High mean entropy calculated from cardiac MRI texture analysis is associated with anti-tachycardia pacing failure

Short Title: Mean entropy and ATP failure

Authors:

Justin Gould MBBS[1,2]–corresponding author

Bradley Porter MBChB[1,2]

Baldeep S Sidhu BM[1,2]

Simon Claridge PhD [1,2]

Zhong Chen PhD[1,2]

Benjamin J Sieniewicz MBChB[1,2]

Mark Elliott MBBS[1,2]

Vishal Mehta MBBS[1,2]

Fernando O Campos PhD[2]

Martin J Bishop DPhil[2]

Caroline Mendonca Costa PhD[2]

Steven Niederer DPhil[2]

Balaji Ganeshan PhD[3]

Reza Razavi MD[1,2]

Amedeo Chiribiri PhD FSCMR[1,2]

Christopher A Rinaldi MD FHRS[1,2]

Affiliations:

[1]Cardiology Department, Guy's and St Thomas' NHS Foundation Trust, London, UK

[2]School of Biomedical Engineering and Imaging Sciences, King's College London, UK

[3]Institute of Nuclear Medicine, University College London, UK

Correspondence:

[1]Cardiology Department, South Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE17EH, UK

+44(0)2071887188;justin.s.gould@kcl.ac.uk

Word count: 3463

Disclosures

This work was supported by the Wellcome/Engineering and Physical Sciences Research Council Centre for Medical Engineering[WT203148/Z/16/Z]. Outside of the submitted work JG has received project funding from Rosetrees Trust, JG and BP have received fellowship funding from Abbott, BSS has received fellowship funding from Medtronic and BJS has received a British Heart Foundation project grant. MJB acknowledges the Medical Research Council through a New Investigator Research Grant[MR/N011007/1]. BG is a director and part-time employee of Feedback Medical LTD and shareholder of Feedback PLC (Cambridge, UK), who develops and commercializes TexRAD software described in this manuscript. AC has received research support outside the submitted work from Philips Healthcare and Siemens Healthineers. CAR receives research funding and/or consultation fees from Abbott, Medtronic, Boston Scientific, Spectranetics and MicroPort outside of the submitted work.

Abstract

Background: Anti-tachycardia pacing (ATP), which may avoid unnecessary ICD shocks, does not always terminate ventricular arrhythmias (VAs). Mean entropy calculated using cardiac magnetic resonance texture analysis (CMR-TA) has been shown to predict appropriate ICD therapy. We examined whether scar heterogeneity, quantified by mean entropy, is associated with ATP failure and explore potential mechanisms using computer modelling.

Methods: A sub-analysis of 114 patients undergoing CMR-TA where the primary endpoint was delivery of appropriate ICD therapy (ATP or shock therapy) was performed. Patients receiving appropriate ICD therapy (n=33) were dichotomized into 'successful ATP' versus 'shock therapy' groups. *In silico* computer modelling was used to explore underlying mechanisms.

Results: A total of 16/33 (48.5%) patients had successful ATP to terminate VA and 17/33 (51.5%) required shock therapy. Mean entropy was significantly higher in the shock versus successful ATP group (6.1±0.5 vs. 5.5±0.7, p=0.037). Analysis of patients receiving ATP (n=22) showed significantly higher mean entropy in the 6/22 patients that failed ATP (followed by rescue ICD shock) compared to 16/22 that had successful ATP (6.3±0.7 vs. 5.5±0.7, p=0.048). Computer modelling suggested inability of the paced wavefront in ATP to successfully propagate from the electrode site through patchy fibrosis as a possible mechanism of failed ATP.

Conclusions: Our findings suggest lower scar heterogeneity (mean entropy) is associated with successful ATP whereas higher scar heterogeneity is associated with more aggressive VAs unresponsive to ATP requiring shock therapy which may be due to inability of the paced wavefront to propagate through scar and terminate the VA circuit.

Keywords

Ventricular arrhythmia; scar heterogeneity; entropy; ATP failure; ICD risk stratification

Introduction

Implantable cardioverter-defibrillators (ICDs) reduce mortality from ventricular arrhythmias (VAs) but are associated with complications including inappropriate shocks.[1] Mortality rates are higher in patients receiving ICD shock therapy[2,3] and may lead to heart failure progression.[4] A recent large meta-analysis including almost 200,000 patients demonstrated mortality was greater for appropriate compared to inappropriate shock therapy but both were associated with reduced survival with multiple shocks predicting worse outcomes.[3,5] Anti-tachycardia pacing (ATP) may terminate ventricular tachycardia (VT) avoiding shock therapy and represents an effective treatment of some but not all VA.[6] ATP has been shown to reduce unnecessary shocks and inappropriate shocks[2] and is therefore important in preserving ICD battery longevity and reducing the psychological impact of ICD shocks.[7] Furthermore, Sweeney et al. demonstrated ATP failure with subsequent ICD shocks was 18 times higher in patients who died at follow-up suggesting failed ATP therapy may be a marker of substrate severity.[5,8] Predicting patients more likely to have failed ATP and require shock therapy may therefore be of significant benefit in pre-counselling patients, ICD selection and programming. Quantifying microchannels within surviving areas of scar tissue (responsible for re-entrant VA) may be possible using cardiac magnetic resonance texture analysis (CMR-TA) to quantify scar heterogeneity from late gadolinium enhancement (LGE) imaging.[9] We previously demonstrated mean entropy, calculated using CMR-TA, predicts appropriate ICD therapy in patients undergoing ICD implantation.[9] In this current work, we hypothesized that scar heterogeneity (mean entropy) would be higher in patients that received appropriate ICD shock therapy compared to those that received successful ATP. We used scar heterogeneity analysis to predict ICD shock therapy by performing a sub-analysis on patients with mixed etiology cardiomyopathy that received appropriate ICD therapy (ATP or shock therapy). Additionally, we hypothesized that scar heterogeneity would be higher in patients with failed ATP compared to those receiving successful ATP and used *in silico* modelling based on CMR-derived scar geometry to explore potential mechanisms why ATP might fail.

Methods

Study population

Between May 2011-January 2013, consecutive patients undergoing primary and secondary prevention ICD implantation were prospectively enrolled from two tertiary centers. We previously reported the utility of mean entropy to predict appropriate ICD therapy (combined ATP/shock therapy) in this cohort.[9] All patients had heart failure and/or antiarrhythmic therapies optimized and underwent coronary angiography and CMR assessment prior to device implantation. Standard criteria defined ischemic cardiomyopathy (ICM); prior myocardial infarction; epicardial coronary artery stenosis >75%; or coronary revascularization with a scar pattern consistent with myocardial infarction on CMR. Absence of these criteria defined non-ischemic cardiomyopathy NICM. Primary prevention was defined as ICD implantation to reduce sudden cardiac death in at-risk individuals who had not yet experienced a life-threatening VA or aborted cardiac arrest. Secondary prevention implants were in those patients who had already experienced a life-threatening VA or aborted cardiac arrest where no reversible cause was identified or treatable. The study protocol was approved by the South East London Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

CMR protocol and analysis

Our CMR protocol has been previously detailed.[9–11] CMR imaging was performed using a 1.5 Tesla (T) scanner with a 32-channel cardiac phased array surface coil (Philips Healthcare, Best, The Netherlands). Following a look-locker acquisition to identify optimum inversion time, an inversion-recovery gradient-echo pulse sequence was used to acquire a stack of short axis slices 10-15 minutes after Gadobutrol 0.2mmol/kg body weight contrast injection (Bayer-Schering Pharma, Berlin, Germany) for LGE assessment from which CMR-TA was performed. Two independent CMR experts blinded to the study endpoint evaluated the LGE images separately and resolved any discrepancies mutually.

Cardiac Magnetic Resonance Tissue Analysis (CMR-TA)

We have previously described our CMR-TA methodology.[9,12] Patients without visible scar were excluded from analysis. All areas of visible scar throughout the short axis left ventricular (LV) stack were manually segmented and analysed using TexRAD research software (Feedback Medical LTD, Cambridge, UK). Manual

segmentation was performed by a CMR-trained cardiologist blinded to patient identifiers and study endpoints. CMR-TA was performed as previously described with regions of interest drawn around all visible LGE, carefully incorporating scar borders and excluding surrounding myocardium.[9,12] CMR-TA was performed using a Laplacian of Gaussian band-pass filter to extract and augment image features corresponding to a medium scar texture (spatial scale filter of 4mm radius), from which histogram analysis of pixel intensity calculated mean entropy as previously described.[9,12]

Follow-up and primary endpoint

All patients underwent implantation of an ICD or cardiac resynchronization therapy defibrillator (CRT-D). A standardized program for appropriate VA detection and ICD therapy with ATP or shock therapy was used as previously described.[9–11] VAs >170 beats/minute (detection count >16 intervals) were treated with ATP initially (x3 burst escalating to x3 ramp protocols where required), followed by shock therapy for unsuccessful ATP. First-line shock therapy was used for VAs >210 beats/min (detection count 24/30 intervals). Patients were followed up at three-month intervals by experienced cardiac physiologists who evaluated recorded events with an electrophysiologist, both blinded to the CMR data.

A total of 114 patients underwent CMR-TA in the original study where the primary endpoint was delivery of appropriate ICD therapy. In the present study, we performed a retrospective sub-analysis of the 33 patients receiving appropriate ICD therapy and dichotomized patients into those that received appropriate ICD shock therapy versus successful ATP (without shock therapy) and evaluated whether mean entropy predicted ICD shock therapy. We also evaluated whether mean entropy values were higher in patients that received unsuccessful ATP (and required rescue shock therapy) versus those that received successful ATP.

Computer modelling of left ventricular scar

In silico computer modeling was performed to explore potential mechanistic explanations underlying the clinical findings using a simplified two-dimensional finite element geometry representing an idealized scar with a protected diastolic isthmus with mesh resolution 200um (Figures 1A,1D). The infarct region comprised two semi-circular segments representing necrotic scar, transcended by a 4mm wide conducting isthmus. The

necrotic scar was set to be insulating with no-flux boundary conditions on the intracellular potential. Patchy fibrosis, of variable density, was included in the protected isthmus by randomly replacing myocytes by non-conducting fibrotic tissue. For each density (*dFib*), 10 different topologies, with slightly different (random) fibrosis distributions were generated. Figure 1 shows one specific topology of fibrosis distribution for an isthmus containing 10%(A) and 50%(D) fibrosis. Tissue electrophysiology was represented by the monodomain model, with cellular dynamics represented by the ten Tusscher ventricular cell model.[13] Additional simulations with impaired excitability in the isthmus were conducted by reducing the maximum channel conductance of the fast sodium current (INa). Simulations were conducted using Cardiac Arrhythmia Research Package.[14] Tissue was stimulated *in silico* at a site proximal to the isthmus mouth (entry site of potential VT re-entry circuit), as shown in Figure 1B. Three steady-state stimuli were delivered at a basic cycle length of 500ms; followed by a premature stimulus at a coupling interval of 320ms delivered at the same location. The standard definition of Shannon entropy was used to define an effective entropy score within the isthmus region for the cases of differing fibrosis densities.

Statistical analysis

Discrete data are presented as n values with corresponding percentages in parentheses and continuous data as mean±1SD. Time to events are shown as median[interquartile range]. Discrete demographic variables were compared using Fisher's exact test. Normally distributed data were compared with an independent samples t-test. Non-normally distributed data were compared using Wilcoxon signed-rank testing. The first episode of appropriate ICD therapy defined the index event. Univariable and multivariable Cox proportional hazard regression models were performed to determine predictors of ICD shock therapy in patients receiving appropriate ICD therapy. Statistically significant variables at univariable analysis and important clinical covariates were used as the basis for multivariable analysis. To avoid overfitting, multivariable analysis was restricted to four variables. Hazard ratios for continuous variables represent the relative increased risk of endpoint per unit increase (e.g. per one unit increase in mean entropy). For all tests, $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences (Macintosh V 24.0.0.1, 2017, Armonk, NY, IBM Corporation).

Results

Of the 33 patients receiving appropriate ICD therapy, 17/33 (51.5%) received successful ICD shock therapy and 16/33 (48.5%) had successful ATP without requiring shocks. Median time to first appropriate ICD therapy was 329[116-529] days and was similar between those that received shock therapy vs. successful ATP therapy (290[89-357] vs. 388[143-593], p=0.154). Patients receiving appropriate ICD shock therapy had a significantly higher mean entropy value compared to those that had successful ATP only (6.1±0.5 vs. 5.5±0.7, p=0.037). Otherwise, patient characteristics were balanced between groups (Table 1). In the group that received successful shock therapy (n=17), 11 patients were treated for ventricular fibrillation (VF), 4 patients had failed ATP during charging for fast VT in the VF zone and a further 2 patients had failed ATP for VT at 190bpm and 210 bpm respectively. In the successful ATP group (n=16), VAs fell within the device VT zone.

Predictors of ICD shock therapy

Univariable analysis showed only secondary prevention and mean entropy were associated with ICD shock therapy (Figure 2A). In a multivariable Cox proportional hazard regression model adjusting for significant and important clinical covariates (LV ejection fraction≤35%, ICM and secondary prevention), mean entropy was an independent predictor of ICD shock therapy (HR 3.50, 95% CI 1.29-9.54, p=0.014) as was secondary prevention (Figure 2B).

Analysis of patients receiving ATP therapy

A total of 22 patients received initial ATP for their index event with 16/22 of these patients receiving successful ATP without requiring shock therapy. In the remaining 6 patients receiving failed ATP prior to the delivery of a successful ICD shock, mean entropy values were significantly higher compared to the successful ATP therapy group (6.3 ± 0.7 vs. 5.5 ± 0.7, p = 0.048) (Figure 3). Patient characteristics were balanced between those receiving successful ATP compared to those receiving 'failed ATP' (Table 2).

***In silico* modelling results**

Computational simulations using the idealized infarct model were used to explore the clinical findings reported in Figure 3. We modelled how penetration of the re-entrant circuit was affected by the fibrotic

tissue texture forming the protected isthmus. With a high degree of patchy fibrosis (50%) at slower pacing rates, the ATP pacing stimulus was able to successfully penetrate the isthmus (Figure 1E) albeit with reduced conduction velocity due to the tortuous course taken around the fibrotic regions.[15] At more rapid pacing rates (similar to VT cycle lengths) activation failed to penetrate the isthmus blocking at its mouth (Figure 1F). Notably with lower degrees of fibrosis (10% fibrosis within the isthmus) the paced activation wavefront was able to penetrate the isthmus at both slow (Figure 1B) and fast (Figure 1C) pacing rates. Shannon entropy was seen to peak at a level of 50% fibrosis (0.35) and fall to 0.21 for 10% fibrosis. The probability of conduction blocking at the mouth of the isthmus (corresponding with the entry site of VA) was also seen to be a function of excitability of the surviving tissue within the isthmus itself as well as fibrosis density, evidenced by the fact that as excitability was further impaired (by blocking INa) the probability of rate-dependent conduction block increased for all levels of fibrosis (Figure 1G).

Discussion

The results of the present study build upon our previous findings that mean entropy predicts appropriate ICD therapy (ATP or shock therapy) in patients with ICM or mixed etiology cardiomyopathy undergoing ICD implantation.[9] To the best of our knowledge, this is the first analysis demonstrating the novel finding that scar heterogeneity, quantified by mean entropy, predicts ICD shock therapy compared to those receiving successful ATP. Furthermore, patients receiving unsuccessful ATP prior to the delivery of a successful ICD shock had significantly higher mean entropy values compared to those receiving successful ATP. This may be of particular clinical importance as it implies that a higher degree of scar heterogeneity (quantified by a higher mean entropy) may be associated with a more aggressive VA requiring shock therapy to terminate. Our *in silico* computer modelling provides a physiologically plausible mechanism to explain our results i.e. ATP failure in the presence of greater scar heterogeneity/fibrosis due to inability of the paced wavefront to propagate into the critical VT isthmus especially at more rapid pacing rates that are generally required for pace termination of VAs.

In addition, secondary prevention was predictive of appropriate ICD therapy (ATP or shock therapy) supporting the consensus that this cohort of patients are at high risk of further ventricular arrhythmias. This consensus is based on historical trials including Antiarrhythmic Versus Implantable Defibrillators (AVID),[16] Cardiac Arrest Study Hamburg (CASH)[17] and Canadian Implantable Defibrillator (CIDS)[18] which demonstrated the effectiveness of ICD therapy in secondary prevention of sudden arrhythmic death and is in keeping with current AHA/ACC/HRS (2017)[19] and ESC (2015)[20] clinical guidelines.

Potential mechanistic explanations for ATP failure

The reasons why higher mean entropy values predict a more aggressive VA requiring shock therapy may lie in the mechanistic differences in arrhythmogenesis between varying scar heterogeneity. A higher degree of myocardial scar tissue heterogeneity (higher mean entropy) may support a greater number of microchannels within scar facilitating micro re-entry circuits stable enough to form sustained VT or VF that do not spontaneously abort and are more difficult to terminate with ATP requiring shock therapy to restore a stable heart rhythm. For ATP to be successful, the stimulus from the pacing electrode must successfully reach and

penetrate the reentrant circuit, closing-down the excitable gap.[21] The re-entrant circuit in sustained monomorphic VT often contains regions of patchy fibrosis, particularly in the diastolic isthmuses through which conduction is known to be impaired and which directly contribute to the arrhythmogenic substrate within the infarcted region. Thus, an important aspect of ATP success may be the ability of the paced wavefront to successfully propagate through patchy fibrosis within the isthmus, rendering it unexcitable when the reentrant wave subsequently arrives. It has been shown that activation propagating through patchy fibrotic regions is susceptible to rate-dependent conduction block[15] with the wavefronts forced to take convoluted and tortuous pathways as they attempt to navigate their way through the patchy fibrotic regions, undergoing frequent rapid tissue expansions and experiencing significant electrotonic source-sink mismatches. Under steady-state conditions, tissue is sufficiently excitable to allow propagation to traverse such regions, albeit with a modulated conduction velocity.[22] However, during rapid pacing, tissue has impairing excitability, and thus electrotonic current source-sink mismatches may reach a threshold to prevent downstream activation, causing unidirectional block. Our computer modelling confirms that high levels of patchy fibrosis within the diastolic isthmus may be susceptible to rate-dependent unidirectional conduction block, which may play an important role in preventing an ATP-paced wavefront from penetrating the critical reentrant channels within the infarct. Such a mechanism, driven by the electronic source-sink mismatch within the patchy fibrotic areas, may be exacerbated during compromised excitability at more rapid pacing rates. This is further supported by the augmentation of unidirectional block seen in situations where excitability (via INa) was further directly compromised (Figure 1G). The amount of patchy fibrosis in a given region, as detected on an LGE image, is related to the level of entropy i.e. quantifying the degree of disorder, or how dissimilar a particular voxel is from its neighbor. Our *in silico* results suggest that regions with moderate patchy fibrosis levels (approximately 50%) have correspondingly higher entropy scores, compared to areas with lower fibrosis levels and provides a physiologically plausible mechanism for how infarcts with lower entropy scores may be more susceptible to successful ATP therapy whereas higher entropy regions may be more susceptible to ATP failure due to rate-dependent block.

Comparison with previous studies

Previous work on entropy and LGE is limited and has focussed on predicting appropriate ICD therapy (combined ATP or shock therapy). Androulakis et al. (2019) recently reported LV entropy as a measure of scar heterogeniety in post myocardial infarction patients and found that high entropy within scar was associated with ICD therapy (ATP or shock therapy for monomorphic VT or VF),[23] and in keeping with our previous findings.[9] Androulakis et al. found entropy of the entire LV myocardium was not a predictor of appropriate ICD therapy[23] in contrast to the findings of Muthalaly et al. (2018) who found it was a predictor of ICD therapy in 130 patients with dilated cardiomyopathy.[24] There is no standardized method for scar segmentation to derive entropy, although in the ICM population, segmenting all visible scar or a selection of visible scar seems appropriate. The findings from these recent studies suggest entropy of LV scar is useful in predicting ICD therapy in patients with ICM and entropy of the entire LV myocardium is useful in predicting ICD therapy in patients with NICM. Notably, Androulakis et al. identified that high entropy of the entire LV myocardium was associated with mortality which may reflect a fibrosis pattern associated with adverse remodelling. Similarly, we have previously shown that $T1^{-native}$ values derived from the mid-septum outside of visible scar are predictive of appropriate ICD therapy in patients with NICM, supporting the use of $T1^{-native}$ values as an inherent tissue-specific index that is effective in differentiating healthy myocardium from diffusely diseased tissue.[9–11]

Clinical importance

Our work supports the hypothesis that patients with greater scar heterogeneity are at higher risk of malignant VAs that may ultimately require shock therapy to restore a stable heart rhythm. Furthermore, these findings substantiate previous computer modelling work that correlates the risk of VAs occurring with increasing heterogeneity of fibrosis.[25] Predicting which patients are at higher risk of receiving ICD shocks may be of significant benefit in counselling of ICD patients (helping to quantify the risk of shock therapy), device programming (using more aggressive ATP therapy in those likely to respond and less in those unlikely to respond) and also in device selection. Greater use of stand-alone subcutaneous ICDs (that are currently unable to deliver ATP) in patients unlikely to benefit or respond to ATP therapy may reduce the transvenous and mediastinal lead burden and subsequently reduce morbidity and mortality from systemic infection from indwelling leads in the circulation/mediastinum as well as from transvenous lead extraction, offering

additional long-term economic benefits to healthcare systems. Another potential application is the development of novel lead technologies to deliver ATP. If, as our results suggest, ATP success is dependent on local myocardial properties/degree of fibrosis in relation to the stimulus location relative to the re-entrant circuit, then delivery of ATP at potentially more favourable sites could be achieved with guided lead placement or multipolar leads that may offer an advantage over current techniques to deliver ATP. Since CMR-TA has the potential to identify patients at high risk of ATP failure and ICD shock therapy, it may also be useful in guiding prophylactic VT ablation in high-risk patients.

Limitations

The results of this study are subject to the innate limitations of non-randomized controlled studies. Furthermore, the sample size is insufficient to draw firm conclusions and larger randomized multicentre studies are required to further evaluate our findings. The morphology and cycle length of VT was not captured in the prospective database which may have provided further mechanistic insights allowing evaluation of the differences in the type of VT responding to ATP versus shock therapy. A standardized device therapy protocol was used according to our institutional guidelines at the time when the study began. The subsequent findings of the MADIT-RIT analysis showed optimized ICD programming which may potentially have reduced the event rate in this study.[2] However, given the standardisation of our ICD programming, it is unlikely that device programming would have introduced systemic bias in the associations studied. We also acknowledge that there may be other potential mechanisms related to higher entropy in infarcted regions which could explain our findings that were not investigated with our computer modelling. Primarily, more complex scar (with additional bystander channels) could result in a more complex VT circuit that is harder to treat with bystander channels being responsible for VT sustenance upon interaction with the paced ATP wavefront that could facilitate the degeneration into more complex VT/VF. Three-dimensional patient specific models of the subjects in this cohort to investigate VA circuits in relation to scar heterogeneity was not possible, due to the coarse out-of-plane resolution of the CMR data, meaning that full 3D realization of the infarct anatomy, including microscopic channels that might support VT, was not possible. Finally, correlation with histopathologic specimens in future studies would also be important to validate our findings.

Conclusion

A higher degree of scar heterogeneity, quantified by mean entropy, predicts ICD shock therapy in a high-risk group of ICD recipients. Our novel findings suggest that high mean entropy may be associated with more aggressive VAs unresponsive to ATP requiring shock therapy. Furthermore, our *in silico* computer modelling proposes a physiologically plausible mechanism to explain ATP failure in the presence of greater scar heterogeneity that may aid clinical decision making in patients more likely to benefit from early shock therapy.

References

1. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. *N Engl J Med* 2002; 346: 877–883.
2. Moss AJ, Schuger C, Beck CA, et al. Reduction in Inappropriate Therapy and Mortality through ICD Programming. *N Engl J Med* 2012; 367: 2275–2283.
3. Proietti R, Labos C, Davis M, et al. A systematic review and meta-analysis of the association between implantable cardioverter-defibrillator shocks and long-term mortality. *Can J Cardiol* 2015; 31: 270–7.
4. Moss AJ, Greenberg H, Case RB, et al. Long-Term Clinical Course of Patients After Termination of Ventricular Tachyarrhythmia by an Implanted Defibrillator. *Circulation* 2004; 110: 3760–3765.
5. Li A, Kaura A, Sunderland N, et al. The Significance of Shocks in Implantable Cardioverter Defibrillator Recipients. *Arrhythmia Electrophysiol Rev* 2016; 5: 110–6.
6. Maria E De, Giacopelli D, Borghi A, et al. Antitachycardia pacing programming in implantable cardioverter defibrillator: A systematic review. *World J Cardiol* 2017; 9: 429.
7. Sears SF, Todaro JF, Lewis TS, et al. Examining the psychosocial impact of implantable cardioverter defibrillators: A literature review. *Clin Cardiol* 1999; 22: 481–489.
8. Sweeney MO, Sherfesee L, DeGroot PJ, et al. Differences in effects of electrical therapy type for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients. *Heart Rhythm* 2010; 7: 353–360.
9. Gould J, Porter B, Claridge S, et al. Mean entropy predicts implantable cardioverter-defibrillator therapy using cardiac magnetic resonance texture analysis of scar heterogeneity. *Heart Rhythm* 2019; 16: 1242–1250.
10. Chen Z, Sohal M, Voigt T, et al. Myocardial tissue characterization by cardiac magnetic resonance imaging using T1 mapping predicts ventricular arrhythmia in ischemic and non–ischemic cardiomyopathy patients with implantable cardioverter-defibrillators. *Heart Rhythm* 2015; 12: 792–801.
11. Claridge S, Mennuni S, Jackson T, et al. Substrate-dependent risk stratification for implantable cardioverter defibrillator therapies using cardiac magnetic resonance imaging: The importance of T1 mapping in nonischemic patients. *J Cardiovasc Electrophysiol* 2017; 28: 785–795.

12. Gibbs T, Villa ADM, Sammut E, et al. Quantitative assessment of myocardial scar heterogeneity using cardiovascular magnetic resonance texture analysis to risk stratify patients post-myocardial infarction. *Clin Radiol*. Epub ahead of print 27 September 2018. DOI: 10.1016/J.CRAD.2018.08.012.

13. ten Tusscher KHWJ, Panfilov A V. Alternans and spiral breakup in a human ventricular tissue model. *Am J Physiol Circ Physiol* 2006; 291: H1088–H1100.

14. Vigmond EJ, Hughes M, Plank G, et al. Computational tools for modeling electrical activity in cardiac tissue. *J Electrocardiol* 2003; 36: 69–74.

15. Engelman ZJ, Trew ML, Smaill BH. Structural heterogeneity alone is a sufficient substrate for dynamic instability and altered restitution. *Circ Arrhythm Electrophysiol* 2010; 3: 195–203.

16. McAnulty J, Halperin B, Kron J, et al. A Comparison of Antiarrhythmic-Drug Therapy with Implantable Defibrillators in Patients Resuscitated from Near-Fatal Ventricular Arrhythmias. *N Engl J Med* 1997; 337: 1576–1584.

17. Kuck K-H, Cappato R, Siebels J, et al. *Randomized Comparison of Antiarrhythmic Drug Therapy With Implantable Defibrillators in Patients Resuscitated From Cardiac Arrest The Cardiac Arrest Study Hamburg (CASH)*. 2000.

18. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS). *Circulation* 2000; 101: 1297–1302.

19. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary. *Circulation*; 138. Epub ahead of print 25 September 2018.

20. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. ESC GUIDELINES 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Eur Heart J* 2015; 36: 2793–2867.

21. Sweeney MO. Antitachycardia Pacing for Ventricular Tachycardia Using Implantable Cardioverter Defibrillators: Substrates, Methods, and Clinical Experience. *Pacing Clin Electrophysiol* 2004; 27: 1292–1305.

22. Fast VG, Kléber AG. Cardiac tissue geometry as a determinant of unidirectional conduction block:

assessment of microscopic excitation spread by optical mapping in patterned cell cultures and in a computer model. *Cardiovasc Res* 1995; 29: 697–707.

23. Androulakis AFA, Zeppenfeld K, Paiman EHM, et al. Entropy as a Novel Measure of Myocardial Tissue Heterogeneity for Prediction of Ventricular Arrhythmias and Mortality in Post-Infarct Patients. *JACC Clin Electrophysiol* 2019; 5: 480–489.

24. Muthalaly RG, Kwong RY, John RM, et al. Left Ventricular Entropy Is a Novel Predictor of Arrhythmic Events in Patients With Dilated Cardiomyopathy Receiving Defibrillators for Primary Prevention. *JACC Cardiovasc Imaging*. Epub ahead of print 2018. DOI: 10.1016/j.jcmg.2018.07.003.

25. Kazbanov I V, ten Tusscher KHWJ, Panfilov A V. Effects of Heterogeneous Diffuse Fibrosis on Arrhythmia Dynamics and Mechanism. *Sci Rep* 2016; 6: 20835.

Figure legends

Figure 1: A specific topology example of fibrosis distribution for an isthmus containing 10%(**A**) and 50%(**D**) fibrosis. The tissue was stimulated at a lower site proximal to the isthmus mouth(**B, C, E & F**). With 10% fibrosis within the isthmus, the paced activation wavefront is able to penetrate the isthmus at both slow(**B**) and fast(**C**) pacing rates. With 50% patchy fibrosis within the diastolic isthmus, activation at slow pacing rates is able to successfully penetrate the isthmus(**E**). At more rapid pacing rates, similar to VT cycle lengths, activation fails to penetrate the isthmus, blocking at its mouth(**F**). The probability of conduction blocking at the mouth of the isthmus was also seen to be a function of both the fibrosis density and also the excitability of the surviving tissue within the isthmus itself(**G**).

Figure 2: Univariable**(A)** and multivariable**(B)** Cox regression analyses to determine predictors of appropriate ICD shock therapy for patients (n=33) receiving appropriate ICD therapy (ATP or shock therapy).

AF=atrial fibrillation; LVEF=left ventricular ejection fraction; CRT=cardiac resynchronization therapy; MI=myocardial infarction; ICM=ischemic cardiomyopathy; CAD=coronary artery disease.

Figure 3: Box and whisker plots showing difference in 'mean entropy' between patients receiving successful ATP (no shock therapy) versus failed ATP (with rescue ICD shock).

+ = mean values of 'mean entropy'

Whiskers represent minimum and maximum absolute values of 'mean entropy'