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Prognostic value of left ventricular reverse remodeling and performance improvement after cardiac resynchronization therapy: A prospective study

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ABSTRACT

Background: The present study was designed to evaluate the respective value of left ventricular (LV) reverse remodeling (changes in LV end-systolic volume relative to baseline (ΔLVESV)) or LV performance improvement (ΔLV ejection fraction (ΔLVEF) or ΔGlobal longitudinal strain (GLS)) to predict long-term outcome in a prospective cohort of consecutive patients receiving routine cardiac resynchronization therapy (CRT).
Methods: One hundred and seventy heart failure patients (NYHA classes II–IV, LVEF ≤ 35%, QRS width ≥ 120 ms) underwent echocardiography before and 9 months after CRT. The relationships between ΔLVESV, ΔLVEF, ΔGLS and outcome (all-cause mortality and/or CHF hospitalization, overall mortality, cardiovascular mortality, CHF hospitalization) were investigated.
Results: During a median follow-up of 32 months, 20 patients died and 27 were hospitalized for heart failure. ΔLVESV, ΔLVEF or ΔGLS were significantly associated with all-cause mortality or CHF hospitalization (adjusted hazard's ratio (HR) per standard deviation 0.58 (0.43–0.77), 0.39 (0.27–0.57) or 0.55 (0.37–0.83) respectively, all $p < 0.01$) and all other endpoints (all $p < 0.01$). Patients with ΔLVESV ≥ 15%, ΔLVEF ≥ 10% and ΔGLS ≥ 1% had a reduced risk of mortality or CHF hospitalization (adjusted HR = 0.25 (0.12–0.51), $p < 0.001$, adjusted HR = 0.26 (0.13–0.54), $p < 0.001$ and adjusted HR 0.38 (0.19–0.75), $p = 0.006$ respectively). Overall performance of multivariate models was better using ΔLVESV or ΔLVEF compared with ΔGLS. Interobserver agreement was excellent for ΔLVESV (Intraclass correlation coefficient — ICC-0.91) and ΔGLS (ICC 0.90) but modest for ΔLVEF (ICC 0.76) in a sample of 20 patients from the study population.
Conclusions: LV reverse remodeling assessed by ΔLVESV is a strong and reproducible predictor of outcome following CRT. Compared with ΔLVESV, ΔLVEF and ΔGLS have important shortcomings: poorer reproducibility or lower predictive value.

1. Introduction

Cardiac resynchronization therapy (CRT) is currently recommended to improve symptoms, and prognosis in patients with moderate-to-severe heart failure, left ventricle (LV) systolic dysfunction and prolonged QRS duration [1]. Identification of 'responders' and 'non-responders' to CRT has attracted considerable attention as 20 to 40% of patients fail to respond to CRT [2]. The CRT response can be measured in terms of clinical outcome or alternatively, in terms of LV response. Numerous studies have shown a significant reduction in left ventricle end-systolic volume (LVESV) after CRT [3–5] which translated consistently into a more favorable outcome [3,6]. Although mechanically attractive, the relationship between LV performance improvement assessed by changes in LV ejection fraction (LVEF) and outcome in heart failure remains a matter of debate [7], with studies reporting conflicting results in patients receiving CRT [8–10]. Lastly, one report from a post hoc analysis of the randomized control MADIT-CRT trial suggested that LV performance improvement as assessed by changes in speckle tracking-derived global longitudinal strain (GLS) may be powerfully

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linked to an improved outcome on top of changes in LVESV and LVEF [11]. Accordingly, the present study was designed to evaluate the respective prognostic value of each of these parameters (changes (Δ) in LVESV, LVEF and GLS) in a prospective cohort of patients receiving CRT according to current guidelines in the context of routine clinical practice.

2. Methods

2.1. Study population

The cohort included ambulatory patients with stable heart failure with indication for CRT according to the European Society of Cardiology guidelines consecutively referred to the Saint Philibert Catholic University Hospital for CRT implantation. Briefly, CRT was considered for patients whose LVEF was ≤35% who remained in New York Heart Association (NYHA) classes II, III and ambulatory IV despite optimal medical treatment and QRS duration ≥120 ms in case of left bundle branch block (LBBB) morphology or with QRS duration ≥150 ms in case of a non-LBBB morphology, as recommended by current guidelines [1].

Exclusion criteria were (1) myocardial infarction, acute coronary syndrome, or coronary revascularization during the previous 3 months; (2) primary mitral or aortic valvular disease; (3) uncontrolled rapid atrial fibrillation; and (4) poor echocardiographic window. The study was approved by the Lille Catholic University ethics committee for non-interventional research. Informed consent was obtained for all patients.

2.2. Echocardiography

Echocardiography was performed the day before CRT implantation and at nine-month follow-up. All exams were performed on a GE Vivid E9 ultrasound system with a M5S probe (GE Healthcare, Velizy, France) by experienced echocardiographers. All echocardiographic data were stored on a PACS. All measurements were off-line performed on a dedicated EchoPAC workstation equipped with the BT12 version (GE Medical Systems). Three cardiac cycles were stored for each measurement for subsequent off-line analysis by one investigator blinded for the clinical status of the patient. LVEF was obtained by Simpson biplan method. LVESV was obtained by contouring LV end systolic volume in two orthogonal plans. All standard echocardiographic data were obtained according to current ASE/EACVI recommendations for performance of echocardiography [12].

Apical chamber views recorded at a frame rate between 55 and 90 frames per second (65 ± 10 fps) were used for strain analysis. Longitudinal strain values were computed after determining aortic valve opening and closure onset using Doppler recordings. Automatic tracking of the endocardial contour on an end-systolic frame was carefully verified and the region of interest was manually corrected to ensure optimal tracking and to cover the entire thickness of the LV myocardium. GLS was the average of segmental peak systolic longitudinal strains from the three apical views.

ΔLVEF and ΔGLS were defined as the differences between baseline and nine-month follow-up values. ΔLVESV was defined as the extent of reduction in LVESV between baseline and nine-month follow-up relative to baseline LVESV.

Interobserver variability of ΔLVESV, ΔLVEF and ΔGLS was tested in a randomly selected set of 20 patients from the study population.

2.3. Clinical data

Clinical data included age, sex, documented history of hypertension, hypercholesterolemia (patients on cholesterol-lowering medication or with a low-density lipoprotein cholesterol concentration greater than 160 mg/dL in the absence of treatment), diabetes mellitus (fasting blood glucose greater than 126 mg/dL on two occasions or patients currently receiving an oral hypoglycemic medication or insulin). Body mass index was calculated as weight in kilogram divided by height in meter square. Significant coronary artery disease was defined as the presence of a luminal narrowing greater than 50% on coronary angiography.

Patients received maximum tolerated doses of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and spironolactone, as recommended by current guidelines. Blood was sampled in the supine position for serum creatinine on the day before CRT device implantation.

2.4. CRT device implantation

Boston Scientific (Natick, MA), Medtronic (Minneapolis, MN), St. Jude (St Paul, MN), Sorin (Milan, Italy), and Biotronik (Berlin, Germany) CRT devices were implanted by electrophysiologists targeting a basal lateral, antero-lateral or postero-lateral coronary sinus vein for LV lead positioning. To promote biventricular pacing, CRT devices were commonly programmed with short atrioventricular delays. Interventricular timing was set to zero. Other parameters were set to nominal values or at the clinician's discretion. Using pulsed Doppler mitral inflow, the atrioventricular delay was selected before hospital discharge to allow adequate E-wave and A-wave separation and termination of the A-wave before mitral valve closure.

2.5. Outcomes

During follow-up, patients were monitored by their personal physicians. Events were ascertained by clinical interviews and/or by phone calls to physicians, patients, and (if necessary) next of kin. The endpoint of the study was all-cause mortality and/or congestive heart failure (CHF) hospitalization. Follow-up was complete in 100% of cases.

2.6. Statistical analysis

Quantitative data are presented as mean ± standard deviation or median [25–75th]. Qualitative data are presented as absolute numbers and percentages. Student paired t-test was performed for paired continuous variables.

For the sake of clarity, ΔGLS has been converted in absolute value in all presented analyses [13]. As a consequence, ΔGLS ("improvement in GLS") positively correlates with improvement in LV systolic function in the present report.

The mean duration of follow-up was computed using the reverse Kaplan–Meier method. Univariate Cox regression survival analysis was used to identify the relationship between ΔLVESV, ΔLVEF and ΔGLS and occurrence of events during follow-up. We used a time-to-first-event approach for composite criteria. Cox regression multivariable survival analysis was thus performed; we did not use model building techniques, and entered covariates that were considered of potential prognostic impact on an epidemiological basis in the models. These covariates were: QRS width, NYHA III or IV, age, coronary artery disease, creatinine serum levels and baseline LVEF (%). The proportional hazards assumption was confirmed using statistics and graphs on the basis of Schoenfeld residuals. Cut-off values for ΔLVESV and ΔLVEF were based on cut-offs from previous published reports [14,15]. In the absence of previously published cut-offs for ΔGLS, the cut-off value was chosen as the value minimizing the Bayesian Information Criteria (BIC) in Cox regression analysis. Univariate survival curves using these categorical values were obtained using the Kaplan–Meier method. To allow comparison of ΔLVESV, ΔLVEF and ΔGLS used as continuous variables, all hazard ratios (HRs) of all Cox models were rescaled by the within-study standard deviation to represent a standardized change in the value of each parameter (either ΔLVESV, ΔLVEF and ΔGLS). Each model discrimination was assessed using Harrell's C statistics. Goodness of fit of Cox multivariate models was assessed by using the R^2. Intraclass correlation coefficient (ICC) was obtained to assess interobserver agreement of ΔLVESV, ΔLVEF and ΔGLS. For all tests, a 2-tailed p-value of 0.05 or less was considered statistically significant. Statistical analysis was performed with R 3.0.3 (Youngstown, Ohio, USA).

3. Results

3.1. Clinical characteristics, EKG, biological and echocardiographic data

One hundred and eighty two patients were initially enrolled in the present study. However, 12 patients died before the nine-month echocardiography examination. The final study population consisted in 170 patients (mean age 70 ± 11 years, 71% male) with heart failure due to LV systolic dysfunction (mean LVEF 26 ± 5%, mean GLS −8.0 ± 2.8%) who received CRT (CRT-P 13%, CRT-D 87%). Clinical characteristics, ECG, biological and echocardiographic data are summarized in Table 1. Fifty percent of the patients were in NYHA functional class III or IV. Mean QRS width was 162 ± 26 ms, 74% of patients had QRS width of ≥150 ms and 81% had a LBBB. Mean values of LVESV, LVEF and GLS at baseline and 9 months of follow-up are detailed in Table 2. Among the 3060 myocardial segments studied at baseline, longitudinal strain analysis was feasible in 3001 (98%). Similarly, among the 3060 myocardial segments studied at nine-month follow-up, longitudinal strain analysis was feasible in 3002 (98%). ΔGLS poorly correlated with ΔLVEF ($r = 0.45$, $p < 0.001$) and ΔLV ESV ($r = 0.48$, $p < 0.001$). In contrast ΔLVEF strongly correlated with ΔLVESV ($r = 0.80$, $p < 0.001$). Mean NYHA functional class decreased from baseline to 9-month follow-up from 2.5 ± 0.6 to 1.9 ± 0.7 ($p < 0.0001$) in the overall study population. Among patients in NYHA functional classes III–IV at baseline, 78% experienced an improvement in one or more NYHA functional class at 9-month follow up. Among patients in NYHA functional class II, 35% experienced an improvement in NYHA functional class at 9-month follow-up. At 9 month follow-up, median [25–75th] biventricular pacing rate was 99 [98;100] %. Seventy nine percent of the study patients achieved biventricular pacing of >97%.