The Extent of Left Ventricular Scar Quantified by Late Gadolinium Enhancement MRI Is Associated With Spontaneous Ventricular Arrhythmias in Patients With Coronary Artery Disease and Implantable Cardioverter-Defibrillators

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Background—Characterization of sudden cardiac death (SCD) risk remains a challenge in the application of implantable cardioverter-defibrillator (ICD) therapy. Late gadolinium enhancement cardiac MRI (LGE-CMR) can accurately identify myocardial scar. We performed a retrospective, single-center observational study to evaluate the association between the extent and distribution of left ventricular scar, quantified using LGE-CMR, and the burden of ventricular arrhythmias in patients with coronary artery disease and ICDs.

Methods and Results—All patients included (2006 to 2009) had undergone LGE-CMR before ICD implantation. Scar (defined as myocardium with a signal intensity \(\leq 50\%\) of the maximum in scar tissue) was characterized in terms of percent scar, scar surface area, and number of transmural left ventricular scar segments. The end point was appropriate ICD therapy. Sixty-four patients (mean age, 66\(\pm\)11 years; male sex, 51) were included. During 19\(\pm\)10 months follow-up, appropriate ICD therapy occurred in 19 (30\%) patients. In Cox regression analyses, both percent scar (hazard ratio per 10\%, 1.75; 95\% CI, 1.09 to 2.81; \(P=0.02\)) and number of transmural scar segments (hazard ratio per segment, 1.40; 95\% CI, 1.15 to 1.70; \(P=0.001\)) were significantly associated with the occurrence of appropriate ICD therapy.

Conclusions—In this pilot study, the extent of myocardial scar characterized by LGE-CMR was significantly associated with the occurrence of spontaneous ventricular arrhythmias. We hypothesize that scar quantification by LGE-CMR may prove a valuable risk stratification tool for the occurrence of ventricular arrhythmias, which may have implications for patient selection for ICD therapy. (Circ Arrhythm Electrophysiol. 2011;4:324-330.)

Key Words: implantable cardioverter-defibrillators ■ MRI ■ coronary artery disease ■ death sudden ■ arrhythmias cardiac
consecutive patients with CAD who had undergone LGE-CMR before ICD implantation over a 4-year period (2006 to 2009).

**Definition of CAD**
CAD was defined as ≥70% stenosis in at least 1 epicardial coronary vessel on angiography, history of myocardial infarction (MI) or coronary revascularization, or both. All patients underwent diagnostic coronary angiography, with images reviewed by a consultant cardiologist.

**ICD Details**
All patients received an ICD according to national guidelines. Patients also meeting criteria for cardiac resynchronization therapy received a combined cardiac resynchronization device. Patients received either a combined cardiac resynchronization device (Consulta, Concerto [Medtronic; Minneapolis, MN]; Cognis [Boston Scientific; Natick, MA]; Contak Renewal [Boston Scientific]; Ovatio [Sorin Group; Milan, Italy]; or Atlas [St Jude Medical; St Paul, MN]) or a dual- or single-chamber ICD (Secura, Virtuoso [Medtronic]; Teligen [Boston Scientific]; Ovatio [Sorin Group]; or Atlas [St Jude Medical]).

**CMR Data Acquisition**
All scans were performed with a dedicated 1.5-T Avanto MRI system (Siemens Medical Systems; Erlangen, Germany). After initial localizer sequences, a stack of steady-state free-precession cine images were acquired in the short-axis plane from the level of the mitral valve annulus to the LV apex. After this acquisition, 0.15 mmol/kg gadobenate dimeglumine (Multihance; Bracco SpA; Milan, Italy) was administered intravenously. Short-axis LGE images were acquired using a 3D segmented inversion recovery fast gradient echo sequence in 2 breathholds. An appropriate time to inversion was selected to null the normal myocardium.

**CMR Analysis**
EF and volumes were analyzed on commercially available postprocessing software. Short-axis cine images were used to measure end-diastolic volume, end-systolic volume, and LVEF by standard methods. Papillary muscles were regarded as part of the ventricular cavity.

Scarf analysis was performed using semiautomated software developed at our institution as a plugin to the open-source DICOM viewer OsiriX (OsiriX Project; Geneva, Switzerland) (Figure 1). Endocardial and epicardial LV myocardial borders were manually delineated on the short-axis LGE-CMR images. For each patient, the maximum signal intensity (SI) within an infarct region in each image of the LV stack was automatically determined, and scar was defined as myocardium with an SI ≥50% of the maximum SI. Scar was automatically segmented, and any areas identified as scar by the software but not deemed to be scar by the user were excluded manually. Three complementary aspects of scar were quantified: (1) the amount of scar, quantified as a percentage of the total LV myocardial volume; (2) the total scar surface area (including epicardial and endocardial surfaces); and (3) the transmural extent of scar. For the transmural scar assessment, scar transmurality was split into quartiles (1% to 25%, 26% to 50%, 51% to 75%, and 76% to 100%), and the number of segments of myocardium were quantified based on a standard American Heart Association 17-segment model to enable transmurality assessment.

**Study Follow-Up and End Point**
All patients were followed every 3 to 6 months through a hospital visit or a remote patient management system. Patients under remote follow-up also were seen at the hospital every 6 months. At each hospital visit, the patient was clinically assessed and the device interrogated. The occurrence of any ICD therapy was recorded. Appropriate ICD therapy was defined as follows: (1) antitachycardia pacing therapy for ventricular tachycardia (VT); (2) shock therapy for VT or ventricular fibrillation; and (3) correct arrhythmia detection or discrimination confirmed by analysis of stored electrograms by 2 electrophysiologists blinded to the CMR analysis.

Appropriate ICD therapy was chosen as the study end point as a surrogate for the potential to benefit from ICD therapy, including SCD risk reduction. However, we recognize that appropriate ICD therapy does not equate to SCD prevention in all patients and that in some patients, prevention of SCD does not translate into a significant increase in life expectancy because some patients subsequently will die of pump failure or another cause.

**Statistics**
Categorical variables are expressed as percentages (numbers) and compared using Fisher exact test. Normally distributed continuous variables are expressed as mean±SD and compared using Student t test. Variables not normally distributed are expressed as median (lower quartile to upper quartile).

The association among clinical, electrocardiographic, and CMR variables and the study end point were assessed in univariable Cox proportional hazard analyses. Because the aim of the study was to explore the association between the extent of LV scar and appropriate ICD therapy, a multivariable model was constructed with number of transmural scar segments as the scar variable and amiodarone use, any previous pre-ICD revascularization, and LVEF as the covariates. These covariables were chosen based on the univariable analysis results as well as on previous studies and were necessarily limited due to the small number of patients who received appropriate ICD therapy (n=19). In view of the strong correlation between percent scar and number of transmural scar segments (Pearson correlation, 0.8; P<0.001), only the scar variable with the strongest association with the study end point (number of transmural scar segments) was used in the multivariable model. The proportional hazards assumption was checked by plotting the Schoenfeld residuals against rank time and fitting a smooth curve with 95% confidence bands as well as plotting log(-log[survival probability]) against time for different variables to ensure that the curves were parallel. Unadjusted and adjusted hazard ratios (HRs) with their corresponding 95% CIs are reported.
To explore the relationship between ventricular arrhythmia burden and the extent of scar, the ventricular arrhythmia rate (number of appropriate ICD therapies per year) for each patient was calculated, and the association between arrhythmia rate and scar variables (percent scar and number of transmural scar segments) was assessed using Spearman rank correlation. For scar variables with a significant association with the study end point (percent scar and number of transmural scar segments), the study population was divided into 2 groups based on the observed median value for each variable, and event rates were analyzed by Kaplan-Meier survival curves. Differences in event rate between groups over time were compared using the log-rank test.

Intraobserver and interobserver agreement for scar quantification measurements were calculated using the intraclass correlation coefficient for absolute agreement. Statistical analyses were performed on SPSS version 17 (SPSS Inc; Chicago, IL) software. In all analyses, a P<0.05 was considered significant.

## Results

### Patient Characteristics

During the study period, there were 257 new ICD implants for CAD of which 64 (25%) patients had an LGE-CMR before device implantation and were included in the study. The characteristics of the included patients were broadly similar to those who did not have an LGE-CMR (Table 1). However, patients who did not have an LGE-CMR were significantly more likely to have had a previous MI (92% versus 77%, P=0.003).

Baseline demographics of the included patients are shown in Table 1. There was a balanced distribution of primary and secondary indication patients (48% versus 52%). Patients were on optimal medical therapy for heart failure (86%; angiotensin-converting enzyme inhibition/angiotensin receptor blockers, 88%). The ICD VT treatment zone lower setting was similar in patients who did and did not experience the study end point (147±26 versus 149±23 beats/minute, respectively; P=0.83).

In all patients, LGE-CMR was performed to guide the need for potential revascularization before ICD implantation. This included an assessment of myocardial viability in all patients as well as an assessment of ischemic burden in the majority (73%, n=47) of patients.

### Assessment of Ischemic Burden

Of the 47 patients who had an assessment of ischemic burden performed as part of their LGE-CMR, 15 had evidence of reversible ischemia. In 9 of these patients, it was considered clinically appropriate to perform surgical or percutaneous revascularization before ICD implantation.

### Clinical Outcomes

During a mean follow-up period of 19±10 months, 19 (30%) patients received appropriate ICD therapy, and 5 (8%) patients died. The distribution of appropriate ICD therapies was as follows: no episodes of appropriate ICD therapy, n=45; appropriate ICD therapy for VT (rate <182 beats/minute) only, n=10; appropriate ICD therapy for fast VT (rate ≥182 beats/minute),18 n=8; and appropriate ICD therapy for ventricular fibrillation, n=1. For the 19 patients who received appropriate ICD therapy, the median number of episodes per patient was 3, and the median rate of appropriate ICD therapies per patient was 2.1 therapies per year. Seven patients were treated with shock therapy, and the remaining 12 with ATP only.
increase, 1.75; 95% CI, 1.09 to 2.81; \( P = 0.02 \)), number of transmural scar segments (HR per segment, 1.40; 95% CI, 1.15 to 1.70; \( P = 0.001 \)), amiodarone use (HR, 0.12; 95% CI, 0.02 to 0.97; \( P = 0.04 \)), and any previous pre-ICD revascularization (HR, 0.30; 95% CI, 0.09 to 0.95; \( P = 0.04 \)) (Table 2).

The associations with both percent scar (HR per 10%, 1.80; 95% CI, 1.07 to 3.02; \( P = 0.03 \)) and number of transmural scar segments (HR per segment, 1.41; 95% CI, 1.15 to 1.74; \( P = 0.001 \)) remained significant when the 6 patients without myocardial scar were excluded. Notably, LVEF (\( P = 0.86 \)), QRS width (\( P = 0.13 \)), and scar surface area (\( P = 0.15 \)) were not associated with the study end point. After adjustment for multiple covariates (amiodarone use, any previous pre-ICD revascularization, and LVEF) (see Methods section), number of transmural scar segments remained strongly associated with the occurrence of appropriate ICD therapy (HR per segment, 1.48; 95% CI, 1.18 to 1.84; \( P = 0.001 \)) (Table 2).

### MRI Scar and Kaplan-Meier Analysis
Survival curves were compared between patient groups stratified by scar indices (percent scar and number of transmural scar segments). For percent scar, patients were separated into 2 groups based on the median value (12.6%). Using Kaplan-Meier analysis, appropriate ICD therapy occurred in 15 of 33 patients with >12.6% scar compared to only 4 of 31 patients with ≤12.6% scar (\( P = 0.02 \)) (Figure 2A). For number of transmural scar segments, patients were again separated into 2 groups based on the median value (2 segments). Using Kaplan-Meier analysis, appropriate ICD therapy occurred in 15 of 33 patients with ≥2 segments of transmural scar compared to only 4 of 31 patients with <2 segments (\( P = 0.016 \)) (Figure 2B).

### Discussion
In a small, retrospective, observational pilot study, we have shown that indices of LV scar, quantified by LGE-CMR, are associated with the occurrence of appropriate ICD therapy in patients with CAD, independently of LVEF. In an analysis including clinical, biochemical, and CMR variables, the number of transmural scar segments had the strongest association with the occurrence of appropriate ICD therapy. Furthermore, the burden of ventricular arrhythmias was significantly associated with scar burden. These findings are consistent with those of previous studies. The amount of myocardial scar identified by LGE-
CMR has been shown to predict all-cause mortality in a range of patient groups, including those with a previous MI, an ischemic cardiomyopathy, and vascular risk factors but without clinical evidence of a prior MI.4–7,19 Because SCD accounts for a large proportion of deaths in patients after MI and with heart failure, it is plausible that scar quantification predicts the occurrence of ventricular arrhythmias.20–22 Scar quantification also has been shown to predict inducibility of ventricular arrhythmias on electrophysiological study, thus identifying patients with the substrate for sustained VT. Bello et al13 quantified scar using LGE-CMR in 48 patients with CAD and reduced LVEF undergoing electrophysiological study. Eighteen of these patients had inducible monomorphic VT, and infarct mass (as a percentage of the LV) (P=0.009) and infarct surface area (P=0.002) were the strongest predictors of inducibility. The mechanistic relationship between ventricular scar and arrhythmogenesis is well established, and postmortem studies have suggested that scar burden may reflect susceptibility to VT.9,24–26

In the present study, although percent scar was associated with the occurrence of appropriate ICD therapy, the strongest association was with the number of myocardial segments with full-thickness (76% to 100%) scar. The transmural extent of scar, as assessed by LGE-CMR, has been shown to predict both the long-term improvement in contractile function after MI and the response to revascularization.27,28 Interestingly, scar transmurality also predicts mortality in patients with a previous MI. Roes et al8 quantified myocardial scar with LGE-CMR in 231 patients with a healed MI. Over a mean follow-up period of 1.7 years, 19 patients died. The amount of transmural scar, defined as extending from 51% to 100% of the LV wall thickness, was a significant predictor of death (P=0.003). These findings were confirmed by Kwon et al7 in 349 patients with CAD and significantly reduced LVEF. During a mean follow-up of 2.6 years, there were 56 events (51 deaths and 5 cardiac transplantations), and the amount of transmural scar, defined as the number of segments in a 17-segment model with scar covering 51% to 100% of the LV wall thickness, was significantly higher in patients with an event (P=0.004).

Although the majority of previous LGE-CMR studies have used a binary approach to classify myocardium as scar or normal (remote) myocardium, a few studies have used a more graduated approach.29–31 It has been suggested that the border zone around an infarct (perifarct zone), which has an intermediate LGE-CMR SI between the bright scar and dark remote myocardium, contains an admixture of normal and viable myocardium.29 The quantification of this perifarct zone by LGE-CMR has been found to predict mortality, inducibility of ventricular arrhythmias, and the occurrence of appropriate ICD therapy.29–31 However, there are a number of possible mechanisms that may contribute to the intermediate SIs found in this perifarct zone, and the histological extent of viable and scar tissue compared with the LGE-CMR findings needs validation.32

Several methods are available for the measurement of LGE-CMR scar, ranging from a simple visual assessment to quantitative assessment by planimetry of hyperenhanced areas.33 However, these methods can be time consuming and are relatively operator dependent. More recently, semiautomated methods have been developed in an attempt to improve objectivity. However, these methods also have limitations.33 One problem with the semiautomated quantification of MI by LGE-CMR is the lack of a standard definition of scar. Many studies have defined scar as having a mean SI of more than a multiple of SDs (usually 2 or 3) above an area of remote user-defined viable myocardium.19,29 However, use of this definition in our data set resulted in a large overestimation of infarct size, which may be partly due to suboptimal signal suppression of remote myocardium or image artifacts. Instead, we defined scar as myocardium with an SI ≥50% of the maximum SI within an infarct region. This definition has been used by other researchers and has been shown to correlate most accurately with infarct size in postmortem studies.31,34 There may be considerable clinical benefit in the development of accurate tools to enable 3D modeling of scar tissue for quantification.

Although LGE-CMR scar quantification is associated with outcomes independently of LVEF, it is unclear whether it gives incremental prognostic information in addition to other available complementary risk stratification tools, such as electrophysiological study, the presence of ventricular arrhythmias on ambulatory monitoring, and the assessment of cardiac sympathetic denervation.2,35 In addition, a consistent
problem with most risk stratification tests designed to guide ICD use is their lack of specificity for SCD prediction. Although indicative of raised SCD risk, most risk stratification tools are also strong predictors of non-SCD mortality, which in the post-MI population often is due to pump failure. No studies have evaluated the relationship of LGE-CMR scar quantification with non-SCD mortality, and its specificity remains unknown.

Limitations
The present study has several limitations. First, it is an observational study and has all the limitations inherent in such a study design. Second, we included only a small number of patients with a short follow-up. The results need to be confirmed in a larger prospective cohort with a longer follow-up period. Third, during the 4-year study period, only 25% of patients with new ICD implants for CAD had an LGE-CMR before device implantation. Although the baseline demographics of ICD recipients who did and did not have an LGE-CMR were broadly similar, LGE-CMR is an expensive investigation, and there may well be some selection bias related to local referral patterns not adequately captured by these baseline demographic data. In addition, we included patients with both primary and secondary prevention indications; therefore, our cohort does not fully reflect the patient population (primary prevention patients) in whom risk stratification tests are most needed. Both of these factors may limit the generalizability of our results. Fourth, in our study, the median LVEF at 30% is relatively high, likely reflecting the high proportion (52%) of secondary prevention patients included. Consequently, there may be a relative underrepresentation of patients with low LVEF in our study. This limitation is significant, and in view of the small number of patients included, may limit the generalizability of our results to the low LVEF population. Finally, although we have demonstrated that scar quantification using our methodology is reproducible, it is unclear how well it correlates with infarct size in our data set. This problem is a general limitation of the methodology of scar quantification using semiautomated tools and would benefit from a standardized scar definition as well as from further anatomic validation in additional data sets. However, this study is hypothesis generating, and to our knowledge, it is the first to show correlation between scar burden and ventricular arrhythmia burden.

Conclusions
In this single-center pilot study of patients with CAD and ICDs, the extent of myocardial scar characterized by LGE-CMR is strongly associated with the occurrence of spontaneous ventricular arrhythmias. Its association is independent of LVEF. We hypothesize that LGE-CMR may be a valuable risk stratification tool to guide optimal ICD use. However, its specificity for SCD and its incremental prognostic value when used in addition to other available risk stratification tests are unknown and need to be evaluated by an appropriately powered study using improved tools for automated and accurate scar quantification.

Acknowledgments
We thank Scott Harris, medical statistician, University of Southampton, for his advice about the statistical analysis.

Sources of Funding
This work was supported by an unrestricted educational grant from Medtronic.

Disclosures
Dr Scott is supported by an educational grant from Medtronic. Drs Morgan and Roberts have received honoraria and research grants from Medtronic, St Jude, Sorin, and Boston Scientific. Dr Murday has previously been supported by unrestricted educational grants from Medtronic and Boston Scientific. Dr Curzen has received honoraria and research grants from Boston Scientific, Medtronic, Cordis, Abbott Vascular, St Jude Medical, Sorin, GlaxoSmithKline, Hemometrics, AstraZeneca, Lilly, Schering-Plough, The Medicines Company, and Pfizer. Drs Carroll, Feebles, and Harden report no conflicts of interest.

References
The identification of patients at high risk for sudden cardiac death remains a challenge in the application of implantable cardioverter-defibrillator (ICD) therapy. Late gadolinium enhancement cardiac MRI (LGE-CMR) can accurately and reproducibly identify areas of myocardial scar, and the amount of left ventricular scar quantified by LGE-CMR has been shown to predict overall mortality in patients with coronary artery disease independently of LV ejection fraction. In the present study, 64 consecutive patients (average age, 66±11 years; male sex, 51%) with coronary artery disease who had undergone LGE-CMR before receiving an ICD were studied. The extent of left ventricular scar on LGE-CMR was characterized in terms of percent scar, scar surface area, and number of transmural scar segments. The primary end point was appropriate ICD therapy (as a surrogate for sudden cardiac death). During a mean follow-up period of 19 months, 19 (30%) patients received appropriate ICD therapy. In an analysis including clinical, biochemical, and CMR variables, the number of transmural scar segments had the strongest association with the occurrence of appropriate ICD therapy. Furthermore, the burden of ventricular arrhythmias was significantly associated with scar burden. These data suggest that scar quantification by LGE-CMR may be a valuable risk stratification tool for the occurrence of ventricular arrhythmias, which may have implications for patient selection for ICD therapy.

**CLINICAL PERSPECTIVE**

The identification of patients at high risk for sudden cardiac death remains a challenge in the application of implantable cardioverter-defibrillator (ICD) therapy. Late gadolinium enhancement cardiac MRI (LGE-CMR) can accurately and reproducibly identify areas of myocardial scar, and the amount of left ventricular scar quantified by LGE-CMR has been shown to predict overall mortality in patients with coronary artery disease independently of LV ejection fraction. In the present study, 64 consecutive patients (average age, 66±11 years; male sex, 51%) with coronary artery disease who had undergone LGE-CMR before receiving an ICD were studied. The extent of left ventricular scar on LGE-CMR was characterized in terms of percent scar, scar surface area, and number of transmural scar segments. The primary end point was appropriate ICD therapy (as a surrogate for sudden cardiac death). During a mean follow-up period of 19 months, 19 (30%) patients received appropriate ICD therapy. In an analysis including clinical, biochemical, and CMR variables, the number of transmural scar segments had the strongest association with the occurrence of appropriate ICD therapy. Furthermore, the burden of ventricular arrhythmias was significantly associated with scar burden. These data suggest that scar quantification by LGE-CMR may be a valuable risk stratification tool for the occurrence of ventricular arrhythmias, which may have implications for patient selection for ICD therapy.
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_Circ Arrhythm Electrophysiol._ 2011;4:324-330; originally published online April 14, 2011; doi: 10.1161/CIRCEP.110.959544

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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