

Infarct Tissue Heterogeneity by Magnetic Resonance Imaging Identifies Enhanced Cardiac Arrhythmia Susceptibility in Patients With Left Ventricular Dysfunction

André Schmidt, MD*; Clerio F. Azevedo, MD*; Alan Cheng, MD; Sandeep N. Gupta, PhD; David A. Bluemke, MD, PhD; Thomas K. Foo, PhD; Gary Gerstenblith, MD; Robert G. Weiss, MD; Eduardo Marbán, MD, PhD; Gordon F. Tomaselli, MD; João A.C. Lima, MD; Katherine C. Wu, MD

Background—The extent of the peri-infarct zone by magnetic resonance imaging (MRI) has been related to all-cause mortality in patients with coronary artery disease. This relationship may result from arrhythmogenesis in the infarct border. However, the relationship between tissue heterogeneity in the infarct periphery and arrhythmic substrate has not been investigated. In the present study, we quantify myocardial infarct heterogeneity by contrast-enhanced MRI and relate it to an electrophysiological marker of arrhythmic substrate in patients with left ventricular (LV) systolic dysfunction undergoing prophylactic implantable cardioverter defibrillator placement.

Methods and Results—Before implantable cardioverter defibrillator implantation for primary prevention of sudden cardiac death, 47 patients underwent cine and contrast-enhanced MRI to measure LV function, volumes, mass, and infarct size. A method for quantifying the heterogeneous infarct periphery and the denser infarct core is described. MRI indices were related to inducibility of sustained monomorphic ventricular tachycardia during electrophysiological or device testing. For the noninducible versus inducible patients, LV ejection fraction ($30\pm 10\%$ versus $29\pm 7\%$, $P=0.79$), LV end-diastolic volume (220 ± 70 versus 228 ± 57 mL, $P=0.68$), and infarct size by standard contrast-enhanced MRI definitions ($P=NS$) were similar. Quantification of tissue heterogeneity at the infarct periphery was strongly associated with inducibility for monomorphic ventricular tachycardia (noninducible versus inducible: 13 ± 9 versus 19 ± 8 g, $P=0.015$) and was the single significant factor in a stepwise logistic regression.

Conclusions—Tissue heterogeneity is present and quantifiable within human infarcts. More extensive tissue heterogeneity correlates with increased ventricular irritability by programmed electrical stimulation. These findings support the hypothesis that anatomic tissue heterogeneity increases susceptibility to ventricular arrhythmias in patients with prior myocardial infarction and LV dysfunction. (*Circulation*. 2007;115:2006-2014.)

Key Words: myocardial infarction ■ arrhythmia ■ cardiomyopathy ■ diagnosis
■ imaging ■ magnetic resonance imaging

We developed and reported a method to evaluate tissue heterogeneity in the infarct periphery by contrast-enhanced MRI (ceMRI).¹ Recent work based on our methodology describes an association between the extent of the peri-infarct zone by ceMRI and all-cause mortality in patients with coronary artery disease,² highlighting the potential clinical significance of tissue heterogeneity within an infarct. A mechanism explaining the adverse prognosis was postulated to involve arrhythmogenesis in the peri-infarct region.² The present work provides support for this premise. We

Clinical Perspective p 2014

aimed to relate the extent of tissue heterogeneity in the infarct border with susceptibility for cardiac arrhythmias. The underlying hypothesis posits that tissue heterogeneity increases susceptibility to ventricular arrhythmia and that such heterogeneity can be indexed by ceMRI. In the present study, we chose a high-risk population, namely, patients with prior myocardial infarction (MI) and left ventricular (LV) dysfunction referred for implantable car-

Received April 29, 2005; accepted February 20, 2007.

From the Division of Cardiology, Department of Medicine (A.S., C.F.A., A.C., D.A.B., G.G., R.G.W., E.M., G.F.T., J.A.C.L., K.C.W.) and Department of Radiology (D.A.B., R.G.W., J.A.C.L.), Johns Hopkins University; and the Applied Science Laboratory, GE Healthcare Technologies (S.N.G., T.K.F.), Baltimore, Md.

*The first 2 authors contributed equally to this work.

Clinical trial registration information—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00181233.

Presented in part at the 77th Scientific Sessions of the American Heart Association, New Orleans, La, November 7–10, 2004, and published in abstract form (*Circulation*. 2004;110[suppl III]:III-644).

Reprint requests to Katherine C. Wu, MD, Division of Cardiology, Johns Hopkins Hospital, 600 N Wolfe St, Carnegie 568, Baltimore, MD 21287. E-mail kwu@jhmi.edu

© 2007 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.106.653568

dioverter defibrillator (ICD) device placement for primary prevention of sudden cardiac death.

Although numerous approaches directed at risk stratification in this patient population have explored the triggers for lethal arrhythmias and the electrophysiology of the myocardial substrate,^{3,4} few have assessed the detailed structure of the ventricular myocardium as a marker of risk. The presence of infarcted tissue or scar forms the substrate for malignant reentrant arrhythmias,^{3,5,6} and ceMRI can, in principle, detect such a substrate by its ability to delineate necrotic myocardium at all stages of infarct healing.^{7–11} Previous approaches to interpreting and analyzing ceMRI images treat the infarcted region as a uniform tissue bed that does not explicitly account for inhomogeneity. Infarcts can have marked spatial heterogeneity, with areas of necrosis interspersed with bundles of viable myocytes, particularly in the border zones and periphery of the infarct.^{12–14} Tissue heterogeneity in these regions may create areas of slow conduction that generate the substrate for the development of lethal reentrant arrhythmias.^{14–16}

In the present study, we examine the utility of ceMRI in identifying patients with increased vulnerability to ventricular arrhythmias. Using ceMRI, we relate a marker of myocardial infarct heterogeneity, based on the quantitative characterization of the infarct periphery, to an electrophysiological marker of the arrhythmic substrate.

Methods

Patients

Forty-seven patients referred for ICD placement for primary prevention of sudden cardiac death were prospectively enrolled between August 2003 and August 2005. The target population was patients with known history of coronary artery disease and prior MI >1 month previously, LV ejection fraction ≤ 0.35 , and no other indications for ICD placement (eg, syncope, cardiac arrest, and sustained ventricular arrhythmias). Exclusions were based on those of the Multicenter Automatic Defibrillator Implantation Trial (MADIT) I¹⁷ and MADIT II.¹⁸ The study protocol was approved by the Johns Hopkins Hospital Institutional Review Board, and all patients gave written informed consent.

MRI Protocol

Patients underwent ceMRI with a 1.5-T scanner (Signa CV/i, GE Healthcare Technologies, Waukesha, Wis), with a 4-element cardiac phased-array receiver coil placed anteriorly and posteriorly on the chest. Ten to 14 contiguous short-axis slices were prescribed to cover the entire LV. Cine images were acquired with a steady state free precession pulse sequence: repetition time (TR) 3.8 ms, echo time 1.6 ms, average in-plane resolution 1.5×2.4 mm, flip angle $\alpha=45^\circ$, 8-mm slice thickness, 2-mm gap, and temporal resolution 40 ms. Late gadolinium-enhanced images were acquired 15 to 30 minutes after a total injection of 0.2 mmol/kg gadodiamide (Omniscan, GE Healthcare Technologies) with an inversion recovery fast gradient-echo pulse sequence^{9,19} in the same short-axis locations as the cine images. Imaging parameters²⁰ were as follows: TR 5.4 ms, echo time 1.3 ms, average in-plane spatial resolution 1.5×2.4 mm, 8-mm slice thickness, 2-mm gap, inversion time (TI) 175 to 250 ms (adjusted to null the signal of normal myocardium), 2 excitations, 1 R-R interval imaging, flip angle 20°, 350-ms time delay after the R wave, and 24 views per segment. These parameters yielded an image acquisition window of 130 ms. In 20 successive patients, a subset of late gadolinium-enhanced short-axis slices (average of 2 per patient) was

reimaged 10 minutes later to evaluate whether assessment of infarct heterogeneity varied with time from contrast bolus.

In a subset of patients with optimal first-pass perfusion image quality (n=8), wash-in contrast characteristics within the different regions were assessed by signal-intensity (SI) analysis of first-pass perfusion during the first few minutes after an initial 0.1-mmol/kg contrast bolus, before late gadolinium enhancement. The sequence used was an ECG-gated saturation recovery interleaved gradient-echo echo-planar sequence²¹: TR=7.2 ms; echo time=1.6 ms, flip angle 20°, field of view 36 to 40 cm, average in-plane spatial resolution 2.8×3.4 mm, 8-mm slice thickness, 2-mm gap, and 6 to 8 slices acquired every other R-R interval. Slice locations were matched as closely as possible to those obtained for the cine and late gadolinium-enhanced sequences.

Electrophysiological Evaluation

Patients underwent programmed ventricular stimulation in an electrophysiological study (n=12 [26%]) or through the ICD (n=35 [74%]) at the time of implantation, 4±7 (range 0 to 28) days after ceMRI. Results of the electrophysiological evaluation were not known to those performing the MRI analysis and did not determine study eligibility. The stimulation protocol consisted of 3 extrastimuli at 2 different drive cycle lengths delivered from the right ventricular apex alone (ICD) or the right ventricular apex and outflow tract (electrophysiological study). Inducibility by electrophysiological evaluation was defined as the induction of sustained monomorphic ventricular tachycardia that lasted ≥ 30 seconds or required cardioversion for hemodynamic compromise.

Data Analysis

All MRI analyses were performed with DICOM (Digital Imaging and Communications in Medicine) images with a custom software package, CINetool (GE Healthcare Technologies) and were performed by investigators blinded to the results of the electrophysiological evaluation. Cine images were used to measure LV ejection fraction, volumes, and mass by standard methods.²² Late gadolinium-enhanced images were used for infarct characterization. The primary aim of the study was to explore the use of a marker that would quantify the heterogeneity of the SI differences within the hyperenhanced region (Figures 1 and 2). We prespecified the definitions of 2 SI thresholds that would distinguish the dense, infarct core from the heterogeneous infarct periphery and applied them to the study group. We used a simplified version of the recently described full-width half-maximum method⁹ to define the infarct "core." After the endocardial and epicardial borders were traced by a trained observer, the myocardial segment containing the region of high SI myocardium was outlined, and the maximum SI within this region was determined. The infarct core was then defined as myocardium with SI >50% of the maximal SI.⁹ A region of interest (ROI) was then placed by a trained observer in the remote myocardium in an area free of artifacts and with uniform myocardial suppression.^{2,9,23} The peak, mean, and SD of the SI within the remote ROI were determined.⁹ Tissue heterogeneity within the infarct periphery (or "gray zone") was defined as the myocardium with SI >peak remote SI but <50% of maximal SI of the high SI myocardium (Figures 1 and 2). For each patient, the hyperenhanced regions in each short-axis slice were planimetered, and the size was expressed as grams of myocardium.^{9,19}

To evaluate for variations in the gray zone extent at 2 time points after contrast bolus, measurements were performed on a per-slice basis and reported as a cross-sectional area (mm²). Interobserver variability was assessed by 2 independent observers using 40 cross-sectional slices and is also reported as a cross-sectional area (mm²).

To thoroughly evaluate total infarct size by previously described definitions, the hyperenhanced region was characterized with different thresholds based on SI values within the remote region.^{2,7,9,23} Using the mean and SD of SI within the remote ROI, as described above, abnormally enhanced myocardium was first defined as high SI regions with SI 1 SD above the mean remote SI; the area of this region was then planimetered for all slices and expressed in grams of

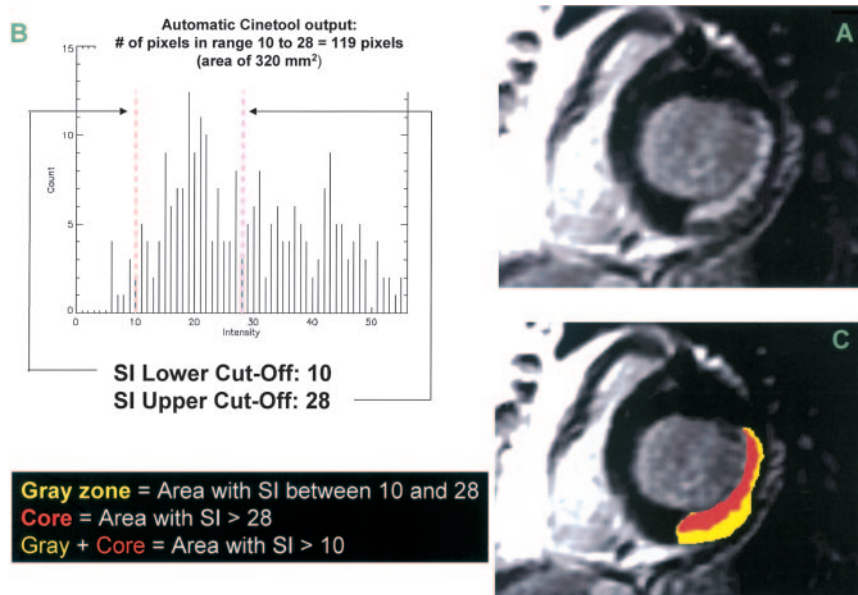


Figure 1. Algorithm for determining the gray zone. Basal short-axis delayed enhanced magnetic resonance image (A) shows the infero-lateral infarct as high SI and the normal myocardium as dark SI. To define the gray zone, the following algorithm was used: the endocardial and epicardial borders were drawn by a trained observer. The observer then planimetered an ROI in the remote, noninfarcted myocardium, and the upper limit of normal SI was defined as peak remote SI (peak remote SI=10 in the example shown). The myocardial segment containing the hyperenhanced region was loosely outlined. Using peak remote SI as the lower SI cutoff for abnormal myocardium, the actual region of abnormal late gadolinium enhancement (LGE) was determined by automatic thresholding (ie, any region with SI > peak remote SI is hyperenhanced). The SI profile (B) for this hyperenhanced region is displayed with SI value on the x-axis and number of pixels on the y-axis. The peak infarct (LGE) SI is displayed (peak LGE SI=56 in the example shown). The upper SI cutoff for the gray zone was calculated as 50% of peak LGE SI ($0.5 \times 56 = 28$ in the example). The gray zone extent was automatically determined as the region (C, shown in yellow) with SI between peak remote SI and 50% of peak LGE SI (between 10 and 28 in the example). The core region (C, shown in red) is the area with SI > 50% of peak SI.

myocardium. This process was repeated for SI cutoff values of 2 to 6 SDs above the mean remote SI.

The transmural extent of hyperenhancement was measured by standard techniques.²⁴ Each short-axis slice was segmented circumferentially into 12 wedges. For each segment, the transmural extent of total hyperenhancement was expressed as percentage of total segment area. For each patient, the percentage of segments with transmural extents of hyperenhancement within each quartile (0% to 25%; 26% to 50%; 51% to 75%; or >75%) was determined.²⁴

To describe regional perfusion in the gray zone, the wash-in characteristics of the gray zone, infarct core, and remote regions were assessed from first-pass perfusion images. Myocardial SI curves were generated in each ROI, as described previously.²⁵ ROIs were defined from the delayed enhancement images. With the image from the perfusion acquisition that best matched the slice location of the late gadolinium enhancement, the ROI was positioned in a similar location by a trained observer. SI was plotted against time with CINetool.

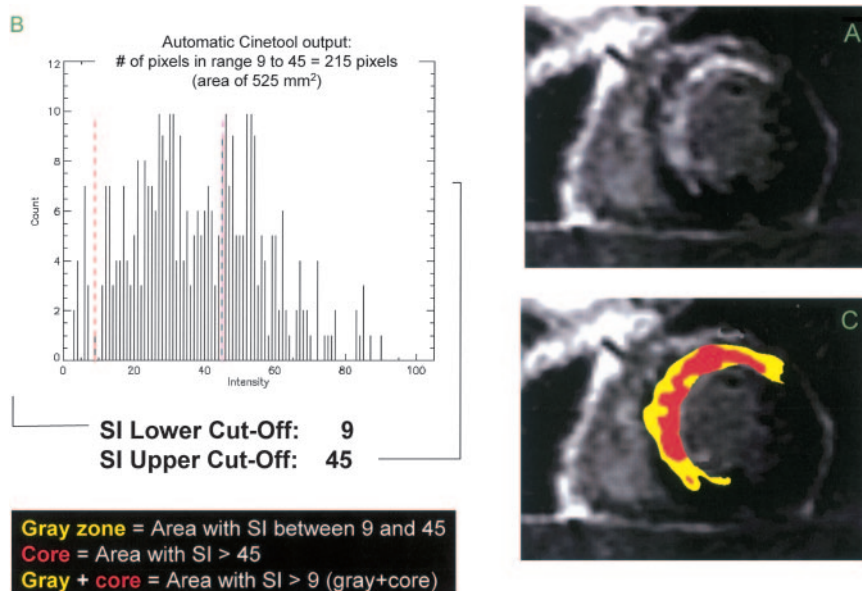


Figure 2. Gray zone measurement. A, Late gadolinium-enhanced short-axis magnetic resonance image of a patient with an anterior infarct. The peak SI within the remote, noninfarcted region was 9 in this example. Abnormal enhancement was defined as SI > 9. The histogram of SI within the hyperenhanced region is displayed in B. Peak SI within the high SI region is 90 in this example. The upper threshold for gray zone extent is 50% of the peak SI (or $90 \times 0.50 = 45$ in this example). The gray zone (C, yellow area) is the region with SI between 9 and 45. The core region (C, red area) is the region with SI > 45.

Statistical Analysis

Continuous variables are expressed as mean \pm SD. Student *t* test (SPSS version 11.0, SPSS Inc, Chicago, Ill) was used to compare group differences in continuous variables according to inducibility status. For the SI curve analysis, repeated-measures ANOVA was used to test the hypothesis that SI over time varied among the 3 different ROIs. For noncontinuous variables, Fisher exact test or χ^2 for trends was used. Variables that could relate to inducibility status by univariate analysis were included in a stepwise logistic regression model to evaluate which were significant. Variables entered the model if $P<0.05$ and exited the model if $P>0.1$. To assess whether quantification of the gray zone varied with time from contrast bolus and between observers, Bland-Altman repeatability analysis was used. A 2-tail probability value <0.05 defined statistical significance.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Patients

Twenty patients (43%) had inducible sustained monomorphic ventricular tachycardia with cycle length 231 ± 37 ms. Non-inducible and inducible groups had similar baseline characteristics except for a larger proportion of whites in the inducible group (Table 1).

MRI Indices and Inducibility

All patients had late gadolinium enhancement by ceMRI that supported the presence of prior MI. Global LV function, LV volumes, infarct location, and infarct transmural extent were similar in both groups (Table 2). On the basis of previously explored definitions of infarct size (ie, total hyperenhancement) and a cutoff of *n* SDs (*n* ranging from 1 to 6) above mean remote SI, no group differences were observed. The recently described criterion of between 2 and 3 SDs of mean remote SI to define the infarct periphery² did not distinguish the 2 groups.

Gray Zone Assessment

The primary end point of gray zone extent was strongly associated with inducibility ($P=0.015$ by Student *t* test; Table 2). This association was confirmed by stepwise logistic regression modeling in which anatomic variables postulated to be relevant to inducibility (namely, gray zone extent, infarct location, core extent, LV ejection fraction, and LV end-diastolic volume) were included (model $P=0.02$). Gray zone extent remained the only significant variable ($P=0.03$). The extent of the infarct core region was not significantly different between groups ($P=0.95$), and neither was the sum of the gray zone and infarct core ($P=0.17$). For both groups (noninducible versus inducible), late gadolinium-enhanced images were acquired with similar inversion times (202 ± 33 versus 194 ± 28 ms, $P=0.39$) and time from contrast bolus (23 ± 9 versus 22 ± 8 minutes, $P=0.53$).

To determine whether the time of data acquisition after contrast administration affected gray zone assessment, we repeated imaging in 20 patients (average of 2 slices per patient) at 2 time points (20 ± 6 and 30 ± 7 minutes after gadolinium administration). The SI histograms were unchanged between these times, a period during which late

TABLE 1. Baseline Clinical Variables According to Inducibility Status at Electrophysiology Study

| Variable | Noninducible for MVT (n=27) | Inducible for MVT (n=20) | P |
|------------------------------------------|-----------------------------|--------------------------|-------|
| Age, y | 61 \pm 11 | 63 \pm 10 | 0.46 |
| Male gender, n (%) | 20 (74) | 15 (75) | 1.00 |
| White, n (%) | 21 (78) | 20 (100) | 0.03 |
| Time from most recent MI, y | 7.5 \pm 6.5 | 8.3 \pm 7.4 | 0.72 |
| Entry ejection fraction (non-MRI method) | 0.25 \pm 0.07 | 0.29 \pm 0.08 | 0.09 |
| CHF class, n (%) | | | 0.28 |
| Class I | 5 (19) | 8 (40) | |
| Class II | 13 (48) | 6 (30) | |
| Class III | 9 (33) | 6 (30) | |
| Medication use, n (%) | | | |
| Aspirin | 26 (96) | 18 (90) | 0.57 |
| ACEI or ARB | 23 (85) | 18 (90) | 1.00 |
| β -Blocker | 25 (93) | 19 (95) | 1.00 |
| Lipid lowering | 27 (100) | 19 (95) | 0.43 |
| Antiarrhythmics (amiodarone) | 2 (7) | 1 (5) | 1.00 |
| Extent of mitral regurgitation, n | | | 0.11 |
| None | 9 | 7 | |
| Mild | 14 | 9 | |
| Mild to moderate | 0 | 4 | |
| Moderate | 2 | 0 | |
| Moderate-severe | 2 | 0 | |
| Severe | 0 | 0 | |
| EP stimulation protocol, n (%) | | | 0.01* |
| EP study | 3 (11) | 9 (45) | |
| NIPS | 24 (89) | 11 (55) | |

MVT indicates monomorphic ventricular tachycardia; CHF, congestive heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EP, electrophysiology; and NIPS, noninvasive programmed electrical stimulation.

*When logistic regression was used to control for the method of electrophysiological evaluation, gray zone extent remained significant in predicting inducibility ($P=0.02$).

gadolinium enhancement is typically performed clinically. Hence, the lower and upper SI thresholds used to define the gray zone at the 2 time points were similar (lower SI cutoff 11 ± 3 versus 10 ± 3 , $P=0.10$; upper SI cutoff 73 ± 24 versus 71 ± 21 , $P=0.30$). Bland-Altman analysis revealed close agreement of gray zone surface area quantification during the measured time interval, with bias of -1 mm² and coefficient of repeatability of 28 mm² (Figure 3). Given the time interval between the 2 sets of images, inversion times were adjusted to null normal myocardium, as is done clinically, and differed between the 2 acquisitions (193 ± 12 versus 215 ± 19 ms, $P<0.001$).

To evaluate interobserver variability, 2 independent observers assessed a subset of short-axis cross sections ($n=40$) for gray zone extent. Reproducibility was high by Bland-Altman analysis, with low bias of 2 mm² and coefficient of reproducibility of 16 mm² (Figure 4).

TABLE 2. MRI Indices According to Inducibility Status at Electrophysiology Study

| Variable | Noninducible for MVT (n=27) | Inducible for MVT (n=20) | P |
|----------------------------------------------------------------------------------|-----------------------------------|--------------------------------|-------|
| MRI LVEF | 0.30±0.10 | 0.29±0.07 | 0.79 |
| LV end-diastolic volume, mL | 220±70 | 228±57 | 0.68 |
| LV end-systolic volume, mL | 156±61 | 162±44 | 0.71 |
| LV end-diastolic mass, g | 146±46 | 132±30 | 0.23 |
| Infarct location, n (%) | | | 0.23 |
| Anterior±other territory | 15 (56) | 15 (75) | |
| Inferior and/or lateral only | 12 (44) | 5 (25) | |
| No. of coronary territories with hyperenhancement (%) | | | 0.1* |
| Single vessel | 21 (78) | 19 (95) | |
| Two vessel | 6 (22) | 1 (5) | |
| Transmural infarct extent: % of sectors grouped by quartiles of transmurality | | | |
| No infarct | 51±15 | 45±9 | 0.11 |
| 1% to 25% infarct transmurality | 8±4 | 7±2 | 0.61 |
| 26% to 50% infarct transmurality | 8±3 | 8±5 | 0.88 |
| 51% to 75% infarct transmurality | 11±5 | 12±5 | 0.39 |
| 76% to 100% infarct transmurality | 23±14 | 28±11 | 0.17 |
| Extent of hyperenhancement, g | | | |
| Total (core+gray) | 34±17 | 40±11 | 0.17 |
| Infarct core | 21±10 | 21±5 | 0.95 |
| Gray zone | 13±9 | 19±8 | 0.015 |

*With a logistic regression model in which gray zone extent and number of coronary territories with hyperenhancement were included, only gray zone extent was statistically significant in predicting inducibility ($P=0.03$).

Wash-In Characteristics

The subset of patients with optimal first-pass perfusion image quality (n=8) had similar clinical characteristics (eg, age, time from MI, LV ejection fraction, and New York Heart Association congestive heart failure class) as the overall study population. The pooled SI curves over time in these 8 patients are shown in Figure 5. Repeated-measures ANOVA showed a significant difference among the 3 myocardial SI patterns ($P<0.001$). By Bonferroni post hoc analysis, we determined that the difference was between the remote and infarct core ($P<0.001$) and the gray zone and core ($P<0.001$), with no difference between the remote and gray zones ($P=NS$). Thus, early wash-in kinetics of the gray zone were not intermediate between the remote and infarcted regions but matched those of the remote region, and both were significantly more rapid than in the infarct core.

Discussion

The present study demonstrates that tissue heterogeneity is quantifiable in human infarcts by ceMRI and is associated with inducibility for monomorphic ventricular tachycardia by programmed electrical stimulation. By assessing SI distribution within the scar, we have focused on the region of intermediate-intensity contrast hyperenhancement, which is prominent at the periphery of the scar that we

term the “gray zone.” In this group of patients, all of whom had dilated LVs with significantly reduced ejection fractions associated with large, predominantly anterior, transmural infarctions, a larger extent of gray zone tissue correlates with an increased susceptibility to ventricular arrhythmias.

Although ceMRI has been increasingly used to delineate infarcts, the tissue characterization potential of the technique has not been fully explored; image interpretation has generally been binary, with hyperenhancement signifying necrosis and lack of enhancement depicting viable myocardium.^{7,10} However, in experimentally induced MI, heterogeneity within the bright region suggests variable contrast enhancement⁹ and perhaps variable tissue perfusion and viability.^{26,27} In such experiments, the infarct core is characterized by significantly brighter SI than the periphery,⁹ consistent with increased gadolinium concentrations in the core.^{26,27} The periphery has SI intermediate between normal myocardium and the infarct core and exhibits faster contrast wash-out.²⁷ These SI differences across the infarct bed may explain the overestimation of infarct size found when a criterion of 2 SDs above mean remote is used.^{9,23} In fact, it was recently shown that pathological assessment of infarction was best approximated by the full-width half-maximum criterion of defining the infarct,⁹ as was used to quantify the infarct core in

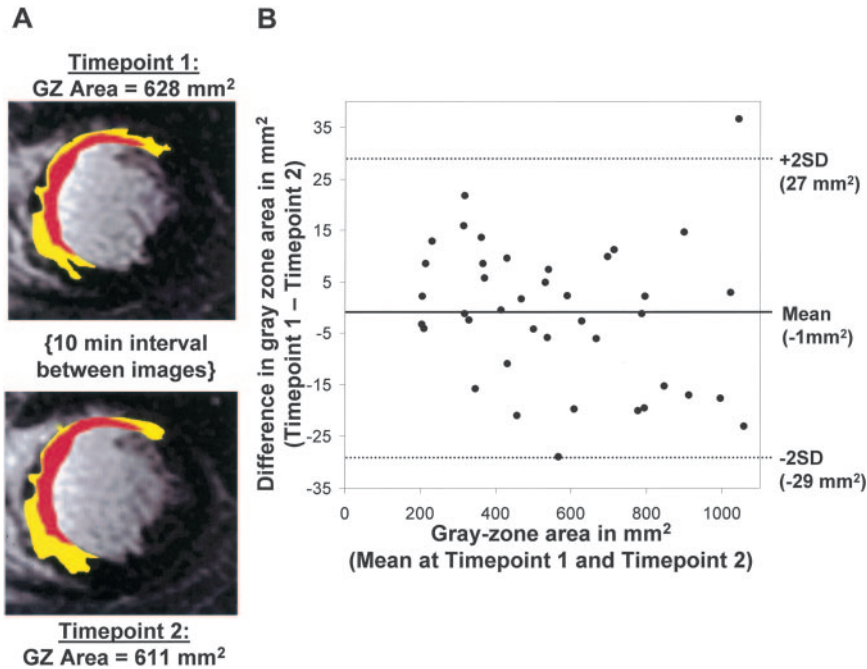


Figure 3. Time course of gray zone (GZ) extent. A, Representative short-axis late gadolinium-enhanced magnetic resonance image of an anterior infarct, imaged at 2 time points, 10 minutes apart. The SI cutoffs for determining the gray zone and the resultant gray zone extent are similar (9 and 47 for time point 1 and 11 and 47 for time point 2). B, Bland-Altman plot for gray zone quantification at 2 time points from contrast bolus (see text).

the present study. Relating extents of the regions of intermediate SI to an arrhythmic end point has not been considered previously.

A recent report in a relatively diverse group of patients with coronary artery disease highlighted the potential clinical significance of the peri-infarct zone as a marker of mortality.² The results of the present study support a potential pathophysiological explanation, namely, that larger regions of mixed tissue at the infarct border may provide the potential substrate for reentrant ventricular arrhythmias. In both studies, the definition of the peri-infarct or gray zone was prespecified but differed. Both were based in part on previously described thresholds for defining abnormal hyperenhancement.^{9,23} Differing thresholds to define the peri-infarct border likely detect varying admixtures of nonviable and viable tissue. Our definition

allowed the detection of regions in the periphery with sufficiently preserved microvascular perfusion (see discussion of contrast kinetics below). Specific definitions may depend on the relative mix of tissue detectable within the constraints of the particular MRI pulse-sequence parameters and across multiple MRI sites with larger numbers of patients. In addition, as noted by others,^{2,28} future studies are needed to determine the optimal thresholds for predicting various clinical outcomes. Nonetheless, the importance of an index of tissue heterogeneity is supported.

Another recent study found a significant relationship between infarct surface area and total size with inducibility.²⁹ Tissue heterogeneity was not assessed in that study.

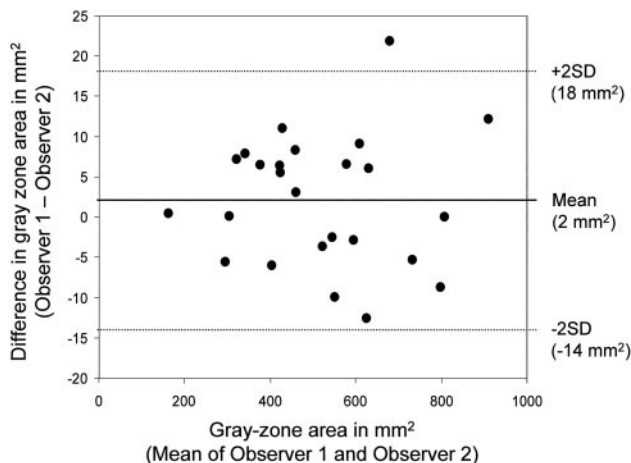


Figure 4. Interobserver variability of gray zone extent. Bland-Altman plot for interobserver variability of gray zone quantification.

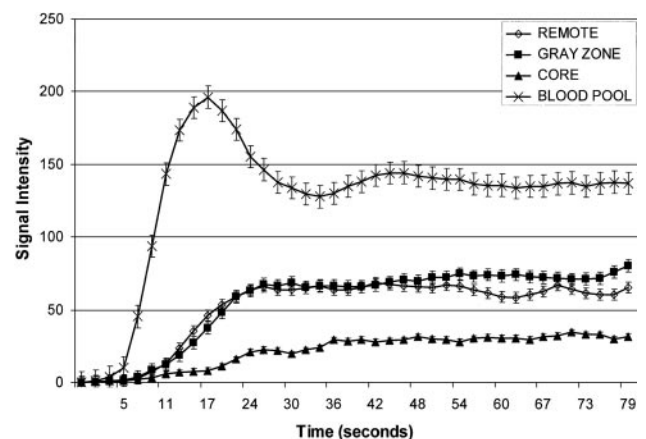


Figure 5. SI curves over time in myocardial regions of interest. Absolute SI (y-axis) in the remote, gray, and infarct core regions over time after contrast bolus from 8 patients. A significant difference exists among the 3 regions (ANOVA $P < 0.001$). However, the difference is between the remote and core ($P < 0.001$) and gray zone and core ($P < 0.001$); the wash-in pattern for the remote and gray zone was not significantly different over this time frame ($P = \text{NS}$).

The patient population and stimulation protocol differed as well. Because many of the patients in the present study were referred for ICD implantation on the basis of established primary prevention criteria, device-based programmed stimulation was often used instead of full electrophysiology studies (see Study Limitations). The present study group included only patients with prior infarction and LV dysfunction with no prior arrhythmic symptoms or indications for ICD other than risk stratification. All of the patients in the present study had evidence of late gadolinium enhancement, and ejection fractions were lower, particularly in the noninducible group. Hence, in a more uniform population with significant LV dysfunction, such as in the present study, total infarct size appears less well-associated with inducibility. In such a situation, quantification of the tissue mix in the infarct border may yield important information.

Two potential and interrelated categories of mechanisms exist to explain the intermediate SI of the infarct border zone: the partial volume effect and differences in contrast wash-in/wash-out kinetics. These mechanisms are discussed below.

Partial Volume Effect

Partial volume effect relates to the 3-dimensional spatial resolution of the image. If a given voxel at the infarct periphery contains an admixture of both infarcted (high SI) and noninfarcted (low SI) tissue, the 2 different SIs will be averaged, and this particular voxel will be represented by an intermediate SI (gray). However, this admixture of tissues causing intermediate SI can occur in 2 different ways. First, it could result merely from the volume-averaging effects of an area of uniformly fibrotic tissue (dense infarct scar) with an adjacent area of completely preserved, viable myocardium, particularly in situations in which spatial resolution is limited.^{7,28,30} In this case, anatomically, there would be a single border between fibrotic scar and viable myocardium, and the limited spatial resolution would render an apparent intermediate SI in that border region. Certainly, partial volume effects because of this averaging effect of normal and necrotic tissue have been demonstrated by cMRI in experimental animal studies^{7,28,30} and are contributory. However, a second possibility is that intermediate SI arises from the intermingling of discrete areas of preserved myocardium with bundles of fibrotic, infarcted scar within the same voxel. In this case, there would be a more gradual anatomic transition from dense, infarct core to preserved tissue beyond the infarct periphery. The latter mechanism is supported by pathological data.^{14,31} The architecture of the infarct border zones can be heterogeneous and nonuniform, and in certain situations, it is the juxtaposition and intermingling of normal and infarcted tissue that likely serves as the substrate for reentrant arrhythmias.^{14–16} Because of the admixture of surviving muscle bundles with collagen in the infarct periphery, the volume of distribution for gadolinium may be significantly less than that in the infarct core,²⁶ which has densely packed collagen fibers.

Contrast Kinetics

Differences in wash-in and wash-out kinetics of gadolinium within the infarcted territory have been noted in *ex vivo* experimental models.²⁷ Although by late gadolinium enhancement imaging, the gray zone had intermediate SI between that of normal and infarcted regions, gray zone wash-in kinetics were identical to that of the normal, remote myocardium during the first minute after contrast bolus. This suggests sufficiently preserved capillary perfusion and/or density within the gray zone, which differs significantly from the core region. Subsequently, the SI of the gray zone becomes brighter than that of the remote region but not as high as that of the infarct core on delayed enhancement images up to 30 minutes after contrast bolus. Although contrast kinetics washout was not explicitly studied, the stability of the SI histograms and gray zone areas between 20 and 30 minutes after contrast bolus allows for reproducible quantification of the infarct interface (gray zone).

Study Limitations

Extrapolation of these findings to other patient populations with smaller infarcts or nonischemic myocardial injury may require alternate algorithms. In addition, the anatomic basis of these clinical observations and the relationship of the induced reentrant circuits to the MRI gray zone are currently not known. Insight into these questions may be obtained from integration of the magnetic resonance images with electroanatomic mapping in experimental models with histopathological correlation and in clinical studies.

The present electrophysiological evaluation has several limitations. Many of the patients in the present study had noninvasive programmed stimulation through the device at the time of implantation. Device-based testing can potentially underestimate the inducibility of the cohort, because programmed stimulation is performed from a single site. However, when logistic regression was used to control for the method of electrophysiological evaluation, the extent of gray zone remained significant ($P=0.02$). Furthermore, the present findings relating larger gray zones to inducibility have been corroborated independently in a study in which all patients received conventional electrophysiological testing.³² The use of inducibility of monomorphic ventricular tachycardia at electrophysiological study as the primary outcome differs from other studies and was used because it is a reliable marker of the presence of a substrate for ventricular tachycardia. Although larger peri-infarct regions were recently associated with a greater risk of all-cause mortality,² extrapolation of the present data for use in stratifying patients according to risk and predicting sudden cardiac death is currently limited. Further prospective investigation is required to determine whether or not the gray zone, alone or in combination with other high-risk parameters in a multivariate model, is associated with other end points suggestive of increased sudden cardiac death risk, such as appropriate ICD firings for malignant ventricular arrhythmias and overall mortality. This possi-

bility will require longer clinical follow-up of the present patient group.

In conclusion, by measuring differences in SI distribution with ceMRI, it is possible to identify and measure regions of heterogeneity within human infarcts. This “gray zone,” which reflects tissue heterogeneity within the infarct periphery, strongly correlates with inducibility of ventricular tachycardia in patients with prior MI and LV dysfunction. Further studies are required to explore the reproducibility, clinical significance, and prognostic potential of these findings in a broad range of infarct populations.

Acknowledgments

We thank research coordinators Angela Steinberg, BSN, and Barbara Butcher, CCRN, and magnetic resonance technologists Donna Green, RT, and Cheryl Shoats, RT, for their efforts.

Sources of Funding

Financial support for this study was provided by the Donald W. Reynolds Foundation and the National Heart, Lung, and Blood Institute, National Institutes of Health (K23 HL04444 to Dr Wu).

Disclosures

Drs Foo and Gupta are employed by GE Healthcare Technologies. The remaining authors report no conflicts.

References

1. Azevedo C, Lima JA, Silva C, Bluemke DA, Weiss RG, Gerstenblith G, Thiemann DR, Halperin H, Steinberg T, Nazarian S, Berger R, Marban E, Wu KC. Tissue heterogeneity by contrast-enhanced MRI as a marker for sudden cardiac death in ischemic cardiomyopathy. *Circulation*. 2004;110(suppl III):III-644. Abstract.
2. Yan AT, Shayne AJ, Brown KA, Gupta SN, Chan CW, Luu TM, Di Carli MF, Reynolds HG, Stevenson WG, Kwong RY. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation*. 2006;114:32–39.
3. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98:2334–2351.
4. Josephson ME, Callans DJ, Buxton AE. The role of the implantable cardioverter-defibrillator for prevention of sudden cardiac death. *Ann Intern Med*. 2000;133:901–910.
5. Stevenson WG, Friedman PL, Sager PT, Saxon LA, Kocovic D, Harada T, Wiener I, Khan H. Exploring postinfarction reentrant ventricular tachycardia with entrainment mapping. *J Am Coll Cardiol*. 1997;29:1180–1189.
6. Bruckhorst CB, Delacretaz E, Soejima K, Maisel WH, Friedman PL, Stevenson WG. Identification of the ventricular tachycardia isthmus after infarction by pace mapping. *Circulation*. 2004;110:652–659.
7. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. 1999;100:1992–2002.
8. Rochitte CE, Lima JA, Bluemke DA, Reeder SB, McVeigh ER, Furuta T, Becker LC, Melin JA. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. *Circulation*. 1998;98:1006–1014.
9. Amado LC, Gerber BL, Gupta SN, Rettmann DW, Szarf G, Schock R, Nasir K, Kraitichman DL, Lima JA. Accurate and objective infarct sizing by contrast-enhanced magnetic resonance imaging in a canine myocardial infarction model. *J Am Coll Cardiol*. 2004;44:2383–2389.
10. Mahrholdt H, Wagner A, Judd RM, Sechtem U. Assessment of myocardial viability by cardiovascular magnetic resonance imaging. *Eur Heart J*. 2002;23:602–619.
11. Grebe O, Paetsch I, Kestler HA, Herkommer B, Schnackenburg B, Hombach V, Fleck E, Nagel E. Optimal acquisition parameters for contrast enhanced magnetic resonance imaging after chronic myocardial infarction. *J Cardiovasc Magn Reson*. 2003;5:575–587.
12. Damle RS, Robinson NS, Ye DZ, Roth SI, Greene R, Goldberger JJ, Kadish AH. Electrical activation during ventricular fibrillation in the subacute and chronic phases of healing canine myocardial infarction. *Circulation*. 1995;92:535–545.
13. Peters NS, Wit AL. Myocardial architecture and ventricular arrhythmogenesis. *Circulation*. 1998;97:1746–1754.
14. Deneke T, Muller KM, Lemke B, Lawo T, Calcum B, Helwing M, Mugge A, Grewe PH. Human histopathology of electroanatomic mapping after cooled-tip radiofrequency ablation to treat ventricular tachycardia in remote myocardial infarction. *J Cardiovasc Electrophysiol*. 2005;16:1246–1251.
15. de Bakker JM, van Capelle FJ, Janse MJ, Wilde AA, Coronel R, Becker AE, Dingemans KP, van Hemel NM, Hauer RN. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. *Circulation*. 1988;77:589–606.
16. Verma A, Marrouche NF, Schweikert RA, Saliba W, Wazni O, Cummings J, Abdul-Karim A, Bhargava M, Burkhardt JD, Kilicaslan F, Martin DO, Natale A. Relationship between successful ablation sites and the scar border zone defined by substrate mapping for ventricular tachycardia post-myocardial infarction. *J Cardiovasc Electrophysiol*. 2005;16:465–471.
17. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M; Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med*. 1996;335:1933–1940.
18. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883.
19. Azevedo CF, Amado LC, Kraitichman DL, Gerber BL, Edvardsen T, Osman NF, Rochitte CE, Wu KC, Lima JA. The effect of intra-aortic balloon counterpulsation on left ventricular functional recovery early after acute myocardial infarction: a randomized experimental magnetic resonance imaging study. *Eur Heart J*. 2005;26:1235–1241.
20. Garot J, Lima JA, Gerber BL, Sampath S, Wu KC, Bluemke DA, Prince JL, Osman NF. Spatially resolved imaging of myocardial function with strain-encoded MR: comparison with delayed contrast-enhanced MR imaging after myocardial infarction. *Radiology*. 2004;233:596–602.
21. Slavin GS, Wolff SD, Gupta SN, Foo TK. First-pass myocardial perfusion MR imaging with interleaved notched saturation: feasibility study. *Radiology*. 2001;219:258–263.
22. Bellenger NG, Pennell DJ. Assessment of cardiac function. In: Manning WJ, Pennell DJ, eds. *Cardiovascular Magnetic Resonance*. 1st ed. Philadelphia, Pa: Churchill Livingstone; 2002:99–111.
23. Bondarenko O, Beek AM, Hofman MB, Kuhl HP, Twisk JW, van Dockum WG, Visser CA, van Rossum AC. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. *J Cardiovasc Magn Reson*. 2005;7:481–485.
24. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343:1445–1453.
25. Judd RM, Lugo-Olivieri CH, Arai M, Kondo T, Croisille P, Lima JA, Mohan V, Becker LC, Zerhouni EA. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. *Circulation*. 1995;92:1902–1910.
26. Arheden H, Saeed M, Higgins CB, Gao DW, Ursell PC, Bremerich J, Wytenbach R, Dae MW, Wendland MF. Reperfused rat myocardium subjected to various durations of ischemia: estimation of the distribution volume of contrast material with echo-planar MR imaging. *Radiology*. 2000;215:520–528.
27. Kim RJ, Chen EL, Lima JA, Judd RM. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. *Circulation*. 1996;94:3318–3326.

28. Klocke FJ, Wu E, Lee DC. "Shades of gray" in cardiac magnetic resonance images of infarcted myocardium: can they tell us what we'd like them to? *Circulation*. 2006;114:8–10.
29. Bello D, Fieno DS, Kim RJ, Pereles FS, Passman R, Song G, Kadish AH, Goldberger JJ. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. *J Am Coll Cardiol*. 2005;45:1104–1108.
30. Hsu LY, Natanzon A, Kellman P, Hirsch GA, Aletras AH, Arai AE. Quantitative myocardial infarction on delayed enhancement MRI, part I: animal validation of an automated feature analysis and combined thresholding infarct sizing algorithm. *J Magn Reson Imaging*. 2006;23:298–308.
31. Freeman I, Grunwald AM, Robin B, Rao PS, Bodenheimer MM. Effect of early reperfusion on use of triphenyltetrazolium chloride to differentiate viable from non-viable myocardium in area of risk. *Cardiovasc Res*. 1990;24:109–114.
32. Iwuchuku C, Siddiqi S, Hitender J, Mathew S, McLaughlin J, Schapiro W, Han J, O'Donnell T, Wang Y, Greenberg SM, Schechter S, Jayam V, Hoch DH, Levine J, Reichek N. Arrhythmic risk in MADIT II patients: role of infarct size and heterogeneity. *Circulation*. 2006;114(suppl II):II-382. Abstract.

CLINICAL PERSPECTIVE

Approaches to risk stratification for sudden cardiac death in patients with prior myocardial infarction have focused on global left ventricular dysfunction and electrophysiological factors. Little attention has been given previously to detailed characterization of the infarcted myocardium itself, which provides the substrate for potential arrhythmogenesis. Gadolinium contrast-enhanced MRI is capable of imaging the myocardium with high spatial resolution and tissue contrast. In the present study, we describe a method of differentiating the dense infarct core from the peri-infarct region or "gray zone" and relate it to arrhythmic substrate by electrophysiological evaluation. We found that gray zones were quantifiable in human infarcts and likely reflect tissue heterogeneity. Larger extents of gray zone were the single factor associated with inducibility for monomorphic ventricular tachycardia. This lends mechanistic support to the findings of a recent study that reported an association between the size of the infarct periphery and mortality: Tissue inhomogeneity in the infarct borders may provide the substrate for potential reentrant arrhythmias that can lead to sudden cardiac death. Future studies are required to explore the potential utility of detailed infarct characterization in prognosis, risk stratification, and therapeutic interventions after myocardial infarction over and above left ventricular ejection fraction and infarct size alone.

Infarct Tissue Heterogeneity by Magnetic Resonance Imaging Identifies Enhanced Cardiac Arrhythmia Susceptibility in Patients With Left Ventricular Dysfunction

André Schmidt, Clerio F. Azevedo, Alan Cheng, Sandeep N. Gupta, David A. Bluemke, Thomas K. Foo, Gary Gerstenblith, Robert G. Weiss, Eduardo Marbán, Gordon F. Tomaselli, João A.C. Lima and Katherine C. Wu

Circulation. 2007;115:2006-2014; originally published online March 26, 2007;

doi: 10.1161/CIRCULATIONAHA.106.653568

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2007 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/115/15/2006>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>