Electrotonic remodeling following myocardial infarction in dogs susceptible and resistant to sudden cardiac death

Carlos L. del Rio,1,2 Patrick I. McConnell,3 Monica Kukielka,1 Roger Dzwonczyk,4 Bradley D. Clymer,2,5 Michael B. Howie,4 and George E. Billman1,6

Departments of 1 Physiology and Cell Biology, 2 Electrical and Computer Engineering, 3 Surgery, 4 Anesthesiology, and 5 Biomedical Engineering, and 6 Dorothy M. Davis Heart and Lung Research Institute, The Ohio State University, Columbus, Ohio

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del Rio CL, McConnell PI, Kukielka M, Dzwonczyk R, Clymer BD, Howie MB, Billman GE. Electrotonic remodeling following myocardial infarction in dogs susceptible and resistant to sudden cardiac death. J Appl Physiol 104: 386–393, 2008. First published November 29, 2007; doi:10.1152/japplphysiol.01106.2007.—Passive electrical remodeling following myocardial infarction (MI) is well established. These changes can alter electrotonic loading and trigger the remodeling of repolarization currents, a potential mechanism for ventricular fibrillation (VF). However, little is known about the role of passive electrical markers as tools to identify VF susceptibility post-MI. This study investigated electrotonic remodeling in the post-MI ventricle, as measured by myocardial electrical impedance (MEI), in animals prone to and resistant to VF. MI was induced in dogs by a two-stage left anterior descending (LAD) coronary artery ligation. Before infarction, MEI electrodes were placed in remote (left circumflex, LCX) and infarcted (LAD) myocardium. MEI was measured in awake animals 1, 2, 7, and 21 days post-MI. Subsequently, VF susceptibility was tested by a 2-min LCX occlusion during exercise; 12 animals developed VF (susceptible, S) and 12 did not (resistant, R). The healing infarct had lower MEI than the normal myocardium. This difference was stable by day 2 post-MI (287 ± 32 Ω vs. 425 ± 62 Ω, P < 0.05). Significant differences were observed between resistant and susceptible animals 7 days post-MI; susceptible dogs had a wider electrotonic gradient between remote and infarcted myocardium (R: 89 ± 60 Ω vs. S: 180 ± 37 Ω). This difference increased over time in susceptible animals (252 ± 53 Ω at 21 days) due to post-MI impedance changes on the remote myocardium. These data suggest that early electrotonic changes post-MI could be used to assess later arrhythmia susceptibility. In addition, passive-electrical changes could be a mechanism driving active-electrical remodeling post-MI, thereby facilitating the induction of arrhythmias.

myocardial ischemia; myocardial electrical impedance; ventricular fibrillation

HEALED MYOCARDIAL INFARCTION (MI) is one of the most important structural substrates of sudden cardiac death (SCD; Ref. 38). Fatal arrhythmias [ventricular fibrillation (VF)] arising from the boundary of scarred myocardium are the cause of sudden death in a significant percentage of deceased patients with a known cardiac lesion. Despite substantial stratification and therapeutic advances, the risk of sudden death remains the highest in the first 30 days after MI (6, 39). Moreover, common arrhythmia risk-stratification variables have limited predictive power identifying patients at risk of SCD after MI (1, 19, 22). Hence, research on both mechanisms and new markers of arrhythmia susceptibility, especially in the setting of healing myocardial infarction, is needed.

A potential mechanism for VF and sudden cardiac death following MI is remodeling of repolarization currents, leading to increased action potential duration (APD) and dispersion of repolarization (2, 30). Recently, it has been shown in vitro that changes in electrotonic loading, which may occur from passive electrical heterogeneities in the ventricle, can trigger the remodeling of these sarcolemmal currents (24). Notably, the remodeling of myocardial structures (e.g., gap junctions) mediating passive electrical coupling/loading in ventricles prone to arrhythmias is well established after MI (see Ref. 44 for review). Several investigations suggest that discontinuities in coupling resistance between neighboring myocardial regions can lead, by itself, to unidirectional conduction block, a critical factor for reentrant arrhythmias (7, 11). Moreover, Sahakian et al. (33) showed (in silico) that conduction block is more likely to occur with steeper electrotonic gradients (differences) and/or when propagation encounters an abrupt decrease in coupling resistance. Interestingly, healing/healed myocardial infarction has lower electrical impedance than normal noninfarcted myocardium (8, 12, 14, 34, 36, 45, 46) as a consequence of ischemic sarcolemmal rupture (31). For example, Fallert et al. (14) reported that following infarction (in sheep), scar impedance was ~60% of the noninfarcted tissue. Nonetheless, the prognostic value of this electrotonic disparity as a tool to assess the susceptibility to ischemia-induced arrhythmias following MI has not been established.

Thus, it was the purpose of this study to investigate electrotonic coupling in the post-MI heart, as measured by myocardial electrical impedance (MEI), and its relationship to arrhythmia susceptibility. In particular, the hypothesis that post-MI hearts with the highest degree of ventricular electrotonic (MEI) heterogeneity also exhibited the greatest susceptibility to VF was tested.

MATERIALS AND METHODS

The principles governing the care and treatment of animals, as expressed by the American Physiological Society, were followed at all times during this study. In addition, the animal protocols and experimental procedures were approved by the Institutional Laboratory Animal Care and Use Committee at this institution, and they adhered to the statutes of the Animal Welfare Act and the guidelines of the Public Health Service.

Chronic model of ischemia-induced VF. The studies were performed on a well characterized canine model of SCD, known to mimic...
the main clinical features associated with the disease: healed myocardial ischemic injury, acute myocardial ischemia, and cardiac autonomic activation. The surgical preparation for this model was initially presented by Billman, Schwartz and Stone (3, 35), and it has been subsequently described in detail (4, 5).

In short, forty-three (n = 43) heartworm-free, purpose-bred, mixed-breed dogs weighing 16.0–25.7 kg (20.1 ± 2.7 kg) were sedated (morphine sulfate 15 mg im, thiopental sodium 20 mg/kg iv) and connected to a respirator via an endotracheal-cuffed tube. Anesthesia was maintained with inhaled isoflurane (1–1.5%) mixed with oxygen (100%). Under sterile conditions, the chest was opened via a left thoracotomy (fifth intercostal space). The heart was exposed and suspended with a pericardial cradle. Subsequently, a large anterolateral MI was created by ligation of the left anterior descending (LAD) coronary artery, proximal to its first diagonal branch; to limit acute ischemic arrhythmias and increase survival, a modified (3, 35) two-stage LAD occlusion was used. Briefly, as described by Harris (17), two silk snare were loosely placed around the LAD coronary artery; these sutures were used first to constrict the vessel by tying a suture against a 20-gauge hypodermic needle that was then removed (stage I), and 20 min later to occlude this vessel completely (stage II). In addition, the left circumflex (LCX) coronary artery was dissected free of the surrounding tissue near its origin (under the edge of the left auricular appendage) and chronically instrumented with a 20-MHz Doppler flow probe and a hydraulic coronary artery occluder. Inflation of this balloon would later render a portion of the LCX distribution acutely ischemic (see Arrhythmia susceptibility).

Before infarction, as required for MEI measurements (see Myocardial electrical impedance), two bipolar pacing electrodes (Medtronic, model Streamline 6495) were placed (one each) in the distal LAD and LCX coronary artery distributions. These two regions are referred to as the ischemic/infarcted and the remote/noninfarcted myocardium, respectively. Each lead was placed (parallel to the local fiber alignment) into the mid-myocardial wall, downstream of the respective ligation/occlusion site (i.e., LAD ligatures/LCX hydraulic occluder), and firmly secured in place with nonabsorbable sutures (prolene 2-0). After acute LAD coronary ligation (infarction), the ischemic/infarcted electrodes were visually confirmed to be in the center of the region rendered ischemic (i.e., cyanotic/diskinetic) during coronary occlusion. The pericardial cradle was released, and the chest was closed in layers and evacuated of air, restoring the negative intrathoracic pressure. All leads were tunneled under the skin, exited at the neck, and carefully bandaged.

To reduce mortality during the acute infarction phase, the procedures were performed under prophylactic anti-arrhythmic therapy instituted both before surgery (procaainamide 500 mg im) and during each stage of the coronary occlusion (lidocaine HCl 60 mg iv, bolus). In addition, the dogs were given a broad-spectrum antibiotic postoperatively (amoxicilin, 500 mg by mouth twice per day for 7 days) to reduce the risk of infection. Nonetheless, out of the 43 animals that were surgically prepared, 17 did not complete the experimental procedures (and were excluded from analysis) due to either premature death (n = 11) or to failure of the MEI electrodes (n = 6, see Experimental protocol).

Arrhythmia susceptibility. The surviving animals were allowed to recover for 3–4 wk and were trained to run on a motor-driven treadmill. Subsequently, the susceptibility to ischemia-induced ventricular fibrillation was assessed by means of a standardized protocol, generally referred as the “exercise-plus-ischemia” test (3, 4, 35). Briefly, after a 3-min warm-up period (4.8 km/h, 0% grade), the dogs ran (6.4 km/h) for 15 min with the grade (incline) increased every 3 min (i.e., 0, 4, 8, 12, and 16%) to activate the autonomic nervous system and to achieve a submaximal (~70%) heart rate of 210 beats/min. During the last minute of exercise (i.e., while running at 6.4 km/h, 16%), the animals were subjected to a brief (2 min) LCX occlusion. This combination of exercise plus ischemia yields two stable and well-differentiated populations of animals: one susceptible to ischemia-induced ventricular fibrillation and the other resistant (see Ref. 4 for review). In this study, 12 animals developed VF (susceptible, 5) and 12 did not (resistant, 7) during the exercise-plus-ischemia test. Two animals (n = 2) could not be classified due to equipment failure. A single-lead electrocardiogram (ECG) was recorded at the time of classification (30.8 ± 8.0 days).

Myocardial electrical impedance. As has previously been described (13), a computer-controlled circuit developed in this laboratory (18) was used to measure the complex electrical impedance of the myocardium. In short, via a bipolar pacing lead (see Chronic model of ischemia-induced VF) the myocardium was probed with a subthreshold zero-mean bipolar current, consisting of two rectangular pulses of alternating polarity (± 5 μA, 100 μs wide) generated 200 ms apart. Measurements were made only with the first pulse of each stimulation pair; the subsequent pulse (of opposite polarity) was used to mitigate possible artifacts introduced by the electrode-tissue interface (e.g., polarization; see Limitations). The complex MEI spectrum was calculated in the frequency domain as the ratio (at each frequency) of the current and voltage spectra resulting from the combined averages of ten stimulus pulses and their respective (voltage) responses. The mean modulus of the complex MEI spectrum in the 0.27- to 5.90-kHz frequency range was examined.

Experimental protocol. As described above, animals were instrumented with MEI electrodes in remote (noninfarcted) and ischemic/infarcted myocardium. Through these leads, MEI was recorded from each myocardial region (distribution) either intraoperatively (under anesthesia, open chest), at end of surgery (under anesthesia, closed chest) and/or during recovery (awake, unsedated, at rest). As mentioned before, six animals (n = 6) were excluded from the chronic study due to lead malfunction (i.e., dislodgement).

Thus, the studies were performed on twenty-six dogs (n = 26). To study the early time course of electrotonic (MEI) remodeling after MI, MEI measurements were collected from a group of animals (n = 14) regardless of arrhythmia susceptibility (5 R, 7 S, and 2 unable to be classified), both acutely (i.e., at end of surgery, and chronically (i.e., on days 1, 2, 7, and 21) after MI (LAD ligation). From the remaining animals (n = 12), consisting of both VF-resistant (n = 7) and VF-susceptible (n = 5) dogs, MEI data were recorded only on post-MI day 7 and day 21. Subsequently, to study the differences between animals susceptible (n = 12) and resistant (n = 12) to ischemia-induced arrhythmias, data collected at post-MI day 7 and day 21 time points were pooled among all dogs successfully classified with the exercise-plus-ischemia test (n = 24). The susceptibility to ischemia-induced arrhythmias was evaluated at the end of the study, i.e., 4 wk (30.8 ± 1.6 days) after MI. In all cases, chronic post-MI data were collected from unrestrained, awake, unsedated animals at rest (in a dimly lit, quiet room) and averaged over at least 1 min (for each myocardial region).

As mentioned before, a modified (3, 35) Harris two-stage occlusion (17) was used to create an anterior myocardial infarction. Notably, although the electrotonic derangements triggered by a single-stage acute coronary occlusion have been well described (7, 11, 13, 18, 21), no study to date has evaluated the passive electrical changes that follow a two-stage procedure. Thus, in a subset of animals (n = 10), MEI was continuously recorded (every 3 s) intraoperatively during the 2-stage LAD ligation. MEI data were collected distal to the LAD snares (ischemic region), and are reported (averaged over 30 s) at eight time points before and during the ischemic insult; preischemic (baseline) values were taken 2 min before coronary constriction (at t = 0 min). Following the onset of occlusion, ischemic minutes 2, 5, 10, 20 (onset of LAD ligation), 22, 25, and 30 were studied. It should be noted that given the unknown electrotonic effects of anesthesia, acute (i.e., collected during or at the end of surgery) and chronic MEI measurements were not compared.

Data analysis. ECG signals were band-pass filtered and digitally recorded (at 500 Hz) by means of a data acquisition system (Biopac Systems, model MP-100). Stored waveforms were analyzed offline,
and fiducial points were determined with the aid of personal computer software (Biopac Systems, Acknowledge). As such, heart rate (HR), R–R interval, and QT interval durations were measured. Since repolarization duration (QT) is rate dependent, QT was corrected for HR values (QTC = QT/R – R0.5). Data were averaged over five consecutive beats at rest.

All data are presented as means ± SD. Statistical analyses were performed with SigmaStat (Systats Software) and NCSS (NCSS). Mean impedance differences between values recorded before/after acute two-stage coronary occlusion (i.e., during surgery) were tested via ANOVA with repeated measures. The time course of electrotonic (MEI) remodeling after MI was evaluated via two-way (time: days 1, 2, 7, and 21 post-MI, distribution: infarct/remote) ANOVA with repeated measures on both factors. Similarly, intergroup comparisons (i.e., resistant vs. susceptible) were made via three-way (time: days 1 and 21 post-MI, distribution: infarct/remote, group: susceptible/resistant) ANOVA with repeated measures on two factors (time/distribution). A significant second-order interaction (time × distribution × group) was found (F1215 = 24.69, P < 0.001), and four two-way ANOVAs were subsequently performed to investigate this effect: two group × distribution (at each time-point) and two distribution × time (within each group) tests were done. In addition, the group-wise interaction (contrast) between remote and infarct impedance (ΔMEI), reflecting the degree of electrotonic heterogeneity within the myocardium, was studied over time via two-way (time/group) ANOVA with repeated measures on one factor (time). If significant F-values were observed, post hoc pairwise comparisons were made via the Tukey test; P < 0.05 was considered to be statistically significant (a priori). The repeated-measures sphericity assumption (i.e., homogeneity of the covariance matrix) was verified by means of Mauchley’s test (NCSS). Receiver-operator characteristic (ROC) curves were generated for the ΔMEI values measured 7 and 21 days post-MI. The area under these ROC curves (AUC) was calculated with a binormal model (NCSS) and is reported (with its standard error, SE_AUC) as an overall measure of diagnostic accuracy (48).

RESULTS

Acute ischemia (two-stage coronary artery occlusion). During the two-stage ischemic insult, MEI increased rapidly (2–5 min) following the initial vessel constriction (stage I), but subsequently recovered (10–20 min). Subsequently, the complete ligation of the LAD coronary artery (stage II) led to a sustained impedance rise (>20 min). These data are displayed in Fig. 1.

Chronic ischemia (infarction). As expected, healing myocardial infarct tissue had significantly lower MEI than normal myocardium (see Fig. 2 and Table 1). This difference was stable by day 2 post-MI (2.3 ± 0.6 days), when the infarct impedance had reached 70 ± 12% of that recorded in noninfarcted tissue (MI: 287 ± 32 Ω vs. LCX: 425 ± 62 Ω, n = 14, P < 0.05), coinciding (temporally) with the peak number of premature deaths; five animals (5/8) died 48–72 h after coronary ligation. One week after MI (7.2 ± 0.6 days), significant differences were observed between resistant and susceptible animals (see Fig. 3 and Table 2); susceptible dogs had a wider electrotonic disparity (ΔMEI) between remote (nonischemic) myocardium and the infarcted tissue (R: 89 ± 60 Ω vs. S: 180 ± 37 Ω, P < 0.05). Three weeks after MI (21.5 ± 1.7 days), this difference had increased significantly, but only in VF-susceptible animals (R: 62 ± 101 Ω vs. S: 252 ± 53 Ω, P < 0.001; see Table 2). It is likely that remodeling of remote (LCX) myocardium (R: 435 ± 78 Ω vs. S: 585 ± 91 Ω, P < 0.001) was responsible for this increased electrotonic dispersion, as no intergroup differences were found among impedance measurements recorded in infarcted tissue (R: 373 ± 69 Ω vs. S: 333 ± 77 Ω, P = 0.3, not significant).

The diagnostic accuracy of ΔMEI for predicting arrhythmia susceptibility was studied from ROC curves for measurements made on days 7 and 21 post-MI; the areas under the ROC curves were 90.3% (SE_AUC = 6.2%; see Fig. 4) and 95.3% (SE_AUC = 4.9%), respectively. The optimal impedance difference for classification 1 wk after MI (i.e., ΔMEI, ~145 Ω) was selected at the point of intersection of the sensitivity and specificity curves (~83%), providing positive/negative predictive values of 82.8% (see Fig. 4, inset).

Furthermore, at the time of classification (29.3 ± 4.9 days post-MI), animals prone to ischemia-induced arrhythmias had longer QTc intervals (R: 323 ± 4.2 ms vs. S: 341 ± 6.3 ms, P < 0.001) despite comparable heart rates (R: 119 ± 18.8 beats/min vs. S: 130 ± 20.0 beats/min, P = 0.16, not significant). These data are consistent with prolonged repolarization in the VF-susceptible dogs.

DISCUSSION

The present study investigated chronic electrotonic remodeling in the left ventricle following an anterior myocardial infarction, as described by the electrical impedance of both
ischemic and remote (noninfarcted) myocardium. Unlike prior studies (8, 14, 34, 36, 45, 46), these passive electrical changes were studied in awake animals and, importantly, in dogs that were subsequently shown to be susceptible/resistant to ischemia-induced VF. In agreement with previous reports (8, 14, 34, 36, 45, 46), the healing infarction had a lower impedance than did the remote, noninfarcted myocardium. In addition, dogs prone to VF had a wider electrotonic gradient (impedance difference, ∆MEI) between these myocardial regions. This broader “impedance mismatch” between infarcted and noninfarcted myocardium was observed as early as 1 wk following infarction, and more importantly, provided a reliable marker for subsequent susceptibility to VF. Furthermore, in animals prone to arrhythmias this “mismatch” increased over time due to MEI changes (increase) in the noninfarcted myocardium, facilitating the impedance-based classification of arrhythmic susceptibility.

Acute MEI changes (two-stage coronary artery occlusion). The present study also evaluated (for the first time) the passive electrical changes that follow an acute Harris two-stage LAD coronary artery occlusion. Following the initial constrictive ischemic insult (stage I), MEI increased rapidly but subsequently recovered. A larger and sustained rise was observed after the complete ligation of the LAD (stage II). In short, after 20 min of constriction and 10 min of coronary occlusion (30 min of combined ischemia), MEI rose 81 ± 41.3 Ω from the preischemic value of 812 ± 106.6 Ω (i.e., +10.0 ± 5.2%, \( P < 0.05 \)). In a previous study, performed also in isoflurane-anesthetized dogs, MEI was shown to increase 24.1 ± 5.4% (from 809 ± 133 Ω) after a 30-min (single-stage) acute LAD occlusion (18). Taken together, these observations suggest that the two-stage occlusion procedure attenuated the MEI progression (electrotonic uncoupling) during ischemia. Interestingly, interventions that delay the passive electrical changes triggered by acute coronary occlusion are known to limit ischemia-induced arrhythmias (e.g., see Ref. 9). Thus, although further research is needed, these results suggest that the attenuation of ischemia-induced electrotonic changes (MEI increase) may be a

![Fig. 2. Early time course of MEI following acute LAD coronary artery ligature (myocardial infarction, MI). Note that in contrast to acutely ischemic tissue (shaded area), healing infarct (chronically ischemic) has lower impedance than remote (noninfarcted) myocardium, resulting in an electrotonic gradient dispersion (∆MEI). Remote values were measured on the distal left circumflex (LCX) coronary artery distribution.](#)

![Fig. 3. A: MEI of infarcted and remote (noninfarcted) myocardium 1 wk after LAD coronary artery ligation. Note the wider electrotonic dispersion, i.e., larger impedance difference between remote and ischemic myocardium (∆MEI), in animals later found susceptible to ischemia-induced malignant arrhythmias. B: individual ∆MEI values 7 days post-MI. Remote values were measured on the LCX coronary artery distribution. Data were collected in awake, unsedated animals at rest.](#)

### Table 1. MEI of ischemic/infarcted and remote (noninfarcted) myocardium following LAD coronary artery ligation

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Acute MI</th>
<th>Infarct Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 1</td>
</tr>
<tr>
<td>Remote (LCX), Ω</td>
<td>765±88</td>
<td>447±72</td>
</tr>
<tr>
<td>Infarct (LAD), Ω</td>
<td>917±139†</td>
<td>340±48†</td>
</tr>
<tr>
<td>RatioLAD/LCX, %</td>
<td>121±19</td>
<td>79±15</td>
</tr>
</tbody>
</table>

Values are means ± SD; \( n = 14 \), except for day 21 where \( n = 12 \) due to equipment failure in 2 dogs. Acute myocardial infarction (MI) measurements were obtained in anesthetized animals (at the end of the surgical preparation/LAD ligation). Chronic post-MI measurements (infarct healing; days 1, 2, 7, and 21) were taken in awake, unsedated animals. MEI, myocardial electrical impedance; LAD, left anterior descending; LCX, left circumflex coronary artery. *\( P < 0.05 \) vs. days 1, 2, and 7. †\( P < 0.05 \) vs. infarct.
mechanism that mediates the antiarrhythmic protection of the two-stage Harris occlusion.

Chronic MEI changes (infarction remodeling). Following infarction, the nonischemic myocardium is known to undergo adaptive processes resulting in detrimental mechanical and electrical changes (1, 30). In agreement with the present observations, clinical and experimental data suggest that the extent of this maladaptation, or remodeling, is well correlated with the risk of ventricular arrhythmias (39, 42). During post-MI cardiac remodeling, impulse conduction in the surviving myocardium is altered by changes in both passive electrical coupling and tissue architecture, leading to highly heterogeneous tissue that may serve as an arrhythmogenic trigger/substrate (32, 37).

For example, in surviving postinfarct myocardium, disarray and downregulation of the gap junctions mediating cell-to-cell electrotonic communication have been shown to correlate spatially with pathways of reentry (28). In a canine model of healed MI, Luke and Saffitz (25) reported that myocytes at the scar border presented not only less interconnections but also smaller gap junctions, limiting intercellular current transfer. Notably, intercellular resistance, and therefore whole-tissue impedance, is determined partially by the conductance properties of the gap junctions (7, 11, 21).

Similarly, post-MI changes in cellular and interstitial space morphology also can alter electrotonic coupling and action potential propagation properties. Cooklin et al. (10), for instance, showed that preparations from hypertrophied ventricles, characterized by larger myocytes, had higher longitudinal impedance than those from sham-operated controls. Interestingly, Swann et al. (43), using the same animal model as the present study, reported that susceptible but not resistant animals exhibited a significant hypertrophy (by echocardiography) of noninfarcted myocardial regions. Thus, it is plausible that more severe remodeling, involving both abnormal (decreased) gap-junction coupling and increased cell size, could underlie the higher impedance recorded from regions remote to a myocardial infarction in animals prone to ischemia-induced VF. In agreement with this hypothesis, post-MI patients with severe left ventricular remodeling (hypertrophy) have the highest risk for sudden cardiac death due to lethal arrhythmias (39, 42).

Regardless of the underlying mechanism(s), passive-electrical changes following MI, as assessed by the myocardial electrical impedance, were able to differentiate between animals later shown to be either prone to or resistant to malignant arrhythmias. In particular, the degree of electrotonic dispersion, or impedance disparity (ΔMEI) between the remote (nonischemic) myocardium and the healing infarct, identified VF-susceptible dogs with high sensitivity and specificity, even when measured just 7 days post-MI (see Fig. 4). Notably, the risk of sudden death remains the highest in the first 30 days after MI (6, 39), and the prognostic significance of early intervention/therapy is well documented. Thus, although a direct comparison with indexes of post-MI arrhythmic-risk currently used in the clinic is difficult (and perhaps unwarranted at this time given the relatively small sample), the results of the present study suggest that markers of electrotonic remodeling (especially in the surviving myocardium) could be valuable in identifying patients vulnerable to arrhythmic events earlier. Furthermore, several groups have presented clinically applicable catheter-based impedance mapping techniques [e.g., Cinca and colleagues (34, 45), Wolf et al. (46)] that could be used concurrently with existing methods investigating active-electrical remodeling post-MI (e.g., indices dispersion of repolarization and/or programmed electrical stimulation protocols), thereby providing a more complete evaluation/understanding of the electrical substrate for arrhythmias.

Interestingly, electrotonic remodeling, occurring as a consequence of MI, could also play a role triggering and/or modulating pro-arrhythmic adaptive processes affecting active electrical properties (i.e., ionic currents). For example, Libbus et al. (24) found that changes in electrotonic loading acutely reduced early (phase 1) action potential repolarization in the epicardium, consistent with remodeling (attenuation) of the transient outward potassium current (Ito). Downregulation of Ito, as well as other repolarizing currents, provides the cell with the capacity to deliver greater electrotonic current to partially uncoupled cells downstream of the conduction (40), thereby acting as...
an intrinsic “impedance matching” (or load balancing) mechanism allowing “optimal” source-load coupling.

Thus, a wider electrotonic gradient (impedance mismatch) following infarction, as observed in animals that either died early (data not shown) or survived but were susceptible to VF, could mediate a more severe attenuation/remodeling of these sarcolemmal ionic currents. Notably, Yao et al. (47) reported that changes in repolarizing potassium currents (such as \( I_{K} \)) were detectable just 3 days after infarction, coinciding with the onset of impedance heterogeneities as reported in the present study. Furthermore, it is generally accepted that post-MI slowing of repolarization prolongs action potential duration (APD) and increases heterogeneities in the time course of repolarization (30). Swann et al. (43) reported that compared with VF-resistant animals, VF-susceptible dogs presented marked ventricular repolarization heterogeneities. In the present study, QTc was longer in VF-susceptible animals, an observation consistent with slowed/heterogeneous repolarization. Furthermore, at the cellular level, animals prone to ischemia-induced VF were found to have longer (and more disperse) APDs compared with either control and/or VF-resistant animals (41). Taken together, these observations further strengthen the potential role of electrotonic remodeling of the nonischemic myocardium as a substrate for VF in postinfarct hearts.

**Study limitations.** Mongrel dogs subjected to coronary artery occlusion-induced myocardial ischemia/infarction were used in this study. It is well established that dogs possess a well-developed coronary collateral system (26), and therefore are more resistant to supply ischemia than other species lacking such innate protection (e.g., pigs). As a result, the effects of infarction on the chronic passive electrical properties of the myocardium may have been underestimated in the present study. For example, Legato (23) reported that in this canine model “infarcts were almost never completely homogeneous, but consisted of patches of fibrosis separated by grossly normal tissue”. Schwartzman et al. (36) found that the electrical impedance of inhomogeneous infarct, where myocytes and collagen bundles coexist, has a higher value (380 ± 60 \( \Omega \cdot \text{cm} \)) than that of densely infarcted myocardium (160 ± 30 \( \Omega \cdot \text{cm} \)). As such, although the impedance values obtained in this study for infarcted myocardium (e.g., 320 ± 46 \( \Omega \) at day 7 post-MI) are consistently higher than those previously reported in the literature for other species (e.g., 110 ± 30 \( \Omega \cdot \text{cm} \) by Cinca et al. (Ref. 8), 90 ± 29 \( \Omega \cdot \text{cm} \) by Fallert et al. (Ref. 14), 122 ± 26 \( \Omega \cdot \text{cm} \) by Salazar et al. (Ref. 34)), the higher infarct impedances are consistent with the observations of Legato (23) and the presence of a prominent coronary collateral density in dogs.

The chronic measurement of the myocardial passive electrical properties in vivo also has limitations. To track electrotonic changes following myocardial infarction, MEI electrodes were implanted chronically, and measurements were taken over several weeks. However, as pointed out by Grill and Mortimer (16) the electrical properties of the tissue surrounding implanted electrodes changes over time. MEI, as measured in this study, results from the combination of the true impedance of the myocardium and that of the electrode-tissue interface. As such, the results reported in the present study could be confounded not only by changes occurring over time at the electrode-tissue interface (e.g., electrode encapsulation) but also by polarization artifacts characteristic of this metal-electrolyte boundary. Similarly (although each animal served as its own control), any confounding electrotonic remodeling triggered by the electrode implantation/surgical procedure alone (i.e., besides the MI) could not be resolved, as no sham-operated (i.e., noninfarcted) controls were studied.

However, several studies demonstrate that chronic MEI measurements are stable and remain sensitive to pathologies known to alter electrotonic coupling in the myocardium (ischemia, see Ref. 12; rejection, see Refs. 15, 29). For example, both Grauhan et al. (15) and Pfitzmann et al. (29) measured MEI chronically in noninfarcted (sham) dogs by means of a two-pole technique similar to that employed in this study, reporting that after an initial decrease following implantation (2 days, as observed in the present study), impedance values were not only “completely stable” for up to 40 days, but also that polarization artifacts were negligible. Furthermore, the experiments in the present study were designed to mitigate the possible bias introduced by concomitant changes or artifacts at the electrode-tissue interface: e.g., relative comparisons were made between different regions of the heart via identical stimuli (currents, frequency) and electrodes (size, surface area), either over time for each animal (remote vs. infarct), or at a given time-point between different animals (S vs. R). Moreover, as described above, the bipolar current stimuli used to measure myocardial impedance were charge balanced. This technique reduces residual electrical charge at the tissue-metal interface, improving the signal-to-noise ratio and reducing polarization at the interface resistances of chronically implanted electrodes (20, 27). Therefore, it seems unlikely that the reported MEI differences between animals susceptible and resistant to VF reflected group-specific changes mediated by the electrode-tissue interface, the surgical procedure, or by polarization artifacts, rather than by the remodeling of electrotonic coupling (in remote myocardium) following infarction.

In summary, animals prone to ischemia-induced VF and characterized by prolonged QTc intervals following MI were found to have a wider electrotonic gradient (impedance difference) between infarcted and noninfarcted myocardium than was noted in those animals resistant to malignant arrhythmias. These differences were obvious as early as 7 days following MI (becoming progressively greater over time) and allowed the stratification of later arrhythmic susceptibility. Furthermore, this electrotonic (impedance) mismatch could provoke remodeling of ionic currents and could thereby lead to repolarization heterogeneities. Thus the results of the present study suggest that early passive electrical changes following MI could be used to assess later arrhythmia susceptibility. In addition, such electrotonic changes could be a mechanism contributing to the active-electrical remodeling in the ventricles following MI, creating a substrate that favors arrhythmia formation.

**GRANTS**

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