A Novel Surface Electrocardiogram Based Marker of Ventricular Arrhythmia Risk in Patients with Ischemic Cardiomyopathy

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Abstract

Background: Better sudden cardiac death risk markers are needed in ischemic cardiomyopathy (ICM). Increased heterogeneity of electrical restitution is an important mechanism underlying the risk of ventricular arrhythmia (VA). The aim was to develop and test a novel quantitative surface electrocardiogram based measure of ventricular arrhythmia risk in patients with ischemic cardiomyopathy, the Regional Restitution Instability Index (R2I2).

Methods and Results: R2I2, mean of standard deviation of residuals from the mean gradient for each ECG lead at a range of diastolic intervals, was measured retrospectively, from high resolution 12 lead ECG recorded during an electrophysiology study (EPS). Patient groups were: Study group: 26 ICM patients being assessed for implantable defibrillator; Control group: 29 supraventricular tachycardia patients undergoing EPS; Replication group: 40 further ICM patients. R2I2 was significantly higher in the Study group than Controls (mean±SEM: 1.09±0.06 vs. 0.63±0.04, $p<0.001$). Over median follow-up of 23months, 6/26 Study group patients had VA/death. R2I2 predicted VA/death independent of demographic factors, EPS result, left ventricular ejection fraction or QRS duration (Cox model, $p=0.029$). R2I2 correlated with peri-infarct zone assessed by cardiac magnetic resonance imaging ($r=0.51$, $p=0.024$). The Replication group replicated findings: R2I2 was significantly higher in 11/40 Replication patients experiencing VA (1.18±0.10 vs. 0.92±0.05, $p=0.019$). In combined analysis of ICM cohorts, R2I2>1.03 identified subjects with significantly higher risk of VA/death (43%) compared with R2I2 below 1.03 (11%) ($p=0.004$).

Conclusions: In this pilot study, we have developed a novel VA risk marker, R2I2, and shown that it correlated with a structural measure of arrhythmic risk and predicted risk of VA/death in patients with ICM. R2I2 may improve risk stratification and merits further evaluation.

Key Words:

death, sudden; electrical restitution; risk factors; implantable cardioverter defibrillator; electrocardiography

Abbreviations:

APD = action potential duration

CMR = cardiac magnetic resonance imaging

ECG = electrocardiogram

EPS = electrophysiological study

ICD = implantable cardioverter defibrillator

ICM = ischemic cardiomyopathy

PIZ = peri-infarct zone

QTp = QRS onset to T wave peak

QTe = QRS onset to T wave end

R2I2 = regional restitution instability index

SCD = sudden cardiac death

TpQ = T wave peak to QRS onset

TpTe = T wave peak to T wave end

VA = ventricular arrhythmia

Introduction

Sudden cardiac death (SCD) is responsible for over 3 million deaths per year worldwide.[1] Implantable cardioverter defibrillators (ICDs) are of proven benefit in preventing SCD. However, SCD risk assessment has considerable limitations despite 20 years of research.[2] In MADIT II and SCD-HeFT <40% of patients received appropriate ICD shock therapy during the first 4 years of follow up(3,4), while the majority of SCD occurs in the large population of people who, based on current evidence, are stratified as being at "low risk".[3]

Ventricular arrhythmia (VA) risk is known to be associated with heterogeneity of repolarisation.[4,5] Increasing evidence from computer and animal models now implicates increased heterogeneity of electrical restitution as an important arrhythmogenic mechanism.[6] Action potential duration (APD) restitution describes a myocardial property whereby APD is determined by the preceding diastolic interval. Body surface measurement of APD restitution has been shown to be possible in a small canine study using a single electrocardiogram (ECG) lead and has been correlated with epicardial unipolar electrograms.[7,8]

The aim of this retrospective study was to develop a new electrophysiological measure of electrical restitution heterogeneity using the surface ECG: the Regional Restitution Instability Index (R2I2), to assess its correlation with cardiac magnetic resonance (CMR) features of increased VA risk and to test and replicate its utility in predicting risk of VA/death in patients with ischemic cardiomyopathy (ICM) who were candidates for ICD therapy.[9–11]

Methods

Subjects

Ethical approval for this study was sought but deemed unnecessary by the Leicestershire Research Ethics Committee and the study protocol was approved by the Research and Development Office of

the University Hospitals of Leicester National Health Service Trust. The Primary Study group was identified by screening the Cardiology Department's audit databases for patients with a history of ICM who had undergone an electrophysiology study (EPS) with programmed electrical stimulation between 1st January 2005 and 31st July 2009 as part of clinical risk stratification for ICD implantation (in accordance with UK guidelines) and who had also had a CMR scan within 6 months of their EPS.[12] This identified 43 patients. EPS recordings were unavailable for 9 patients and 4 more patients were excluded because only 6 lead surface ECGs had been recorded. Of the 30 patients for whom EPS data was available 3 were excluded from analysis because of insufficient data due to non-captured beats and 1 could not be analysed because the drive cycle length was changed midway through the protocol. CMR data was then sought for the remaining 26 patients. Late gadolinium enhanced CMR images were not acquired for 3 patients because of difficulties gating (1) and breath holding (2) and 4 patients could not be analysed because of an incompatibility between the acquisition and peri-infarct zone analysis software. Late gadolinium enhanced CMR images were available for 19/26 patients.

A 30 patient Control group was selected from patients who had had an EPS for supraventricular tachycardia in 2010. Case matching was performed where possible on the basis of age and gender. Controls were excluded prior to data analysis if they had: insufficient surface ECG data recorded, an abnormal echocardiogram, atrial fibrillation, family history of SCD or diabetes mellitus (because of potential for associated autonomic dysfunction and silent ischemic heart disease). During data analysis one Control was excluded because it was apparent that the quadripolar catheter had moved from the right ventricular apex during the study. All Control subjects had normal left ventricular function as judged by visual assessment of 2D transthoracic echoes. The Replication ICM group was selected in the same way as the Primary Study group, except that only patients who had ICD implantation were selected and a CMR scan was not required; this identified 40 patients.

Electrophysiological Study

EP studies were performed as per the standard departmental protocol, which did not change for the duration of the study. Fasting subjects were studied with minimal sedation and with antiarrhythmic drug cessation 4-5 half-lives prior to the procedure. Data was recorded using a 6F quadripolar catheter advanced transvenously to the right ventricular apex; other catheters were positioned as appropriate to the clinical procedure. Standard 12 lead electrocardiograms were recorded using LabSystem Pro (BARD, Lowell) at 1 kHz sampling rate with a low pass filter set to 50Hz and high pass filter set to 0.01Hz. The study protocol used an 8 or 10 beat train at drive cycle lengths of 600ms and 400ms. A single extrastimulus protocol was followed with decrements of 20ms. If breakthrough beats were seen in the drive train the drive cycle length was reduced. The S1S2 coupling interval is the period between the last beat of the drive train and the first extrastimulus, the R2I2 was derived from measurements taken from the last S1 and the S2 beats. Programmed electrical stimulation was performed in the Primary Study and Replication cohorts; a modified Wellens protocol was used (two drive trains, drive cycle length 600ms and 400ms, at the right ventricular apex and one, drive cycle length 400ms, at the right ventricular outflow tract coupled with up to 3 extrastimuli with each drive train).[13] Monomorphic ventricular tachycardia of duration greater than 30 seconds or associated with hemodynamic compromise was recorded as positive; the test was otherwise recorded as negative.

Analysis of the R2I2

The surface electrocardiograms were exported at 16-bit digital resolution for analysis in custom software written in MATLAB (Mathworks, Natick) by WBN. The timing of the QRS onset and T wave peak were analysed automatically and all data points were manually verified by WBN, a senior electrophysiology research fellow. The T wave peak was chosen in preference to the end of the T wave because of the known difficulties in measuring the end of the T wave.[14] The R2I2 is derived from the QRS onset and T wave peak measurements. Intra and inter-operator reproducibility was

assessed using a representative sample of 242 paced ECG points from the dataset and was performed independently by two electrophysiology research fellows (WBN and PDB). Mean intra-operator variability for measurement of the QRS onset and T wave peak was 5.0ms (SD 7.6ms) vs. inter-operator 6.0ms (SD 7.9ms).

Data points were censored according to predetermined rules: 1. Breakthrough beat occurring after beat 6 of the drive train (146/1114 drive train beats censored), 2. Point indeterminate due to artefact, baseline wander or unclear morphology (536/11758 points). For each S1 S2 coupling interval the diastolic interval was taken as the period from T wave peak on the last beat of the drive train to the S2 QRS onset (TpQ), as shown in Figure 1; note the possibility for negative T wave peak to QRS onset interval as measured in this way. The body surface surrogate for the action potential duration was taken as the period from S2 QRS onset to the S2 T wave peak(QTp). These body surface surrogates were measured for each S2 performed at the right ventricular apex; where possible drive trains with drive cycle length 600ms were used but if not present or unusable due to breakthrough beats an alternative drive cycle length was selected.

The focus of the study was on regional electrical heterogeneity assessed by APD restitution gradient. For each lead of the surface ECG the QTp was plotted as a function of TpQ and gradients were fitted using 40ms overlapping least squares linear segments as described previously by Taggart et al. (Figure 2).[15] For each lead, in each 40ms segment, the difference of the gradient from the mean gradient in that 40ms segment was calculated. The standard deviation of these values was taken as a measure of APD heterogeneity in each lead. The mean of this was then taken as the R2I2 (no units). A small number of non-physiologically steep gradients result from points that have near or identical TpQ (measured to the nearest millisecond). To avoid skewing of the data, gradients exceeding ±10 were censored (1.5% of gradients).

Measurement of T wave peak to T wave end Interval and QT Dispersion

The exported ECGs were also used to measure non-paced T wave peak to T wave end intervals (TpTe) and QT dispersion. As described by Chugh et al. TpTe was measured in lead V5, or if V5 was not suitable due to noise or low amplitude V4 or V6 were used in that order.[16] Tend was taken to be the intersection of the tangent to the down slope of the T wave and the isoelectric line. If a U wave followed the T wave, the T-wave offset was measured as the nadir between the T and U waves. The QT interval was measured from the earliest onset of the QRS complex to the end of the T wave. The QT dispersion for each ECG recording was defined as the difference between the longest and shortest measured QT interval.[17]

Late Gadolinium Enhanced Cardiac Magnetic Resonance Imaging Protocol

The ICM patients in the Primary Study cohort underwent late gadolinium enhanced CMR as per Departmental protocol within a median of 35 days [inter-quartile range 105 days] of their EPS. Comprehensive CMR imaging was performed using a 1.5-T scanner (Siemens Magnetom, Avanto) with ECG triggering and a 6 channel phased array cardiac coil. After scout imaging, steady-state free precession (TrueFISP) cine images were acquired in 4, 3 and 2 chamber-views and a series of short axis slices were obtained covering the left ventricle from base to apex, with 1 slice every 10mm.[18] A gadolinium-based contrast agent (0.1-0.2mmol/kg) was administered intravenously as a bolus and late gadolinium enhanced images were obtained approximately 10 minutes later with the use of an inversion-recovery, segmented gradient echo sequence.[19,20]

CMR analysis

All analysis was performed offline blinded to patient details using commercially available software. Volumetric analysis was performed by manual tracing of endocardial and epicardial contours; left ventricular end-diastolic volume, end-systolic volume, stroke volume, left ventricular ejection fraction and left ventricular end-diastolic mass were calculated. Late gadolinium enhanced images

were analysed for scar and peri-infarct zone mass using a modification of the Schmidt et al technique.[11] All voxels with signal intensity greater than 50% of peak infarct core were recorded as scar. PIZ was defined as all pixels in the region of the myocardial infarction with signal intensity >2 standard deviations above mean intensity in an area of normal myocardium and below 50% of the peak intensity (Figure 3). CMR volumes and mass were indexed to height. Scar size is presented as percent of left ventricular mass and PIZ as mass in grams, percent of left ventricular mass and percent of infarct size.

Statistical analysis

Parametric data are expressed as mean ± standard error of the mean and analysed using Student's t-test; non-parametric data as median [inter-quartile range] and analysed using the Mann-Whitney U test. Proportions were analysed using a two sided Fisher's exact test. A receiver operator characteristic curve using the R2I2 was constructed in the Primary Study cohort for identification of the optimal R2I2 cut-off and for comparison in the Replication cohort. A Kaplan-Meier survival curve was drawn using this cut-off value, combining the Primary Study and Replication groups; comparison of cumulative endpoints was based on logarithmic transformations. Survival was recorded as time to first endpoint or the end of follow up. Pearson rank correlation was used to look for correlation between the R2I2 and PIZ and between age and R2I2 within the Control, Primary Study and Replication groups and between R2I2 and TpTe in the combined ICM cohorts. Spearman's rank correlation was used to look for correlation between R2I2 and QT dispersion in the combined ICM cohorts. A single Cox proportional hazards model was used to look for independence of the R2I2, programmed electrical stimulation result, left ventricular ejection fraction and QRS duration in the Primary Study group. A p-value <0.05 was considered statistically significant. All analyses were performed using STATA (StataCorp LP, College Station).

Results

The clinical characteristics, and relevant ECG characteristics including mean R212 values for the 26 Primary Study group patients, the 29 Controls and the 40 Replication group patients are summarised in Table 1. Given that the Controls underwent an EPS because of a different indication (supraventricular tachycardia), there were significant differences in their clinical characteristics and left ventricular ejection fraction compared to the two other groups. Individual level R2I2 values for subjects of all three groups are shown in Figure 4. R2I2 was significantly greater in the Primary Study group compared with the Controls (1.09±0.05 vs. 0.63±0.04 $p<0.001$). No correlation was seen between age or gender and the R2I2 within the Primary Study, Control or Replication groups.

Median follow up in the Primary Study group was 23 months [18] during which 6 patients reached the endpoint of VA/death: 3 VA and 4 deaths (1 patient had successful ICD therapy for VA and subsequently died). Following programmed electrical stimulation 12/26 Primary Study group patients had ICDs implanted and 2/4 deaths occurred in patients who did not have ICDs. Characteristics of the Primary Study Group patients partitioned on the basis of the primary endpoint are shown in Table 2. Patients who reached an endpoint had significantly higher mean R2I2 than those that did not (1.30±0.10 vs. 1.03±0.06 $p=0.037$). Age and programmed electrical stimulation result also trended towards an association with VA/death but were not correlated with R2I2. Cox multivariate analysis including the R2I2, programmed electrical stimulation result, left ventricular ejection fraction and QRS duration showed that the R2I2 was an independent predictor of VA/death ($p=0.029$).

The percentage of CMR PIZ was significantly associated with VA/death (15.6% [4.6] vs. 7.4% [8.0], $p=0.016$) and exhibited significant correlation with the R2I2 ($r=0.51$, $p=0.024$, Figure 5). Other CMR parameters such as scar percentage were also significantly associated with VA/death (22.0% [3.8] vs.

8.7% [13.5], p=0.042, Table 2). A receiver operating characteristic analysis of the Primary Study Group showed that a R2I2 cut-off of 1.03 provided the greatest discrimination between those who had a primary endpoint and those without an event during follow-up (area under curve of 0.792, Figure 6). Interestingly, none of the Control patients had a R2I2 value above 1.03 (Figure 4).

The Replication group did not differ significantly from the Primary Study group in the main clinical characteristics (Table 1). The Replication cohort subjects were selected on the basis of ICD implant; therefore the endpoint of VA was chosen. Median follow up in the Replication cohort was 40 months [22] during which 11 patients reached the primary endpoint of VA and 7 patients died. The Replication cohort replicated the findings of the Primary Study group: patients reaching the endpoint of VA had a significantly higher mean R2I2 (1.18±0.10 vs. 0.92±0.05 p=0.019). A R2I2 cut-off value of 1.03 identified 7/11 patients who suffered an endpoint, the receiver operating characteristic area under curve was 0.740.

In a combined analysis of the ICM subjects from the Primary Study and Replication groups, an R2I2≥1.03 identified subjects with a significantly higher risk of VA/death (43%, 13/30) compared with those with an R2I2 below 1.03 (11%, 4/36) (p=0.004, Fisher's exact). A survival curve of the combined ICM groups partitioned by an R2I2 value of 1.03 is shown in Figure 7; a highly significant difference (p=0.003, log rank) was observed. Side-by-side analysis of the R2I2 against TpTe and QT dispersion was performed using the combined ICM cohorts. In comparison of ICM patients experiencing VA/death versus ICM patients not reaching endpoint, neither TpTe (88.8 [32.7] vs. 77.2 [34.5], p=0.644) nor QT dispersion (66.3±32.8 vs. 60.0±25.9, p=0.428) were associated with endpoint. There was also no correlation between R2I2 and TpTe (r=-0.004, p=0.978) or between R2I2 and QT dispersion (r=-0.207, p=0.096).

Discussion

In this paper we report the development and characterisation of R2I2 as a potential prognostic marker in patients with ICM at risk of SCD. Despite considerable effort no definitive surface ECG marker of SCD risk has emerged to date. For example, microvolt T-wave alternans showed initial promise but in the 490 patient sub-study of SCD-HeFT, no significant difference in event free survival was found between microvolt T-wave alternans positive and negative patients (hazard ratio 1.24, 95% CI 0.60 to 2.59, P=0.56).[21] Another technique is the signal-averaged ECG which combines a series of QRS complexes to detect ventricular late potentials which are thought to correlate with VA risk. However, in CABG Patch, a 900 patient ICD prophylaxis trial, the signal-averaged ECG was unhelpful in identifying a high-risk group of patients.[22] R2I2 is a novel approach, founded on improved basic science understanding of VA,[6,23] which has the potential to be further refined and offer clinical utility.

In the Primary Study group the R2I2 was significantly higher in patients with ischemic cardiomyopathy who subsequently had a VA or died. This result was replicated using a Replication cohort of patients with ICM and the predefined endpoint of VA. The R2I2 electrical measure of risk showed a significant, moderate correlation with an anatomic measure of arrhythmic substrate, the extent of PIZ. Importantly R2I2 was independent of programmed electrical simulation result, left ventricular ejection fraction and QRS duration suggesting that it may add value to existing markers of VA / death risk.

Simulation studies of ventricular fibrillation suggest that it is initiated by breaking of the depolarisation wave into multiple wavelets that spread chaotically.[24] Wavelets are extinguished if they collide with each other or are blocked by refractory tissue. Hence, according to this paradigm ventricular fibrillation is maintained by the constant genesis of new wavelets. The electrical

restitution properties of the heart have been linked to increased susceptibility to wavelet breakdown and generation of ventricular fibrillation. The relationship of the APD and conduction velocity of a certain beat to the diastolic interval from the previous beat has been shown both mathematically to be important and biologically to support a link with arrhythmogenesis.[6,25] Regional heterogeneity of APD restitution adds to this electrical instability.[23] Chronic myocardial infarction creates a complex milieu of heterogeneities in these electrical restitution properties. First, there is an underlying normal variation in APD restitution that is seen from base to apex, epicardium to endocardium and left to right ventricle. Heterogeneous behaviour of APD restitution in different regions of the heart has been demonstrated using intracardiac catheters and also with an epicardial sock of electrodes in patients undergoing cardiac surgery, with significant differences seen between patients with ischemic heart disease and aortic valve disease.[23,26,27] Second, there is the anatomical heterogeneity related to interdigitation of infarcted and viable tissue and the effects of fibrosis on myofibril disarray and in particular conduction velocity restitution.[28–30] Finally there are the many sequelae of ischaemia and myocardial insufficiency, for example, on APD and conduction velocity restitution curves and on the secretion of nerve growth factor leading to cardiac nerve sprouting and sympathetic hyperinnervation.[30,31]

A high resolution 12 lead electrocardiogram describes the summation of myocyte electrical activity along specific vectors. Cardiac depolarisation flows in a complex 3 dimensional wave that is influenced by static factors such as myocardial scar and dynamic factors that exert their influence through APD and conduction velocity restitution. The diastolic interval, which itself has a spatial gradient, affects the excitability of individual myocytes, regional conduction velocity and also repolarisation. These effects alter the depolarisation wavefront, the consequence of this being dependent on whether the resulting wavelets propagate or are extinguished. In turn these effects will create spatial dispersion of repolarisation and potentially discordant alternans.[32,33] The R2I2 attempts to use the 12 lead ECG to measure regional manifestations of this irreducibly complex

cardiac choreography. Figure 8 shows an example of regional differences in repolarisation developing as the S1-S2 coupling interval shortens in a Primary Study group patient who went on to develop VA; these changes cause substantial heterogeneity in the restitution gradient and a high R2I2 (1.63).

The R2I2 uses the T wave peak as a surrogate for end repolarisation rather than the more typically used T wave end as detection of the former is more accurately determined than the latter. Antzelevitch et al. suggest that the T wave peak correlates with end repolarisation of epicardial cells with the difference between the Tpeak and Tend (TpTe) reflecting transmural heterogeneity. [34] Other authors consider the TpTe to reflect total left ventricular dispersion of repolarisation.[35] It may be that the QTp interval is as reflective of the intracardiac APD as the QT end interval; the measures corresponding to different components of the signal. Sundqvist et al. investigated the relationship between QTp and QTe during exercise in healthy subjects and found that the QTp and QTe decrease in parallel with increasing heart rate and that the majority of the decrease is in the QTp rather than the TpTe.[36] Haapalahti et al. have constructed QTp/heart rate slopes in control subjects and found them to be no different from QTe/heart rate slopes; they go on to find QTp autonomic responses in long QT syndrome 1 carriers to be more impaired than QTe responses.[37,38] Important further work is needed to clarify the relationship between the R2I2 and intracardiac heterogeneity of restitution. Clinical studies by Chugh et al. and others have shown the TpTe interval to be a potentially useful predictor of sudden cardiac death and we will be actively assessing this measure and the QTe interval in future work.[16]

For the electrophysiologist, the recent interest of the CMR community in assessing arrhythmia vulnerability through measurement of the PIZ is conceptually attractive. While this approach is still at an early stage, it has been shown in a study of 144 patients post myocardial infarction to be independent of left ventricular ejection fraction in its association with all cause mortality (p=0.005)

and it has also been found that PIZ predicted a positive programmed electrical stimulation test in 47 patients (p=0.015).[11] Importantly late gadolinium enhanced CMR anatomical data has been shown to correlate with intracardiac CARTO voltage data, histology and cellular biochemical pathology.[39–41] Limitations of PIZ quantification include spatial resolution of CMR (typically >1mm) the range of methods used to delineate it, the different ways in which measured PIZ is expressed and the tendency of PIZ research to use programmed electrical simulation result as an endpoint.[10,11,39] In the current study we found a statistically significant correlation between PIZ and the R2I2 that offers further support for our hypothesis that R2I2 is an appropriate measure of electrical heterogeneity and of SCD risk.

The Replication cohort provided independent support for the efficacy of the R2I2 in predicting VA risk. While this is encouraging, further work is needed to identify the potential role of the R2I2 in ICD risk stratification, especially in prospective studies. It would be interesting to perform side-by-side analysis of the R2I2 with other ECG markers of SCD, for example, QT variability and T-wave alternans. This being a retrospective study, analysis of comparators was limited but it is of note that there is no correlation between QT dispersion, a conceptually flawed measure of repolarisation heterogeneity, and the R2I2.[42] There has recently been interest in use of TpTe measurements with Chugh et al. presenting encouraging data.[16] In the current study, which represents a comparatively small cohort, TpTe values are higher in patients experiencing VA/death but the result does not approach significance. The R2I2 does not correlate with the TpTe; the indices are substantially different with R2I2 using TpQ and QTp to measure restitution gradient heterogeneity across the 12 lead ECG and TpTe measuring repolarisation heterogeneity in a single lead. However, the TpTe component of repolarisation is potentially important and as previously mentioned we will be investigating TpTe and QTe in future work. There is scope for refining R2I2 and improving its accuracy. For example, decreasing the S1S2 coupling interval in 10ms steps from 300ms could provide more detail in the steep portion of the curve. Work is also needed to validate the R2I2

against intracardiac data. Finally, whether determination of R2I2 could be undertaken entirely non-invasively using exercise or chronotropic medication to induce a range of heart rates needs to be tested.

Limitations

This is a small retrospective study and has several limitations. The R2I2 in its current form is invasive, requiring intracardiac pacing to create a spectrum of diastolic intervals. Only 19/26 patients' CMR scans were analysable. If the R2I2 data had been collected prospectively we would have used a longer drive train and repeated drive trains that had breakthrough beats in addition to performing a dynamic restitution protocol. Multivariate analysis was limited by the small numbers.

Conclusions

This pilot study suggests that the R2I2 is capable of extracting information on regional restitution heterogeneity and that this is increased in patients with ICM and associated with VA / death. Further work is needed to refine the technique and explore the correlation between the R2I2 and intracardiac APD and conduction velocity restitution and their clinical significance in patients with ICM.

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Disclosures

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References

1. Myerburg RJ Mitrani RM, Kessler KM, Castellanos A. IAJ. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol*. 1997; 80:10F-19F.

2. Kusmirek SL, Gold MR. Sudden cardiac death: the role of risk stratification. *Am Heart J*. 2007; 153:25-33.

3. Sanders GD, Al-Khatib SM, Berliner E, Bigger JT, Buxton AE, Califf RM, Carlson M, Curtis AB, Curtis JP, Domanski M, Fain E, Gersh BJ, Gold MR, Goldberger J, Haghighi-Mood A, Hammill SC, Harder J, Healey J, Hlatky MA, Hohnloser SH, Lee KL, Mark DB, Mitchell B, Phurrough S, Prystowsky E, Smith JM, Stockbridge N, Temple R. Preventing tomorrow's sudden cardiac death today: part II: Translating sudden cardiac death risk assessment strategies into practice and policy. *Am Heart J*. 2007; 153:951-9.

4. Han J, Moe GK. Nonuniform recovery of excitability in ventricular muscle. *Circulation Research*. 1964; 14:44-60.

5. Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation*. 1983; 67:1356-1367.

6. Clayton RH, Taggart P. Regional differences in APD restitution can initiate wavebreak and re-entry in cardiac tissue: a computational study. *BioMed Eng OnLine*. 2005; 4:54.

7. Fossa AA, Wisialowski T, Crimin K. QT prolongation modifies dynamic restitution and hysteresis of the beat-to-beat QT-TQ interval relationship during normal sinus rhythm under varying states of repolarization. *J Pharmacol Exp Ther*. 2006; 316:498-506.

8. Jiang H, Zhao D, Cui B, Lu Z, Lü J, Chen F, Bao M. Electrical restitution determined by epicardial contact mapping and surface electrocardiogram: its role in ventricular fibrillation inducibility in swine. *Journal of Electrocardiology*. 2008; 41:152-9.

9. Schuleri KH, Centola M, George RT, Amado LC, Evers KS, Kitagawa K, Vavere AL, Evers R, Hare JM, Cox C, McVeigh ER, Lima JAC, Lardo AC. Characterization of Peri-Infarct Zone Heterogeneity by Contrast-Enhanced Multidetector Computed Tomography: A Comparison With Magnetic Resonance Imaging. *J. Am. Coll. Cardiol.* 2009; 53:1699-1707.

10. 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.

11. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK, Gerstenblith G, Weiss RG, Marban E, Tomaselli GF, Lima JAC, Wu KC. Infarct Tissue Heterogeneity by Magnetic

Resonance Imaging Identifies Enhanced Cardiac Arrhythmia Susceptibility in Patients With Left Ventricular Dysfunction. *Circulation*. 2007; 115:2006-2014.

12. National Institute for Health and Clinical Excellence. January 2006. Implantable cardioverter defibrillators for arrhythmias Review of Technology Appraisal 11. TA95. London: National Institute for Health and Clinical Excellence. Available from: http://guidance.nice.org.uk/TA95/guidance/pdf/English.

13. Zehender M, Brugada P, Geibel A, Waldecker B, Stevenson W, Wellens HJJ. Programmed electrical stimulation in healed myocardial infarction using a standardized ventricular stimulation protocol. *Am J Cardiol*. 1987; 59:578-585.

14. Murray A, McLaughlin NB, Bourke JP, Doig JC, Furniss SS, Campbell RW. Errors in manual measurement of QT intervals. *Br Heart J*. 1994; 71:386-390.

15. Taggart P, Sutton P, Chalabi Z, Boyett MR, Simon R, Elliott D, Gill JS. Effect of adrenergic stimulation on action potential duration restitution in humans. *Circulation*. 2003; 107:285-9.

16. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, Gunson K, Jui J, Chugh SS. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2011; 4:441-7

17. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *British Heart Journal*. 1990; 63:342-4.

18. Petersen SE, Jung BA, Wiesmann F, Selvanayagam JB, Francis JM, Hennig J, Neubauer S, Robson MD. Myocardial tissue phase mapping with cine phase-contrast mr imaging: regional wall motion analysis in healthy volunteers. *Radiology*. 2006; 238:816-826.

19. Simonetti OP, Kim RJ, Fieno DS, Hillenbrand HB, Wu E, Bundy JM, Finn JP, Judd RM. An improved MR imaging technique for the visualization of myocardial infarction. *Radiology*. 2001; 218:215-223.

20. Selvanayagam JB, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, Neubauer S. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation*. 2004; 110:1535-1541.

21. Gold MR, Ip JH, Costantini O, Poole JE, McNulty S, Mark DB, Lee KL, Bardy GH. Role of microvolt T-wave alternans in assessment of arrhythmia vulnerability among patients with heart failure and systolic dysfunction: primary results from the T-wave alternans sudden cardiac death in heart failure trial substudy. *Circulation*. 2008; 118:2022-8.

22. Bigger JT. Prophylactic Use of Implanted Cardiac Defibrillators in Patients at High Risk for Ventricular Arrhythmias after Coronary-Artery Bypass Graft Surgery. *N Engl J Med*. 1997; 337:1569-1575.

23. Ng GA, Mantravadi R, Walker WH, Ortin WG, Choi BR, de Groat W, Salama G. Sympathetic nerve stimulation produces spatial heterogeneities of action potential restitution. *Heart Rhythm*. 2009; 6:696-706.

24. Chen PS, Garfinkel A, Weiss JN, Karagueuzian HS. Spirals, chaos, and new mechanisms of wave propagation. *PACE*. 1997; 20:414-21.

25. Ng GA, Brack KE, Patel VH, Coote JH. Autonomic modulation of electrical restitution, alternans and ventricular fibrillation initiation in the isolated heart. *Cardiovasc Res*. 2007; 73:750-760.

26. Yue AM, Franz MR, Roberts PR, Morgan JM. Global Endocardial Electrical Restitution in Human Right and Left Ventricles Determined by Noncontact Mapping. *J. Am. Coll. Cardiol.* 2005; 46:1067-1075.

27. Nash MP, Bradley CP, Paterson DJ. Imaging Electrocardiographic Dispersion of Depolarization and Repolarization During Ischemia: Simultaneous Body Surface and Epicardial Mapping. *Circulation*. 2003; 107:2257-2263.

28. Derksen R, van Rijen HVM, Wilders R, Tasseron S, Hauer RNW, Rutten WLC, de Bakker JMT. Tissue Discontinuities Affect Conduction Velocity Restitution: A Mechanism by Which Structural Barriers May Promote Wave Break. *Circulation*. 2003; 108:882-888.

29. Cao J-M, Qu Z, Kim Y-H, Wu T-J, Garfinkel A, Weiss JN, Karagueuzian HS, Chen P-S. Spatiotemporal Heterogeneity in the Induction of Ventricular Fibrillation by Rapid Pacing: Importance of Cardiac Restitution Properties. *Circ Res.* 1999; 84:1318-1331.

30. Dilly SG, Lab MJ. Electrophysiological alternans and restitution during acute regional ischaemia in myocardium of anaesthetized pig. *Journal of Physiology*. 1988; 402:315-333.

31. Zhou S, Chen LS, Miyauchi Y, Miyauchi M, Kar S, Kangavari S, Fishbein MC, Sharifi B, Chen P-S. Mechanisms of Cardiac Nerve Sprouting After Myocardial Infarction in Dogs. *Circ Res.* 2004; 95:76-83.

32. Gilmour Jr. RF, Gelzer AR, Otani NF. Cardiac electrical dynamics: maximizing dynamical heterogeneity. *J Electrocardiol*. 2007; 40:S51-5.

33. Watanabe MA, Fenton FH, Evans SJ, Hastings HM, Karma A. Mechanisms for discordant alternans. *J Cardiovasc Electrophysiol*. 2001; 12:196-206.

34. Antzelevitch C, Shimizu W, Yan GX, Sicouri S, Weissenburger J, Nesterenko VV, Burashnikov A, Di Diego J, Saffitz J, Thomas GP. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electr*. 1999; 10:1124-52.

35. Opthof T, Coronel R, Janse MJ. Is there a significant transmural gradient in repolarization time in the intact heart?: Repolarization Gradients in the Intact Heart. *Circ Arrhythm Electrophysiol.* 2009; 2:89-96.

36. Sundqvist K, Sylvén C. Cardiac repolarization properties during standardized exercise test as studied by QT, QT peak and terminated T-wave intervals. *Clin Physiol.* 1989; 9:419-25.

37. Haapalahti P, Viitasalo M, Perhonen M, Mäkijärvi M, Väänänen H, Oikarinen L, Hekkala A-M, Salorinne Y, Swan H, Toivonen L. Ventricular repolarization and heart rate responses during cardiovascular autonomic function testing in LQT1 subtype of long QT syndrome. *Pacing Clin Electrophysiol.* 2006; 29:1122-9.

38. Haapalahti P, Viitasalo M, Perhonen M, Väänänen H, Mäkijärvi M, Swan H, Toivonen L. Comparison of QT peak and QT end interval responses to autonomic adaptation in asymptomatic LQT1 mutation carriers. *Clin Physiol Funct. Imaging*. 2011; 31:209-14.

39. Amado LC, Gerber BL, Gupta SN, Rettmann DW, Szarf G, Schock R, Nasir K, Kraitchman DL, Lima JAC. 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.

40. Codreanu A, Odille F, Aliot E, Marie P-Y, Magnin-Poull I, Andronache M, Mandry D, Djaballah W, Regent D, Felblinger J, de Chillou C. Electroanatomic Characterization of Post-Infarct Scars: Comparison With 3-Dimensional Myocardial Scar Reconstruction Based on Magnetic Resonance Imaging. *J. Am. Coll. Cardiol.* 2008; 52:839-842.

41. Hu Q, Wang X, Lee J, Mansoor A, Liu J, Zeng L, Swingen C, Zhang G, Feygin J, Ochiai K, Bransford TL, From AH, Bache RJ, Zhang J. Profound bioenergetic abnormalities in peri-infarct myocardial regions. *Am J Physiol Heart Circ Physiol*. 2006; 291:H648-57

42. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J. Am. Coll. Cardiol.* 2000; 36:1749-1766.

Figure Legends

Figure 1. Technique for measurement of diastolic interval surrogate: T wave peak to QRS onset (TpQ) and action potential duration surrogate: QRS onset to T wave peak (QTp). A. When an S2 arrives after the T wave peak the TpQ and QTp are measured as shown on the left of the diagram. B. If the S2 occurs before the T wave peak the TpQ is effectively negative. In this case it is measured by subtracting the QTp_{-1} interval (QTp for the last drive cycle beat) from the QQ, in the example above this would give a TpQ close to zero.

Figure 2. Explanation of the R2I2 calculation and demonstration of the body surface restitution relation. A. Plot of QRS onset to T wave peak (QTp) against T wave peak to QRS onset (TpQ) for representative ECG leads: I (lateral), II (inferior) and V2 (anterior) to explain the Regional Restitution Instability Index (R2I2) calculation in a typical study patient. For each lead, the QTp / TpQ gradient (least squares regression) was calculated over a 40 ms segment of TpQ range. This segment was then scanned over the range of TpQ with available data to produce gradients at 10 ms intervals (example gradients are shown for lead V2). The difference of the gradient from the mean gradient in each 40ms segment was calculated. The standard deviation of these values was taken as a measure of action potential duration restitution heterogeneity in each lead. The mean of this was then taken as the R2I2. B. Mean data points for the individual ECG leads from the combined ICM cohorts were calculated and an area graph of the standard error of the mean has been plotted for the same representative leads as in A.

Figure 3. Endocardial and epicardial borders are drawn; then a large representative area of “normal myocardium” and a small area of “peak scar” are selected as shown in A. Software analysis identifies all voxels with signal intensity >2 standard deviations above “normal myocardium” mean

intensity and voxels with signal intensity >50% of the "peak scar" are subtracted from this to obtain the peri-infarct zone. Identified voxels that are not in the region of an infarct are discarded.

Figure 4. Scatter plot for Regional Restitution Instability Index (R2I2) in Control, Primary Study and Replication groups, the line indicates the value chosen to separate a positive and negative R2I2 result and filled squares identify patients who reached the endpoints of ventricular arrhythmia / death (Primary Study group) or ventricular arrhythmia (Replication group) during follow up.

Figure 5. Plot of Regional Restitution Instability Index (R2I2) against peri-infarct zone (PIZ) in each of the 19 Primary Study group patients for whom paired data was available. Lines are drawn at the optimal cut-off values for both parameters. A least-squares regression line demonstrates significant correlation ($r= 0.51$, $p=0.024$).

Figure 6. Receiver operating characteristic curve for Regional Restitution Instability Index (R2I2) in Primary Study group: ventricular arrhythmia (VA) / death vs. ventricular arrhythmia free survival.

Figure 7. Kaplan-Meier survival curve for combined Primary Study and Replication groups showing a significantly higher rate of ventricular arrhythmia in a "high risk" group with Regional Restitution Instability Index (R2I2) >=1.03 compared with the "low risk" group with R2I2 < 1.03 ($p=0.003$, log rank test).

Figure 8. Diagram shows the last beat of the drive train and the S1 S2 coupling interval at 400, 380, 360 and 340ms for leads V2 and III. Demonstration of regional heterogeneity in repolarisation: little change is seen in V2 and the QRS onset to T wave peak (QTp) is stable, while lead III is seen to fragment with two peaks and variable QTp. This Primary Study group patient had an R2I2 of 1.63 and had VA during follow up.

Table 1. Main characteristics of the Primary Study, Control and Replication groups.

Variable	Primary Study Group (n=26)	Controls (n=29)	p	Replication Group (n=40)
Age (years)	66.2±1.9	45.3±2.5	<0.001	66.2±1.5
Sex (% male)	96	59	0.001	88
QRSD (ms)	107±3.8	104±3.7	0.63	120±4.9
LVEF (%)	29±2.7	64±1.0	<0.001	30-35%*
R2I2	1.09±0.06	0.63±0.04	<0.001	0.99±0.05

Parametric data are expressed as mean±standard deviation. (Abbreviations: QRSD QRS duration, LVEF left ventricular ejection fraction, R2I2 regional restitution instability index). *The Replication group LVEF measurements were obtained from clinical echocardiogram reports that specify a LVEF range.

Table 2. Baseline characteristics of the Primary Study group split by endpoint.

Variable	No VA / Death (n=20)	VA / Death (n=6)	p
Age (years)	64.5±2.2	71.8±3.5	0.120
Sex (% male)	95	100	…
QRSD (ms)	107±4.7	108±6.3	0.889
LVEF (%)	30.5±3.3	25.3±3.0	0.414
PES result (positive/total)	7/20	4/6	0.348
R2I2	1.03±0.06	1.30±0.10	0.037
EDV index (ml/cm)	1.43±0.12	1.44±0.23	0.958
SV index (ml/cm)	0.37±0.04	0.39±0.06	0.790
Mass index(gm/cm)	0.80±0.04	0.72±0.04	0.342
Height (cm)	170±1.7	173±2.2	0.383
Follow up (months)	24[17]	19 [12]	0.273
PIZ %*	7.4[8.0]	15.6[4.6]	0.016
PIZ mass (gm)*	7.4[7.9]	20.1 [7.5]	0.033
PIZ mass/Scar Mass %*	66[64]	72[26]	0.643
Scar % LV mass*	8.7[13.5]	22.0[3.8]	0.042

Parametric data are expressed as mean ± standard deviation; non-parametric data as median [inter-quartile range]. (Abbreviations: QRSD QRS duration, LVEF left ventricular ejection fraction, PES programmed electrical stimulation, R2I2 regional restitution instability index, EDV left ventricular end diastolic volume, SV stroke volume, PIZ peri-infarct zone). *CMR peri-infarct zone data was available for 19/26 patients.

Figures

Figure 1

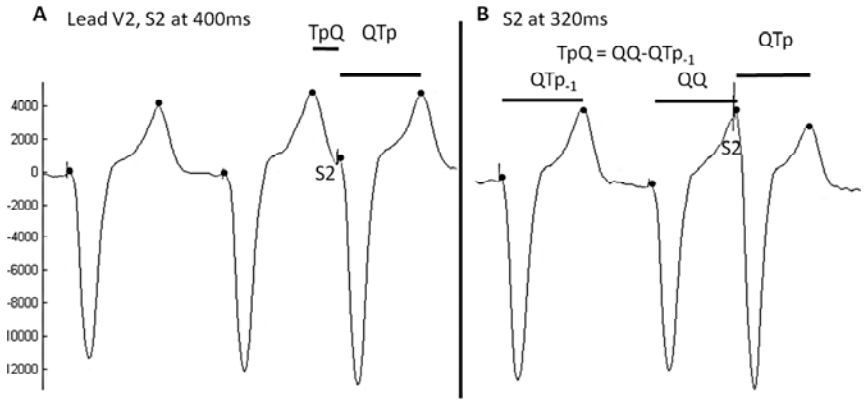

Figure 2

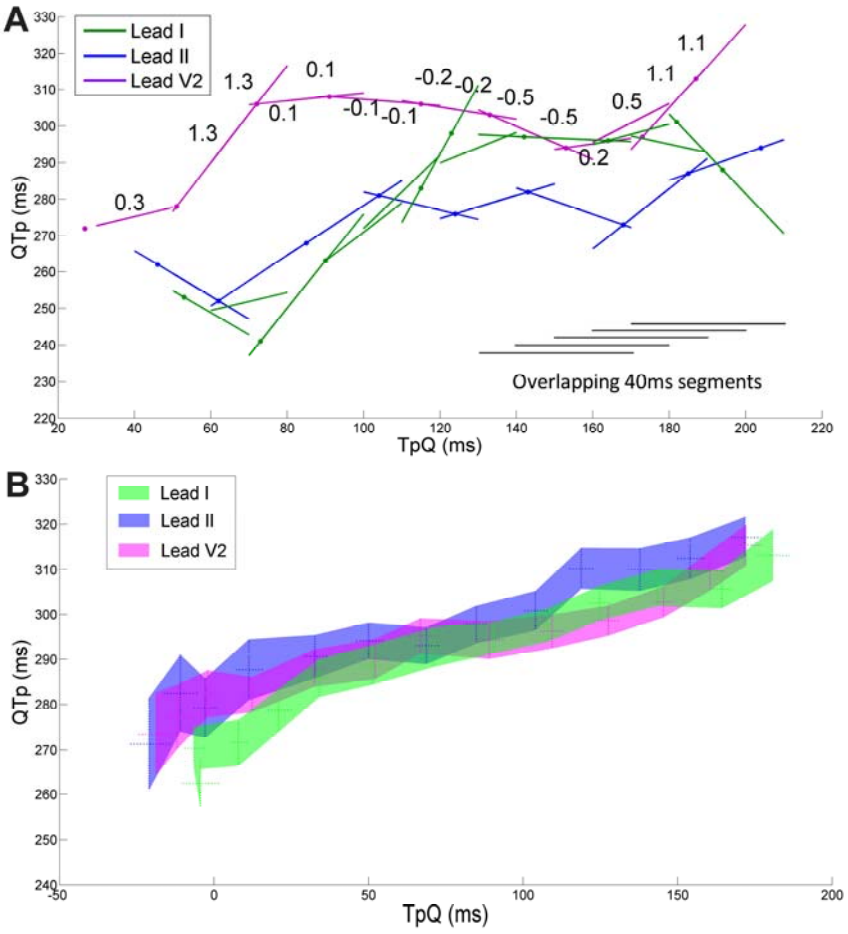
A
Lead I
Lead II
Lead V2
1.3
0.1
-0.2
-0.2
-0.5
1.1
1.1
0.5
1.3
0.1
-0.1
-0.1
-0.5
0.2
0.3
Overlapping 40ms segments
QTp (ms)
TpQ (ms)
B
Lead I
Lead II
Lead V2
QTp (ms)
TpQ (ms)

Figure 3

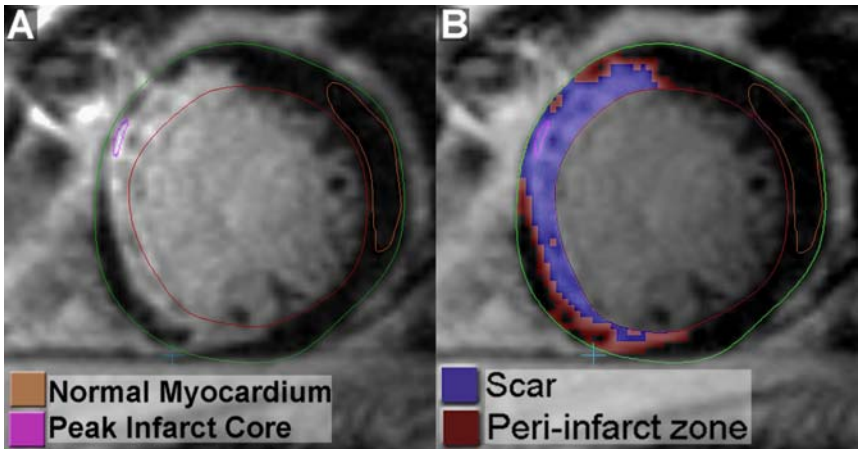
A
B
Normal Myocardium
Peak Infarct Core
Scar
Peri-infarct zone

Figure 4

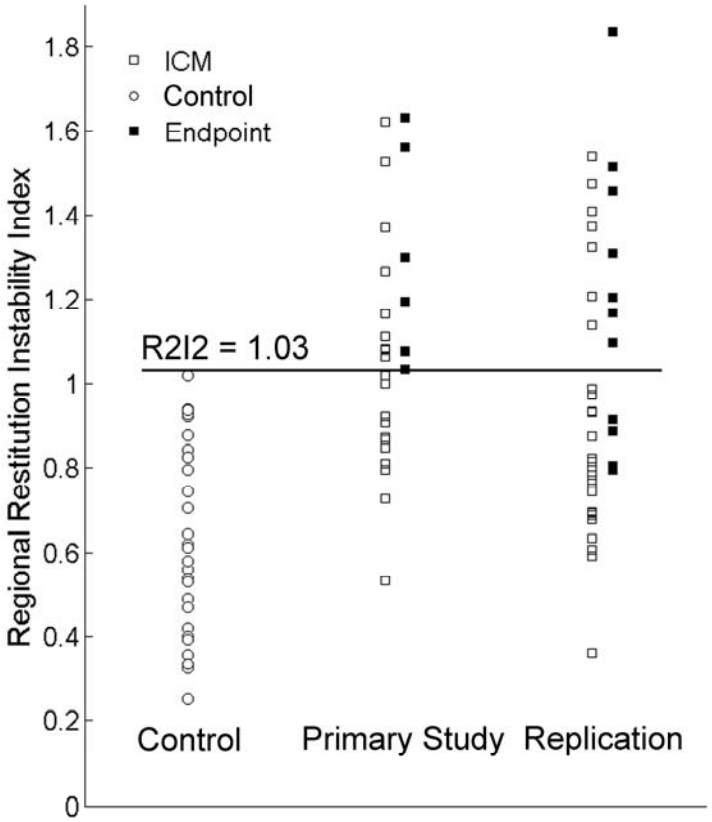
ICM
Control
Endpoint
R2I2 = 1.03
Regional Restitution Instability Index
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Control
Primary Study
Replication

Figure 5

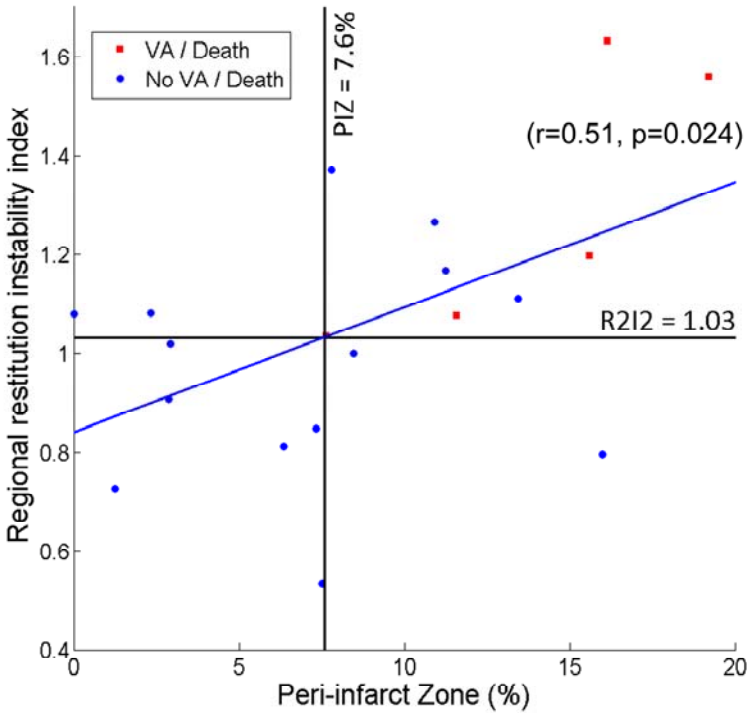
VA / Death
No VA / Death
PIZ = 7.6%
(r=0.51, p=0.024)
R2I2 = 1.03
Regional restitution instability index
Peri-infarct Zone (%)
1.6
1.4
1.2
1
0.8
0.6
0.4
0
5
10
15
20

Figure 6

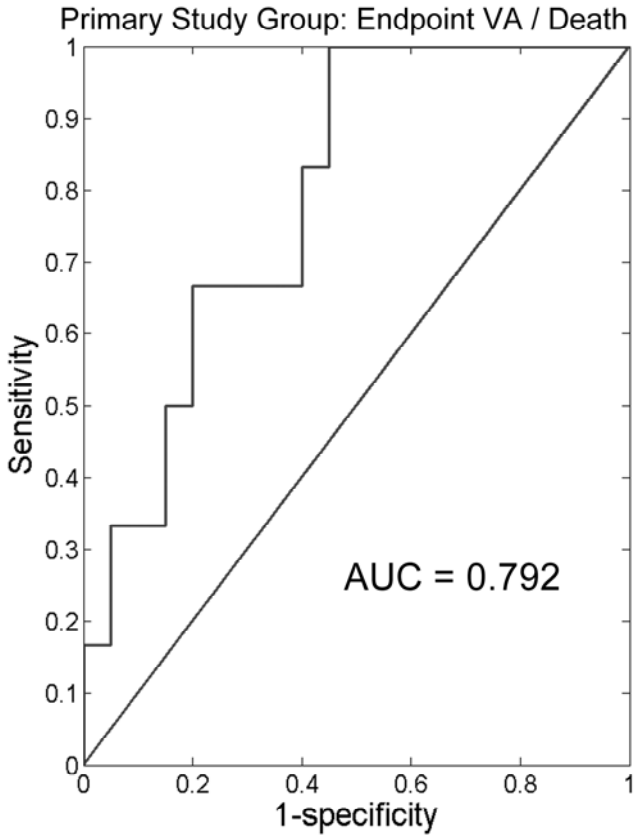
Primary Study Group: Endpoint VA / Death
Sensitivity
1-specificity
AUC = 0.792
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.2
0.4
0.6
0.8
1

Figure 7

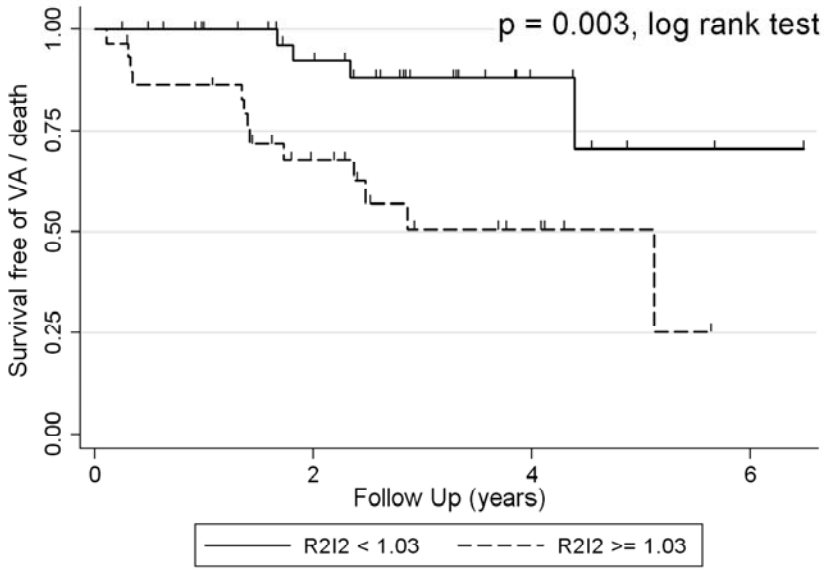
p = 0.003, log rank test
Survival free of VA / death
0.00
0.25
0.50
0.75
1.00
0
2
4
6
Follow Up (years)
R2I2 < 1.03
R2I2 >= 1.03

Figure 8