Left ventricular lead position, mechanical activation, and myocardial scar in relation to left ventricular reverse remodeling and clinical outcomes after cardiac resynchronization therapy: A feature-tracking and contrast-enhanced cardiovascular magnetic resonance study

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BACKGROUND Late mechanical activation (LMA) and viability in the left ventricular (LV) myocardium have been proposed as targets for LV pacing during cardiac resynchronization therapy (CRT).

OBJECTIVE The purpose of this study was to determine whether an LV lead position over segments with LMA and no scar improves LV reverse remodeling (LVRR) and clinical outcomes after CRT.

METHODS Feature-tracking and late gadolinium enhancement images were analyzed retrospectively in patients with heart failure (HF) (n = 89; mean age 66.8 ± 10.8 years; LV ejection fraction = 23.1% ± 9.9%) who underwent cardiovascular magnetic resonance (CMR) scanning before CRT implantation. Lead positions were classified as concordant (no scar and LMA [time to peak systolic circumferential strain]) or nonconcordant (scar and/or no LMA).

RESULTS LVRR occurred in 68% and 24% of patients with concordant and nonconcordant LV lead positions, respectively ($P < .001$). Over a median of 4.4 years (range 0.1–8.7 years), LV lead concordance predicted cardiac mortality (adjusted odds ratio [aOR] 0.27; 95% confidence interval [CI] 0.12–0.62) and cardiac mortality or HF hospitalizations (aOR 0.26, 95% CI 0.12–0.58). "No scar" in the paced segment predicted cardiac mortality (aOR 0.24; 95% CI 0.11–0.52) and cardiac mortality or HF hospitalizations (adjusted aOR 0.24; 95% CI 0.12–0.49).

CONCLUSION LV lead deployment over nonscarred LMA segments was associated with better LVRR and clinical outcomes after CRT. LVRR was primarily related to LMA, whereas events were primarily related to scar. These findings support the use of late gadolinium enhancement CMR and feature-tracking CMR in guiding LV lead deployment.

KEYWORDS Heart failure; Cardiac resynchronization therapy; Feature-tracking cardiovascular magnetic resonance; Late gadolinium enhancement; Cardiovascular magnetic resonance

ABBREVIATIONS **aOR** = adjusted odds ratio; **CI** = confidence interval; **CMR** = cardiovascular magnetic resonance; **CRT** = cardiac resynchronization therapy; **HF** = heart failure; **FT** = feature-tracking; **LGE** = late gadolinium enhancement; **LMA** = latest mechanical activation/latest mechanically activated; **LR** = log rank; **LV** = left ventricle/ventricular; **LVEDV** = left ventricular end-diastolic volume; **LVEF** = left ventricular ejection fraction; **LVESV** = left ventricular end-systolic volume; **LVRR** = left ventricular reverse remodeling; **NYHA** = New York Heart Association; **OR** = odds ratio; **STARTER** = Speckle Tracking Assisted Resynchronization Therapy for Electrode Region; **TARGET** = Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy

Introduction

Cardiac resynchronization therapy (CRT) is a standard treatment for patients with heart failure (HF), impaired left ventricular (LV) systolic function, and a wide QRS complex. In addition to prolonging survival,[1,2] CRT reduces HF hospitalizations and improves symptoms, including exercise capacity and quality of life.[1–3] As with any other therapy, [4]

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CRT leads to a variable treatment response. This has led to the concept of "nonresponders."[5]

While patient selection is important in reducing "nonresponders," the response to CRT is still variable and unpredictable, even when the LV lead is deployed in fluoroscopically "optimal" LV pacing positions. This variability is not surprising, as fluoroscopy is opaque to biological properties of the LV myocardium. Echocardiographic studies have suggested that better LV resynchronization, LV reverse remodeling (LVRR), and clinical outcomes after CRT can be achieved by pacing the latest mechanically activated (LMA) LV segments.[6,7] Feature-tracking (FT) cardiovascular magnetic resonance (CMR),[8] the CMR equivalent of speckle-tracking echocardiography, has been validated against the criterion standard of CMR tagging for the assessment of myocardial deformation.[9]

Studies using late gadolinium enhancement (LGE) CMR[10–12] and nuclear scintigraphy[13] have shown that myocardial scarring in the segment subtended by the LV lead leads to a suboptimal response to CRT. These findings are consistent with the observation that pacing scar is associated with increased duration[14] and fragmentation of the QRS complex, as well as suboptimal resynchronization.[15] Moreover, myocardial scars are not readily excitable[16] and effectively reduce the volume of the myocardium available for LV pacing.[17] We hypothesized that deployment of the LV lead over nonscarred segments with LMA, assessed using LGE CMR and FT CMR, leads to a better LVRR response and outcomes after CRT.

Methods

Patients

Q7 Patients who underwent successful CRT device implantation and who had a preimplantation CMR scan were recruited through a dedicated HF device clinic at a single center (Good Hope Hospital, Birmingham, UK). Inclusion criteria were as follows: HF in New York Heart Association (NYHA) class II-IV; optimum pharmacological therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, and mineralocorticoid receptor antagonists; a QRS duration of ≥120 ms and any QRS morphology; and an LV ejection fraction (LVEF) of ≤35%. Exclusion criteria were as follows: contraindications to cardiac pacing; myocardial infarction or acute coronary syndrome within the previous month; severe structural valvular heart disease; preexisting cardiac implantable electronic devices; presence of comorbidities likely to threaten survival for 12 months. The diagnosis of ischemic cardiomyopathy was made if LV systolic dysfunction was associated with a history of myocardial infarction[18] and if there was angiographically documented coronary heart disease (>50% stenosis in ≥1 coronary arteries). The findings of LGE CMR were also used in the assessment of the etiology of HF. Accordingly, LV dysfunction in combination with transmural or subendocardial LGE was regarded as ischemic cardiomyopathy, whereas LV dysfunction and no LGE, patchy uptake, or mid-wall LGE was regarded as non–ischemic cardiomyopathy.[19] The study conforms to the Declaration of Helsinki. This study was approved by the local ethics committee.

Study design

This study consisted of patients who underwent CRT device implantation on the basis of accepted indications from September 2000 to June 2009. As national guidance and funding for cardiac resynchronization therapy with defibrillation (CRT-D) in the United Kingdom was not issued Q8 until 2007, cardiac resynchronization-pacing (CRT-P) was the predominant therapy.

A clinical assessment was performed on the day before implantation and at 1, 3, and every 6 months after implantation. Echocardiography was performed within 1 month before implantation, at 6 weeks after implantation, and every 6 months thereafter. CMR scanning was performed within 1 month before implantation. In patients who died, clinical and echocardiographic data at follow-up pertains to the latest available follow-up. FT CMR and LGE CMR images were analyzed retrospectively by an investigator who was blinded to the clinical outcome data.

Clinical assessment and echocardiography

The preimplantation clinical assessment included assessment of NYHA functional class and a 6-minute hall walk test.[20] *Response in terms of the composite clinical score* was defined as survival for 1 year after implantation free of HF hospitalizations and improvement by ≥1 NYHA classes or by ≥25% in 6-minute walking distance. Two-dimensional echocardiography was performed using a Vivid Systems 5 and 7 scanners (General Electric Healthcare Worldwide, Slough, UK). *LVRR* was defined as a ≥15% reduction in LV end-systolic volume (LVESV) at 6-month follow-up. Echocardiography operators were blinded to other study data.

Device therapy

CRT device implantation was performed using cephalic, subclavian, or femoral transvenous approaches. The right ventricular lead was deployed at the apex. The LV lead was positioned in a coronary vein overlying the LV free wall. For patients in permanent atrial fibrillation, right ventricular and LV leads were implanted and a CRT generator was used, plugging the atrial port. For patients in sinus rhythm, backup atrial pacing was set at 60 beats/min and the pacing mode was set to DDD with an interventricular delay of 0–4 ms, depending on the manufacturer. A ventricular-triggered mode was adopted in patients with atrial fibrillation. Atrioventricular optimization was performed using the iterative echocardiographic method at 6 weeks after implantation and every 6 months thereafter.

CMR

CMR scanning was performed using a 1.5-T Signa (GE Healthcare Worldwide, Slough, United Kingdom) scanner and a phased-array cardiac coil. Horizontal long-axis and