DOI:
10.1016/j.hrthm.2018.11.013

Document Version
Peer reviewed version

Accepted Manuscript

Left ventricular activation-recovery interval variability predicts spontaneous ventricular tachyarrhythmia in heart failure patients

Bradley Porter, MBChB, Martin J. Bishop, PhD, Simon Claridge, LLB, MBBS, Nicholas Child, MBBS, Stefan Van Duijvenboden, PhD, Julian Bostock, PhD, Benjamin J. Sieniewicz, MBChB, Justin Gould, MBBS, Baldeep Sidhu, MBBS, Ben Hanson, PhD, Zhong Chen, MBBS, PhD, Christopher A. Rinaldi, MD, Peter Taggart, MD, DSc, Jaswinder S. Gill, MD

PII: S1547-5271(18)31145-7

DOI: https://doi.org/10.1016/j.hrthm.2018.11.013

Reference: HRTHM 7815

To appear in: *Heart Rhythm*

Received Date: 15 June 2018

Please cite this article as: Porter B, Bishop MJ, Claridge S, Child N, Van Duijvenboden S, Bostock J, Sieniewicz BJ, Gould J, Sidhu B, Hanson B, Chen Z, Rinaldi CA, Taggart P, Gill JS, Left ventricular activation-recovery interval variability predicts spontaneous ventricular tachyarrhythmia in heart failure patients, *Heart Rhythm* (2019), doi: https://doi.org/10.1016/j.hrthm.2018.11.013.

Left ventricular activation-recovery interval variability predicts spontaneous ventricular tachyarrhythmia in heart failure patients.

Short Title: ARI variability and ventricular tachyarrhythmia

Authors: Bradley Porter, MBChB,[a] * Martin J Bishop, PhD,[a] Simon Claridge, LLB, MBBS,[a] Nicholas Child, MBBS, [b] Stefan Van Duijvenboden, PhD,[d] Julian Bostock, PhD,[b] Benjamin J Sieniewicz, MBChB,[a] Justin Gould, MBBS,[a] Baldeep Sidhu, MBBS,[a] Ben Hanson, PhD,[d] Zhong Chen, MBBS, PhD,[a] Christopher A Rinaldi, MD,[b] Peter Taggart, MD, DSc,[c] Jaswinder S Gill, MD,[b]

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

[b] Guy's and St Thomas' Hospital, London, UK.

[c] Department of Cardiovascular Sciences, University College London, UK

[d] Department of Mechanical Engineering, University College London, UK

Corresponding author: Dr Bradley Porter, School of Biomedical Engineering and Imaging Sciences, St Thomas' Hospital, London, SE1 7EH, U.K. Email: bradley.porter@kcl.ac.uk

Word count: 4999

Sources of Funding: BP is funded by an Abbott educational grant. MJB acknowledges support from the UK Medical Research Council (NIRG).

Disclosures: None

ABSTRACT

Background: Enhanced beat-to-beat variability of repolarization (BVR) is strongly linked to arrhythmogenesis and is largely due to variation in ventricular action potential duration (APD). Previous studies in humans have relied on QT interval measurements; however, a direct relationship between beat-to-beat variability of APD and arrhythmogenesis in humans has yet to be demonstrated.

Objectives: This study aimed to explore the beat-to-beat repolarization dynamics within a heart failure population at the level of ventricular APD.

Methods: 43 patients with heart failure and implanted cardiac resynchronization therapy defibrillator devices were studied. Activation-recovery intervals (ARI) as a surrogate for APD were recorded from the left ventricular epicardial lead while pacing from the right ventricular lead to maintain constant cycle length.

Results: During mean follow-up of 23.6±13.6 months, 11 patients sustained VT/VF and received appropriate implantable cardioverter-defibrillator therapies (Anti-Tachycardia Pacing or shock therapy). ARI variability (ARIV) was significantly greater in patients with subsequent VT/VF vs. those without VT/VF (3.55±1.3 ms vs. 2.77±1.09 ms, p=0.047). Receiver operating characteristic curve analysis (AUC 0.71, p=0.046) suggested high and low risk ARIV groups for VT/VF. The Kaplan–Meier survival analysis demonstrated that the time until first appropriate therapy for VT/VF was significantly shorter in the high-risk ARIV group (p=0.028). ARIV was a predictor for VT/VF in the multivariate Cox model (HR, 1.623; 95% CI, 1.1 to 2.393; p=0.015).

Conclusions: Increased left ventricular ARIV is associated with an increased risk of VT/VF in patients with heart failure.

Key words: ventricular arrhythmia, activation-recovery interval, beat-to-beat variability, intracardiac electrogram, cardiac resynchronization therapy defibrillator

INTRODUCTION

Accurate prediction of individuals at risk of ventricular arrhythmia (VA) and sudden cardiac death remains a major challenge.[1] Exaggerated beat-to-beat variability (BBV) of repolarization (BVR) is known to be associated with arrhythmogenesis in animal models[2-5] and humans[6-11] and has been proposed as a potential risk marker.

The activation-recovery interval (ARI) is well validated.[12-14] In vivo it can be obtained from pacing leads in ambulatory patients, invasively during electrophysiology studies, and more recently has been derived from non-invasive cardiac electrophysiology mapping techniques.[15] As such it is readily available for the assessment of ventricular repolarization and therefor a potential adjunct in the prediction of patients at risk of VA. Recent animal studies have demonstrated significant increases in the BBV of ARI prior to the onset of Torsades de pointes and have highlighted its potential for integration into implantable cardiac devices to monitor arrhythmia risk.[16]

In the present study, we have recorded left ventricular (LV) unipolar electrograms (UEGs), while pacing from the right ventricular (RV) lead to maintain a constant cycle length in patients with heart failure. From these electrograms we have calculated ARI variability (ARIV). We hypothesized that higher baseline ARIV would be seen in patients experiencing VA during follow-up.

METHODS

Ethical Approval

The study was approved by the local research ethics committee and conformed to the Declaration of Helsinki (latest revision: 64th WMA General Assembly) standard. Informed consent was obtained in writing from all subjects.

Study population and data acquisition

We retrospectively analyzed the prospectively collected data of 43 consecutive patients who underwent electrogram recordings to study basic ARI within a heart failure population. The study enrolled patients with St. Jude Medical cardiac resynchronization therapy defibrillator (CRT-D) devices for primary or secondary indications of sudden cardiac death (SCD). Patients of either sex, >18 years of age and undergoing CRT-D follow-up at our institution were eligible. During a routine follow-up visit LV UEG recordings were made via the device programmer (Merlin, St. Jude Medical Inc., St Paul, MN). Effects of heart rate variability on repolarization dynamics were removed by establishing fixed cycle length with steady-state pacing (DDD-RV for sinus rhythm or VVI-RV for atrial fibrillation).[17] A constant rate of 10 beats above the patient's intrinsic heart rate was chosen with a minimum adaptation period of 2 minutes.[18] A 30 second recording of LV UEG was made using the device programmer at a sampling frequency of 512 Hz and extracted for off-line analysis. [19,20] **Figure 1** shows examples of raw digital UEGs. Occurrence of VA therapy with either ATP or shock therapy was assessed by CRT-D checks and served as the endpoint. Programming of the CRT-D device was based on clinical evaluation of the attending electrophysiologist. CRT-D interrogation data of recorded events was evaluated by an electrophysiologist blinded to the outcome of the LV UEG data.

Repolarization variability analysis

Raw digital LV UEG traces were analysed off-line using custom built MATLAB software (MathWorks Inc, Mass). Recordings were separately low pass filtered at both 80 and 30 Hz for calculation of activation times (ATs) and repolarization times (RTs), respectively. The choice of two separate frequencies for AT and RT calculation allowed us to maintain the sharp activation gradients required to identify ATs, whilst also successfully preserving the morphology of the slower T-wave to identify RTs. Consecutive ARIs were calculated by identifying AT and RT for each beat using the Wyatt method.[13,14,19,21,22] Automated identification of ATs and RTs removed any observer variability. **Figure 1** shows examples of the identification of ATs and RTs and the resultant ARI across various morphologies of UEG. ARIV over the full 30s recording was then computed as.

$$ARIV = \frac{\sum_{i=1}^{n_{beats}-1} |ARI_{i+1} - ARI_i|}{(\sqrt{2} \times n_{beats})}$$

where n beats is the number of beats contained within the 30s period.[23] To account for the possibility that the magnitude of beat-to-beat changes may depend on the intrinsic ARI duration we introduced the ARIV index. The ARIV index provides a normalized value of the ARIV relative to the mean ARI duration for each patient. The ARIV index was computed as.

$$ARIV\ index = \frac{1}{ARI_{mean}} \times \frac{\sum_{i=1}^{n_{beats}-1} |ARI_{i+1} - ARI_i|}{(\sqrt{2} \times n_{beats})} \quad \text{where} \quad ARI_{mean} = \frac{\sum_{i=1}^{n_{beats}} ARI_i}{n_{beats}}$$

Statistical Analysis

Results are presented as mean±standard deviation for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. The independent-samples t-test was used to compare normally distributed continuous variables; otherwise the Mann-Whitney U test

was used. Categorical variables were compared using Fisher's exact test. ROC analysis was performed using Youden's index to determine the variable cut-off levels with optimal sensitivity and specificity for the endpoint. The estimated cutoff values were retrospectively used to reclassify and dichotomize the study subjects into high and low-risk categories. Kaplan-Meier survival analysis was used to address our hypothesis testing the association between increased ARIV and probability of first appropriate defibrillator therapy for VT/VF. Cox proportional hazards analyses were performed separately for each variable of interest (Mean ARI, ARIV and ARIV index). A *P* value of <0.05 was considered to be statistically significant for all tests. All statistical analyses were performed using SPSS (IBM Switzerland, Switzerland) and Prism (GraphPad Software Inc., California, USA).

RESULTS

Data eligibility

A total of 43 ambulatory heart failure patients underwent UEG recordings. Of these, 6 patients were excluded from the ARIV analysis: 2 due to a >15% ectopy burden during recordings, 3 due to significant electrogram fractionation (**Figure 2A**), 1 due to absence of a well-defined T-wave such that no positive gradient could be identified during repolarization (**Figure 2B**). ARIV analysis was performed in the remaining 37 patients. T-wave morphology remained constant and there were no AV conducted beats throughout the recordings. The median RV pacing rate used during LV UEG recordings was 85 bpm (IQR, 80 to 95). As expected, significant correlation was seen between the pacing rate and mean ARI (r=-0.725, p<0.001). However, there was no correlation between mean ARI and ARIV (r=0.045, p=0.792), nor the pacing rate and ARIV (r=-0.150, p=0.377).

Study population

Of those eligible for ARIV analysis (**Table 1**), 30 were men (81.1%) and 7 women (18.9%) who had undergone CRT-D implantation for primary (29 patients, 78.4%) or secondary (8 patients, 21.6%) prevention of SCD. The patients were enrolled in the study in median time 6.9 months after CRT-D implantation (range, 5.3 to 31.9 months). At the time of data acquisition, no patients had decompensated heart failure. All patients had electrolytes within ranges unexpected to disturb repolarization prior to UEG recordings (sodium 138.1±3.2 mEq/L, potassium 4.7±0.5 mEq/L). During follow-up no patients were initiated on class I or III antiarrhythmic agents, nor underwent coronary intervention/VT ablation prior to meeting the study endpoint or before conclusion of study follow-up.

Comparing patients with ischemic and non-ischemic cardiomyopathy, there was no difference in mean ARI (257.69±26.6 ms vs. 251.21±35.27 ms, p=0.554), ARIV (3.44±1.32 ms vs. 2.67±0.98 ms, p=0.055), nor the ARIV index (1.37±0.6% vs. 1.07±0.36%, p=0.115). LV ejection fraction (LVEF) showed no correlation with mean ARI (r_s=0.021, p=0.901), ARIV (r_s=0.020, p=0.907) nor the ARIV index (r_s=0.039, p=0.818). Between patients with primary and secondary prevention indications for CRT-D there was no difference in mean ARI (257.34±32.35 ms vs. 241.97±26.99 ms, p=0.207). Differences in ARIV approached significance (2.83±1.21 ms vs. 3.62±0.94 ms, p=0.051), and a significantly higher ARIV index was seen in the secondary prevention group (1.12±0.5% vs. 1.49±0.34%, p=0.021). 23 of the patients were CRT responders and 14 non-responders (a CRT responder was defined as a ≥5% improvement in LVEF from pre-implant). Between responders and non-responders there was no observed difference in mean ARI (253.26±35.24 ms vs. 255.26±25.61 ms, p=0.865), ARIV (2.94±1.14 ms vs. 3.11±1.3 ms, p=0.699) nor ARIV index (1.18±0.48% vs. 1.23±0.53%, p=0.817).

Implantable cardioverter-defibrillator therapy

Following LV UEG recordings a mean follow-up of 23.6±13.6 months took place. During follow-up 11 patients of 37 reached the endpoint of appropriate ICD therapy for VT/VF. ATP was attempted and successful in 9 patients with VT. One patient with VT had successful rescue shock therapy. One patient experienced VF with successful shock therapy. One patient died from heart failure before reaching the endpoint. **Table 1** shows a comparison of clinical characteristic of patients with and without subsequent appropriate ICD therapy for VT/VF**.**

ARIV was significantly greater in patients with subsequent VT/VF events vs. those without VT/VF events (3.55±1.3 ms vs. 2.77±1.09 ms, p=0.047). The ARIV index was also significantly greater in

patients with subsequent VT/VF events vs. those without VT/VF events (1.43±0.5% vs. 1.1±0.47%, *p*=0.036). No observed difference between groups was found in mean ARI (249.34±27.91% vs. 256±33.31%, *p*=0.618). Receiver operating characteristic (ROC) curve analysis (**Figure 3**) suggested cut-off levels for ARIV of ≥2.52 ms with 82% sensitivity (95% CI, 48-98%) and 58% specificity (95% CI, 37-77%) (AUC 0.71; 95% CI, 0.53-0.89; *p*=0.046) and ARIV index of ≥1.14% with 64% sensitivity (95% CI, 31-89%) and 65% specificity (95% CI, 44-83%) (AUC 0.72; 95% CI, 0.55-0.9; *p*=0.036) to dichotomize into high/low risk for the endpoint of appropriate ICD therapy.

Table 2 shows the clinical characteristics of patients with ARIV dichotomized at high and low risk of VT/VF. When comparing subjects in the high-risk group for ARIV, 45% experienced an episode of VT/VF by 3 years, compared with 11.8% in the low-risk group. **Figure 4A** demonstrates the separation of the Kaplan-Meier curves at the variable cut-off for ARIV (Mantel-Cox log-rank test, *p*=0.028). When comparing subjects in the high-risk group for ARIV index, 43.8% experienced an episode of VT/VF by 3 years, compared with 19.0% in the low-risk group. **Figure 4B** demonstrates the separation of the Kaplan-Meier curves at the variable cut-off for ARIV index (Mantel-Cox log-rank test, *p*=0.079).

Mean ARI, ARIV and the ARIV index were tested separately in the multivariate Cox proportional-hazards regression model for all VT/VF events, with the significant clinical covariate LVEF. Low LVEF remained a significant predictor of appropriate ICD therapy for VT/VF in all models tested. Mean ARI was not predictive (HR, 0.997; 95% CI, 0.977-1.017; *p*=0.758). ARIV (HR, 1.623; 95% CI, 1.1-2.393; *p*=0.015) and the ARIV index (HR, 3.256; 95% CI, 1.222-8.676; *p*=0.018) were independent predictors of VT/VF (**Figure 5**). After exclusion of patients with secondary indications for ICD therapy both ARIV (HR, 1.518; 95% CI, 1.009-2.285; *p*=0.045) and the ARIV index (HR, 2.87; 95% CI, 1.033-7.975; *p*=0.043) remained independent predictors of VT/VF. After exclusion of patients on amiodarone both

196 ARIV (HR, 1.625; 95% CI, 1.114-2.371; p=0.012) and the ARIV index (HR, 3.259; 95% CI, 1.262-8.411;

197 p=0.015) remained independent predictors of VT/VF.

198

DISCUSSION

To our knowledge, this is the first study to demonstrate an association between VA risk and increased LV BVR. The main findings were: 1) increased ARIV was associated with an independent risk for VT/VF; 2) increased ARIV index (ARIV normalized to mean ARI) remained an independent predictor for VT/VF; 3) there was no association between mean ARI and VT/VF risk.

Relation to prior work on repolarization variability

The potential for stratification of individuals at risk of VA by means of repolarization instability has been demonstrated with QT intervals from the surface ECG and RV intracardiac electrograms. [6-11] Our findings of higher values of BBV of ARI in heart failure patients experiencing VT/VF extends these observations to the level of the ventricular APD and to the assessment of LV BVR. The ROC analysis found ARIV to be more sensitive than the ARIV index in the prediction of ICD therapies. This was highlighted again in the Kaplan-Meier analysis showing less separation in the curves for ARIV index when compared to ARIV. These results would suggest that use of BBV of ARI to assess risk of VT/VF is more reliable without adjustment for basic ARI.

A major component of QTV is heart rate variability and both the QT interval and APD are strongly cycle length dependent [24,25]. As the majority of QTV studies occurred in the absence of controlled cycle length it is technically challenging to separate heart rate driven QTV from actual fluctuations in the QT interval. RV pacing to obtain cycle length control as employed in our study removes the component of BVR due to heart rate variability.

222 It is accepted that the QT interval in a given ECG lead measures the interval between the earliest
223 depolarization and latest repolarization as projected onto the axis of that lead.[26] Given its spatial
224 heterogeneity the use of multi-lead ECG recordings to assess QTV has been suggested but warrants
225 further investigation.[26] The in vivo dispersion of ARIV and correlations to various body surface ECG
226 repolarization indices should be studied and could be invaluable in our understanding of both QTV
227 and ARIV.

228

229 **Relation to prior work on basic APD and QT interval measurements**

230 In the present study, basic ARI in heart failure patients was not predictive of VT/VF events. This is
231 consistent with several studies reporting QT variability as a stronger predictor of arrhythmia than QT
232 prolongation. [2,3,5,7,8] These findings pointing to instability of repolarization as a key factor would be in
233 keeping with a cellular mechanism such as proposed by Johnson et al[27], who also observed
234 dissociation between APD variability and basic APD under certain conditions.

235

236 Shortening of basic APD occurs in responders to CRT, whilst lengthening of basic APD occurs in non-
237 responders. [20] In vivo electrical remodelling in heart failure at the level of BBV-APD needs to be
238 studied prospectively and may offer insight into the impact of CRT on VAs.

239

240 **Mechanisms of beat-to-beat variability of repolarization**

241 Several mechanisms have been proposed for the cellular basis of BBV-APD. Its apparently random
242 nature suggests the involvement of a stochastic process. Stochastic variation of fast sodium current
243 (I_{Na}), L-type calcium current (I_{CaL}), transient outward current (I_{to}), rapid delayed rectifier (I_{kr}) and slow
244 delayed rectifier (I_{ks}) potassium currents has been shown to influence BBV-APD[23,28,29] with
245 considerable interdependence between individual channels.[23] Spontaneous calcium release from the

sarcoplasmic reticulum exhibits BBV and in the presence of calcium overload has been shown experimentally and in silico to generate BBV-APD.[27] This mechanism was due to spontaneous calcium release from the sarcoplasmic reticulum in late diastole reducing the subsequent calcium transient and hence reducing I_{CaL} deactivation and prolonging the APD. However, the extent to which these effects seen in isolated cells may be operative in the whole heart where cells are well coupled is uncertain due to electrotonic interaction between cells.[30] Nevertheless under conditions of calcium overload or reduced repolarization reserve, the effect of stochasticity on channel behavior may be enhanced suggesting that these effects may become operative in pathological conditions. BBV-APD may be arrhythmogenic either by the development of early or delayed afterdepolarizations[27] or by enhanced dispersion of repolarization facilitating re-entry.

Clinical implications and future work

Risk stratification of patients at high risk of sudden cardiac death remains a major challenge. In view of the multiple mechanisms involved it is unlikely that a single test would prove sufficient and that a combination of clinical characteristics with a selection of stratification tools may be more appropriate.[31] In this context, our study builds on the body of evidence highlighting the potential for assessment of baseline BVR to form part of the risk stratification tool.

Wijers et al[16] have highlighted the significance of the temporal behavior of ARI prior to the onset of VA in dogs. Furthermore, this work demonstrated comparable short-term variability of ARI between RV and LV. The potential for automated continuous real-time monitoring of ARIV offers a novel future application for ICDs. However, the optimal recording location is unknown and further work is needed to compare ARIV across multiple simultaneous recording sites within the heart. Paroxysmal

atrial arrhythmias may result in variable ventricular filling in BiV paced patients and as such their influence on the ventricular ARI within a CRT population should be studied.

Limitations

The study population was relatively small and as a single tertiary centre study the patient group may not be representative of the usual CRT-D population. These results should be validated in a larger multicenter prospective study of a primary prevention ICD indication cohort. As ischemia testing was not conducted as part of the protocol we are unable to determine the influence of ischemia on BBV of ARI. Our observations are confined to a single LV epicardial site. Regional variation of the electrophysiological properties throughout the ventricular myocardium makes it possible that other regions may have demonstrated differing results. Short and long-term variation in ARIV should be studied in order to determine the optimal duration and frequency of recordings for its use as a predictor of VA.[32] Whilst strategies to analyze fractionated electrograms have been proposed,[33] a clear consensus in their interpretation does not exist. In the context of the assessment of BVR this could prove a challenge. Furthermore, the presence of a high ectopy burden or the lack of a gradient to define repolarization time could exclude some patients altogether. In our study 14.0% of patients were excluded due to these limitations thus highlighting an area for future work.

Conclusion

In patients with heart failure, increased ARIV is associated with increased risk of spontaneous VT/VF. These results accord with observations in QTV and extend observations to assessment of left ventricular BVR and specifically to the level of ventricular APD. Our findings are supportive of the possible utility of BVR as an adjunct to risk stratification of patients at risk of ventricular arrhythmia.

Acknowledgements

This work was supported by the Wellcome/EPSRC Centre for Medical Engineering [WT 203148/Z/16/Z]. The research was funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

REFERENCES

1. Køber L, Thune JJ, Nielsen JC, et al.: Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med Massachusetts Medical Society, 2016; 375:1221–1230.

2. Thomsen MB, Verduyn SC, Stengl M, Beekman JDM, de Pater G, van Opstal J, Volders PGA, Vos MA: Increased short-term variability of repolarization predicts d-sotalol-induced torsades de pointes in dogs. Circulation American Heart Association, Inc, 2004; 110:2453–2459.

3. Gallacher DJ, Van de Water A, van der Linde H, Hermans AN, Lu HR, Towart R, Volders PGA: In vivo mechanisms precipitating torsades de pointes in a canine model of drug-induced long-QT1 syndrome. Cardiovasc Res 2007; 76:247–256.

4. Abi-Gerges N, Valentin J-P, Pollard CE: Dog left ventricular midmyocardial myocytes for assessment of drug-induced delayed repolarization: short-term variability and proarrhythmic potential. Br J Pharmacol Blackwell Publishing Ltd, 2010; 159:77–92.

5. Jacobson I, Carlsson L, Duker G: Beat-by-beat QT interval variability, but not QT prolongation per se, predicts drug-induced torsades de pointes in the anaesthetised methoxamine-sensitized rabbit. J Pharmacol Toxicol Methods 2011; 63:40–46.

6. Atiga WL, Calkins H, Lawrence JH, Tomaselli GF, Smith JM, Berger RD: Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. J Cardiovasc Electrophysiol 1998; 9:899–908.

7. Haigney MC, Zareba W, Gentlesk PJ, Goldstein RE, Illovsky M, McNitt S, Andrews ML, Moss AJ, Multicenter Automatic Defibrillator Implantation Trial II investigators: QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. Journal of the American College of Cardiology 2004; 44:1481–1487.

8. Hinterseer M, Beckmann B-M, Thomsen MB, et al.: Usefulness of short-term variability of QT intervals as a predictor for electrical remodeling and proarrhythmia in patients with nonischemic heart failure. The American Journal of Cardiology Elsevier, 2010; 106:216–220.

9. Oosterhoff P, Tereshchenko LG, van der Heyden MAG, Ghanem RN, Fetics BJ, Berger RD, Vos MA: Short-term variability of repolarization predicts ventricular tachycardia and sudden cardiac death in patients with structural heart disease: a comparison with QT variability index. Heart Rhythm 2011; 8:1584–1590.

10. Tereshchenko LG, Fetics BJ, Domitrovich PP, Lindsay BD, Berger RD: Prediction of ventricular tachyarrhythmias by intracardiac repolarization variability analysis. Circ Arrhythm Electrophysiol American Heart Association, Inc, 2009; 2:276–284.

11. Tereshchenko LG, Ghanem RN, Abeyratne A, Swerdlow CD: Intracardiac QT integral on far-field ICD electrogram predicts sustained ventricular tachyarrhythmias in ICD patients. HRTHM Elsevier Inc, 2011; 8:1889–1894.

12. Haws CW, Lux RL: Correlation between in vivo transmembrane action potential durations and activation-recovery intervals from electrograms. Effects of interventions that alter repolarization time. Circulation 1990; 81:281–288.

13. Coronel R, de Bakker JMT, Wilms-Schopman FJG, Opthof T, Linnenbank AC, Belterman CN, Janse MJ: Monophasic action potentials and activation recovery intervals as measures of ventricular action potential duration: experimental evidence to resolve some controversies. Heart Rhythm Elsevier, 2006; 3:1043–1050.

14. Potse M, Vinet A, Opthof T, Coronel R: Validation of a simple model for the morphology of the T wave in unipolar electrograms. Am J Physiol Heart Circ Physiol American Physiological Society, 2009; 297:H792–H801.

15. Andrews CM, Srinivasan NT, Rosmini S, Bulluck H, Orini M, Jenkins S, Pantazis A, McKenna WJ, Moon JC, Lambiase PD, Rudy Y: Electrical and Structural Substrate of Arrhythmogenic Right Ventricular Cardiomyopathy Determined Using Noninvasive Electrocardiographic Imaging and Late Gadolinium Magnetic Resonance Imaging. Circ Arrhythm Electrophysiol American Heart Association, Inc, 2017; 10:e005105.

16. Wijers SC, Sprenkeler DJ, Bossu A, Dunnink A, Beekman JDM, Varkevisser R, Hernández AA, Meine M, Vos MA: Beat-to-beat variations in activation-recovery interval derived from the right ventricular electrogram can monitor arrhythmic risk under anesthetic and awake conditions in the canine chronic atrioventricular block model. Heart Rhythm 2018; 15:442–448.

17. Bueno-Orovio A, Hanson BM, Gill JS, Taggart P, Rodríguez B: Slow adaptation of ventricular repolarization as a cause of arrhythmia? Methods Inf Med Schattauer Publishers, 2014; 53:320–323.

18. Franz MR, Swerdlow CD, Liem LB, Schaefer J: Cycle length dependence of human action potential duration in vivo. Effects of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady-state frequencies. J Clin Invest American Society for Clinical Investigation, 1988; 82:972–979.

19. Hanson B, Child N, Van Duijvenboden S, Orini M, Chen Z, Coronel R, Rinaldi CA, Gill JS, Gill JS, Taggart P: Oscillatory behavior of ventricular action potential duration in heart failure patients at respiratory rate and low frequency. Front Physiol Second Edition. Frontiers, 2014; 5:414.

20. Chen Z, Hanson B, Sohal M, et al.: Coupling of ventricular action potential duration and local strain patterns during reverse remodeling in responders and nonresponders to cardiac resynchronization therapy. Heart Rhythm Elsevier, 2016; 13:1898–1904.

21. Wyatt RF, Burgess MJ, Evans AK, Lux RL, Abildskov JA, Tsutsumi T: Estimation of ventricular transmembrane action potential durations and repolarization times from unipolar electrograms. The American Journal of Cardiology Elsevier, 1981; 47:488.

22. Hanson B, Gill J, Western D, Gilbey MP, Bostock J, Boyett MR, Zhang H, Coronel R, Taggart P: Cyclical modulation of human ventricular repolarization by respiration. Front Physiol Frontiers, 2012; 3:379.

23. Pueyo E, Dangerfield CE, Britton OJ, Virág L, Kistamás K, Szentandrássy N, Jost N, Varró A, Nánási PP, Burrage K, Rodríguez B: Experimentally-Based Computational Investigation into Beat-To-Beat Variability in Ventricular Repolarization and Its Response to Ionic Current Inhibition. PLoS ONE Public Library of Science, 2016; 11:e0151461.

24. Boyett MR, Jewell BR: A study of the factors responsible for rate-dependent shortening of the action potential in mammalian ventricular muscle. J Physiol (Lond) Wiley-Blackwell, 1978; 285:359–380.

25. Zaza A, Malfatto G, Schwartz PJ: Sympathetic modulation of the relation between ventricular repolarization and cycle length. Circ Res 1991; 68:1191–1203.

26. Baumert M, Porta A, Vos MA, Malik M, Couderc J-P, Laguna P, Piccirillo G, Smith GL, Tereshchenko LG, Volders PGA: QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrophysiology. Europace 2016; 18:925–944.

27. Johnson DM, Heijman J, Bode EF, Greensmith DJ, van der Linde H, Abi-Gerges N, Eisner DA, Trafford AW, Volders PGA: Diastolic spontaneous calcium release from the sarcoplasmic reticulum increases beat-to-beat variability of repolarization in canine ventricular myocytes after β-adrenergic stimulation. Circ Res American Heart Association, Inc, 2013; 112:246–256.

28. Tanskanen AJ, Greenstein JL, O'Rourke B, Winslow RL: The role of stochastic and modal gating of cardiac L-type Ca2+ channels on early after-depolarizations. Biophys J Elsevier, 2005; 88:85–95.

29. Heijman J, Zaza A, Johnson DM, Rudy Y, Peeters RLM, Volders PGA, Westra RL: Determinants of beat-to-beat variability of repolarization duration in the canine ventricular myocyte: a computational analysis. PLoS Comput Biol Public Library of Science, 2013; 9:e1003202.

30. Zaniboni M, Pollard AE, Yang L, Spitzer KW: Beat-to-beat repolarization variability in ventricular myocytes and its suppression by electrical coupling. Am J Physiol Heart Circ Physiol 2000; 278:H677–H687.

31. Dagres N, Hindricks G: Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? Eur Heart J 2013; 34:1964–1971.

32. Guduru A, Lansdown J, Chernichenko D, Berger RD, Tereshchenko LG: Longitudinal changes in intracardiac repolarization lability in patients with implantable cardioverter-defibrillator. Front Physiol Frontiers, 2013; 4:208.

33. Ellis WS, Eisenberg SJ, Auslander DM, Dae MW, Zakhor A, Lesh MD: Deconvolution: a novel signal processing approach for determining activation time from fractionated electrograms and detecting infarcted tissue. Circulation 1996; 94:2633–2640.

410

411 **Table 1.** Baseline characteristics of patients with and without subsequent appropriate ICD therapy

412 for VT/VF. NYHA, New York Heart Association.

Variables	**No VT/VF event (n=26)**	**VT/VF events at follow-up (n=11)**	***P* value**
Age (IQR), years	68 (63-77)	63 (52-66.5)	0.059
Male, n (%)	19 (73.1)	11 (100)	0.080
Ischemic cardiomyopathy, n (%)	12 (46.2)	4 (36.4)	0.723
Ejection fraction ±SD, %	38.9 ± 11.7	26 ± 11.2	**0.004**
NYHA class ≥ 2, n (%)	16 (61.5)	9 (81.8)	0.279
Secondary prevention ICD, n (%)	6 (23.1)	2 (18.2)	1
Diabetes mellitus, n (%)	8 (30.8)	4 (36.4)	1
Hypertension, n (%)	8 (30.8)	5 (45.5)	0.465
Atrial fibrillation, n (%)	6 (23.1)	4 (36.4)	0.442
Beta-blockade, n (%)	21 (80.8)	11 (100)	0.295
ACE inhibitor, n (%)	24 (92.3)	11 (100)	1
Aldosterone antagonists, n (%)	15 (57.7)	4 (36.4)	0.295
Digoxin, n (%)	4 (15.4)	3 (27.3)	0.403
Amiodarone, n (%)	3 (11.5)	0 (0)	0.540
Biventricular pacing percentage (IQR), %	99 (97-99)	98 (94-99)	0.377
Pacing rate for EGM recording (IQR), bpm	80 (80-95)	90 (82.5-92.5)	0.780

413

414 **Table 2.** Clinical characteristics of patients with ARIV dichotomized as per ROC suggested optimal

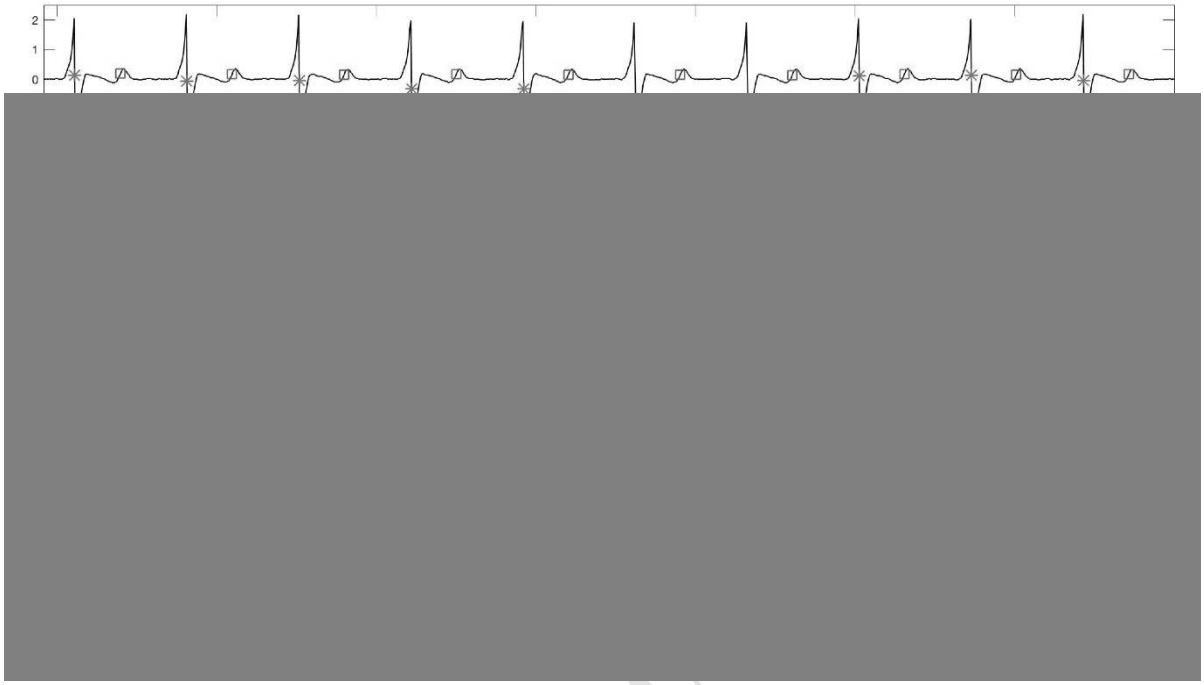
415 cut-off values. NYHA, New York Heart Association.

Variables	**ARIV low-risk (n=17)**	**ARIV high-risk (n=20)**	***P* value**
Age (IQR), years	68 (62-76)	66 (56-75)	0.279
Male, n (%)	12 (70.6)	18 (90)	0.212
Ischemic cardiomyopathy, n (%)	5 (29.4)	11 (55)	0.185
Ejection fraction ±SD, %	35.5 ± 13.6	34.8 ± 12.5	0.857
NYHA class ≥ 2, n (%)	10 (58.8)	15 (75)	0.482
Secondary prevention ICD, n (%)	1 (5.9)	7 (35)	**0.048**
Diabetes mellitus, n (%)	7 (41.2)	5 (25)	0.482
Hypertension, n (%)	2 (11.8)	11 (55)	**0.014**
Atrial fibrillation, n (%)	6 (35.3)	4 (20)	0.460
Beta-blockade, n (%)	14 (82.4)	18 (90)	0.644
ACE inhibitor, n (%)	16 (94.1)	19 (95)	1
Aldosterone antagonists, n (%)	11 (64.7)	8 (40)	0.191
Digoxin, n (%)	5 (29.4)	2 (10)	0.212
Amiodarone, n (%)	0 (0)	3 (15)	0.234
Biventricular pacing percentage ±SD, %	99 (98-99)	98 (94-99)	0.368
Pacing rate for EGM recording ±SD, bpm	90 (80-100)	80 (80-90)	0.148

416

417 **Figure 1.** Unipolar electrograms recorded from the left ventricular lead of 3 separate patients

418 demonstrating local activation (star) and repolarization (square).



419

420 **Figure 2.** Two pitfalls of ARIV analysis: (**A**) fractionation, (**B**) neutral gradient during repolarization.

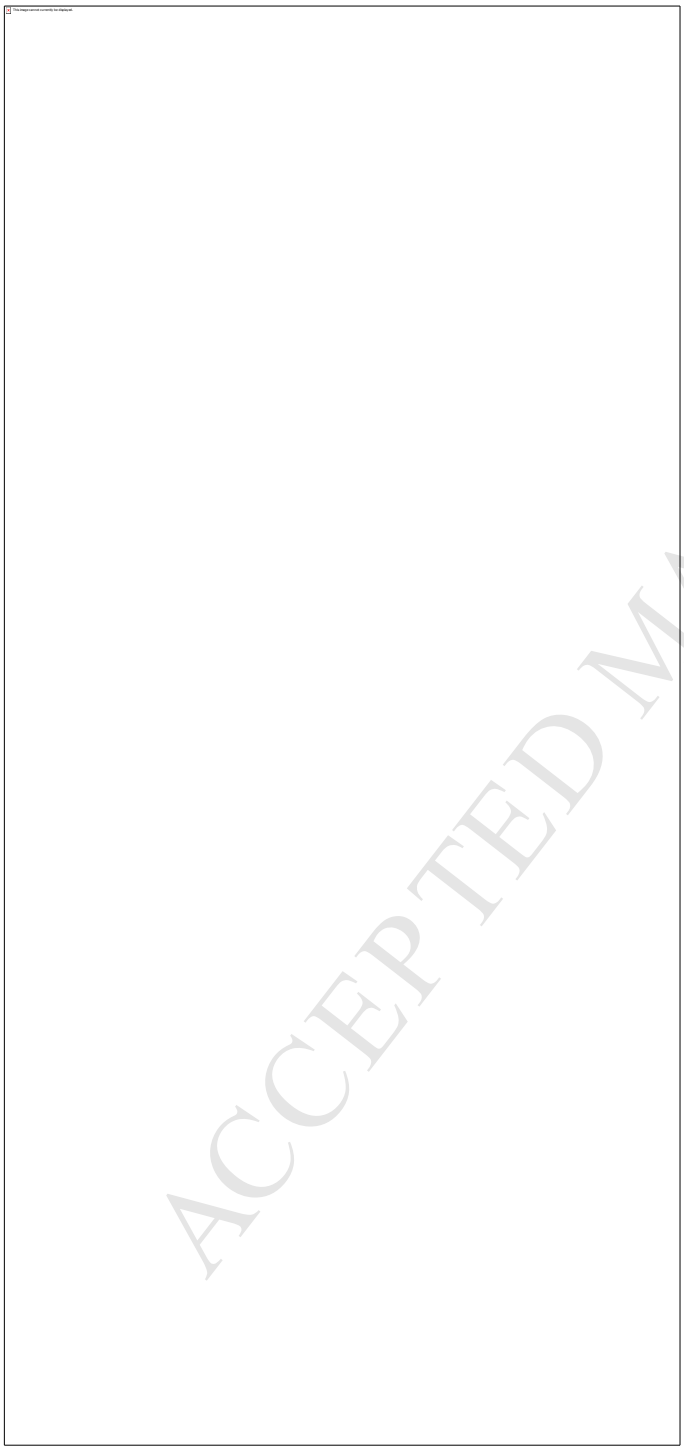
421

422

423 **Figure 3.** Receiver operating characteristic analysis for (**A**) ARIV and (**B**) ARIV index to predict VT/VF.

424 Optimal cut-off levels determined by Youden's index.

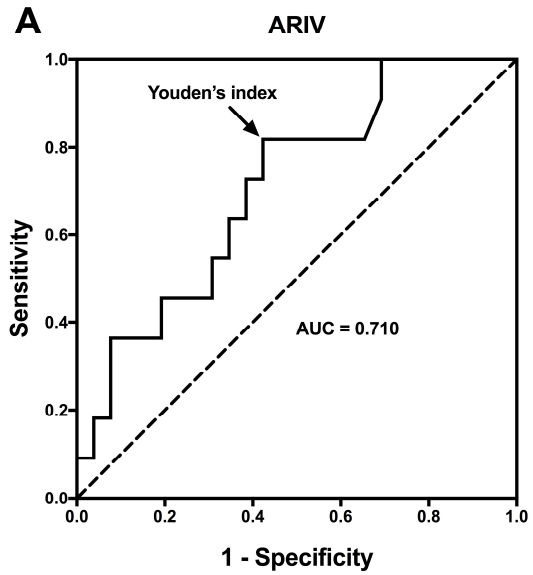
425

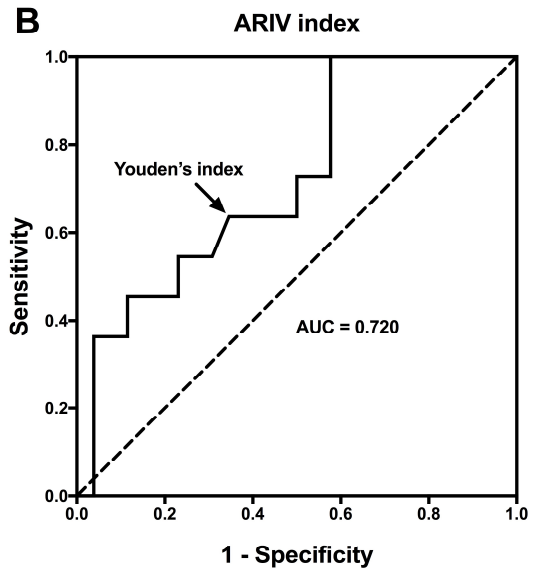


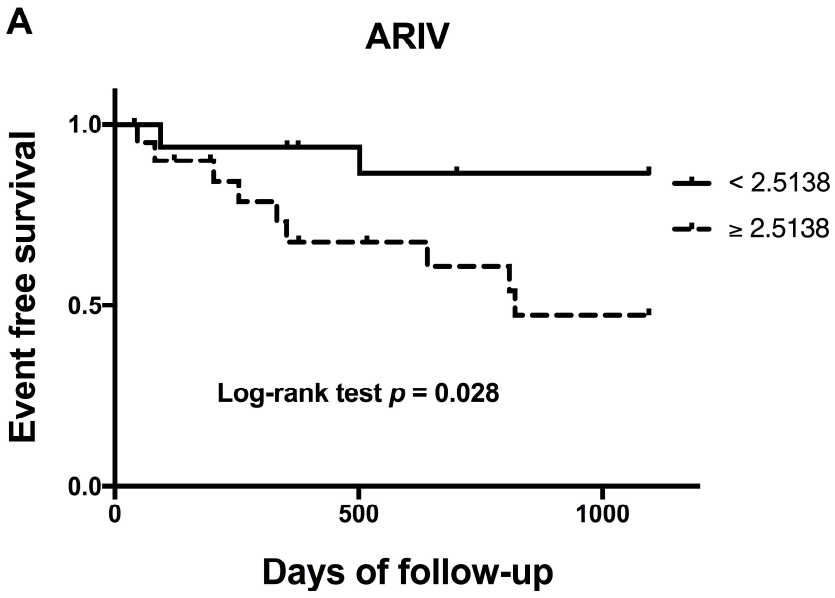
426

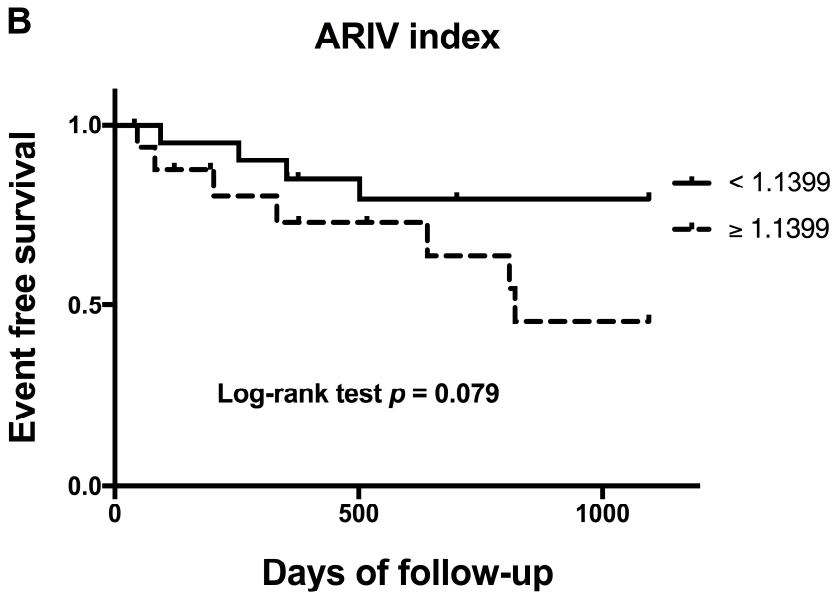
Figure 4. Kaplan-Meier curves for freedom from VT/VF events in patients dichotomized by ROC derived optimal cut-off values for (**A**) ARIV and (**B**) ARIV index.

Figure 5. Hazard ratios (adjusted for LVEF) for the association of mean ARI, ARIV and ARIV index with appropriate ICD therapy for VT/VF.






A
ARIV
Event free survival
1.0
0.5
0.0
0
500
1000
Days of follow-up
< 2.5138
≥ 2.5138
Log-rank test p = 0.028


B
ARIV index
Event free survival
1.0
0.5
0.0
0
500
1000
Days of follow-up
< 1.1399
≥ 1.1399
Log-rank test p = 0.079