Journal of Electrocardiology 57 (2019) 69–76

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

# Non-invasive electrocardiographic imaging in patients with idiopathic premature ventricular contractions from the right ventricular outflow tract: New insights into arrhythmia substrate

Leonor Parreira *, Pedro Carmo, Pedro Adragão, Joana Pinho, Margarita Budanova, Stepan Zubarev, Diogo Cavaco, Rita Marinheiro, João Carmo, Francisco Costa, Hugo Marques, Pedro Goncalves

*Hospital Luz Lisboa, Av Lusiada 1500-650, Lisboa, Portugal*

ARTICLE INFO

*Keywords:*
Non-invasive electrocardiographic imaging
ARI
Idiopathic premature ventricular contractions
Catheter ablation

ABSTRACT

*Aims:* The aim of this study was to use non-invasive electrocardiographic imaging (ECGI) to study the electrophysiological properties of right ventricular outflow tract (RVOT) in patients with frequent premature ventricular contractions (PVCs) from the RVOT and in controls.
*Methods:* ECGI is a combined application of body surface electrocardiograms and computed tomography or magnetic resonance imaging data. Unipolar electrograms are reconstructed on the epicardial and endocardial surfaces. Activation time (AT) was defined as the time of maximal negative slope of the electrogram (EGM) during QRS, recovery time (RT) as the time of maximal positive slope of the EGM during T wave, Activation recovery interval (ARI) was defined as the difference between RT and AT. ARI dispersion (Δ ARI) and RT dispersion (Δ RT) were calculated as the difference between maximal and minimal ARI and RT respectively. We evaluated those parameters in patients with frequent PVCs from the RVOT, defined as >10.000 per 24 h, and in a control group.
*Results:* We studied 7 patients with frequent RVOT PVCs and 17 controls. Patients with PVCs from the RVOT had shorter median RT than controls, in the endocardium and in the epicardium, respectively 380 (239–397) vs 414 (372–448) ms, $p = 0.047$ and 275 (236–301) vs 330 (263–418) ms, $p = 0.047$. The dispersion of ARI and of RT in the epicardium was higher than in controls, Δ ARI of 145 (68–216) vs 17 (3–48) ms, $p = 0.001$ and Δ RT of 201 (160–235) vs 115 (65–177), $p = 0.019$.
*Conclusion:* In this group of patients we found a shorter median RT in the endocardium and in the epicardium of the RVOT and a higher dispersion of the ARI and RT across the epicardium in patients with PVCs from the RVOT when comparing to controls.



## Introduction

It has been accepted for years that idiopathic premature ventricular contractions (PVCs) with origin in the right ventricular outflow tract (RVOT) are benign in the absence of structural heart disease [1]. They are thought to result from triggered activity and most studies do not describe abnormal findings on the electroanatomical mapping. However, we have previously reported the presence of low voltage electrograms in patients with PVCs from the RVOT and apparently normal hearts. The presence of low voltage was associated with the presence of coved type ST elevation in V1 obtained in the second intercostal space [2].

Body surface electrocardiographic mapping was firstly used almost thirty years ago. That system consisted of eighty-seven unipolar electrodes recording simultaneously from the surface of the thorax [3]. Those authors studied with that system the patterns of depolarization and repolarization in a number of pathological situations. Subsequently, experimental work done in isolated pig hearts has demonstrated that the activation recovery interval (ARI), estimated from unipolar electrograms recorded at the surface of the heart, is independent of the activation time (AT), and can be used as an appropriate surrogate of action potential duration (APD) and repolarization [4,5].

ARI has been defined as the difference between recovery time (RT) measured at the steepest ascending slope of the T wave in the unipolar electrogram and the AT, measured at the steepest downslope of the QRS in the unipolar electrogram. In a recent study, ARI measurement was assessed with a type of non-invasive electrocardiographic imaging similar to ours. The values obtained non-invasively correlated with the intracardiac measurements [6].

* Corresponding author at: Av Dr António Rodrigues Manito, 114 2900-064 Setúbal, Portugal.
*E-mail address:* leonor.parreira@gmail.com (L. Parreira).

https://doi.org/10.1016/j.jelectrocard.2019.08.046
0022-0736/

Depolarization and repolarization have been extensively studied in Brugada syndrome, to explain the occurrence of the ST elevation, giving rise to two different theories, the depolarization [7] and the repolarization theory [8]. Zhang et al. [9], obtained panoramic maps of activation and repolarization of patients with Brugada syndrome using a non-invasive electrocardiographic imaging system (ECGI) different from ours. The ECGI is not the same as body surface electrocardiographic mapping, since the former is capable of reconstructing and displaying the unipolar electrograms on the surface of the heart. Using the ECGI, the authors concluded that both abnormal repolarization and abnormal conduction are present in the substrate, leading to steep repolarization gradients and delayed activation. The same group also studied the repolarization pattern in patients with early repolarization [10], and observed the presence of steep repolarization gradients caused by localized shortening of APD.

Recently, a new ECGI system has emerged, which has the ability of obtaining simultaneous epicardial and endocardial unipolar electrograms [11]. This system has been validated for mapping of PVCs [12] and structural ventricular tachycardia [13]. The evaluation of repolarization using this system was first reported by Rudic et al. [14] in patients with Brugada syndrome and with right bundle branch block.

In the current study, using the same ECGI system as reported in the previous study, we characterized the epicardial and endocardial electrophysiological substrate of RVOT in patients with frequent PVCs originating in that region.

## Material and methods

### *Study patients*

From February 2018 to February 2019, we retrospectively studied 24 consecutive patients, 7 patients with frequent PVCs from the RVOT, defined as >10.000 per 24 h, and a control group of 17 patients without PVCs or with PVCs from another location. Patients underwent electrophysiological study and catheter ablation of the arrhythmia and had an ECGI performed before the ablation. All patients underwent transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler echocardiography and 12-lead electrocardiograms (ECG), and whenever there were symptoms that might suggest the presence of coronary heart disease, a treadmill exercise test was done. All patients with PVCs from the RVOT had a cardiac magnetic resonance imaging (cMRI) performed to exclude the presence of RVOT anomalies.

Patients were excluded if the intrinsic rhythm was not sinus rhythm, if the ECG showed conduction abnormalities or the investigation, including cardiac magnetic resonance imaging, suggested presence of disease in the RVOT.

We studied with the ECGI the endocardial and epicardial electrophysiological substrate of the RVOT in both groups.

### *12 lead ECG*

All patients performed a standard ECG, and we assessed the presence of negative T wave beyond V1, the presence of ST elevation in V1 and the presence of a coved-type shaped ST segment.

### *Non-invasive electrocardiographic imaging*

The ECGI was performed with the novel non-invasive epicardial and endocardial electrocardiographic imaging system, Amycard 01C EP (EP Solutions SA, Switzerland), before the invasive electrophysiological study. This method has been previously described [11]. However, briefly it consists of a multichannel ECG amplifier recorder that analyses up to 224 electrodes placed on the patient's torso. For the purpose of this study the ECG recordings were analyzed during sinus rhythm in all patients with PVCs from RVOT and controls. They were recorded with a 0.05- to 500-Hz bandpass filter, were digitized with the sampling rate of 1000 samples/s and exported to the Amycard laboratory software. The map was done with a single beat and, except for patients with bigeminy we used a beat at least three cycles away from the previous PVC.

Afterwards, with the electrodes in place, an ECG-gated computed tomography (CT) scanning of the heart and thorax with intravenous contrast, was performed with a third-generation 192-slice dual-source SOMATOM Force (Siemens Healthcare). Scanning of the torso and heart was performed simultaneously. The CT data was imported in the DICOM format into the Amycard laboratory software, and a 3-dimensional torso and heart model was obtained from the CT segmentation (Supplementary Fig. A1). Body surface ECG data were processed by Amycard system, using its inverse problem solution software [11] in combination with heart and torso anatomy, allowing for reconstruction of unipolar electrograms at approximately 2500 points on epicardium and endocardium.

We obtained the maps in the advanced mode based on the first derivative of the unipolar electrogram (Fig. 1). In that mode, the system performs automatic assessment of the local AT and RT and displays in a color-coded fashion the ARI maps, based on automatic ARI measurements (Fig. 2). The evaluation of AT, RT and ARI with the ECGI system used in our study has been performed previously in patients with right bundle brunch block, Brugada syndrome and normals [14]. Validation of noninvasive reconstruction unipolar electrograms at the

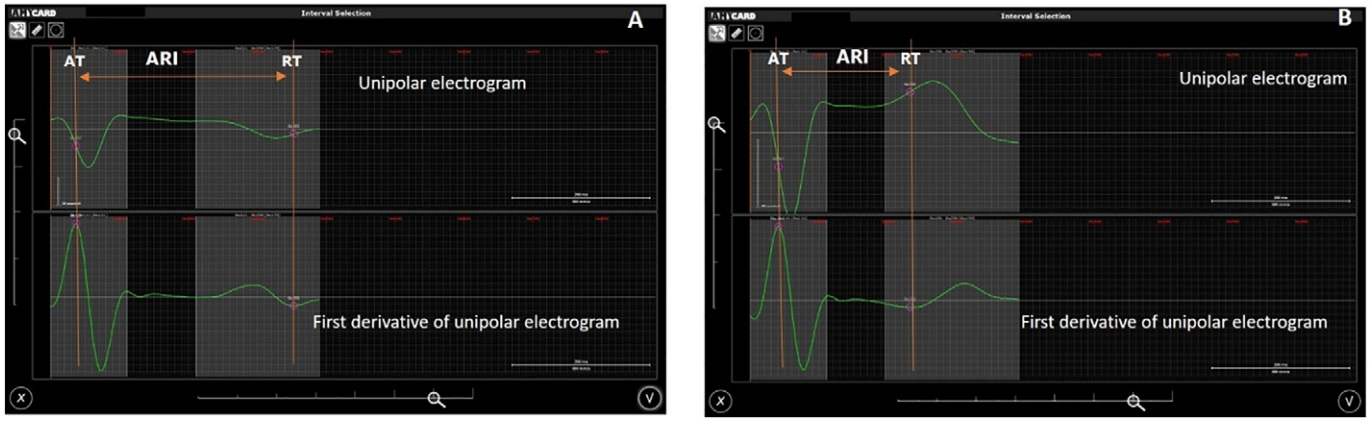


**Fig. 1.** Advanced mode based on the first derivative of the unipolar electrogram. Panel A advanced mode based on the first derivative of the unipolar electrogram with a negative T wave (above). The RT is measured in the ascending limb of the T wave. Panel B ARI measurement in case of a unipolar electrogram with a positive T wave (above). The RT is measured in the ascending limb of the T wave as well. The ARI is shorter in the positive T wave electrogram. AT: activation time; RT recovery time; ARI: activation recovery interval.

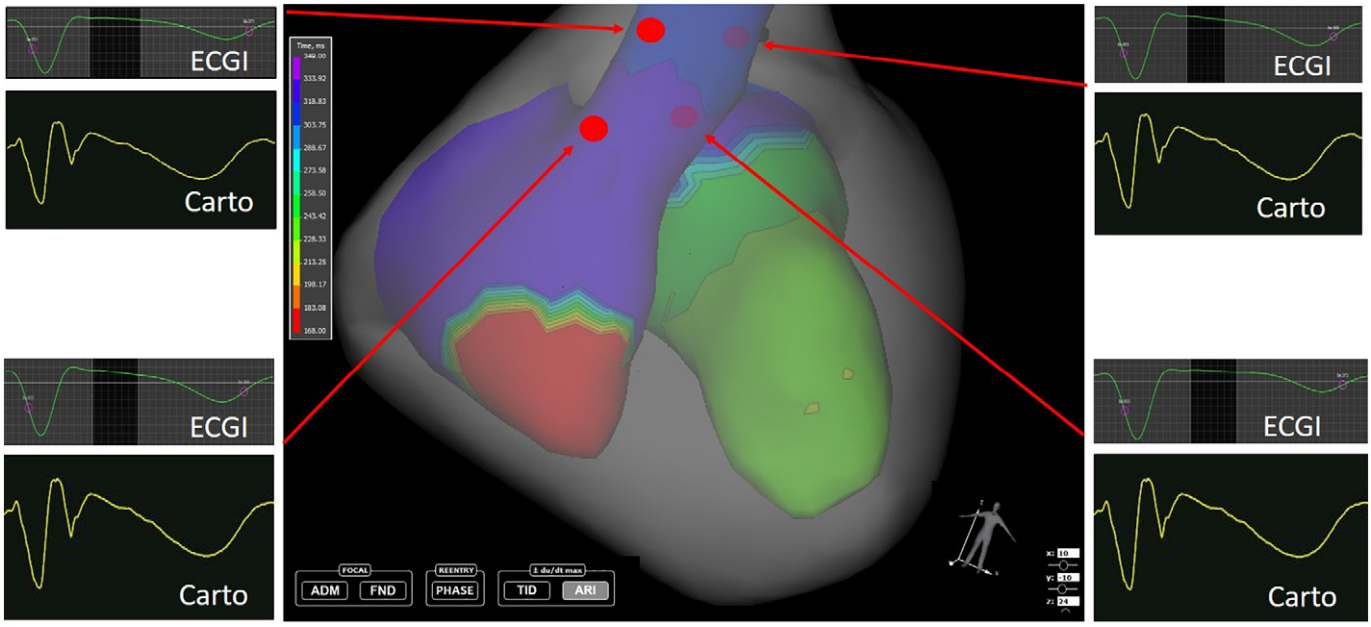


**Fig. 2.** Automatic ARI map. Automatic ARI map in the endocardium showing absence of ARI dispersion (ARI varies between 330 and 320 ms). Red dots correspond to the endocardial points collected both with the ECGI and Carto invasive mapping (arrows). ARI: activation recovery interval.

epicardial surface when assessing repolarization, has been performed before [15]. Our system has not been systematically validated for repolarization assessment, but a previous study has shown some limited data on its validation [14].

The accuracy of the automatic measurements depends on the quality of the unipolar electrogram and, additional filtering can help to attenuate noise and improve the reliability of the measures. Usually, when studying the depolarization an additional 50 Hz filter is used [11]. However, when studying the repolarization, a 30 Hz filter is advised [16]. Duijvenboden et al. [ 16], have demonstrated experimentally that the best accuracy is obtained when using a filter at a cutoff frequency of 10 to 15 Hz. We customized the filter between 30 and 15 Hz in order to obtain the best signal to noise ratio of the unipolar electrograms (Supplementary Figs. A2 and A3).

Spatial properties of the EP substrate were determined by dividing the RVOT in 24 segments, 16 in the endocardium and 8 in the epicardium. The RVOT endocardium was divided into free wall and septum. Each wall was further divided into an anterior and posterior part, and finally from pulmonary valve to the assumed location of the His bundle area, was divided in 4 segments [17]. The RVOT epicardium was divided in anterior and posterior wall and each wall further divided in 4 segments from the pulmonary valve to the assumed location of the His bundle area (Fig. 3).

We evaluated the presence of T wave inversion, ST segment elevation defined as elevation of >1 mV above the baseline and the presence of a coved-type ST segment in the unipolar electrogram in any of the 24 segments.

AT, referenced to the beginning of the QRS in ECG lead II, was determined by the maximal negative slope of the EGM during QRS. RT, referenced to the beginning of the QRS in ECG lead II, was determined by the maximal positive slope of the EGM during T wave, regardless the morphology of the T wave (Fig. 1).

Epicardial and endocardial activation duration (AD) was defined as the interval between the earliest and the latest AT.

For the epicardium and the endocardium separately, we calculated the median, maximal and minimal values of AT, RT and ARI for all segments. ARI dispersion and RT dispersion were calculated as the difference between maximal and minimal ARI and RT respectively, in the endocardium and the epicardium (Δ ARI) and (Δ RT).

### *Statistical analysis*

SPSS version 23 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis. A Kolmogorov-Smirnov test was performed to test for the normality of continuous variables and in the presence of normality, data is expressed as medium and standard deviation and, in its absence, as median and interquartile range (IQR). Data is present as frequencies and percentages for categorical variables. Categorical variables were compared with the use of Fischer's exact-test or the chi-square test as appropriate. Continuous variables were compared with the use of Student's t-test or Mann Whitney test, as appropriate. The Wilcoxon test for continuous variables and the McNemar test for categorical variables were used to compare values from epicardial and endocardial measurements. Linear regression was used to evaluate the effect of AT and RT on ARI. A value of $p < 0.05$ was considered statistically significant.

### *Ethics*

All patients signed the informed consent form and the study was approved by the Ethics Committee for Health of Hospital da Luz. The study is in compliance with the Helsinki Declaration.

## Results

### *Study population*

24 patients were enrolled, 7 patients with PVCs from the RVOT, and 17 patients in the control group (9 with PVCs outside the RVOT and 8 patients with supraventricular arrhythmias). Two subjects had structural heart disease both in the control group, 1 had a mitral prothesis and the second had a previous history of myocarditis without involvement of the right ventricle. The two groups did not differ in relation to age or gender (Table 1).

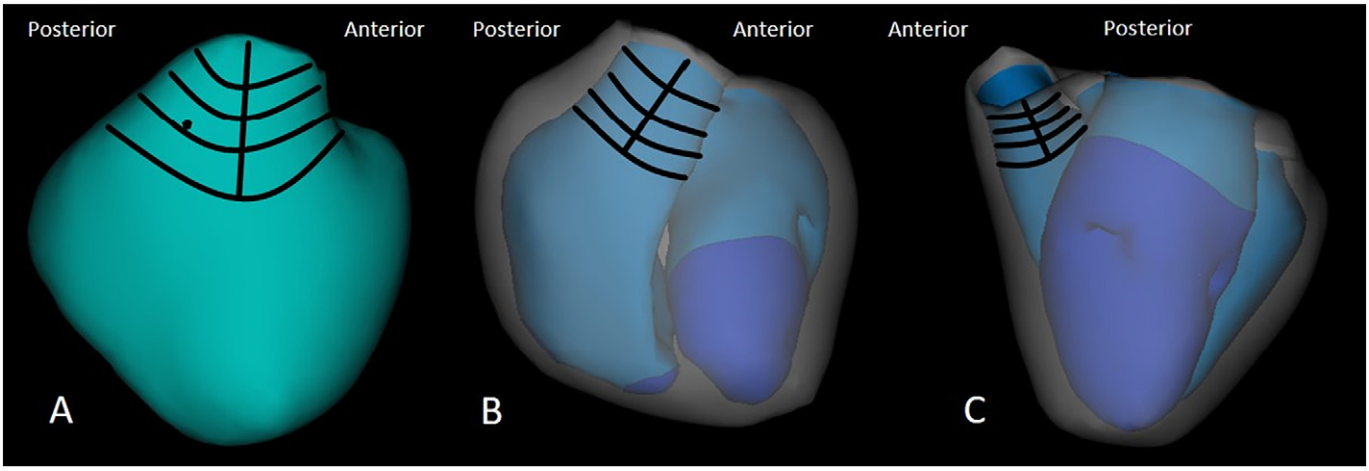


**Fig. 3.** RVOT segmentation. Schematic display of the 24 segments analyzed. Epicardium of the RVOT (A), free wall of the RVOT (B) and septal wall of the RVOT (C). RVOT: right ventricular outflow tract.

*12 lead ECG*

Patients with PVCs from the RVOT had more frequently ST elevation in the V1-V3 leads 71% versus 18%, $p = 0.021$. (Table 1).

*Non-invasive electrocardiographic imaging*

*Endocardium*

ST segment elevation was observed in at least one segment of the endocardium in all patients with PVCs from the RVOT versus 7 patients (41%) in the control group, $p = 0.019$. This ST elevation was also present in the intracardiac unipolar electrograms obtained with Carto (Fig. 4 and Supplementary Fig. A4). Presence of negative T waves or coved-type ST elevation was not significantly different in both groups (Table 2). The median AT was not significantly different between groups and the activation was almost simultaneous across the RVOT, in both groups, with AD of approximately of 0 ms. Patients with PVCs from the RVOT had a shorter median RT of 380 (239–397) versus 414 (372–448) ms, $p = 0.047$, but the ARI was not significantly different, and we found no ARI or RT dispersion across the endocardium in both groups.

*Epicardium*

The two groups did not differ in relation to the presence of ST elevation or T wave inversion. The median AT was not significantly different between groups. The median RT was shorter in the epicardium, in patients with PVCs from the RVOT as well as the minimal ARI, respectively, 275 (236–301) versus 330 (263–418) ms, $p = 0.047$ and 170 (154–196) versus 222 (200−320) ms, $p = 0.004$.

We observed the presence of RT and ARI dispersion in the epicardium of the RVOT in patients with PVCs from the RVOT, that was not present in controls, Δ RT of 201 (160–235) vs 115 (65–177), $p = 0.019$ and Δ ARI of 145 (68–216) versus 17 (3–48) ms, $p = 0.001$ (Fig. 4).

*Epicardium-endocardium differences*

Presence of a negative T wave in the unipolar electrogram of at least one segment of the RVOT, was more frequent in the endocardium that in the epicardium as was the case of ST elevation (Table 3). As would be expected the median AT was significantly shorter in the endocardium 55 (46–66) versus 63 (53–69) ms, $p < 0.0001$. The AD in the endocardium was also shorter leading to an almost simultaneous activation of the RVOT, with an AD of 0 (0–0.75) versus 8 (2.3–17) ms, $p < 0.0001$ (Table 3). The RT and ARI were significantly shorter in the epicardium, respectively 303 (261–386) versus 396 (360–439), $p = 0.001$ and 234 (199–342) versus 335 (319–354) ms, $p = 0.001$. Dispersion of RT and ARI was observed only in the epicardium.

*Association between ARI and AT or RT*

ARI was linearly associated with RT, $R^2 = 0.864$, $p < 0.0001$ for the endocardium and $R^2 = 0.831$, $p < 0.0001$ for the epicardium), but not with the AT (Fig. 5).

**Table 1**
Baseline characteristics in the two groups.

| | Overall sample ($n = 24$) | RVOT PVCs ($n = 7$) | Controls ($n = 17$) | P value[a] |
|---|---|---|---|---|
| Demographic data | | | | |
| Age mean (SD) in years | 57 (12) | 58 (10) | 57 (13) | 0.824 |
| Male gender, n (%) | 16 (67) | 4 (57) | 12 (71) | 0.647 |
| Structural heart disease, n (%) | 2 (8) | 0 (0) | 2 (12) | 0.9999 |
| Medications | | | | 0.9999 |
| No medication, n (%) | 16 (67) | 5 (71) | 11 (65) | |
| Betablockers, n (%) | 5 (20) | 1 (14) | 4 (23) | |
| Sotalol, n (%) | 1 (4) | 0 (0) | 1 (6) | |
| Propafenone, n (%) | 1 (4) | 1 (14) | 0 (0) | |
| Amiodarone, n (%) | 1 (4) | 0 (0) | 1 (6) | |
| ECG | | | | |
| (−) T wave beyond V1, n (%) | 3 (13) | 2 (29) | 1 (6) | 0.194 |
| Coved-type ST segment, n (%) | 6 (25) | 3 (57) | 3 (43) | 0.397 |
| V1-V3 ST elevation, n (%) | 8 (33) | 5 (71) | 3 (18) | **0.021** |

Values are presented as mean (standard deviation) and n (%).
RVOT: right ventricular outflow tract; PVCs: premature ventricular contractions.
[a] $p$ values were calculated using the $t$-test for continuous variables and the Fisher test for categorical variables.

## Discussion

This is the first study in man, reporting on simultaneous epicardial and endocardial electrocardiographic mapping, to evaluate the electrophysiological substrate of idiopathic PVCs from the RVOT. Yang et al. [6] have previously studied the distribution of ARI in patients with PVCs from the RVOT, however those authors assessed the ARI during the PVCs instead of during sinus rhythm.

The usefulness of the ECGI to evaluate repolarization, is that it allows a panoramic view of global segmental repolarization. In our study, patients with PVCs from the RVOT as well as controls, displayed negative

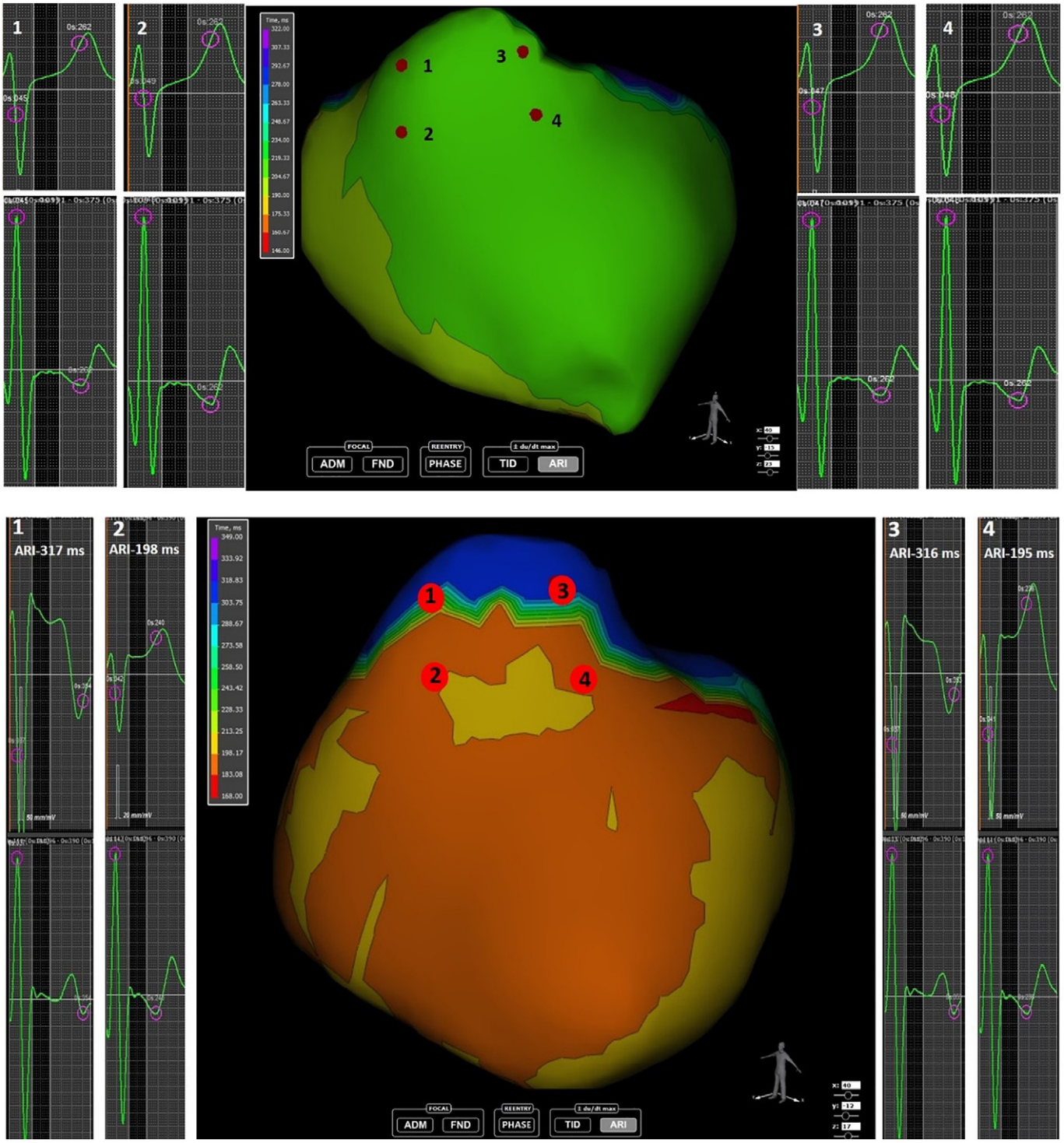


**Fig. 4.** Automatic ARI map in a control patient and in a patient with PVCs from the RVOT. Epicardial automatic ARI map of a control patient showing absence of ARI dispersion in the RVOT (top panel), dots correspond to the respective ECGI unipolar electrogram and below its first derivative. In the bottom panel a patient with PVCs from the RVOT showing a dispersion of ARI with higher values in the upper RVOT [1 and 3] segments and significantly lower values in the segments below (2and 4). ARI: activation recovery interval; RVOT: right ventricular outflow tract; PVCs: premature ventricular contractions.

T waves in at least one segment in the endocardium or in the epicardium in most cases. It has been suggested that the presence of negative T waves may disqualify the calculation of RT and ARI [18]. According to those authors the methodology of measuring the RT at the ascending limb of the T wave may lead to overestimation of the RT and consequently of ARI. However, several experimental studies indicate the contrary [19,20]. The time instant of maximal dV/dt of the T wave on epicardial unipolar electrograms, closely corresponds to the instant of local ventricular recovery independently of T wave morphology. More recently, Coronel et al. [4], have elegantly demonstrated that repolarization time in the local unipolar electrogram is to be measured at the positive slope of the T wave. Those authors measured ARI as the interval between dV/dt minimum of the QRS complex and the dV/dt maximum of the T wave (irrespective of the polarity of the T wave). In all instances,

**Table 2**
Non-invasive electrocardiographic imaging data in the two groups.

| | Overall sample ($n = 24$) | RVOT PVCs (n = 7) | Control (n = 17) | P value[a] |
|---|---|---|---|---|
| Endocardium of RVOT | | | | |
| ST elevation, n (%) | 14 (58) | 7 (100) | 7 (41) | **0.019** |
| Negative T wave, n (%) | 22 (92) | 5 (71) | 17 (100) | 0.076 |
| Coved-type ST segment, n (%) | 11 (46) | 4 (57) | 7 (41) | 0.659 |
| Median ST elevation (IQR) in mV | 1(0.12–1) | 1 (1–2) | 0.5 (0–1) | **0.013** |
| Median AT (IQR) in ms | 55 (46–66) | 55 (41–61) | 56 (49–94) | 0.455 |
| AD, median (IQR) in ms | 0 (0–0.75) | 0 (0–1) | 0 (0–0) | 0.534 |
| Median RT (IQR) in ms | 396 (360–439) | 380 (239–397) | 414 (372–448) | **0.047** |
| Median ARI (IQR) in ms | 335 (319–354) | 322 (253–339) | 337 (323–367) | 0.130 |
| Maximal ARI, median (IQR) in ms | 342 (322–359) | 322 (257–33) | 344 (327–374) | 0.075 |
| Minimal ARI, median (IQR) in ms | 334 (316–353) | 322 (253–339) | 337 (323–367) | 0.099 |
| Δ ARI, median (IQR) in ms | 0 (0–2.50) | 8 (0–1.50) | 0 (0–1.0) | 0.804 |
| Δ RT, median (IQR) in ms | 0.0 (0.0–1.75) | 0.0 (0.0–2.0) | 0.0 (0.0–3.0) | 0.757 |
| Epicardium of RVOT | | | | |
| ST elevation, n (%) | 6 (25) | 3 (43) | 3 (18) | 0.307 |
| Negative T wave, n (%) | 15 (63) | 5 (72) | 10 (59) | 0.669 |
| Coved-type ST segment, n (%) | 5 (21) | 2 (29) | 3 (18) | 0.659 |
| Median ST elevation (IQR) in mV | 0 (0–0) | 0 (0–0.5) | 0 (0–0) | 0,534 |
| Median AT (IQR) in ms | 63 (53–69) | 56 (53–64) | 64 (52–101) | 0.318 |
| AD, median (IQR) | 8 (2.3–17) | 9 (4–14) | 5 (1–19) | 0.455 |
| Median RT (IQR) in ms | 303 (261–386) | 275 (236–301) | 330 (263–418) | **0.047** |
| Median ARI (IQR) in ms | 234 (199–342) | 201 (193–246) | 240 (205–356) | 0.166 |
| Maximal ARI, median (IQR) in ms | 317 (217–391) | 363 (237–391) | 255 (213–390) | 0.619 |
| Minimal ARI, median (IQR) in ms | 205 (182–245) | 170 (154–196) | 222 (200–320) | **0.004** |
| Δ ARI, median (IQR) in ms | 32 (6–140) | 145 (68–216) | 17 (3–48) | **0.001** |
| Δ RT, median (IQR) in ms | 133 (108–222) | 201 (160–235) | 115 (65–177) | **0.019** |

Values are presented as median (interquartile range) or n (%).
RVOT: right ventricular outflow tract; PVCs: premature ventricular contractions; AD: activation duration; AT: activation time; RT: recovery time; ARI: activation recovery interval.
[a] p values were calculated using the Mann-Whitney-*U* test for continuous variables and the Fisher test for categorical variables.

repolarization of the monophasic action potential coincided with positive slope of the T wave.

The first important finding in our study was the observation of ST elevation on the endocardial and epicardial unipolar electrograms more frequently in patients with PVCs from the RVOT that in controls. The difference only reaches statistical significance in the endocardium, and one possible explanation for this may have to do with the small sample size. We have previously described the presence of ST elevation in the 12 lead ECG of patients with PVCs from the RVOT that corresponded to the presence of low voltage in the RVOT assessed with electroanatomical mapping [ 2]. With the ECGI we had the ability to evaluate the presence of ST elevation in the RVOT itself and confirmed this finding. We do not know the reason or the implications of this ST elevation in the genesis of the disease. However, we can speculate that it may have to do with the dispersion of the repolarization as is the case of Brugada [9] or early repolarization syndromes [10]. The presence of ST elevation was associated with ARI dispersion in both Brugada and early repolarization syndromes. These two clinical entities were studied with ECGI to assess the repolarization properties of the epicardium. In the case of Brugada syndrome the authors described the presence of ST elevation and negative T waves in association with an ARI dispersion and prolongation of the RT [9]. In the early repolarization syndrome, the same authors also found ST elevation at local epicardial reconstructed unipolar electrograms at sites with ARI dispersion however in this case, associated with a shortening of the RT and ARI [10]. The ECGI used in these two studies only evaluates epicardial electrograms. Rudic et al. [14] with an ECGI identical to ours studied the epicardial and endocardial repolarization in patients with Brugada syndrome. They reported the presence of ST elevation and T wave inversion in the unipolar electrograms recorded both in the epicardial and endocardial surface of the RVOT [14]. The authors also reported increased AT in the endocardium and significantly prolonged ARI in the epicardium in comparison to controls.

**Table 3**
Endocardial versus epicardial differences in overall sample.

| | Endocardium (n = 24) | Epicardium (n = 24) | P value[a] |
|---|---|---|---|
| Negative T wave, n (%) | 22 (92) | 15 (63) | **0.039** |
| Coved-type ST segment | 11 (46) | 5 (21) | 0.070 |
| ST elevation, n (%) | 14 (58) | 6 (25) | **0.008** |
| Median ST elevation (IQR) in mV | 1 (0.12–1) | 0 (0–0) | **0.036** |
| Median AT (IQR) in ms | 55 (46–66) | 63 (53–69) | <**0.0001** |
| AD, median (IQR) | 0 (0–075) | 8 (2.3–17) | <**0.0001** |
| Median RT (IQR) in ms | 396 (360–439) | 303 (261–386) | **0.001** |
| Median ARI (IQR) in ms | 335 (319–354) | 234 (199–342) | **0.001** |
| Δ ARI, median (IQR) in ms | 0 (0–2.50) | 32 (6–140) | **0.001** |
| Δ RT, median (IQR) in ms | 0.0 (0.0–1.75) | 133 (108–222) | <**0.0001** |

Values are presented as median (interquartile range) or n (%).
AD: activation duration; AT: activation time; RT: recovery time; ARI: activation recovery interval.
[a] p values were calculated using the Wilcoxon test for continuous variables and the McNemar test for categorical variables.

When comparing our endocardial and epicardial results, the finding of an AT shorter in the endocardium or an RT shorter in the epicardium was predictable. It is well known that depolarization starts in the endocardium and the repolarization starts in the epicardium [21] and therefore, some of our findings are expected. Likewise, since the ARI is the difference between the RT and the AT, it was shorter in the epicardium as anticipated. When comparing groups, the AT was not significantly different between the group with PVCs from the RVOT and controls either in the epicardium or the endocardium. However, the median RT was shorter both in the endocardium and the epicardium. Median ARI was also shorter in patients with PVCs from the RVOT but did not reach statistical significance probably due to the small sample dimension.

The reason for this shorter RT is unknown. We hypothesize that just as it is possible that the refractory period may decrease in result of rapid

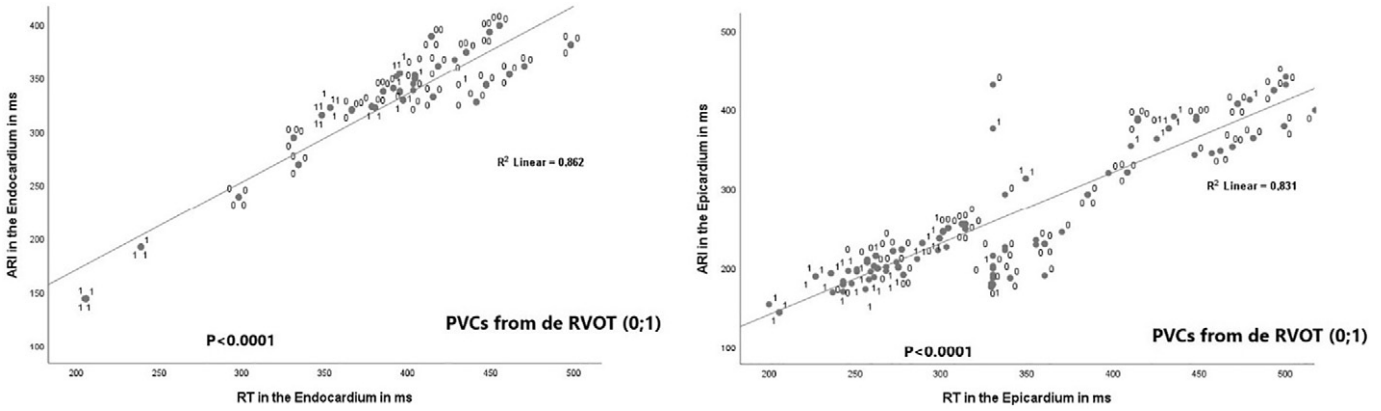


**Fig. 5.** Association between the RT and the value of ARI in the endocardium and epicardium in all segments analysedanalyzed.ARI: activation recovery time; RT: recovery time; PVC: premature ventricular contractions; RVOT: right ventricular outflow tract.0: control patients; 1: patients with PVCs from the RVOT. The rest of the paragraphs are the legends of supplementary figures A1, A2, A3 and A4 each paragraph for each supplementary figure.

pacing [22], it is conceivable that the constant ectopic activation by the PVCs may induce a reduction of the refractory period of the RVOT with time, as a form of electrical remodeling.

Recently Sakamoto et al. [23] described the presence of abnormal repolarization properties in patients with frequent PVCs from the RVOT assessed by the presence of T-wave changes and QRST time integral. This phenomenon involves changes in repolarization properties resulting from abnormal activation sequence [24]. Those T-wave abnormalities were more pronounced in patients with a PVC burden higher than 10.000 PVCs per day, as is the case of our study group, and progressively returned to normal a few weeks after successful ablation. The authors [23] attributed these T-wave changes to cardiac memory. They reported a statistically significant difference in the amplitude of the T-wave in lead V2 when compared to normal subjects and this difference attenuates after successful ablation. Patients with PVCs from the RVOT had also much lower QRST time integral values in V2 than normal subjects [23], although the authors did not comment on those findings.

So, it is possible that the findings obtained from the epicardial reconstructed electrogramas might be associated with the T-wave changes described by these authors and be a consequence of the PVCs. But it could be the other way round, and the repolarization abnormalities being the cause and not the consequence of the PVCs. In fact, the work from Zhang et al. [10] showed that in patients with early repolarization, a shorter RT was present in the epicardial surface. PVCs were present in two of those patients, and in both, the origin of the PVCs was in the area with ST elevation and repolarization abnormalities.

Idiopathic PVCs from the RVOT are thought to be due to delayed after depolarizations (DADs) [25], but this theory has never been proved. DADs result from an increase in intracellular Ca2+, so a critical factor should be the APD. Longer action potentials are associated with more Ca2+ overload and facilitated DADs [24]. Considering the fact that ARI correlates with the APD one would have expected that in patients with PVCs from the RVOT the ARI would be higher than in controls, and we found the opposite.

The most striking finding in our study was the presence of a dispersion of the RT and ARI in the epicardium in patients with PVCs from the RVOT. Hamon et al. [26] studied in a porcine model, the effect of PVCs from the RVOT on electrical stability and on dispersion of repolarization and found a significant increase in the dispersion of the repolarization on the sinus beats immediately after the PVCs, that progressively returned to normal in the subsequent sinus beats. Those authors also studied the effect of PVCs on the cardiac neurons that respond to both afferent and efferent cardiovascular stimuli and demonstrated that almost half of those neurons (46%) responded to PVCs. This fact indicates that PVCs pose a strong and unique stress to intrinsic cardiac nervous system neurons. The RT and ARI dispersion that we observed in our patients may result from the stress to intrinsic cardiac nervous system neurons, imposed by the presence of PVCs from the RVOT [26].

*Limitations*

There has been some concern regarding the accuracy of the electrograms obtained with the ECGI at least with the epicardial ECGI. Recently, Bear et al. [27] performed a validation study in five anesthetized, closed-chest pigs comparing the reconstructed epicardial unipolar electrograms obtained from ECGI with the electrograms directly recorded from the epicardium. The authors concluded that the ECGI provides qualitative information on the origin and spread of epicardial activation, but resolution was poorer than previously thought. Cluitmans et al. [28] also performed a validation study in four anesthetized closed-chest dogs assessing both the depolarization and the repolarization. The authors found a better accuracy of reconstructed activation times than of recovery times and pointed out the improvement obtained by incorporating the local spatiotemporal characteristics of the reconstructed electrograms, which we have not performed. Still, several studies in humans have validated the ECGI system for depolarization and repolarization in different diseases. With our epicardial and endocardial system, the number of studies is inferior, and invasive validation of this system for repolarization has not been performed, except for some limited data presented in the work by Rudic et al. [14]. The results of our study should therefore be interpreted with caution and more validation studies are needed prior to its widespread use to assess repolarization.

## Conclusions

In conclusion, the RVOT in patients with frequent PVCs shows abnormal electrophysiological characteristics.

The reason for these abnormalities is still unknown but we may speculate that the PVCs are in their origin. The abnormalities of repolarization may represent a form of electrical remodeling in response to the abnormal depolarization, or on the contrary, they may be the cause of the PVCs. Either way that is worthy of bigger studies not only before ablation but in the follow-up, to assess the evolution of this abnormalities after successful ablation. Finally, we found the presence of a dispersion of repolarization in the epicardium of the RVOT, however the level of ARI and RT dispersion necessary to pose additional risk of ventricular arrhythmias is still not known.

## Declaration of competing interest

M. Budanova, S. Zubarev are clinical application specialists of EP Solutions Company.

## Acknowledgements

The authors are grateful to Danila Potyagaylo PhD for the revision of the manuscript and to Rafael Jeronimo and Ana Soares for their help in collecting data.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2019.08.046.

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