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

Radu-Gabriel Vatasescu1, Alexandra Vasile1, Corneliu Iorgulescu1, Dana Constantinescu2, Cristina Caldararu3, Dragos Cozma4, Maria Dorobantu1

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±0.7 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. LV 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 sinus, 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 echiocardiografie speckle tracking cu evaluarea deformării radiale intraventriculare (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 parasternală 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 semnificativă 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 cresce semnificativ disincronia de contracție a VS (367±58 ms vs. 312±60, p=<0,001). Stimularea VD a reduș 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 pacienții (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

---

1 Department of Cardiology, Emergency Clinical Hospital, Bucharest, Romania
2 „Monza” Cardiovascular Center, Bucharest, Romania
3 Sanador Hospital, Bucharest, Romania
4 Institute of Cardiovascular Diseases, Timisoara, Romania

Contact address:
Radu Vatasescu, MD
Pacing and Clinical Electrophysiology Lab. Department of Cardiology, Emergency Clinical Hospital, 014451, Bucharest, Romania.
E-mail: radu_vatasescu@yahoo.com
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 (suggested 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 therapy1. Clinical response to CRT is observed in 60% to 70%2 of the patients, while structural response (LV reverse remodeling) is present in only 56% of the patients3. 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 position4. 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 CRT5. Possible explanations could be the weak reproducibility of these parameters6 and complex torsion movement of the asynchronous failing LV. 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 failu-
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)**

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

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)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intrinsic</th>
<th>RV pacing</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration (ms)</td>
<td>180±18</td>
<td>179±35</td>
<td>NS</td>
</tr>
<tr>
<td>LV dyssynchrony (ms)</td>
<td>322±90</td>
<td>350±98</td>
<td>0.08</td>
</tr>
<tr>
<td>Global radial strain (%)</td>
<td>18.3±7.4</td>
<td>13.3±8.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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.
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 change 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\[^{39}\]. 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 change of LV mechanical dyssynchrony pattern induced by RV pacing during CRT may explain why echocardiographic indices of intraventricular dyssynchrony as assessed during sinus rhythm are not well correlated with CRT response.

**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 mechanical dyssynchrony pattern induced by RV pacing during CRT may explain why echocardiographic indices of intraventricular dyssynchrony as assessed during sinus rhythm are not well correlated with CRT response.

![Figure 2. Acute effects of RV pacing on LV mid-ventricular global radial strain.](image-url)
LV radial deformation: Intraventricular dyssynchrony induced and/or augmented by RV pacing alters LV systolic function acutely24,25,28,29 as well as chronically18,26, and this effect is largest in patients with systolic LVD and LBBB29. Present investigation showed that midventricular GRS was significantly reduced during RV pacing, suggestive of an acute reduction in LV systolic function since GRS has been reported to be correlated with LVEF9,33. This also might explain the superior response in HF patients with limited RV pacing during CRT10,34,35.

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 term21,23, 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 interobserver variability in measuring radial strain. Although the latter is in range with other studies (or even smaller)26, 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 patients26, 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.

References

2. Chung ES; Leon AR; Tavazzi L; Sun J-P; Nihooyannopoulos P; Merlino J; et al. Results of the Predictors of Response to CRT (PROSPECT) Trial. Circulation 2008;117:2608-2616.
3. Yu CM; Bleeker GB; Fung JW; Schalij MJ; Zhang Q; van der Wall EE; et al. Left ventricular reverse remodeling but not clinical improvement; predicts long-term survival after cardiac resynchronization therapy. Circulation 2005;112:1580-6.
4. Suffoletto MS; Dohi K; MD; Cannesson M; Saba S; Gorcsan J; Novel Speckle-Tracking Radial Strain From Routine Black-and-White Echocardiographic Images to Quantify Dyssynchrony and Predict Response to Cardiac Resynchronization Therapy. Circulation 2006;113:960-968.
10. Vatasescu R; Burreuoz A; Mont L; Tamborero D; Sitges M; Silva E; et al. Midterm ‘super-response’ to cardiac resynchronization therapy by biventricular pacing with fusion: insights from electro-anatomical mapping. Euro paced. 2009 Dec;11:12:1675-82.
11. Vassallo JA; Cassidy DM; Miller JM; Buxton AE; Marchlinski FE; Josephson ME. Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. J Am Coll Cardiol 1986;7:1228-33.
13. Jia P; Ramanathan C; Ghameen RN; Ryu K; Varma N; Rud Y. Electrocardiographic imaging of cardiac resynchronization therapy in heart failure: Observation of variable electrophysiologic responses. Heart Rhythm 2006;3:296-310.
15. Wilkoff BL; Cook JR; Epstein AE; Greene HL; Hallstrom AP; Hsia H; et al; on behalf of the Dual Chamber and VVI Implantable Defibrillator Trial Investigators. Dual chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID)trial. JAMA 2002;288:3115-23.
16. Steinberg JS; Fischer A; Wang P; Schuger C; Daubert J; McNitt S; et al; MADIT II Investigators. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. J Cardiovasc Electrophysiol 2005;16:359-65.
17. Sweeney MO; Heikkamp AS; Ellenbogen KA; Greenspoon AJ; Freedman RA; Lee KL; et al; MODe Selection Trial Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrilla-