Profound differences in prognostic impact of left ventricular reverse remodeling after cardiac resynchronization therapy relate to heart failure etiology

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BACKGROUND An ischemic etiology of heart failure (HF) has been associated with reduced left ventricular reverse remodeling after cardiac resynchronization therapy (CRT).

OBJECTIVE The purpose of this study was to assess the relationship between the etiology of HF and reverse remodeling and outcome after CRT.

METHODS Consecutive patients undergoing CRT implantation between October 1, 2008 and August 14, 2015 were retrospectively evaluated. Coronary angiography classified ischemic vs nonischemic etiology. *Reverse remodeling* was defined as the changes in left ventricular ejection fraction (LVEF) after 6 months. Clinical outcome was assessed 1 year after implantation using a combined end point of all-cause mortality and HF readmission.

RESULTS A total of 685 patients were included (300/385 for ischemic/nonischemic etiology). Compared with patients with ischemic cardiomyopathy, patients with nonischemic cardiomyopathy exhibited a greater degree of improvement in LVEF (8.4% ± 10.4% vs 15.8% ± 12.3%; $P < .001$). After correcting for differences, an ischemic etiology of HF predicted less reverse remodeling ($P < .001$) and a higher rate of mortality or HF readmission (hazard ratio 1.63; 95% confidence interval [CI] 1.12–2.73; $P = .011$). Nevertheless, in comparison to a greater degree of improvement in LVEF, a lesser degree of improvement in LVEF (0%–5%) was associated with a higher risk of all-cause mortality and HF hospitalization in patients with nonischemic cardiomyopathy (odds ratio 9.78; 95% CI 1.95–49.04; $P = .006$) but not in patients with ischemic cardiomyopathy (odds ratio 3.58; 95% CI 0.85–15.18; $P = .083$). The most accurate cutoff for improvement in LVEF predicting good clinical outcome was 5.5% in ischemic cardiomyopathy vs 10.5% in nonischemic cardiomyopathy.

CONCLUSION CRT results in reverse remodeling in both patients with ischemic and nonischemic cardiomyopathy, but to a lesser extent in the former. Patients with an ischemic etiology are at an intrinsically higher risk of mortality and HF hospitalization, but derive benefit on outcome at a lesser degree of reverse remodeling.

KEYWORDS Ischemic cardiomyopathy; Nonischemic cardiomyopathy; Cardiac resynchronization therapy; Reverse remodeling; Outcome

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Introduction

Cardiac resynchronization therapy (CRT) alleviates electromechanical dyssynchrony in patients with heart failure with reduced ejection fraction (HFrEF), thereby beneficially affecting functional status, cardiac structure (reverse remodeling), and outcome.[1–8] It is clear that more pronounced left ventricular reverse remodeling induced by CRT favorably influences prognosis.[9–11] As a result, it has become increasingly popular in clinical practice to measure left ventricular reverse remodeling as an end point or even a predictor of success in patients undergoing CRT. Randomized controlled trials have consistently pointed out that up to 30% of patients do not exhibit a meaningful effect on left ventricular reverse remodeling.[12] However, such patients may still exhibit some degree of reverse remodeling, but at a lower extent than so-called responders. Nonresponders are known to have a higher risk of heart failure hospitalization and all-cause mortality.[9] However, this group also constitutes of patients with an intrinsically higher risk of heart failure hospitalizations and mortality (ischemic cardiomyopathy, right bundle branch block, etc). Therefore, any potential benefit of CRT might be diminished by their inherently higher risk of adverse outcome. Patients with ischemic

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cardiomyopathy form such a subgroup of patients that have shown a reduced capability to mount a left ventricular reverse remodeling response in randomized controlled trials.[9–11] As a result, physicians might wrongly think that CRT has a diminished effect on outcome in patients with ischemic cardiomyopathy because of the lesser degree of reverse remodeling attained. However, in the CRT trials that have demonstrated a reduction in the combined end point of heart failure hospitalizations and all-cause mortality with CRT, no interaction was seen for ischemic etiology on outcome.[2,3,6,7] As such, the relationship between left ventricular reverse remodeling and outcome in patients with ischemic vs nonischemic cardiomyopathy might be different. This analysis sought to determine the intrinsic relationship between left ventricular reverse remodeling response and clinical outcome according to heart failure etiology in a contemporary population undergoing CRT.

Methods

Study population

Consecutive patients with HFrEF undergoing CRT implantation in a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium) between October 2008 and August 2015 were retrospectively evaluated. CRT indications were in compliance with the European Society of Cardiology guidelines.[13] After implantation, all patients underwent a similar prespecified follow-up and CRT optimization protocol, as published previously by our group.[14,15] Briefly, all patients received identical optimization of heart failure care, including uptitration of neurohormonal blockers, downtitration of loop diuretics, as well as echocardiographically guided AV and VV optimization of their device settings. Patients received a first follow-up appointment 6 weeks after implantation and a second follow-up at 6 months. Afterward, the follow-up intensity was reduced to once every 9 months if clinically stable. For the present analysis, patients were grouped according to heart failure etiology. Differentiation between an ischemic and a nonischemic etiology of HFrEF was made before CRT implantation in all patients on the basis of coronary angiography. The present study is in compliance with the Declaration of Helsinki. Given the retrospective nature of the study design, the need for written informed consent was waived by the local ethics committee. The manuscript was drafted according to the Strengthening the Reporting of Observational Studies in Epidemiology statement for observational studies.[16]

Baseline characteristics and follow-up

Demographic characteristics and clinical data just before CRT placement, medical therapy, baseline laboratory results, baseline electrocardiography, and echocardiography were retrospectively collected from the individual electronic medical record. Cardiac reverse remodeling was evaluated by comprehensive 2-dimensional echocardiography examinations (Philips Medical Systems, iE33w, Andover, MA) performed by experienced cardiac sonographers. Left ventricular reverse remodeling was measured as the change in left ventricular ejection fraction (LVEF) 6 months after CRT implantation. LVEF was obtained using the modified Simpson's biplane method in the apical 2- and 4-chamber views. All reported echocardiography measurements were averaged from 3 consecutive cycles (or 5 if atrial fibrillation was present) and assessed as recommended by the American Society of Echocardiography.[17]

Study specific end points

To assess the relationship between left ventricular reverse remodeling and outcome, the LVEF change from baseline until 6 months of follow-up was handled as a continuous value. *Good clinical outcome* was defined as the absence of all-cause mortality or heart failure readmission after 1 year. *Heart failure hospitalization* was defined as hospitalization for congestion (at least 2 signs or symptoms of congestion), necessitating the use of intravenous diuretics or hospitalization for low-output heart failure lasting at least 24 hours.

Statistics

Continuous variables are expressed as mean ± SD if normally distributed or median (interquartile range) if not normally distributed. Normality was checked using the Shapiro-Wilk statistic. Categorical data were expressed as numbers and percentages and compared using the Pearson χ^2 test or Fisher exact, as appropriate. Continuous variables were compared using the Student t test or Mann-Whitney U test, as appropriate. Linear regression analysis was used to determine the extent of differential left ventricular reverse remodeling (standardized coefficients) attributed to ischemic vs nonischemic etiology after correcting for differences in baseline characteristics. The Kaplan-Meier method was used to construct survival curves, with the log-rank test used for comparison between groups. Adjusted hazard ratios were calculated by Cox regression analysis after correcting for differences in baseline characteristics. Binary logistic regression analysis was used to determine the adjusted odds ratio for discrete categorical groups of LVEF improvement on clinical outcome according to heart failure etiology. The optimal relationship between change in LVEF (continuous variable) and the absence of mortality and heart failure admission after 1 year was investigated using receiver operating characteristics (ROCs). The optimal cutoff point was searched by identifying the Youden index point (sensitivity + specificity – 1). Adjustment of ROC curves for differences in baseline characteristics was done by introducing statistically different baseline variables into a linear regression model and saving the multivariate residual (the linear predictor). Afterwards it was determined if the multivariate residual affected the area under the curve, which was not the case. Thus making ROC-curve adjustment unnecessary. Statistical significance was always set at a 2-tailed probability level of $<.05$. Statistical analyses were performed using SPSS version 22 (IBM Corp, Chicago, IL).