in a significant proportion of patients[26], possibly obscuring the changes in LV activation. However, in the vast majority of the patients the present study showed a shift in the LV dyssynchrony pattern. If we consider also that the AVI used reflects common practice in CRT optimization in many centers, this suggest that present findings might have a significant impact in clinical practice, warranting attention and further research.

CONCLUSIONS

In patients with systolic LVD and LBBB, RV pacing changes the location of maximum LV delay area and, especially for RVA leads, augments intraventricular dyssynchrony, and supplementary impairs LV strain. This might explain the weak correlation between baseline mechanical intraventricular dyssynchrony as assessed during intrinsic rhythm and the response to CRT.

Conflict of interest: none declared.

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