European Heart Journal (2011) **32**, 93–103
doi:10.1093/eurheartj/ehq389

Impact of scar burden by single-photon emission computed tomography myocardial perfusion imaging on patient outcomes following cardiac resynchronization therapy

Evan C. Adelstein*, Hidekazu Tanaka, Prem Soman, Glen Miske, Stephanie C. Haberman, Samir F. Saba, and John Gorcsan III

Cardiovascular Institute, University of Pittsburgh, 200 Lothrop Street, PUH B535, Pittsburgh, PA 15213, USA

Received 19 March 2010; revised 19 July 2010; accepted 14 September 2010; online publish-ahead-of-print 22 October 2010

Aims Ischaemic heart disease negatively impacts response to cardiac resynchronization therapy (CRT), yet the impact of infarct scar burden on clinical outcomes and its interaction with mechanical dyssynchrony have not been well described.

Methods and results We studied 620 NYHA classes III–IV heart failure patients with ejection fraction (EF) $\leq$ 35% and QRS duration $\geq$120 ms referred for CRT. Included were 190 ischaemic cardiomyopathy (ICM) CRT recipients with scar burden quantified by rest–redistribution Tl^{201} myocardial perfusion imaging using a 17-segment (0 = normal to 4 = absence of uptake) summed rest score (SRS). Non-ICM (NICM) CRT recipients ($n = 380$) and 50 patients referred for CRT with unsuccessful LV lead implant comprised the comparison groups. Echocardiographic dyssynchrony analysis was performed in a subgroup of 150 patients. Follow-up left ventricular EF (LVEF) and volumes were examined at 7 $\pm$ 3 months in 143 patients. The outcome of death, cardiac transplant, or mechanical circulatory support was assessed in all. Over 2.1 $\pm$ 1.6 years, ICM patients had significantly worse survival and less LVEF improvement than NICM patients ($P < 0.01$). Ischaemic cardiomyopathy patients with low scar burden (SRS $<$ 27) had favourable survival and LVEF improvement, similar to NICM patients. A high scar burden (SRS $\geq$ 27) was associated with reduced survival and lack of LV functional improvement ($P \leq 0.01$), similar to those with unsuccessful LV lead implant, whereas baseline dyssynchrony was not predictive of outcome in these patients.

Conclusion Extensive scar burden in ICM patients unfavourably affected clinical and LV functional outcomes after CRT, regardless of baseline dyssynchrony measures. Patients with ICM and lower scar burden had significantly better outcomes, similar to NICM patients.

Keywords Heart failure • Pacing • Imaging • Nuclear medicine • Echocardiography

Introduction

Cardiac resynchronization therapy (CRT) has been shown to improve symptoms and prognosis in selected patients with refractory New York Heart Association classes III–IV heart failure (HF), left ventricular (LV) ejection fraction (EF) $\leq$35%, and a QRS duration $\geq$120 ms, regardless of HF aetiology.[1–3] However, approximately 30% of patients do not respond favourably to CRT, and much attention has been focused on prospective predictors of response.[1,4–10] Although previous studies have suggested that CRT provides greater morbidity and mortality benefits to patients with non-ischaemic cardiomyopathy (NICM) when compared with those with ischaemic cardiomyopathy (ICM), conflicting data have been reported.[2,3,11–16] Further evidence suggests that

* Corresponding author. Tel: +1 412 647 6272, Fax: +1 412 647 7979, Email: adelsteinec@upmc.edu

among patients with ICM, significant scar burden related to lead position is also associated with lack of response.[17–19] Although quantification of scar by magnetic resonance imaging is a promising method, resting single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is more commonly utilized in mainstream clinical practice and is safe in patients with previously implanted devices. Accordingly, the objective of this study was to test the hypothesis that scar burden from prior myocardial infarction, as quantified by MPI, is an important determinant of patient outcomes following CRT.

Methods

Patient population

This study examined consecutive patients ($n = 620$) referred to our institution for CRT-defibrillator (CRT-D) implantation between 1998 and 2008 who satisfied one of the following criteria: (i) ICM with a pre-CRT SPECT MPI study, (ii) NICM, or (iii) attempted but unsuccessful LV lead implantation regardless of HF aetiology. The Institutional Review Board approved all research activities, and all subjects provided informed consent. All patients had New York Heart Association classes III–IV HF symptoms refractory to optimal medical therapy, LVEF $\leq$ 35%, and QRS duration $\geq$120 ms (*Table 1*). There were 190 CRT patients characterized as ICM based upon the angiographic finding of >70% stenosis of at least one major epicardial coronary artery or a documented ST-elevation myocardial infarction. A group of 380 CRT recipients were classified as NICM by having major epicardial coronary disease excluded by coronary angiography and included idiopathic, inflammatory, and post-partum aetiologies of chronic HF. Patients with unsuccessful LV lead implant were similarly categorized as ICM ($n = 27$) and NICM ($n = 23$), and all received a standard defibrillator. All patients were managed with optimal tolerated medical therapy, including β-adrenergic antagonists and inhibitors of the renin–angiotensin–aldosterone axis.

Myocardial perfusion imaging

Myocardial scar burden was assessed by Tl^{201} SPECT MPI using a rest–24 h redistribution protocol.[20,21] Patients were injected at rest with 3 mCi of Tl^{201}, with weight-based dosing for patients $\geq$110 kg. Single-photon emission computed tomography imaging was commenced 5 min after radiotracer injection on a dual-headed system (Philips Medical Systems, Andover, MA, USA) using a 180° circular orbit (45° right anterior oblique to 45° left posterior oblique) and a step-and-shoot format with 30 s of imaging at each of 64 total stops. When a perfusion abnormality was present on this early image, a redistribution image was acquired 24 h later using the same acquisition parameters but with 45 s of imaging per stop. Scar burden analysis was performed on the 24 h redistribution image using a standard 17-segment LV model and a five-point, semi-quantitative, visual perfusion score (0 = normal to 4 = absent perfusion; *Figure 1*). A summed rest score (SRS) was calculated as the sum of individual segment scores, which was indicative of the extent and severity of

Table 1 Baseline demographic and clinical characteristics of the study population

	Entire cohort ($n = 620$)	CRT NICM ($n = 380$)	CRT ICM ($n = 190$)	Unsuccessful LV lead implant ($n = 50$)	*P*-value
Demographics					
Age (years)	64 ± 13	62 ± 13	68 ± 10	65 ± 15	<0.001*
Men	438 (70.2%)	242 (63.4%)	164 (85.0%)	32 (65.3%)	<0.001*‡
NYHA class IV	35 (5.6%)	18 (4.7%)	15 (7.8%)	2 (4.1%)	0.266
Diabetes mellitus	209 (33.5%)	104 (27.2%)	84 (43.5%)	21 (42.9%)	<0.001*†
Atrial fibrillation history	306 (49.0%)	166 (43.5%)	115 (59.6%)	25 (51.0%)	<0.05*
Serum creatinine (mg/dL)	1.4 ± 0.8	1.3 ± 0.7	1.5 ± 0.7	1.6 ± 1.1	<0.001*†
ECG characteristics					
QRS duration (ms)	169 ± 33	171 ± 34	166 ± 33	170 ± 31	0.472
Native RBBB	53 (8.6%)	24 (6.4%)	24 (12.5%)	5 (10.4%)	0.063
HF medical therapy					
β-Blocker	496 (79.6%)	308 (80.8%)	151 (78.2%)	37 (75.5%)	0.597
ACE-I or ARB	527 (84.7%)	331 (87.1%)	158 (81.9%)	38 (77.6%)	0.05†
Aldosterone antagonist	151 (24.4%)	102 (26.9%)	38 (19.8%)	11 (22.4%)	0.176
Baseline echocardiography					
LVEF (%)	24 ± 6	23 ± 7	25 ± 6	25 ± 5	0.178
LVEDV (mL)	210 ± 82	204 ± 83	213 ± 80	228 ± 84	0.520
LVESV (mL)	162 ± 71	167 ± 78	159 ± 67	169 ± 71	0.723

NYHA, New York Heart Association; RBBB, right bundle-branch block; ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor-blocker; EDV, end-diastolic volume; ESV, end-systolic volume, NS, not significant. *P*-values reflect a three-way comparison of NICM, ICM, and unsuccessful LV lead implant groups.
Significant differences ($P < 0.05$) in two-way comparisons are annotated as follows.
*NICM vs. ICM.
†NICM vs. unsuccessful LV lead implant.
‡ICM vs. unsuccessful LV lead implant.

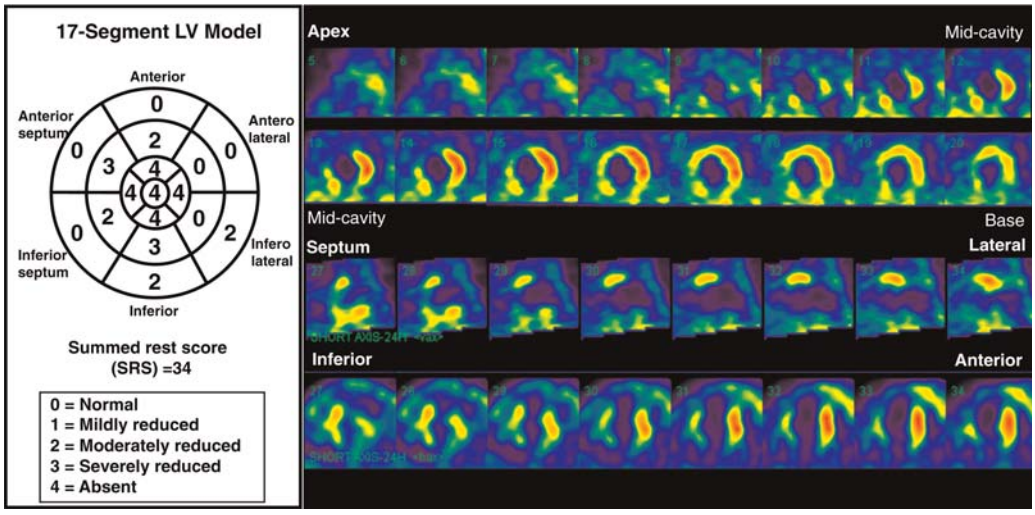

Figure 1 A representative 24 h redistribution Tl^{201} single-photon emission computed tomography scan from an ischaemic cardiomyopathy patient with high scar burden (SRS = 32) who underwent cardiac resynchronization therapy and had a poor outcome. The short-axis (upper two rows), vertical long-axis (third row), and horizontal long-axis slices (bottom row) show extensive perfusion defects in multiple vascular territories. The summed rest score was derived using a standard 17-segment left ventricular model and semi-quantitative perfusion score shown in the left panel.

myocardial infarction.[22] Interobserver variability of SRS was prospectively tested in a sample of 54 randomly selected studies and found to be <10% (Spearman's correlation coefficient 0.901).

Echocardiography

Echocardiographic studies were performed with commercially available imaging systems (VIVID 7, GE-Vingmed, Horten, Norway; Sequoia, Siemens Medical Solutions, Mountain View, CA, USA; or Aplio SSA-770A, Toshiba Medical Systems Corp., Tokyo, Japan). All patients were studied before CRT, and 143 patients had follow-up echocardiograms available for quantitative analysis 7 ± 3 months after CRT. Left ventricular volumes and EF were assessed by biplane Simpson's rule using manual tracing of digital images.[23] A subset of 150 patients had baseline dyssynchrony analysis, including tissue Doppler imaging (TDI) and/or speckle tracking, as previously described in detail (EchoPAC BT08 GE-Vingmed or Research Arena Siemens Medical Solutions).[8,24,25] Briefly, frame rates were 30–100 Hz (mean 65 ± 15 Hz) for grayscale imaging used for speckle tracking and 72–154 Hz for TDI. Longitudinal velocity was determined from digitally stored apical four-chamber, two-chamber, and long-axis views. Ejection intervals were indicated from the LV outflow tract spectral Doppler signal. Colour-coded TDI analysis was performed using regions of interest (7 mm × 15 mm) placed in the basal and mid-segments and adjusted manually to optimize time–velocity curves with the most reproducible peak velocities during ejection.[26] Speckle tracking was performed on routine grayscale images as previously described in detail.[8,27] Longitudinal time–velocity curves were determined towards the LV apex from all three apical views. Longitudinal dyssynchrony was defined as the maximal difference in peak velocity at basal and mid-segments in opposing walls. Significant longitudinal dyssynchrony was defined as the maximal time difference between opposing walls in one view ≥65 ms, using the same cut-off by either software approach. For radial strain, an end-systolic circular region of interest was traced on the endocardial cavity with a second larger circle automatically generated and adjusted near the epicardium.[28] Time–strain curves from each of six standard segments were generated from the short-axis image. Significant radial dyssynchrony was defined as the time difference between the anteroseptal to posterior wall peak strain ≥130 ms.[8] No corrections for heart rate were performed; heart rates were in the range of 50–100 b.p.m.

Device implantation

Patients undergoing CRT implant received a standard active-fixation pacing lead in the right atrium, a high-voltage lead in or near the right ventricular apex, and an LV pacing lead in the coronary venous system, preferentially targeting lateral or posterolateral cardiac veins. In the event that a lead could not be placed transvenously because of anatomic constraints, excessively elevated LV thresholds, and/or low phrenic nerve capture thresholds, epicardial LV leads were surgically implanted via mini-thoracotomy in selected patients ($n = 29$). A group of patients who met standard CRT implant criteria but in whom transvenous LV lead implantation was unsuccessful and no epicardial LV leads were implanted comprised the control group ($n = 50$). The decision to forgo surgical epicardial lead implantation was primarily based on patient refusal. The unsuccessful LV lead implant patients reflected the overall CRT population at our institution with respect to HF aetiology, consisting of 23 patients with NICM and 27 with ICM. All CRT patients received CRT-D, and all unsuccessful LV lead implant patients received a standard cardioverter-defibrillator.

Outcome analysis

The pre-defined principal outcome variable was the combined endpoint of death, cardiac transplant, or the need for mechanical circulatory support (i.e. ventricular assist device). This endpoint was pre-determined because only patients with end-stage HF undergo transplant or ventricular assist device implantation. Follow-up echocardiograms were available in a subset of 143 patients for LVEF as a measure of LV function and LV end-systolic volume as a marker of

reverse remodelling. Left ventricular volume and EF response were pre-specified as a relative ≥15% improvement from baseline values, as utilized in previous studies.[7,8,25]

Statistical analysis

Categorical variables were compared using the χ^2 square test. Continuous variables were observed to approximate a normal distribution and were therefore compared using ANOVA and are reported as means ± 1 SD. The cut-off point for high vs. low scar burden was previously obtained by receiver operating curve analysis when performing logistic regression of LV functional response on the scar burden score.[17] Kaplan–Meier and the multivariate Cox proportional hazard regression were used for time-dependent outcomes. Multivariate analysis of binary discrete endpoints was performed with logistic regression. A combination of forward and backward selection procedures was used to aid in determining the best model of independent predictors. This was followed by forcing potential confounders into the models and determining their effect on the relationship of interest. A *P*-value of ≤0.05 was considered statistically significant, and all tests were two-sided. All statistical calculations were performed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA). The authors had full access to the data and take responsibility for its integrity.

Results

Demographic and clinical characteristics

Baseline characteristics of the study population are shown in *Table 1*. Variables differing ($P \leq 0.05$) among the ICM, NICM, and unsuccessful LV lead implant groups included age, gender, prevalence of diabetes and atrial fibrillation, baseline serum creatinine concentration, and the use of angiotensin-converting enzyme-inhibitors or angiotensin receptor-blockers.

Survival according to heart failure aetiology

The overall follow-up duration was 2.1 ± 1.6 years (median 1.9 years, range 2 days to 10 years) for survival free from transplant or assist device. Follow-up data were 100% complete for the primary endpoint of death, transplant, or assist device implantation, with a total of 155 events overall. There were primary endpoint events in 73 (19%) NICM patients, 65 (34%) ICM patients, and 17 (35%) unsuccessful LV lead implant patients. Survival free from transplant or mechanical circulatory support was significantly longer in NICM patients than in both ICM patients (hazard ratio 1.8, 1.3–2.5, $P < 0.001$; *Figure 2*) and unsuccessful LV lead implant patients (hazard ratio 2.4, 1.4–4.2, $P = 0.001$; *Figure 2*). The significant difference in survival between ICM and NICM patients was retained after adjusting for differences in baseline clinical characteristics detailed in *Table 1* (i.e. age, gender, diabetes, atrial fibrillation, serum creatinine concentration, and use of angiotensin converting-enzyme-inhibitors or angiotensin receptor-blockers). Both ICM (hazard ratio 0.68, 0.48–0.96, $P = 0.03$) and unsuccessful LV lead implant (hazard ratio 0.51, 0.29–0.88, $P = 0.02$) were also significantly associated with increased mortality, transplant, or need for circulatory support in a multivariate model that also included those baseline characteristics individually predictive of this primary endpoint (i.e. NYHA class IV HF, serum creatinine concentration, baseline right bundle-branch block, and use of β-blockers).

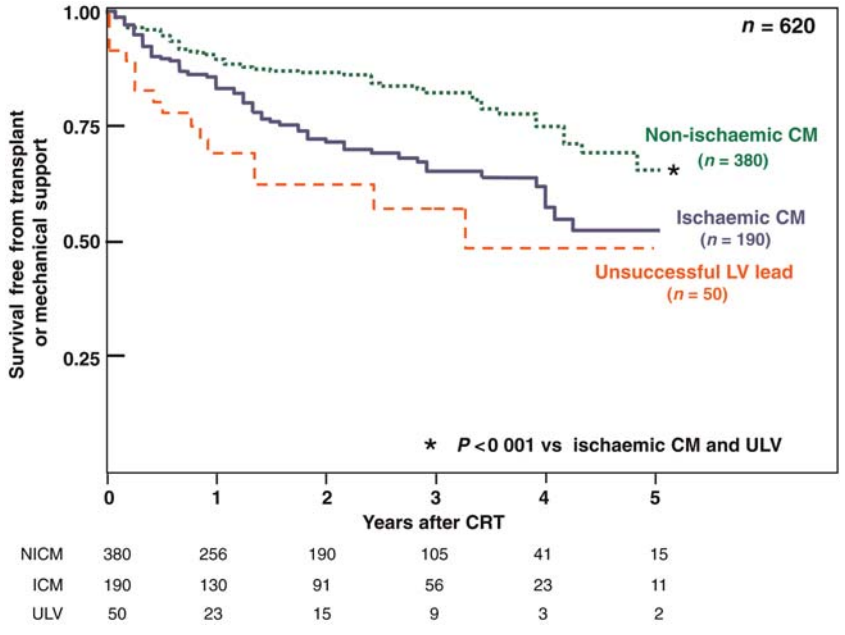

Figure 2 Kaplan–Meier curves depicting survival free from cardiac transplant or mechanical circulatory support in heart failure patients after cardiac resynchronization therapy-defibrillator implantation, stratified according to ischaemic cardiomyopathy or non-ischaemic cardiomyopathy. A third group of patients with attempted but unsuccessful left ventricular lead implant who received a standard cardioverter-defibrillator was included for comparison. Patients with non-ischaemic cardiomyopathy had significantly more favourable event-free survival than the other groups.

Association of survival with scar burden

The ICM cohort was divided according to the extent of MPI scar burden using a pre-defined cut-off SRS value of ≥27, which has previously been shown to delineate LV functional response to CRT among ICM recipients.[17] There were no other baseline differences between the two groups of ICM patients (*Table 2*). Receiver operator characteristic curve analysis using death, heart transplant, or mechanical circulatory support at 1 year as the outcome variable and SRS as the continuous variable confirmed that SRS ≥ 27 has the best predictive value (AUC 0.66, $P = 0.008$). Ischaemic cardiomyopathy patients with SRS < 27 demonstrated better survival free from transplant or assist device than ICM patients with SRS ≥ 27, with similar outcomes as NICM patients (*Figure 3*), even after controlling for potential confounding variables of age, gender, prevalence of atrial fibrillation and diabetes, and baseline serum creatinine concentration (hazard ratio 2.38, 1.44–3.94, $P = 0.02$). Multivariate analysis using individual baseline characteristics associated with the primary endpoint (i.e. NYHA class IV HF, serum creatinine concentration, baseline right bundle-branch block, and β-blocker use) also confirmed that among ICM patients, SRS < 27 is a significant predictor of favourable survival free from transplant or assist device (hazard ratio 2.19, 1.32–3.62, $P = 0.002$).

The cohort with ICM and SRS ≥ 27 was compared separately with unsuccessful LV lead implant patients with ICM. These groups were similar at baseline, differing only in age and serum creatinine concentration (*Table 2*). Survival free from transplant or mechanical circulatory support did not differ (*Figure 3*), even after controlling for age and baseline renal function.

Left ventricular reverse remodelling response

Follow-up LV volume and EF data were available to assess reverse remodelling in a subgroup of 143 patients at an interval of 7 ± 3 months after CRT. These included 62 CRT recipients with ICM, 63 CRT recipients with NICM, and 18 with unsuccessful LV lead implant. Overall, CRT resulted in significant improvements in LV end-systolic volume from 163 ± 73 to 137 ± 80 mL ($P < 0.001$) and LVEF from 24 ± 6 to 33 ± 12% ($P < 0.001$). When examined by HF aetiology, NICM patients had significantly greater reduction in LV end-systolic volumes than ICM patients, decreasing from 167 ± 78 to 130 ± 87 vs. 159 ± 67 to 144 ± 71 mL in the ICM group ($P < 0.001$), and had greater improvement in LVEF, increasing from 23 ± 7 to 34 ± 14 vs. 25 ± 6 to 31 ± 11% in the ICM group ($P < 0.005$; *Figure 4*). Patients with unsuccessful LV lead implant had non-statistically significant changes in both LV end-systolic volume (169 ± 71 ml at baseline vs. 166 ± 56 mL at follow-up) and LVEF (25 ± 5% at baseline vs. 23 ± 9% at follow-up), as expected. Among CRT recipients, ICM patients with SRS ≥ 27 had the least LV reverse remodelling with CRT; group mean LV end-systolic volume increased from 180 ± 86 mL at baseline to 183 ± 84 mL and group mean LVEF changed from 23 ± 5 to 25 ± 9%. (*Figure 5*) Although individual variability in reverse remodelling response was observed, this was similar to the unsuccessful LV lead implant patients.

Table 2 Baseline demographic and clinical characteristics of the subjects with ischaemic cardiomyopathy

	CRT recipients		Unsuccessful LV lead implant with ICM ($n = 27$)	*P*-value
	ICM, SRS < 27 ($n = 123$)	ICM, SRS ≥ 27 ($n = 67$)		
Demographics				
Age (years)	68 ± 10	66 ± 10	72 ± 9	0.03†
Men	105 (85.4%)	57 (85.1%)	6 (22.2%)	0.605
NYHA class IV	7 (5.7%)	8 (11.9%)	2 (7.4%)	0.308
Diabetes mellitus	55 (44.7%)	28 (41.8%)	11 (40.7%)	0.889
Atrial fibrillation history	78 (63.4%)	35 (52.2%)	15 (55.6%)	0.303
Serum creatinine (mg/dL)	1.5 ± 0.7	1.4 ± 0.5	1.9 ± 1.4	0.009*,†
ECG characteristics				
QRS duration (ms)	166 ± 33	169 ± 34	172 ± 32	0.827
Native RBBB	12 (9.8%)	11 (16.4%)	2 (7.7%)	0.322
HF medical therapy				
β-Blocker	98 (79.7%)	50 (74.6%)	21 (77.8%)	0.726
ACE-I or ARB	98 (79.7%)	57 (85.1%)	20 (74.1%)	0.435
Aldosterone antagonist	20 (16.4%)	18 (26.9%)	7 (25.9%)	0.186
Baseline echocardiography				
LVEF (%)	26 ± 6	24 ± 6	26 ± 6	0.186
LVEDV (mL)	209 ± 65	227 ± 99	215 ± 84	0.635
LVESV (mL)	156 ± 55	174 ± 81	161 ± 72	0.460

See Table 1 for abbreviations. *P*-value reflects three-way comparison of ICM SRS ≥ 27, ICM SRS < 27, and unsuccessful LV lead implant with ICM groups. No differences were seen between the two CRT groups.
*$P < 0.05$ between ICM SRS < 27 CRT group and unsuccessful LV lead implant ICM group
†$P < 0.01$ between ICM SRS ≥ 27 CRT group and unsuccessful LV lead implant ICM group.

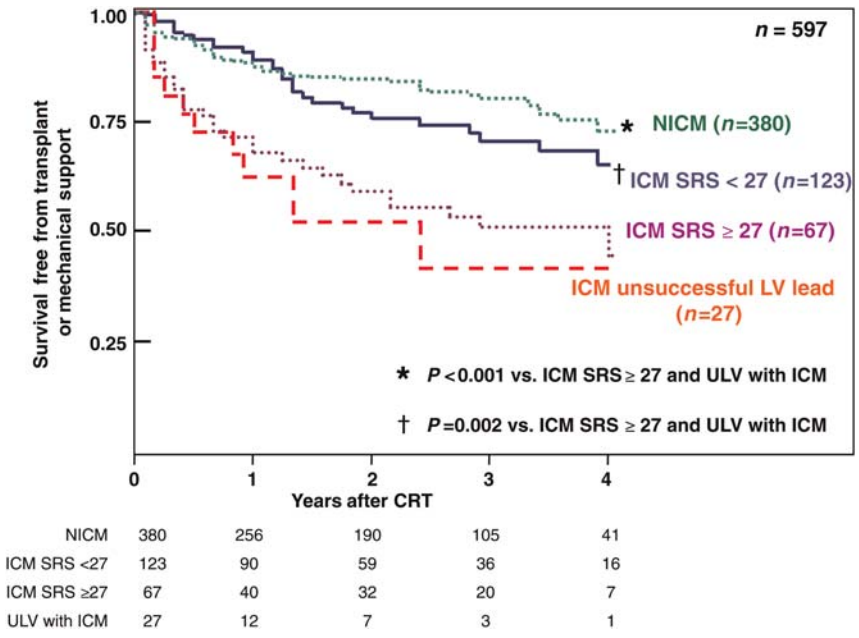

Figure 3 Kaplan–Meier curves depicting survival free from cardiac transplant or mechanical circulatory support in study patients after cardiac resynchronization therapy-defibrillator implantation. Patients were grouped as follows: (1) cardiac resynchronization therapy with non-ischaemic cardiomyopathy, (2) cardiac resynchronization therapy with ischaemic cardiomyopathy and low scar burden by single-photon emission computed tomography imaging (SRS $<$ 27), (3) cardiac resynchronization therapy with ischaemic cardiomyopathy and high scar burden (SRS $\geq$ 27), (4) unsuccessful left ventricular lead implant with ischaemic cardiomyopathy. Patients with non-ischaemic cardiomyopathy or ischaemic cardiomyopathy with SRS $<$ 27 had significantly better survival free from transplant or assist device than ischaemic cardiomyopathy with SRS $\geq$ 27 and unsuccessful left ventricular lead implant ischaemic cardiomyopathy patients.

Relative influence of scar burden and dyssynchrony on echocardiographic response

Of the 150 study patients with available baseline dyssynchrony analysis, 66 were ICM CRT recipients, 80 were NICM CRT recipients, and 4 were unsuccessful LV lead patients. Among CRT recipients, dyssynchrony was more predictive of improvements in LVEF and reverse remodelling in NICM than ICM patients. Defining response as a relative $\geq$15% improvement in LVEF or end-systolic volume, the pre-defined cut-off of $\geq$65 ms for longitudinal velocity opposing wall delay had a sensitivity of 79% and specificity of 89% for NICM patients, in contrast to a lower sensitivity of 67% and lower specificity of 55% for ICM patients. Similarly, the pre-defined cut-off of $\geq$130 ms for radial strain septal to posterior wall delay had a higher sensitivity of 84% and higher specificity of 78% for NICM patients, compared with a sensitivity of 66% and specificity of 65% for ICM patients. One hundred and forty-two (97%) had paired longitudinal and radial dyssynchrony data available, which have been shown previously to predict EF response after CRT.[25] Using the same definition of response as above, significant combined longitudinal and radial dyssynchrony had a sensitivity of 77% and specificity of 89% for NICM patients and both a lower sensitivity of 62% and lower specificity of 65% for ICM patients. Among the 66 ICM patients with complete dyssynchrony analysis, high scar burden (SRS $\geq$ 27) was associated with poor survival free from transplant or assist device, whereas combined dyssynchrony did not predict this primary endpoint (*Figure 6*). Multivariate analysis also demonstrated that high scar burden, not combined dyssynchrony, correlated with lack of echocardiographic response (odds ratio 0.28, 0.09–0.91, $P = 0.03$).

Discussion

This is the first study of a large series of consecutive patients undergoing CRT to demonstrate the important association of scar burden by SPECT MPI with survival, LV functional response, and reverse remodelling. A differential response to CRT was observed with respect to HF aetiology, with NICM patients having better survival and improvement in LVEF and end-systolic volume than ICM patients. Among ICM patients, lesser scar burden by SPECT MPI (SRS $<$ 27) was associated with more favourable survival and reverse remodelling following CRT, with outcomes similar to NICM patients. High scar burden (SRS $\geq$ 27) was associated with the lack of LV functional improvement, absence of reverse remodelling, and worse survival. Furthermore, baseline echocardiographic dyssynchrony, previously associated with LV functional improvement and reverse remodelling following CRT, did not correlate with response in ICM patients with high scar burden. High scar burden by SPECT was the most powerful independent predictor of outcome in these patients.

Multi-centre, randomized trials of CRT have demonstrated significant morbidity and mortality benefit in patients with and without coronary artery disease.[1–3] However, multiple smaller studies have shown that NICM patients derive significantly greater benefit

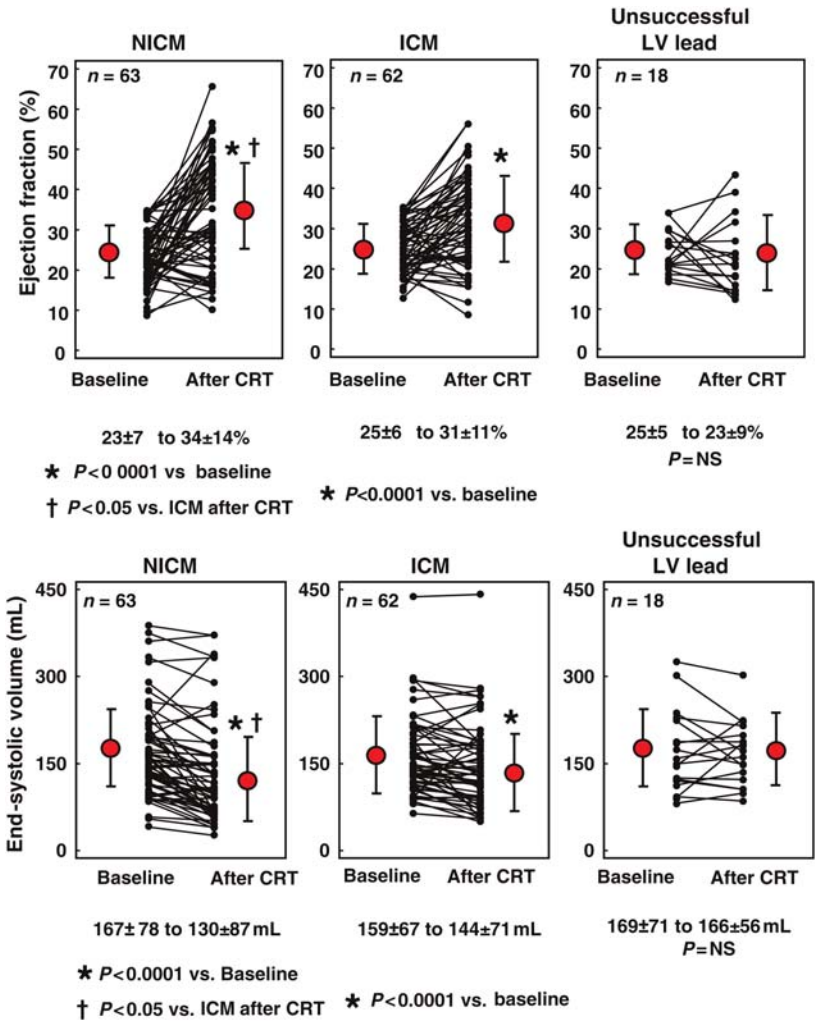

Figure 4 Dot plots of ejection fractions and end-systolic volumes before and after cardiac resynchronization therapy in patients grouped according to ischaemic cardiomyopathy or non-ischaemic cardiomyopathy. A third group of patients with attempted but unsuccessful left ventricular lead implant who received a standard cardioverter-defibrillator was included for comparison. Significant improvements in ventricular function and reverse remodelling were observed in patient groups who received cardiac resynchronization therapy.

than their ICM counterparts, in terms of both symptomatic and ventricular functional improvement.[11–15] No post-CRT survival analysis has differentiated ICM patients based upon scar burden severity, which may be a key determinant of CRT response among those with ICM.[17] Our large single-centre experience using SPECT MPI, which may be more representative of mainstream clinical practice, confirms that ICM portends a less favourable prognosis following CRT compared with NICM. Ischaemic cardiomyopathy alone did not dictate lack of response, but myocardial scar burden by SPECT MPI appeared to differentiate LV reverse remodelling responders from non-responders and survivors from non-survivors.

The present analysis adds to a growing body of data implicating myocardial scar from prior infarction as an impediment to CRT response, whether defined by improvement in functional capacity, cardiac function, or reverse remodelling.[9,29,30] Scar defined by SPECT MPI, in terms of both overall scar burden and scar localized near the LV lead, has been shown previously in smaller studies to predict the lack of clinical response and failure to improve ventricular function after CRT with follow-up limited to 6 months.[17,31] The present study extends these observations to a larger series of CRT patients with longer survival follow-up and corroborates the SRS cut-off value of $\geq$27 described in an earlier work by our group.[17] Myocardial scar delineated by delayed enhancement cardiac magnetic resonance has also been shown to impact CRT outcomes. Bleeker *et al.*[30] first described the effect of scar localized to the posterolateral left ventricle on clinical and echocardiographic parameters in a relatively small series of CRT recipients, concluding that a scar in this region, which corresponded to both the site of the LV lead and the area of latest LV mechanical activation, is associated with lack of functional improvement and reverse remodelling. They observed that posterolateral scar was as predictive of poor outcomes as lack of dyssynchrony. Similar

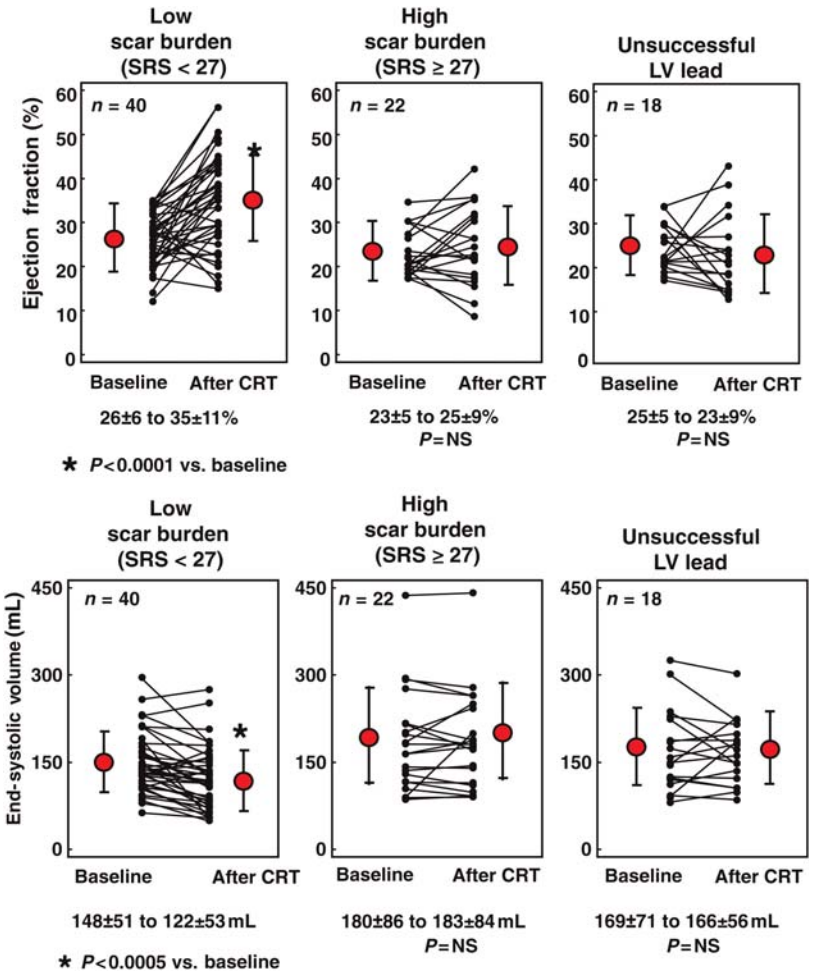

Figure 5 Dot plots of ejection fractions and end-systolic volumes before and after cardiac resynchronization therapy in patients with ischaemic cardiomyopathy grouped by high scar burden (SRS $\geq$ 27) or low scar burden (SRS $<$ 27). Although patients with lesser degrees of scar burden improved, patients with high scar burden failed to demonstrate consistent improvements in ventricular function or reverse remodelling, similar to those with attempted but unsuccessful left ventricular lead implant.

findings have been subsequently described with longer clinical follow-up.[32] A study by White *et al.*[19] utilizing cardiac magnetic resonance imaging demonstrated that $\geq$15% total scar burden predicted lack of CRT response, defined broadly as an improvement in symptoms or LVEF. Bilchick *et al.*[29] more recently used cardiac magnetic resonance imaging to combine the assessment of dyssynchrony and scar burden to predict outcome in CRT patients. Although quantification of scar by magnetic resonance imaging continues to evolve, it is presently less clinically available than SPECT MPI, and incompatibility with previously implanted hardware, such as cardioverter-defibrillators or pacemakers, remains a concern. Accordingly, scar quantification by SPECT MPI remains a practical and realistic approach for current clinical practice and is well validated in the literature.[33]

The negative impact of scar on CRT outcomes may relate mechanistically to overall scar burden, localized scar near the region of LV pre-excitation, and/or persistent increased risk of future ischaemic events. Large amounts of scar may directly prevent CRT-induced reverse remodelling, which has been shown to predict improved survival with CRT.[34] After an acute myocardial infarction, remodelling occurs both within and remote from the affected infarct territory.[35] Densely infarcted areas are replaced by fibrous tissue, forming relatively inert areas of scar. In contrast, non-infarcted segments undergo adverse remodelling in response to the imposed alteration in workload.[36] These regions of myocardium should be susceptible to CRT-induced reverse remodelling, as they are also the target of other life-prolonging HF therapies (e.g. angiotensin-converting enzyme-inhibitors).[37] A large scar burden may be a marker of a greater propensity towards future ischaemic insults or non-arrhythmogenic sudden death (e.g. pulseless electrical activity) that cannot be treated by a defibrillator.[38] Localized non-contractile scar near the LV lead site may directly preclude mechanical resynchronization with the septum[17,30–32] or may excessively slow conduction from the stimulation site, diminishing the amount of myocardium preexcited by the LV lead.[39]

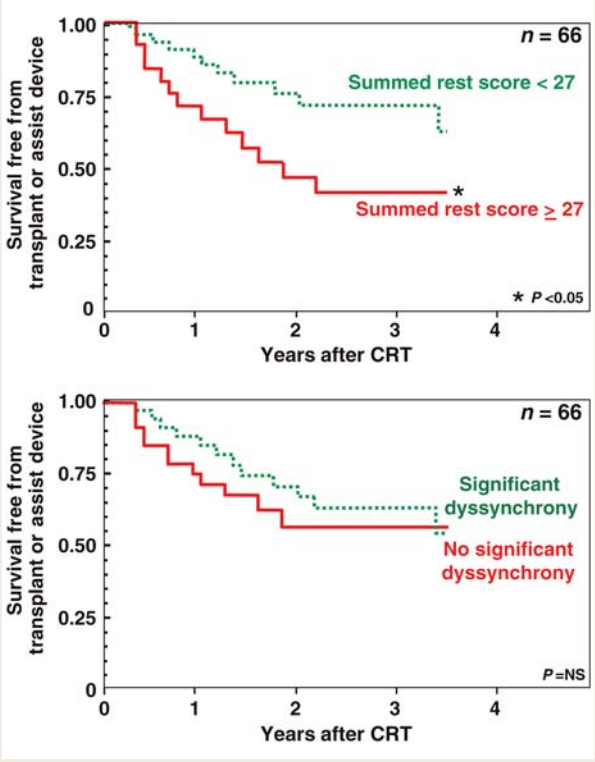

Figure 6 Kaplan–Meier curves depicting survival free from cardiac transplant or mechanical circulatory support in ischaemic cardiomyopathy patients who had both single-photon emission computed tomography perfusion imaging and echocardiographic dyssynchrony analysis before cardiac resynchronization therapy. The top panel demonstrates that high scar burden (SRS ≥ 27) was associated with significantly lower survival. The bottom panel demonstrates that significant dyssynchrony, defined as both positive longitudinal and positive radial dyssynchrony, was not predictive of survival in these patients.

An interesting finding in the present study was that measures of dyssynchrony were less predictive of outcomes in ICM patients compared with those with NICM and did not appear to be predictive in those with high scar burden. Although a large body of literature supports the value of echocardiographic dyssynchrony indices to predict response to CRT,[7,8,10,24,25,40] their ability to predict response is not clear.[6,41] The PROSPECT study examined M-mode, routine Doppler, and tissue Doppler dyssynchrony indices, but was inconclusive for convincingly predicting response to CRT at 6 months.[6] However, speckle-tracking deformation analysis was not evaluated in PROSPECT, nor were patients studied with respect to aetiology of HF or scar burden. Our present study, in contrast to PROSPECT, supports tissue Doppler and speckle tracking dyssynchrony analysis as being predictive of CRT response but less predictive in patients with ischaemic disease when compared with patients with NICM. Furthermore, our findings indicated that patients with high scar burden appear to have an unfavourable outcome after CRT and that scar burden appears to be more importantly associated with outcome than dyssynchrony in this subset of patients.

Study limitations

A limitation of this study was that SPECT MPI studies were performed as the clinical standard of care and not uniformly in all consecutive patients. Although this may represent selection bias, the amount of scar burden was widely distributed within the ICM patient cohort, and baseline LVEF and other important baseline characteristics were similar between the groups. Automated quantitative scoring of scar burden was not used because of the lack of availability of a normal database for 24 h Tl^{201} redistribution studies. Furthermore, semi-quantitative visual scoring has heretofore been most frequently used to provide prognostic data in the literature.[22,42] Another limitation is the comparatively lower spatial resolution of scar quantification by SPECT MPI compared with cardiac magnetic resonance imaging methods. However, our findings would also suggest that the identification of small amounts of scar tissue is unlikely to improve prognostication following CRT. We acknowledge that follow-up LVEF and volume data were only available in a subset of patients who were referred to our institution for CRT implant; many returned to satellite facilities or their remote primary healthcare providers for follow-up echocardiography. Our sample of 143 patients was appropriately distributed among the study groups and statistically powered to demonstrate significant results. Dyssynchrony data were not available on all patients because electrical dyssynchrony (i.e. QRS duration ≥120 ms) not mechanical dyssynchrony is one of the current criteria for considering CRT. Although recent criticism has emerged regarding dyssynchrony analysis for the prediction of response to CRT, the present investigation focuses on differences between NICM and ICM patients and scar burden, and it extends these observations to the use of speckle tracking, which was not tested in the PROSPECT study.[6] Another limitation is that the subgroup of patients with high scar burden was relatively small and possibly insufficiently powered in comparison to the overall study group. Accordingly, future study of dyssynchrony on a larger group of patients with high scar burden would be of interest to confirm these findings.

Conclusions

In conclusion, higher scar burden quantified by SPECT MPI negatively impacts survival free from transplant or mechanical circulatory support and LV functional outcomes following CRT-D among ICM patients. Although the benefits of CRT appeared greater in NICM patients overall, ICM itself is not necessarily predictive of adverse outcomes. Ischaemic cardiomyopathy patients with low scar burden experience similar favourable outcomes as those with NICM. In contrast, ICM patients with high scar burden appear to have an unfavourable prognosis following CRT, regardless of baseline dyssynchrony. These findings merit further prospective study.

Acknowledgements

The authors are grateful to the staffs of the electrophysiology, nuclear cardiology, and echocardiography laboratories of Presbyterian University Hospital, Pittsburgh, PA, for their tireless work and cooperation. We also thank Delia Johnson, PhD, for her expert statistical analysis and guidance.

Funding

J.G. is supported in part by NIH K24 HL04503. J.G. receives modest research grant support from Medtronic, St Jude Medical, and Biotronik.

Conflict of interest: none declared.

References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
3. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
4. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;**44**: 1834–1840.
5. Bax JJ, Abraham T, Barold SS, Breithardt OA, Fung JW, Garrigue S, Gorcsan J III, Hayes DL, Kass DA, Knuuti J, Leclercq C, Linde C, Mark DB, Monaghan MJ, Nihoyannopoulos P, Schalij MJ, Stellbrink C, Yu CM. Cardiac resynchronization therapy: Part 1—issues before device implantation. *J Am Coll Cardiol* 2005;**46**: 2153–2167.
6. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J III, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;**117**:2608–2616.
7. Gorcsan J III, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. *Am J Cardiol* 2004;**93**: 1178–1181.
8. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006;**113**:960–968.
9. Ypenburg C, Roes SD, Bleeker GB, Kaandorp TA, de Roos A, Schalij MJ, van der Wall EE, Bax JJ. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *Am J Cardiol* 2007; **99**:657–660.
10. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;**105**:438–445.
11. Diaz-Infante E, Mont L, Leal J, Garcia-Bolao I, Fernandez-Lozano I, Hernandez-Madrid A, Perez-Castellano N, Sitges M, Pavon-Jimenez R, Barba J, Cavero MA, Moya JL, Perez-Isla L, Brugada J. Predictors of lack of response to resynchronization therapy. *Am J Cardiol* 2005;**95**:1436–1440.
12. Gasparini M, Mantica M, Galimberti P, Genovese L, Pini D, Faletra F, Marchesina UL, Mangiavacchi M, Klersy C, Gronda E. Is the outcome of cardiac resynchronization therapy related to the underlying etiology? *Pacing Clin Electrophysiol* 2003;**26**:175–180.
13. Molhoek SG, Bax JJ, van Erven L, Bootsma M, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Comparison of benefits from cardiac resynchronization therapy in patients with ischemic cardiomyopathy versus idiopathic dilated cardiomyopathy. *Am J Cardiol* 2004;**93**:860–863.
14. Reuter S, Garrigue S, Barold SS, Jais P, Hocini M, Haissaguerre M, Clementy J. Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure. *Am J Cardiol* 2002;**89**: 346–350.
15. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation* 2006;**113**:266–272.
16. Wikstrom G, Blomstrom-Lundqvist C, Andren B, Lonnerholm S, Blomstrom P, Freemantle N, Remp T, Cleland JG. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. *Eur Heart J* 2009;**30**:782–788.
17. Adelstein EC, Saba S. Scar burden by myocardial perfusion imaging predicts echocardiographic response to cardiac resynchronization therapy in ischemic cardiomyopathy. *Am Heart J* 2007;**153**:105–112.
18. Sciagra R, Giaccardi M, Porciani MC, Colella A, Michelucci A, Pieragnoli P, Gensini G, Pupi A, Padeletti L. Myocardial perfusion imaging using gated SPECT in heart failure patients undergoing cardiac resynchronization therapy. *J Nucl Med* 2004;**45**:164–168.
19. White JA, Yee R, Yuan X, Krahn A, Skanes A, Parker M, Klein G, Drangova M. Delayed enhancement magnetic resonance imaging predicts response to cardiac resynchronization therapy in patients with intraventricular dyssynchrony. *J Am Coll Cardiol* 2006;**48**:1953–1960.
20. Soman P. Gated SPECT myocardial perfusion scintigraphy: a multi-faceted tool for the evaluation of heart failure. *J Nucl Cardiol* 2009;**16**:173–175.
21. Soman P, Lahiri A, Mieres J, Calnon D, Wolinsky D, Beller G, Sias T, Burnham K, Conway L, McCullough P, Daher E, Walsh M, Wight J, Heller G, Udelson J. Etiology and pathophysiology of new-onset heart failure: evaluation by myocardial perfusion imaging. *J Nucl Cardiol* 2009;**16**:82–91.
22. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998;**97**:535–543.
23. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**: 1440–1463.
24. Cannesson M, Tanabe M, Suffoletto MS, Schwartzman D, Gorcsan J III. Velocity vector imaging to quantify ventricular dyssynchrony and predict response to cardiac resynchronization therapy. *Am J Cardiol* 2006;**98**: 949–953.
25. Gorcsan J III, Tanabe M, Bleeker GB, Suffoletto MS, Thomas NC, Saba S, Tops LF, Schalij MJ, Bax JJ. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. *J Am Coll Cardiol* 2007;**50**: 1476–1483.
26. Gorcsan J III, Abraham T, Agler DA, Bax JJ, Derumeaux G, Grimm RA, Martin R, Steinberg JS, Sutton MS, Yu CM. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting—a report from the American Society of Echocardiography Dyssynchrony Writing Group endorsed by the Heart Rhythm Society. *J Am Soc Echocardiogr* 2008;**21**:191–213.
27. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain—a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;**17**:1021–1029.
28. Tanaka H, Hara H, Saba S, Gorcsan J III. Prediction of response to cardiac resynchronization therapy by speckle tracking echocardiography using different software approaches. *J Am Soc Echocardiogr* 2009;**22**:677–684.
29. Bilchick KC, Dimaano V, Wu KC, Helm RH, Weiss RG, Lima JA, Berger RD, Tomaselli GF, Bluemke DA, Halperin HR, Abraham T, Kass DA, Lardo AC. Cardiac magnetic resonance assessment of dyssynchrony and myocardial scar predicts function class improvement following cardiac resynchronization therapy. *JACC Cardiovasc Imaging* 2008;**1**:561–568.
30. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, van der Wall EE, Schalij MJ, Bax JJ. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation* 2006;**113**:969–976.
31. Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *Eur Heart J* 2007;**28**:33–41.
32. Chalil S, Stegemann B, Muhyaldeen SA, Khadjooi K, Foley PW, Smith RE, Leyva F. Effect of posterolateral left ventricular scar on mortality and morbidity following cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2007;**30**: 1201–1209.
33. Gibbons RJ, Miller TD, Christian TF. Infarct size measured by single photon emission computed tomographic imaging with (99m)Tc-sestamibi: a measure of the efficacy of therapy in acute myocardial infarction. *Circulation* 2000;**101**: 101–108.

34. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;**112**:1580–1586.
35. Kramer CM, Rogers WJ, Theobald TM, Power TP, Petruolo S, Reichek N. Remote noninfarcted region dysfunction soon after first anterior myocardial infarction. A magnetic resonance tagging study. *Circulation* 1996;**94**:660–666.
36. Cleutjens JP, Blankesteijn WM, Daemen MJ, Smits JF. The infarcted myocardium: simply dead tissue, or a lively target for therapeutic interventions. *Cardiovasc Res* 1999;**44**:232–241.
37. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;**325**:293–302.
38. van der Burg AE, Bax JJ, Boersma E, Pauwels EK, van der Wall EE, Schalij MJ. Impact of viability, ischemia, scar tissue, and revascularization on outcome after aborted sudden death. *Circulation* 2003;**108**:1954–1959.
39. Herweg B, Ilercil A, Madramootoo C, Krishnan S, Rinde-Hoffman D, Weston M, Curtis AB, Barold SS. Latency during left ventricular pacing from the lateral cardiac veins: a cause of ineffectual biventricular pacing. *Pacing Clin Electrophysiol* 2006;**29**:574–581.
40. Bleeker GB, Holman ER, Steendijk P, Boersma E, van der Wall EE, Schalij MJ, Bax JJ. Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol* 2006;**48**:2243–2250.
41. Beshai JF, Grimm RA, Nagueh SF, Baker JH II, Beau SL, Greenberg SM, Pires LA, Tchou PJ. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;**357**:2461–2471.
42. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–2907.