Meta-Analysis of the Relation of Baseline Right Ventricular Function to Response to Cardiac Resynchronization Therapy

Abhishek Sharma, MD[a,*], Jerome J. Bax, MD[b], Ajay Vallakati, MD[c], Sunny Goel, MD[d], Carl J. Lavie, MD[e], John Kassotis, MD[a], Debabrata Mukherjee, MD, MS[f], Andrew Einstein, MD, PhD[g,h], Nikhil Warrier, MD[a], and Jason M. Lazar, MD, MPH[a]

Right ventricular (RV) dysfunction has been associated with adverse clinical outcomes in patients with heart failure (HF). Cardiac resynchronization therapy (CRT) improves left ventricular (LV) size and function in patients with markedly abnormal electrocardiogram QRS duration. However, relation of baseline RV function with response to CRT has not been well described. In this study, we aim to investigate the relation of baseline RV function with response to CRT as assessed by change in LV ejection fraction (EF). A systematic search of studies published from 1966 to May 31, 2015 was conducted using PubMed, CINAHL, Cochrane CENTRAL, and the Web of Science databases. Studies were included if they have reported (1) parameters of baseline RV function (tricuspid annular plane systolic excursion [TAPSE] or RVEF or RV basal strain or RV fractional area change [FAC]) and (2) LVEF before and after CRT. Random-effects metaregression was used to evaluate the effect of baseline RV function parameters and change in LVEF. Sixteen studies (n = 1,764) were selected for final analysis. Random-effects metaregression analysis showed no significant association between the magnitude of the difference in EF before and after CRT with baseline TAPSE ($\beta = 0.005$, $p = 0.989$); baseline RVEF ($\beta = 0.270$, $p = 0.493$); baseline RVFAC ($\beta = -0.367$, $p = 0.06$); baseline basal strain ($\beta = -0.342$, $p = 0.462$) after a mean follow-up period of 10.5 months. In conclusion, baseline RV function as assessed by TAPSE, FAC, basal strain, or RVEF does not determine response to CRT as assessed by change in LVEF. **(Am J Cardiol 2016;117:1315−1321)**

Right ventricular (RV) function is an independent prognostic marker for patients with heart failure (HF) and also plays an important role in determining the response to medical therapy in patients with HF.[1,2] Recently, it has been suggested that baseline echocardiographic parameters of RV function could be helpful in identifying patients who respond more favorably to cardiac resynchronization therapy (CRT).[3,4] However, studies have reported conflicting results, and the relation of baseline RV function with response to CRT remains unclear.[3−19] In this study, we performed a meta-analysis of published studies and investigated the relation of various baseline echocardiographic parameters of RV function with response to CRT, as assessed by change in left ventricular (LV) ejection fraction (EF).

Methods

A systematic review of the reports was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[20] We systematically searched PubMed, CINAHL, Cochran CENTRAL, Embase, Scopus, and Web of Science databases for all studies that reported parameters of RV function at baseline and LVEF before and after CRT implantation. All relevant combinations of the following keywords related to CRT were included in the search: RV function, tricuspid annular plane systolic excursion (TAPSE), RV diameters, RV short-axis diameter, RV long-axis diameter, RV fractional area change (FAC), and LVEF. The search was conducted from the inception of each database to May 31, 2015. No language or age restrictions were applied. Pertinent trials were also searched in *clinicaltrials.gov* and in the proceedings of major international cardiology meetings (American College of Cardiology, American Heart Association, European Society of Cardiology, and Heart Rhythm Society). Studies were included if they met each of the following 3 criteria: (1) human studies with participants of any age requiring CRT for any indication; (2) reported at least one parameter

[a]Division of Cardiovascular Medicine, State University of New York Downstate Medical Center, New York, New York; [b]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; [c]Division of Cardiology, Metrohealth Medical Center, Case Western Reserve University, Cleveland, Ohio; [d]Department of Medicine, Maimonides Medical Center, New York, New York; [e]Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the University of Queensland School of Medicine, New Orleans, Louisiana; [f]Division of Cardiology, Texas Tech University, El Paso, Texas; and [g]Division of Cardiology, Department of Medicine and [h]Division of Cardiology, Department of Radiology, Columbia University Medical Center, New York, New York. Manuscript received December 6, 2015; revised manuscript received and accepted January 19, 2016.

See page 1320 for disclosure information.

*Corresponding author: Tel: (+1) 201-892-6548; fax: (+1) 718-270-2917.

E-mail address: abhisheksharma4mamc@gmail.com (A. Sharma).

0002-9149/16/$ - see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2016.01.029

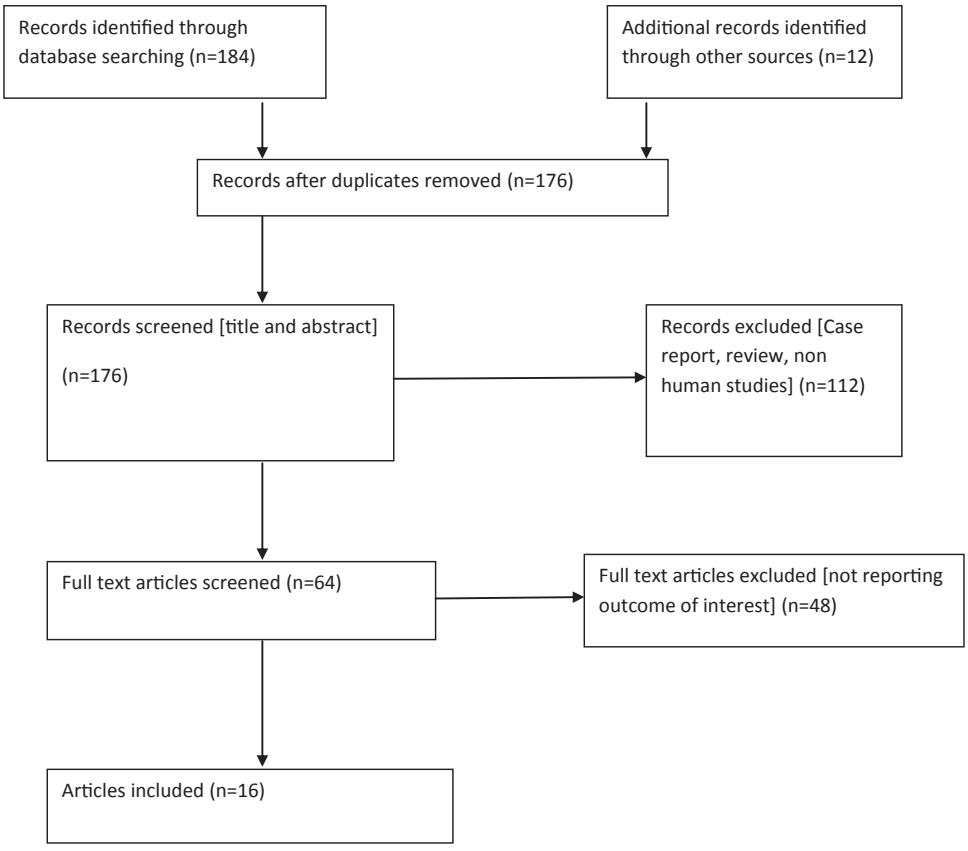

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow sheet.

of baseline RV function (TAPSE, and/or RVEF, and/or RV long-axis diameter, and/or RV basal strain, and/or RVFAC); and (3) reported LVEF before and after CRT. Two independent reviewers (AS and SG) screened the titles and abstracts for relevance. Discrepancies between reviewers were discussed until consensus was reached. The manuscripts of selected titles/abstracts were reviewed for inclusion, and the investigators were contacted if additional data were needed. Using the previously mentioned selection criteria, these 2 reviewers independently determined the studies to be included and excluded, and data from the relevant studies were extracted using predefined extraction forms. Any disagreements in data extraction were discussed until consensus was reached.

In this analysis, Review Manager, version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2008, Copenhagen) was used. A random-effects model with inverse variance weighting was used to calculate pooled mean difference in LVEF and corresponding CI. 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 <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). Open Meta-Analyst software was used to perform random-effects metaregression to evaluate the effect of baseline RV function parameters on change in LVEF.[21]

Results

We identified 17 studies, which reported parameters of baseline RV function and LVEF (Figure 1).[3–19] One study was not included in the final analysis, as it did not provide data in terms of absolute number (and SD) for baseline RV function parameters and LVEF before and after CRT.[19] Sixteen studies were selected for final analysis.[3–18] Details of the studies and baseline characteristics are summarized in Tables 1 and 2.

Pooled analysis of 16 studies reporting LVEF and RV function revealed that CRT led to an absolute increase of 5.82% (95% CI 4.23 to 7.41) in mean LVEF (Figure 2). There was significant heterogeneity across the studies ($p<0.001$, $I^2 = 91\%$). Sensitivity analysis did not demonstrate any significant change in effect size with exclusion of any particular study.

Pooled analysis of the 10 studies that reported the effect of baseline TAPSE on Δ LVEF ($n = 1{,}368$) showed that CRT improved LVEF by 5.96% (95% CI 4.64 to 7.29; Supplementary Figure 1). Random-effects metaregression analysis showed no significant association between the magnitude of the difference in LVEF before and after CRT with baseline TAPSE ($\beta = 0.005$, $p = 0.989$; Figure 3). Similar improvement in LV function was noted after pooling the studies presenting baseline RVEF (5.91%