

# Does the Right Go Wrong During Cardiac Resynchronization Therapy?

Citation for published version (APA):

Lumens, J., Willemen, E., & Prinzen, F. W. (2020). Does the Right Go Wrong During Cardiac Resynchronization Therapy? *JACC-Cardiovascular Imaging*, 13(7), 1485-1488. <https://doi.org/10.1016/j.jcmg.2020.01.009>

## Document status and date:

Published: 01/07/2020

## DOI:

[10.1016/j.jcmg.2020.01.009](https://doi.org/10.1016/j.jcmg.2020.01.009)

## Document Version:

Publisher's PDF, also known as Version of record

## Document license:

Taverne

## Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

## General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

[www.umlib.nl/taverne-license](http://www.umlib.nl/taverne-license)

## Take down policy

If you believe that this document breaches copyright please contact us at:

[repository@maastrichtuniversity.nl](mailto:repository@maastrichtuniversity.nl)

providing details and we will investigate your claim.

EDITORIAL COMMENT

# Does the Right Go Wrong During Cardiac Resynchronization Therapy?\*



Joost Lumens, PhD,<sup>a</sup> Erik Willemen, MSc,<sup>a</sup> Frits W. Prinzen, PhD<sup>b</sup>

About 1 in 3 patients with chronic heart failure (HF) has left bundle branch block (LBBB) (1), a ventricular conduction disorder causing a distinct pattern of electromechanical polarization in the left ventricular (LV) wall, characterized by a decrease of work load in the early activated septum and an increase of work load in the late activated LV lateral wall (2-4). Many clinical studies have shown that LBBB is associated with increased morbidity and mortality (5,6). The introduction of cardiac resynchronization therapy (CRT) has significantly improved the prognosis of patients with HF with reduced LV ejection fraction and hallmarks of LBBB on 12-lead electrocardiogram (i.e., widening and LBBB configuration of the QRS complex) (7). The most popular working mechanism attributed to CRT is its instantaneous reCOORDINATING effect on LV electromechanical function. Through biventricular pacing, CRT can (partially) repair the LV mechanical imbalance by inter- and intraventricular resynchronization of the electric activation (8).

## A CALL FOR FOCUS ON RIGHT VENTRICULAR MECHANICAL FUNCTION

It is important to realize that the vast majority of the studies investigating LBBB and its treatment with CRT has focused on LV mechanics and pump function. The right ventricle, however, is often disregarded in these studies, although it has been known for a long time that a change in the loading condition of either ventricle directly influences the pump function of the other ventricle. Also, several studies have identified right ventricular (RV) systolic dysfunction as an independent predictor of nonresponse to CRT (9). For this reason, the publication of Storsten et al. (10) in this issue of *iJACC* is important, as it provides mechanistic insight into the effects of both LBBB and CRT on RV mechanical function. The work is composed of an elegant combination of animal experimental and human measurements. Echocardiographic longitudinal strain analysis in a group of patients with LBBB with nonischemic cardiomyopathy and normal RV function revealed an abnormal contraction pattern in the RV free wall, characterized by premature systolic shortening before RV ejection. In most patients, this early-systolic RV free wall shortening was significantly reduced or entirely abolished by CRT.

Storsten et al. (10) observed the same premature RV systolic shortening in an animal model as soon as LBBB was induced by radiofrequency ablation of the left bundle branch. Because the intrinsic His-Purkinje conduction of the right ventricle was maintained in this acute model of LBBB, it was concluded that the RV contraction abnormality was a result of a change in direct LV-RV interaction. Interestingly, they also investigated what this change of ventricular interaction means for the distribution of work load over the ventricular walls.

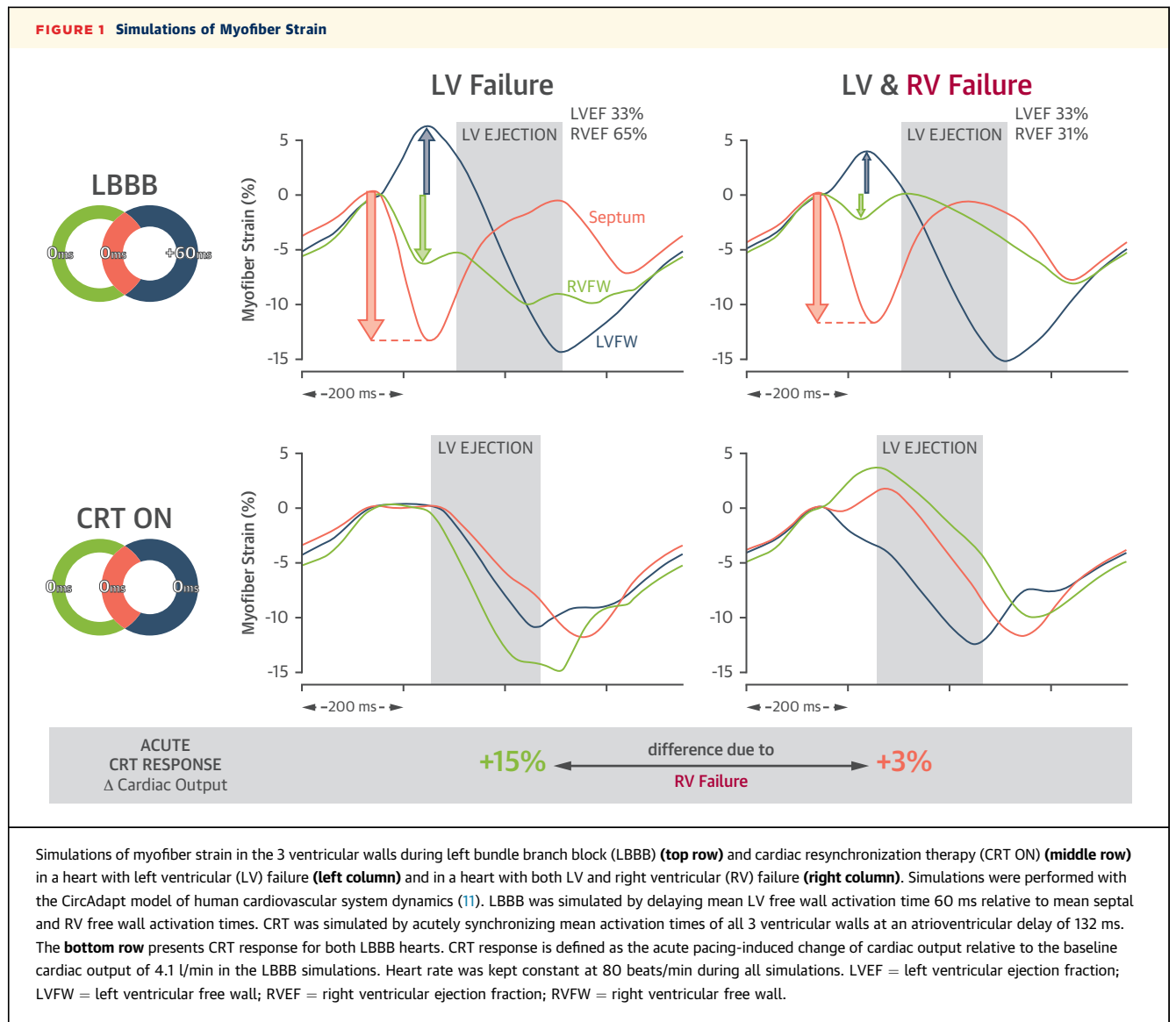
## MYOCARDIAL UNLOADING AND RELOADING DURING LBBB AND CRT

By combining LV and RV pressure measurements with myocardial deformation analysis using

\*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *iJACC* or the American College of Cardiology.

From the <sup>a</sup>Department of Biomedical Engineering, CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, the Netherlands; and the <sup>b</sup>Department of Physiology, CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, the Netherlands. Dr. Lumens has received support from the Dr. Dekker Program of the Dutch Heart Foundation (grant 2015T082), the Netherlands Organisation for Scientific Research (ZonMw, VIDI grant 016.176.340), and the ERA-Net ERACoSysMed program (PUSHCART). Dr. Lumens has received research grants from Medtronic. Dr. Prinzen has received research grants from Abbott, Microport CRM, Biotronik, Medtronic, and EBR Systems. Dr. Willemen has reported that he has no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* [author instructions page](#).



sonomicrometric crystals, the distribution of myocardial work across the ventricular walls was determined during LBBB and CRT. These experimental data corroborate previous experimental and clinical studies (3,12) by showing that LBBB increases myocardial work load in the late activated LV lateral wall and decreases work load in the early activated septum and that CRT (partially) restores the distribution of myocardial work load. Furthermore, the animal experimental data validate previous computer simulation work showing that LBBB reduces work load in the RV free wall and that CRT reverts this unloading effect (3). In other words, CRT instantly

increases the work load of the RV myocardium in a patient with HF with LBBB. Therefore, as Storsten et al. (10) suggest, their study raises the important question whether this pacing-induced change in RV work load can explain the association between baseline RV dysfunction and worse outcome after CRT.

#### IS RV WORK LOAD THE LINK BETWEEN RV FAILURE AND NONRESPONSE TO CRT?

For this editorial, we have performed computer simulations to test this hypothesis. We have used the well-established CircAdapt model of the human heart

and circulation (CircAdapt, Maastricht University, Maastricht, the Netherlands), which has been extensively used for simulation of mechanics and hemodynamic status in the failing heart with LBBB and during its treatment with CRT (3,13). **Figure 1** shows the simulated strain patterns of the 3 ventricular walls during LBBB (**Figure 1**, top row) and during CRT (**Figure 1**, middle row) in a heart with LV failure and normal RV function (**Figure 1**, left column) and in a heart with both LV and RV failure (**Figure 1**, right column). The LBBB simulation with LV failure shows the same early systolic RV and septal shortening and LV pre-stretch as observed by Storsten et al. (10) in dogs and HF patients with LBBB. In addition, the simulations predict that RV failure significantly reduces the amount of early systolic RV shortening and LV pre-stretch in LBBB. In the simulations of CRT (**Figure 1**, middle row), the 3 ventricular walls are synchronously activated. As expected, CRT made the strain patterns of the 3 ventricular walls rather uniform in the heart with LV failure alone. Interestingly, CRT did not lead to such mechanical equilibration in the heart with additional RV failure. Instead, the LV free wall strain pattern showed early systolic shortening, and the RV free wall and septum were stretched before the onset of LV ejection. Given the synchronous electric activation of the 3 ventricular walls during CRT, this mechanical imbalance can be explained only by a marked interventricular difference in contractile strength during early systole, which is due to the pacing-induced redistribution of myocardial work load in the LBBB heart from the LV free wall to the RV free wall. The failing right ventricle cannot handle this acute increase in mechanical work load. The bottom panel of **Figure 1** illustrates the effect of RV failure on hemodynamic response to CRT, in terms of acute change of cardiac output relative to baseline LBBB conduction. The simulations predict that RV contractile failure significantly reduces the potential for acute CRT response.

## RV DEFORMATION PATTERN AS A PREDICTIVE BIOMARKER

In an earlier study, Van Everdingen et al. (14) showed that conventional LV mechanical dyssynchrony indexes (i.e., time to peak strain between the septum and LV lateral wall, interventricular mechanical delay, and septal systolic rebound stretch) do not reflect the negative impact of RV contractile dysfunction on CRT response. The data published by Storsten et al. (10) and the simulations presented in this editorial suggest that the early systolic RV shortening can be of prognostic value, given its sensitivity to the electromechanical LBBB substrate that is amenable to CRT and to the contractile function of the RV free wall, which seems to be a strong determinant of CRT response.

## GOING THE RIGHT WAY WITH CRT

Taking all these data together, we strongly support the notion by Storsten et al. (10) that the diagnostic work-up of patients with HF who are candidates for CRT should include the assessment of baseline RV function. Their combination of patient and animal experimental data as well as the aforementioned computer simulations indicate that the RV free wall, which is mechanically spared in the LBBB heart, should be strong enough to bear the sudden increase in work load imposed by CRT. Future studies are needed to determine how much of the current problem of nonresponse to CRT is due to a lack of RV contractile reserve.

**ADDRESS FOR CORRESPONDENCE:** Dr. Joost Lumens, Department of Biomedical Engineering, CARIM School for Cardiovascular Diseases, Maastricht University, P.O. Box 616, 6200 MD Maastricht, the Netherlands. E-mail: [joost.lumens@maastrichtuniversity.nl](mailto:joost.lumens@maastrichtuniversity.nl).

## REFERENCES

1. Clark AL, Goode K, Cleland JG. The prevalence and incidence of left bundle branch block in ambulant patients with chronic heart failure. *Eur J Heart Fail* 2008;10:696-702.
2. Gjesdal O, Remme EW, Opdahl A, et al. Mechanisms of abnormal systolic motion of the interventricular septum during left bundle-branch block. *Circ Cardiovasc Imaging* 2011;4:264-73.
3. Lumens J, Ploux S, Strik M, et al. Comparative electromechanical and hemodynamic effects of left ventricular and biventricular pacing in dyssynchronous heart failure: electrical resynchronization versus left-right ventricular interaction. *J Am Coll Cardiol* 2013;62:2395-403.
4. Vernooij K, Verbeek XA, Peschar M, et al. Left bundle branch block induces ventricular remodeling and functional septal hypoperfusion. *Eur Heart J* 2005;26:91-8.
5. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J* 2002;143:398-405.
6. Houthuizen P, Van Garsse LA, Poels TT, et al. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. *Circulation* 2012;126:720-8.
7. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;123:1061-72.

8. Prinzen FW, Vernooy K, De Boeck BW, Delhaas T. Mechano-energetics of the asynchronous and resynchronized heart. *Heart Fail Rev* 2011;16:215-24.
9. Damy T, Ghio S, Rigby AS, et al. Interplay between right ventricular function and cardiac resynchronization therapy: an analysis of the CARE-HF trial (Cardiac Resynchronization-Heart Failure). *J Am Coll Cardiol* 2013;61:2153-60.
10. Storsten P, Aalen JM, Boe E, et al. Mechanical effects on right ventricular function from left bundle branch block and cardiac resynchronization therapy. *J Am Coll Cardiol Img* 2020;13:1475-84.
11. Source code CircAdapt model [version Walmsley 2015]. Available at: <http://www.circadapt.org/>. Accessed February 20, 2020.
12. Russell K, Eriksen M, Aaberge L, et al. A novel clinical method for quantification of regional left ventricular pressure-strain loop area: a non-invasive index of myocardial work. *Eur Heart J* 2012;33:724-33.
13. Walmsley J, Arts T, Derval N, et al. Fast simulation of mechanical heterogeneity in the electrically asynchronous heart using the MultiPatch module. *PLoS Comput Biol* 2015;11:e1004284.
14. van Everdingen WM, Walmsley J, Cramer MJ, et al. Echocardiographic prediction of cardiac resynchronization therapy response requires analysis of both mechanical dyssynchrony and right ventricular function: a combined analysis of patient data and computer simulations. *J Am Soc Echocardiogr* 2017;30:1012-20.e2.

---

**KEY WORDS** dyssynchrony, heart failure, right ventricle, strain, ventricular interaction