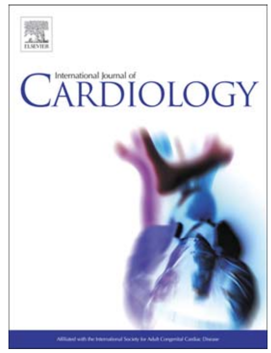
View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by University of Queensland eSpace



Accepted Manuscript

Effect of cardiac resynchronization therapy on right ventricular function

Abhishek Sharma, Jerome J. Bax, Ajay Vallakati, Sunny Goel, Carl J. Lavie, Akash Garg, Debabrata Mukherjee, Edgar Lichstein, Jason M. Lazar

PII: S0167-5273(16)30248-0
DOI: doi: 10.1016/j.ijcard.2016.02.034
Reference: IJCA 22002

To appear in: *International Journal of Cardiology*

Received date: 17 January 2016
Accepted date: 2 February 2016

Please cite this article as: Sharma Abhishek, Bax Jerome J., Vallakati Ajay, Goel Sunny, Lavie Carl J., Garg Akash, Mukherjee Debabrata, Lichstein Edgar, Lazar Jason M., Effect of cardiac resynchronization therapy on right ventricular function, *International Journal of Cardiology* (2016), doi: 10.1016/j.ijcard.2016.02.034

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Effect of Cardiac Resynchronization Therapy on Right Ventricular Function

Abhishek Sharma[1], MD; **Jerome J Bax**[2]**,** MD; **Ajay Vallakati**[3], MD; **Sunny Goel**[4], MD; **Carl J Lavie**[5], MD; **Akash Garg**[6], MD; **Debabrata Mukherjee**[7], MD, MS; **Edgar Lichstein**[4], MD; **Jason M Lazar**[1], MD.

1. Division of Cardiovascular Medicine, State University of New York Downstate Medical Center, NY
2. Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
3. Division of Cardiology, University of Kansas Medical Center, Kansas City, KS
4. Department of Medicine, Maimonides Medical Center, NY
5. Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the University of Queensland School of Medicine, New Orleans, LA
6. Department of Medicine, Saint Peter's University Hospital, NJ
7. Division of Cardiology, Texas Tech University, TX

Corresponding Author: Abhishek Sharma, MD
Postal address: 125 96th street Apt 5B
Brooklyn, NY 11209
Phone# 201-892-6548
Fax: 718-270-2917
Email: abhisheksharma4mamc@gmail.com
Conflict of interest: All authors declare no conflict of interest
Disclosure: None

Word Count: 1057 (excluding references)

Keywords: Cardiac Resynchronization Therapy; Right Ventricular Function

ACCEPTED MANUSCRIPT

Dear Editor,

Cardiac resynchronization therapy (CRT) has been shown to result in improvement in left ventricular (LV) function. However, the effects of CRT on right ventricular (RV) function have not been well described. In this study, we evaluated the effects of CRT on RV function.

A systematic review of the literature was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [1]. We systematically searched PubMed, CINAHL, Cochran CENTRAL, Scopus and Web of Science databases for all studies that reported parameters of RV function before and after CRT implantation. All relevant combinations of following keywords related to cardiac resynchronization therapy, RV function, tricuspid annular plane systolic excursion (TAPSE), RV diameters, RV short axis diameter, RV long axis diameter, RV fractional area change (FAC) were included for database search. The search was conducted from the inception of these databases to October 31, 2015. Studies were included if they met the following criteria: 1) human studies with participants of any age requiring CRT for any indication, 2) reported tricuspid annular plane systolic excursion (TAPSE) or RV basal strain or RV long axis diameter or RV short axis diameter or RV fractional area change (FAC) as absolute number (with standard deviations) before and after CRT. Two independent reviewers (AS, SG) screened the titles and abstracts for relevance. Any disagreements in data extraction were discussed until consensus was reached.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Mix 2.0 Pro (Biostat XL) software was used to analyze the data. A random-effects model with inverse variance weighting was used to calculate pooled mean difference in RV measure and corresponding confidence interval. Heterogeneity between studies was assessed using Cochrane's Q test and I^2 statistic, which denotes the percentage of total variation across studies that is a result of heterogeneity rather than chance. Heterogeneity was considered significant if the p value was less than 0.05. Publication bias was assessed by Begg's test and Egger's regression test. The influence of individual studies was examined by removing each study at a time to assess the degree to which meta-analysis estimate depends on a particular study (exclusion sensitivity analysis).

A total of 13 studies were identified (n=1541) [2-14] (Supplementary figure 1). Baseline characteristics of various studies have been summarized in Supplemental table 1 and 2. Publication bias was not detected by Begg's and Eggers' regression test for any of RV measures. Our results suggest that CRT led to improvements in RV size and function that were consistent across the different measures of RV function. There was a statistically significant increase in TAPSE (Figure 1), RV basal strain (Supplementary figure 2) and RV fractional area change with CRT (Supplementary figure 3). Moreover, CRT led to significant improvements in RV dimensions as determined by RV long axis (Supplementary figure 4) and short axis diameters (Supplementary figure 5).

To our knowledge, this is the first meta-analysis to evaluate the impact of CRT therapy on RV size and function. We reported various parameters of RV function in 1541 patients from 13 studies, with a mean follow- up period of almost 9months. Most of the studies

ACCEPTED MANUSCRIPT

included in our study have used TAPSE as a measure of RV function, which relatively simple echocardiographic measure, which represents RV longitudinal function, which has shown to have a good correlation with more precise measures of RV systolic function, including radionuclide estimation of RV ejection fraction (RVEF) [15]. The exact mechanism of how CRT improves the RV function is not clear, but the most plausible explanation is that CRT leads to favorable LV remodeling, which causes decline in LV volumes and improvements in LV systolic function, which might improve the RV filling and RV systolic function [16]. CRT therapy reduces LV end diastolic pressures, mitral regurgitation and pulmonary artery pressures, which ultimately leads to decreased RV afterload and improvements in RV contractility [17, 18]. The RV shares oblique fibers with the LV within the interventricular septum, which facilitates the augmentation of RV contraction with LV systolic contraction [18]. With declining LV function, there is re-orientation of oblique septal fibers to more transverse position as the LV become more spherical secondary to volume overload. This dramatically reduces the mechanical advantage of RV contractility by these oblique fibers [18]. CRT induces LV remodeling and thereby could lead to repositioning of these fibers and lead to improvements in RV function.

There are several potential limitations in our meta-analysis. First, studies used in our analysis did not use advanced cardiac imaging modalities to evaluate RV function. The RV has a complex geometry and is volume dependent and affected by preloading conditions, which pose a challenge in accurately determining the RV function [15]. Since echocardiography is inexpensive and readily available, it is the most heavily utilized

ACCEPTED MANUSCRIPT

modality to measure RV function. Since one echocardiographic measure might not accurately represent true RV function, we used multiple parameters of RV function. Our results show improvement across all parameters of RV function, including TAPSE and FAC, which have been reported to correlate well with measure of RV function obtained by cardiac MRI. Second, as mentioned above, we could not include a few studies in our analysis, as these studies did not report data in terms of absolute number for RV parameters before and after CRT therapy. One of these studies also showed improvement in RV function with CRT, which is in consensus with our results [19]; another study, however, reported no statistically significant improvement in RV function with CRT [20]. However, this study could have missed the subtle changes in RV function, as it did not report newer echocardiographic RV function parameters such as RV strain, which have been evaluated in our study [20]. Third, there was significant heterogeneity in several parameters of RV function in our study. Thus, precluding a robust conclusion. Large-scale prospective studies will be helpful in further evaluating the response of CRT on RV function. Fourth, it is assumed that patients enrolled in the studies included in our analysis would have had optimal medical management. However, it cannot be claimed conclusively since medical optimization data was missing in few studies included in the meta-analysis.

In conclusion**,** our results suggest that CRT led to improvements in RV size and function as measured by TAPSE, RV FAC, RV basal strain, RV long axis and short axis diameters. Future studies should assess the impact of these changes on symptoms, quality of life and major HF morbidity and mortality.

Author Contributions: Dr. Sharma had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sharma. Acquisition of data: Goel and Sharma. Analysis and interpretation of data: Sharma, Vallakati, Bax, Lavie, Lazar and Mukherjee. Drafting of the manuscript: Sharma, Bax, Garg, Goel, and Vallakati. Critical revision of the manuscript for important intellectual content: Sharma, Lavie, Lazar, Bax, Lichstein and Mukherjee. Administrative, technical, and material support: Sharma and Lichstein. Study supervision: Bax, Lavie, Lichstein, Mukherjee and Lazar

References

1. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151(4):W65-W94.

2. Bleeker GB, Schalij MJ, Nihoyannopoulos P, Steendijk P, Molhoek SG, van Erven L, Bootsma M, Holman ER, van der Wall EE, Bax JJ. Left ventricular dyssynchrony predicts right ventricular remodeling after cardiac resynchronization therapy. J Am Coll Cardiol. 2005 Dec 20;46(12):2264-9.

3. Donal E, Thibault H, Bergerot C, Leroux PY, Cannesson M, Thivolet S, Barthelet M, Rivard L, Chevalier P, Ovize M, Daubert JC, Leclerq C, Mabo P, Derumeaux G. Right

ACCEPTED MANUSCRIPT

ventricular pump function after cardiac resynchronization therapy: a strain imaging study. Arch Cardiovasc Dis. 2008 Jul-Aug;101(7-8):475-84.

4. Scuteri L, Rordorf R, Marsan NA, Landolina M, Magrini G, Klersy C, Frattini F, Petracci B, Vicentini A, Campana C, Tavazzi L, Ghio S. Relevance of echocardiographic evaluation of right ventricular function in patients undergoing cardiac resynchronization therapy. Pacing Clin Electrophysiol. 2009 Aug;32(8):1040-9.

5. D'Andrea A, Salerno G, Scarafile R, Riegler L, Gravino R, Castaldo F, Cocchia R, Limongelli G, Romano M, Calabrò P, Nigro G, Cuomo S, Bossone E, Caso P, Calabrò R. Right ventricular myocardial function in patients with either idiopathic or ischemic dilated cardiomyopathy without clinical sign of right heart failure: effects of cardiac resynchronization therapy. Pacing Clin Electrophysiol. 2009 Aug;32(8):1017-29.

6. Aksoy H, Okutucu S, Aytemir K, Kaya EB, Tulumen E, Evranos B, Fatihoglu SG, Kabakci G, Tokgozoglu L, Ozkutlu H, Oto A. Improvement in right ventricular systolic function after cardiac resynchronization therapy correlates with left ventricular reverse remodeling. Pacing Clin Electrophysiol. 2011 Feb;34(2):200-7.

7. Leong DP, Höke U, Delgado V, Auger D, Witkowski T, Thijssen J, van Erven L, Bax JJ, Schalij MJ, Marsan NA. Right ventricular function and survival following cardiac resynchronisation therapy. Heart. 2013 May;99(10):722-8.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

8. Praus R, Haman L, Tauchman M, Pudil R, Blaha V, Parizek P. Echocardiographic changes after cardiac resynchronisation therapy. Kardiol Pol. 2012;70(12):1250-7.

9. Kusiak A, Wiliński J, Wojciechowska W, Jastrzębski M, Sondej T, Bacior B, Kloch-Badełek M, Czarnecka D. Effects of biventricular pacing on right ventricular function assessed by standard echocardiography. Kardiol Pol. 2012;70(9):883-8.

10. Szulik M, Streb W, Lenarczyk R, Stabryła-Deska J, Kowalski O, Kalarus Z, Kukulski T. The incremental value of right ventricular indices for predicting response to cardiac resynchronization therapy. J Am Soc Echocardiogr. 2011 Feb;24(2):170-179.e3.

11. Sade LE, Özin B, Atar I, Demir Ö, Demirtaş S, Müderrisoğlu H. Right ventricular function is a determinant of long-term survival after cardiac resynchronization therapy. J Am Soc Echocardiogr. 2013 Jul;26(7):706-13.

12. Esmaeilzadeh M, Poorzand H, Maleki M, Sadeghpour A, Parsaee M. Evaluation of Longitudinal Right Ventricular Mechanical Dyssynchrony before and Early after Cardiac Resynchronization Therapy: A Strain Imaging Study. J Tehran Heart Cent. 2011 Winter;6(1):24-30.

13. Vitarelli A, Franciosa P, Nguyen BL, Capotosto L, Ciccaglioni A, Conde Y, Iorio G, De Curtis G, Caranci F, Vitarelli M, Lucchetti P, Dettori O, De Cicco V. Additive value of right ventricular dyssynchrony indexes in predicting the success of cardiac

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

resynchronization therapy: a speckle-tracking imaging study. J Card Fail. 2011 May;17(5):392-402.

14. Knappe D, Pouleur AC, Shah AM, Bourgoun M, Brown MW, Foster E, Pfeffer MA, Moss AJ, Solomon SD; MADIT-CRT Investigators. Acute effects of withdrawal of cardiac resynchronization therapy on left and right ventricular function, dyssynchrony, and contractile function in patients with New York Heart Association functional class I/II heart failure: MADIT-CRT. J Card Fail. 2013 Mar;19(3):149-55.

15. Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J. 1984 Mar;107(3):526-31.

16. Voelkel NF1, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smart FW, Suzuki YJ, Gladwin M, Denholm EM, Gail DB; National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. Circulation. 2006 Oct 24;114(17):1883-91.

17. Ogunyankin KO, Puthumana JJ. Effect of cardiac resynchronization therapy on right ventricular function. Curr Opin Cardiol 2010; 25:464–468.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

18. Schwarz K, Singh S, Dawson D, Frenneaux MP. Right ventricular function in left ventricular disease: pathophysiology and implications. Heart Lung Circ2013; 22:507–511.

19. Campbell P, Takeuchi M, Bourgoun M, Shah A, Foster E, Brown MW, Goldenberg I, Huang DT, McNitt S, Hall WJ, Moss A, Pfeffer MA, Solomon SD; Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) Investigators. Right ventricular function, pulmonary pressure estimation, and clinical outcomes in cardiac resynchronization therapy. Circ Heart Fail. 2013 May;6(3):435-42.

20. Damy T, Ghio S, Rigby AS, Hittinger L, Jacobs S, Leyva F, Delgado JF, Daubert JC, Gras D, Tavazzi L, Cleland JG. 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 May 28;61(21):2153-60.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Figure 1. Forest plot for tricuspid annular plane systolic excursion with cardiac resynchronization therapy