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

Short Title: ARI variability and ventricular tachyarrhythmia

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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.

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.

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Repolarization variability analysis

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77 Raw digital LV UEG traces were analysed off-line using custom built MATLAB software

78 (MathWorks Inc, Mass). Recordings were separately low pass filtered at both 80 and 30 Hz

79 for calculation of activation times (ATs) and repolarization times (RTs), respectively. The

80 choice of two separate frequencies for AT and RT calculation allowed us to maintain the

81 sharp activation gradients required to identify ATs, whilst also successfully preserving the

82 morphology of the slower T-wave to identify RTs. Consecutive ARIs were calculated by

83 identifying AT and RT for each beat using the Wyatt method.[13,14,19,21,22] Automated

84 identification of ATs and RTs removed any observer variability. **Figure 1** shows examples of

85 the identification of ATs and RTs and the resultant ARI across various morphologies of

86 UEG. ARIV over the full 30s recording was then computed as.

87
$$ARIV = \frac{\sum_{i=1}^{n_{beats}-1}|ARI_{i+1} - ARI_i|}{(\sqrt{2} \times n_{beats})}$$

88 where n beats is the number of beats contained within the 30s period.[23] To account for the

89 possibility that the magnitude of beat-to-beat changes may depend on the intrinsic ARI

90 duration we introduced the ARIV index. The ARIV index provides a normalized value of the

91 ARIV relative to the mean ARI duration for each patient. The ARIV index was computed as.

92 $ARIV\ index = \frac{1}{ARI_{mean}} \times \frac{\sum_{i=1}^{n_{beats}-1}|ARI_{i+1}-ARI_i|}{(\sqrt{2} \times n_{beats})}$ where $ARI_{mean} = \frac{\sum_{i=1}^{n_{beats}} ARI_i}{n_{beats}}$
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Statistical Analysis

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97 Results are presented as mean±standard deviation for normally distributed variables and as

98 median and interquartile range (IQR) for non-normally distributed variables. The

99 independent-samples t-test was used to compare normally distributed continuous variables;

100 otherwise the Mann-Whitney U test was used. Categorical variables were compared using

101 Fisher's exact test. ROC analysis was performed using Youden's index to determine the

102 variable cut-off levels with optimal sensitivity and specificity for the endpoint. The estimated

103 cutoff values were retrospectively used to reclassify and dichotomize the study subjects into

104 high and low-risk categories. Kaplan-Meier survival analysis was used to address our

105 hypothesis testing the association between increased ARIV and probability of first

106 appropriate defibrillator therapy for VT/VF. Cox proportional hazards analyses were

107 performed separately for each variable of interest (Mean ARI, ARIV and ARIV index). A *P*

108 value of <0.05 was considered to be statistically significant for all tests. All statistical

109 analyses were performed using SPSS (IBM Switzerland, Switzerland) and Prism (GraphPad

110 Software Inc., California, USA).

111

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.

137   Comparing patients with ischemic and non-ischemic cardiomyopathy, there was no

138   difference in mean ARI (257.69±26.6 ms vs. 251.21±35.27 ms, p=0.554), ARIV (3.44±1.32

139   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).

140   LV ejection fraction (LVEF) showed no correlation with mean ARI (r_s=0.021, p=0.901),

141   ARIV (r_s=0.020, p=0.907) nor the ARIV index (r_s=0.039, p=0.818). Between patients with

142   primary and secondary prevention indications for CRT-D there was no difference in mean

143   ARI (257.34±32.35 ms vs. 241.97±26.99 ms, p=0.207). Differences in ARIV approached

144   significance (2.83±1.21 ms vs. 3.62±0.94 ms, p=0.051), and a significantly higher ARIV

145   index was seen in the secondary prevention group (1.12±0.5% vs. 1.49±0.34%, p=0.021). 23

146   of the patients were CRT responders and 14 non-responders (a CRT responder was defined as

147   a ≥5% improvement in LVEF from pre-implant). Between responders and non-responders

148   there was no observed difference in mean ARI (253.26±35.24 ms vs. 255.26±25.61 ms,

149   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.

150   1.23±0.53%, p=0.817).

151

152   **Implantable cardioverter-defibrillator therapy**

153   Following LV UEG recordings a mean follow-up of 23.6±13.6 months took place. During

154   follow-up 11 patients of 37 reached the endpoint of appropriate ICD therapy for VT/VF. ATP

155   was attempted and successful in 9 patients with VT. One patient with VT had successful

156   rescue shock therapy. One patient experienced VF with successful shock therapy. One patient

157   died from heart failure before reaching the endpoint. **Table 1** shows a comparison of clinical

158   characteristic of patients with and without subsequent appropriate ICD therapy for VT/VF**.**

159

160   ARIV was significantly greater in patients with subsequent VT/VF events vs. those without

161   VT/VF events (3.55±1.3 ms vs. 2.77±1.09 ms, p=0.047). The ARIV index was also

162 significantly greater in patients with subsequent VT/VF events vs. those without VT/VF

163 events (1.43±0.5% vs. 1.1±0.47%, *p*=0.036). No observed difference between groups was

164 found in mean ARI (249.34±27.91% vs. 256±33.31%, *p*=0.618). Receiver operating

165 characteristic (ROC) curve analysis (**Figure 3**) suggested cut-off levels for ARIV of ≥2.52

166 ms with 82% sensitivity (95% CI, 48-98%) and 58% specificity (95% CI, 37-77%) (AUC

167 0.71; 95% CI, 0.53-0.89; *p*=0.046) and ARIV index of ≥1.14% with 64% sensitivity (95% CI,

168 31-89%) and 65% specificity (95% CI, 44-83%) (AUC 0.72; 95% CI, 0.55-0.9; *p*=0.036) to

169 dichotomize into high/low risk for the endpoint of appropriate ICD therapy.

170

171 **Table 2** shows the clinical characteristics of patients with ARIV dichotomized at high and

172 low risk of VT/VF. When comparing subjects in the high-risk group for ARIV, 45%

173 experienced an episode of VT/VF by 3 years, compared with 11.8% in the low-risk group.

174 **Figure 4A** demonstrates the separation of the Kaplan-Meier curves at the variable cut-off for

175 ARIV (Mantel-Cox log-rank test, *p*=0.028). When comparing subjects in the high-risk group

176 for ARIV index, 43.8% experienced an episode of VT/VF by 3 years, compared with 19.0%

177 in the low-risk group. **Figure 4B** demonstrates the separation of the Kaplan-Meier curves at

178 the variable cut-off for ARIV index (Mantel-Cox log-rank test, *p*=0.079).

179

180 Mean ARI, ARIV and the ARIV index were tested separately in the multivariate Cox

181 proportional-hazards regression model for all VT/VF events, with the significant clinical

182 covariate LVEF. Low LVEF remained a significant predictor of appropriate ICD therapy for

183 VT/VF in all models tested. Mean ARI was not predictive (HR, 0.997; 95% CI, 0.977-1.017;

184 *p*=0.758). ARIV (HR, 1.623; 95% CI, 1.1-2.393; *p*=0.015) and the ARIV index (HR, 3.256;

185 95% CI, 1.222-8.676; *p*=0.018) were independent predictors of VT/VF (**Figure 5**). After

186 exclusion of patients with secondary indications for ICD therapy both ARIV (HR, 1.518;

187   95% CI, 1.009-2.285; *p*=0.045) and the ARIV index (HR, 2.87; 95% CI, 1.033-7.975;

188   *p*=0.043) remained independent predictors of VT/VF. After exclusion of patients on

189   amiodarone both ARIV (HR, 1.625; 95% CI, 1.114-2.371; p=0.012) and the ARIV index

190   (HR, 3.259; 95% CI, 1.262-8.411; p=0.015) remained independent predictors of VT/VF.

191

192 **DISCUSSION**

193

194 To our knowledge, this is the first study to demonstrate an association between VA risk and

195 increased LV BVR. The main findings were: 1) increased ARIV was associated with an

196 independent risk for VT/VF; 2) increased ARIV index (ARIV normalized to mean ARI)

197 remained an independent predictor for VT/VF; 3) there was no association between mean

198 ARI and VT/VF risk.

199

200 **Relation to prior work on repolarization variability**

201 The potential for stratification of individuals at risk of VA by means of repolarization

202 instability has been demonstrated with QT intervals from the surface ECG and RV

203 intracardiac electrograms. [6-11] Our findings of higher values of BBV of ARI in heart failure

204 patients experiencing VT/VF extends these observations to the level of the ventricular APD

205 and to the assessment of LV BVR. The ROC analysis found ARIV to be more sensitive than

206 the ARIV index in the prediction of ICD therapies. This was highlighted again in the Kaplan-

207 Meier analysis showing less separation in the curves for ARIV index when compared to

208 ARIV. These results would suggest that use of BBV of ARI to assess risk of VT/VF is more

209 reliable without adjustment for basic ARI.

210

211 A major component of QTV is heart rate variability and both the QT interval and APD are

212 strongly cycle length dependent [24,25]. As the majority of QTV studies occurred in the absence

213 of controlled cycle length it is technically challenging to separate heart rate driven QTV from

214 actual fluctuations in the QT interval. RV pacing to obtain cycle length control as employed

215 in our study removes the component of BVR due to heart rate variability.

216

217 It is accepted that the QT interval in a given ECG lead measures the interval between the

218 earliest depolarization and latest repolarization as projected onto the axis of that lead.[26] Given

219 its spatial heterogeneity the use of multi-lead ECG recordings to assess QTV has been

220 suggested but warrants further investigation.[26] The in vivo dispersion of ARIV and

221 correlations to various body surface ECG repolarization indices should be studied and could

222 be invaluable in our understanding of both QTV and ARIV.

223

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

225 In the present study, basic ARI in heart failure patients was not predictive of VT/VF events.

226 This is consistent with several studies reporting QT variability as a stronger predictor of

227 arrhythmia than QT prolongation. [2,3,5,7,8] These findings pointing to instability of

228 repolarization as a key factor would be in keeping with a cellular mechanism such as

229 proposed by Johnson et al[27], who also observed dissociation between APD variability and

230 basic APD under certain conditions.

231

232 Shortening of basic APD occurs in responders to CRT, whilst lengthening of basic APD

233 occurs in non-responders. [20] In vivo electrical remodelling in heart failure at the level of

234 BBV-APD needs to be studied prospectively and may offer insight into the impact of CRT on

235 VAs.

236

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

238 Several mechanisms have been proposed for the cellular basis of BBV-APD. Its apparently

239 random nature suggests the involvement of a stochastic process. Stochastic variation of fast

240 sodium current (I_{Na}), L-type calcium current (I_{CaL}), transient outward current (I_{to}), rapid

241 delayed rectifier (I_{kr}) and slow delayed rectifier (I_{ks}) potassium currents has been shown to

242   influence BBV-APD[23,28,29] with considerable interdependence between individual channels.[23]

243   Spontaneous calcium release from the sarcoplasmic reticulum exhibits BBV and in the

244   presence of calcium overload has been shown experimentally and in silico to generate BBV-

245   APD.[27] This mechanism was due to spontaneous calcium release from the sarcoplasmic

246   reticulum in late diastole reducing the subsequent calcium transient and hence reducing I_{CaL}

247   deactivation and prolonging the APD. However, the extent to which these effects seen in

248   isolated cells may be operative in the whole heart where cells are well coupled is uncertain

249   due to electrotonic interaction between cells.[30] Nevertheless under conditions of calcium

250   overload or reduced repolarization reserve, the effect of stochasticity on channel behavior

251   may be enhanced suggesting that these effects may become operative in pathological

252   conditions. BBV-APD may be arrhythmogenic either by the development of early or delayed

253   afterdepolarizations[27] or by enhanced dispersion of repolarization facilitating re-entry.

254

Clinical implications and future work

255

256   Risk stratification of patients at high risk of sudden cardiac death remains a major challenge.

257   In view of the multiple mechanisms involved it is unlikely that a single test would prove

258   sufficient and that a combination of clinical characteristics with a selection of stratification

259   tools may be more appropriate.[31] In this context, our study builds on the body of evidence

260   highlighting the potential for assessment of baseline BVR to form part of the risk

261   stratification tool.

262

263   Wijers et al[16] have highlighted the significance of the temporal behavior of ARI prior to the

264   onset of VA in dogs. Furthermore, this work demonstrated comparable short-term variability

265   of ARI between RV and LV. The potential for automated continuous real-time monitoring of

266   ARIV offers a novel future application for ICDs. However, the optimal recording location is

267   unknown and further work is needed to compare ARIV across multiple simultaneous

268   recording sites within the heart. Paroxysmal atrial arrhythmias may result in variable

269   ventricular filling in BiV paced patients and as such their influence on the ventricular ARI

270   within a CRT population should be studied.

271

272   **Limitations**

273   The study population was relatively small and as a single tertiary centre study the patient

274   group may not be representative of the usual CRT-D population. These results should be

275   validated in a larger multicenter prospective study of a primary prevention ICD indication

276   cohort. As ischemia testing was not conducted as part of the protocol we are unable to

277   determine the influence of ischemia on BBV of ARI. Our observations are confined to a

278   single LV epicardial site. Regional variation of the electrophysiological properties throughout

279   the ventricular myocardium makes it possible that other regions may have demonstrated

280   differing results. Short and long-term variation in ARIV should be studied in order to

281   determine the optimal duration and frequency of recordings for its use as a predictor of VA.[32]

282   Whilst strategies to analyze fractionated electrograms have been proposed,[33] a clear

283   consensus in their interpretation does not exist. In the context of the assessment of BVR this

284   could prove a challenge. Furthermore, the presence of a high ectopy burden or the lack of a

285   gradient to define repolarization time could exclude some patients altogether. In our study

286   14.0% of patients were excluded due to these limitations thus highlighting an area for future

287   work.

288

289   **Conclusion**

290   In patients with heart failure, increased ARIV is associated with increased risk of

291   spontaneous VT/VF. These results accord with observations in QTV and extend observations

292   to assessment of left ventricular BVR and specifically to the level of ventricular APD. Our

293   findings are supportive of the possible utility of BVR as an adjunct to risk stratification of

294   patients at risk of ventricular arrhythmia.

295

296   **<u>Acknowledgements</u>**

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421

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

423   therapy 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

424

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

426 optimal 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

427

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

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

430

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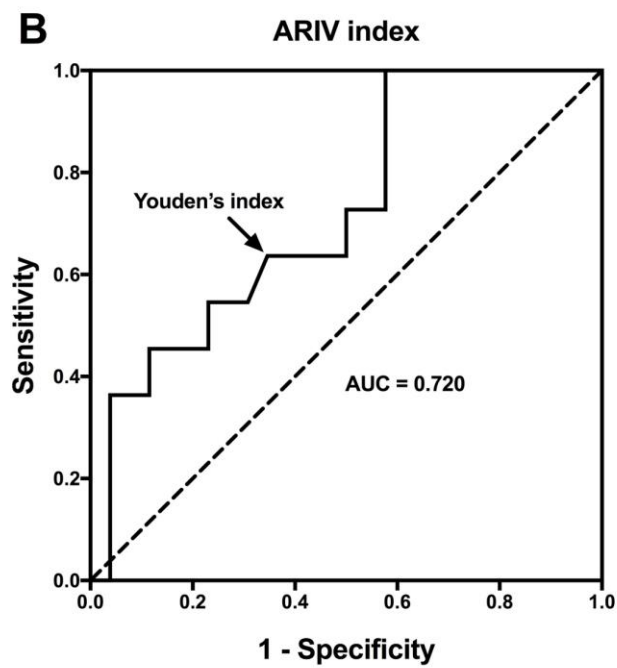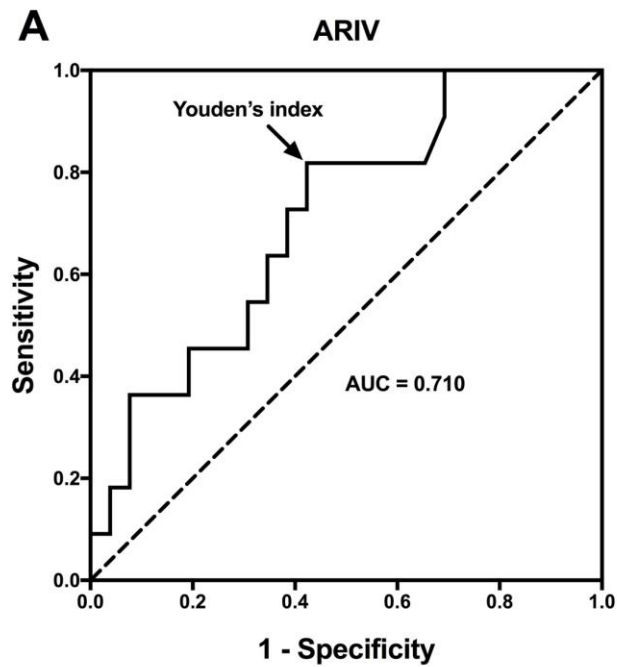
432 repolarization.

433
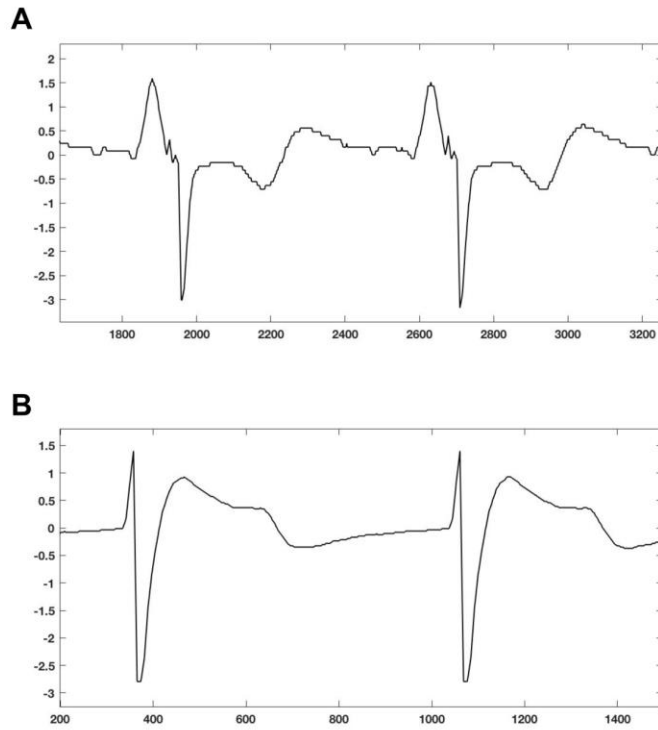
434

435 **Figure 3.** Receiver operating characteristic analysis for (**A**) ARIV and (**B**) ARIV index to

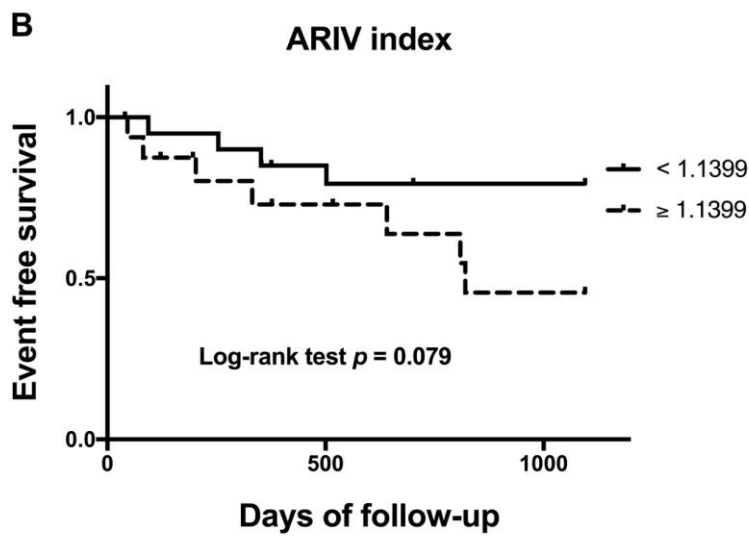436 predict VT/VF. Optimal cut-off levels determined by Youden's index.

437

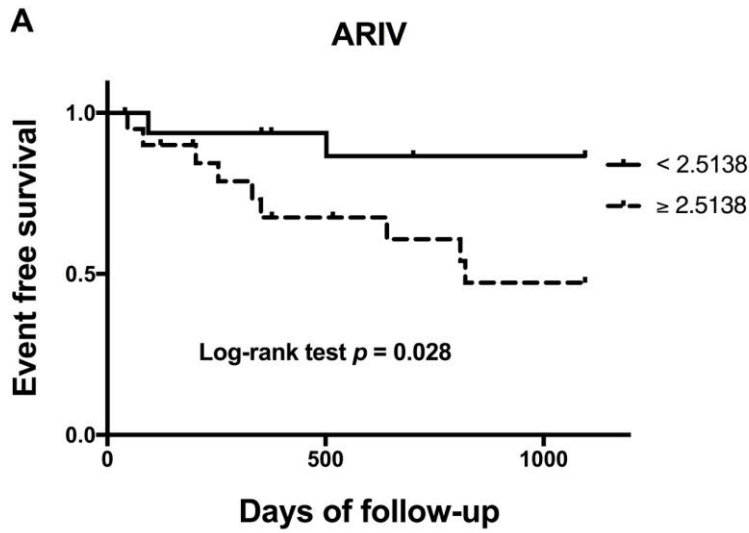

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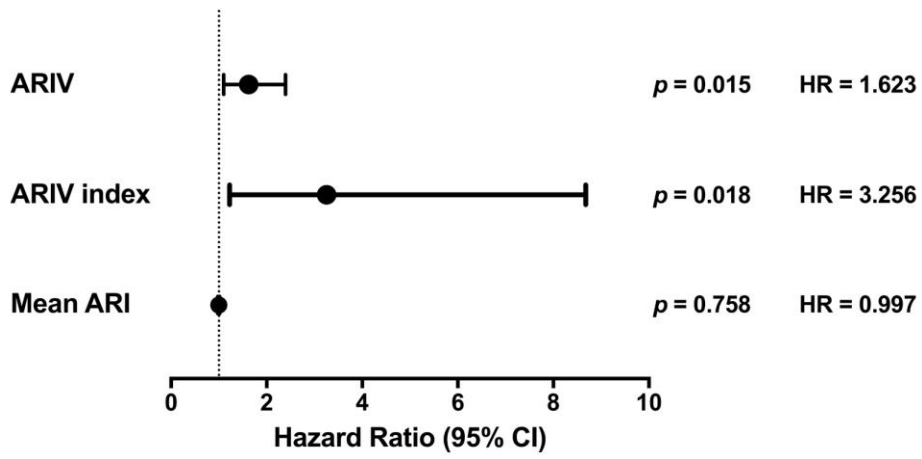440 **Figure 4.** Kaplan-Meier curves for freedom from VT/VF events in patients dichotomized by

441 ROC derived optimal cut-off values for (**A**) ARIV and (**B**) ARIV index.

442

443 **Figure 5.** Hazard ratios (adjusted for LVEF) for the association of mean ARI, ARIV and

444 ARIV index with appropriate ICD therapy for VT/VF.

445

446

447