Terminal QRS axis has the potential to differentiate arrhythmogenic right ventricular cardiomyopathy from right ventricular outflow tract ectopy

Emilie Empsen[1*]; Evelyne Roets[1*]; Pieter Koopman[2,3]

[1] Hasselt University, Hasselt, Belgium

[2] Hasselt Heart Centre, Jessa Hospital, Hasselt, Belgium

[3] Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

* equally contributing authors

Corresponding author:

Pieter Koopman, Cardiology department, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium

Phone: +32 11309447

Email: pieter.koopman@jessazh.be

keywords: Arrhythmogenic right ventricular cardiomyopathy; right ventricular outflow tract tachycardia; terminal QRS axis; right ventricular conduction delay; electrocardiogram

ABSTRACT

Aims

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is associated with delayed electrical activation of the right ventricle (RV). The aim of this study was to assess direction of the terminal axis (TA) of the QRS complex on 12-lead electrocardiogram (ECG) as a new method to add to the pathophysiological understanding of this condition.

Methods and results

We retrospectively determined TA in 170 patients with a clinical diagnosis of ARVC and 26 with RVOT ectopy without structural abnormalities, as compared to 50 normal ECGs. TA was defined as the frontal plane axis of the terminal QRS activation at 20 ms before the end of the QRS and was visualized on a circular diagram. Our results show that TA of ARVC patients has a distinct right-sided direction, whereas TA of control patients and TA of patients with RVOT ectopy is equally distributed on a circular diagram. A right-sided orientated TA yielded a sensitivity of 79% for the diagnosis of ARVC.

Conclusion

TA of ARVC patients is significantly directed right-sided towards the RV inflow and outflow tract, compatible to involvement of RV conduction delay in ARVC pathophysiology. In patients with benign RVOT ectopy, TA does not show this predilection. Determination of TA could be a useful additional criterium in the diagnosis of ARVC and the differentiation with benign RVOT ectopy.

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy is a progressive cardiomyopathy characterized by autosomal dominant inheritance, with a risk of sudden cardiac death (SCD) among young adults due to polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF) (1, 2). On the other hand, RVOT ectopy or tachycardia with no structural heart disease is a benign condition, caused by cyclic adenosine monophosphate (cAMP) mediated triggered activity (3). Both conditions frequently present with premature ventricular contractions (PVC) originating from the right ventricle or right ventricular outflow tract, and VT in ARVC may present with morphological features similar to RVOT VT, notably left bundle-branch block (LBBB) with inferior axis (3). Since benign RVOT ectopy has a different prognosis and treatment than ARVC, adequate differentiation between both pathologies is necessary (4, 5).

The etiology of ARVC is considered to be a mutation in desmosomal genes, leading to fibrofatty replacement of the right ventricular myocardium, resulting in RV conduction delay. Typically the structural changes are confined to certain regions: the inflow tract, outflow tract and apical portions of the RV, also called the triangle of dysplasia, although also affection of LV myocardium is possible (6-8).

Different gene mutations have been described, particularly in the plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2) and plakoglobin (JUP) genes (9, 10). ARVC prevalence is estimated to be 1 in 2000-5000, affecting men more frequently than women, with a ratio of 3:1 (2).

Clinical diagnosis of ARVC is based on the 2010 Task Force Criteria revised by Marcus et al, classified in major and minor criteria. These criteria include 1) RV structural abnormalities or dysfunction measured by means of echocardiography, magnetic resonance imaging (MRI) or RV angiography, including regional RV akinesia, dyskinesia, aneurysm or reduced RV ejection fraction 2) Tissue characterization by RV biopsy indicating fibrofatty replacement 3) Negative T-waves in precordial leads, 4) Conduction abnormalities resulting in the presence of a characteristic epsilon wave in the right precordial leads or late potentials as measured by signal averaged ECG (SAECG), 5) Arrhythmias including RV tachycardia or ectopy of LBBB morphology with superior axis, 6) Family history of premature SCD or diagnosis of ARVC in a first-degree relative who meets current Task Force Criteria, and 7) Pathogenic mutation associated with ARVC. (2, 11, 12)

Prior to development of histological changes in the myocardium, gap junction dysfunction is present, leading to ECG changes, particularly a delayed terminal activation of the RV. We propose a new method consisting of determination of terminal axis (TA) of the QRS trying to characterize the site of conduction delay on the surface 12-lead ECG, and as such differentiate ARVC from controls or benign conditions such as RVOT ectopy, in which we do not expect RV conduction delay.

METHODS

Construction of patient database

We retrospectively reviewed the medical records and electrocardiograms (ECGs) of 246 patients. This population consisted of 3 groups (**Figure 1)**. The first group included all 170 patients from the databases of Jessa Hospital, Hasselt, Belgium and Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands, that underwent genetic testing for a suspected hereditary cardiac disease following a clinical diagnosis of ARVC. The second group included 26 patients with a clinical diagnosis of benign RVOT ectopy that underwent VT ablation in Jessa Hospital, Hasselt, Belgium, since 1/2009. The third group was selected out of all 74 patients that underwent an electrophysiologic examination at the cardiology department in Jessa Hospital, Hasselt, Belgium, from 01/11/2013 to 31/12/2013. From these records 50 control patients were identified that were absent of ischemia, structural heart disease, known hereditary cardiac disease, conduction disorder or other pathology that could alter the QRS complex.

Patient characteristics

Patient characteristics are presented in **Table 1**. Clinical diagnosis of ARVC patients according to the 2010 revised Task Force Criteria requires 2 major criteria, 1 major and 2 minor criteria or 4 minor criteria (2, 11). These criteria were evaluated for all patients. Major criteria include dysfunction and structural changes of the RV, consisting of severe dilatation and reduction of RV ejection fraction and RV aneurysms. Other major criteria are fibrofatty replacement of myocardium, inverted T-waves in right precordial leads, epsilon waves and LBBB-type VT with superior axis. Family history of ARVC is also a major criterium. Minor criteria include mild RV dilatation or mildly reduced ejection fraction, less distinct inverted T-waves in right precordial leads, and positive late potentials (13). Arrhythmogenic changes classified as minor criteria include LBBB-type VT with inferior axis and frequent premature ventricular contractions (PVC). Family history of SCD is also considered a minor criterium.

When RVOT ectopy was present, patients were further characterized by morphology of the 12-lead ECG, patient symptomatology and family history. The first ECG following the respective diagnosis was selected for evaluation. Only ECGs prior to ablation, pacemaker implantation or implantable cardioverter-defibrillator (ICD) implantation were included. ECGs were retrieved from and analyzed through the ECG databases SEMA-200 (Schiller AG, Baar, Switzerland) and MUSE ECG Management System (GE Healthcare, Fairfield, Connecticut, USA). Related patient demographics and characteristics were retrieved from the digital patient databases C2M (Cegeka, Hasselt, Belgium) and SAP Productions (SAP SE, Waldorff, Germany). Evaluation of ARVC patients included RV systolic function and structure, tissue characterization, repolarization abnormality, depolarization abnormality, arrhythmias and family history (**Table 1**).

Determination of terminal QRS axis

We developed a four-step method for accurate measurement and visualization on the ECG of the TA of the QRS complex (**Figure 2**). This technique has previously been validated in Brugada patients, complete right bundle branch block (CRBBB), incomplete right bundle branch block (IRBBB) and control patients (Koopman et al, unpublished).

In a first step, QRS duration was measured and expressed in milliseconds. Automatic measurement of the beginning and the end of the QRS complex by the SEMA-200 or MUSE software, indicated by two vertical calipers, was proven accurate in comparison to manual measurement and could therefore be safely adopted.

Secondly, the ECG was magnified to the fullest extent and the amplitude at 20 ms preceding the end of the QRS in leads I and aVF was measured, relative to the amplitude at the starting point of the QRS. A third step consisted of calculating the TA angle, defined as the arctangent of the previously determined amplitude of lead aVF when divided by the amplitude of lead I, using trigonometry in a right-angled triangle:

$$\alpha = arctan\frac{aVF}{I}$$

The value of the arctangent results in two possible angles. Depending on lead I being positive or negative, the angle can be correctly chosen with or without correction by 180°. This was performed using an automatic function called ATAN2 in the Microsoft Excel software package (Microsoft Corporation, Redmond, Washington, USA).

In a fourth step the TA was visualized on a circular diagram in a frontal plane, corresponding to the frontal plane of the heart in the chest. This circle is obtained by inverting the Y-axis on the goniometric circle. The angle of the TA corresponds to the location of the dot on the circle. The distance from the dot to the center of the circle is a function of the QRS duration. X and Y values of the dots where calculated using the following formula and are expressed in milliseconds.

$$X = \cos\big(\alpha\,(degrees)\big).QRS\ duration\,(ms)$$

$$Y = \sin\big(\alpha\,(degrees)\big).QRS\ duration\,(ms)$$

Statistical analyses

Continuous variables were expressed as mean ± standard deviation. The angular nature of our data necessitated the use of circular statistics. We performed the Rayleigh test of uniformity, assessing the significance of the mean resultant direction of TA. Because the sample size of the RVOT ectopy patient group was smaller than 50, bootstrap test for reflective symmetry was used. 95% confidence intervals were constructed for the mean direction. Watson's goodness of fit test was performed for evaluating the von Mises normal circular distribution. Comparing TA for different ECGs of the same patient was done by Moore's test for paired circular data. Mean direction of TA between groups was compared by Watson's large-sample nonparametric test, assuming that all sample sizes are at least 25.

Homogeneity of the concentration parameter kappa was analysed in our 3 samples of directional data. A univariate analysis was performed to compare clinical and electrocardiographic patient characteristics, using a chi-square test for categorical variables. Continuous variables were

analysed by a one-way ANOVA and one-sample student t-test. For all analyses, a two-sided P-value ≤ 0,05 was considered statistically significant. Analyses were performed using the program R-3.2.0 statistics with the circular package (open source software, Robert Gentleman and Ross Ihaka, Department of Statistics, University of Auckland, Auckland, New-Zealand).

RESULTS

Patient demographics and ECG parameters

The study was part of a protocol approved by both Institutional Ethics Committees. Clinical baseline characteristics and ECG characteristics can be seen in **Table 1**. Men are more frequently affected by ARVC then women, with a 3:1 ratio. This illustrates that our sample is a good representation of the total ARVC population. SCD (p-value: <0.0001) and structural changes, mostly RV dilatation (p-value: <0.0001), are more common in the ARVC patient group when compared to the RVOT patient group. VT with LBBB morphology is a condition represented in both patient groups (p-value: 0.027). Epsilon waves are very specific for ARVC patients but are only present in a minority of patients (12.9%; p-value: <0.0001). Late potentials, as measured with the signal averaged-electrocardiogram (SAECG), are more frequently seen in ARVC patients (19.4%; p-value: <0.0001), highlighting the localized conduction delay. This is in contrast to positive SAECG present in RVOT ectopy and control patients, respectively 7.7% and 0% (p-value: <0.0001). A positive genetic diagnosis for desmosomal gene mutations was present in 31.8% of ARVC patients (p-value: <0.0001).

Terminal Axis distribution

In accordance with the method described above, TA was determined for all patients included in this study (**Figure 3**). According to the Rayleigh test, TA of control patients (p-value: 0.147; CI: [37.953; 143.252]) and patients with benign RVOT ectopy (p-value: 0.114; CI: [348.314; 103.953]) had no significant mean direction and was equally distributed on a circular diagram. In patients with ARVC, TA was significantly directed towards the right side of the heart (p-value: <0.0001; CI: [16.692; 42.129]). This distribution illustrates a significant difference between TA in ARVC patients compared to TA in RVOT ectopy and control patients. The lower value of the concentration parameter kappa in the RVOT (kappa-value: 0.475) and control patient group (kappa-value: 0.299) supports the homogeneity of this distributions. The larger value of kappa in ARVC patients is consistent with the presence of a mean direction (kappa-value: 1.015). Comparison of the mean direction of TA between patients with or without a known pathogenic mutation indicates no significant difference between the two groups (p-value: 0.462).

Sensitivity and specificity were calculated for ARVC in comparison to control and RVOT ectopy patients. A right-sided orientated TA yielded a sensitivity of 79% and a specificity of 37% for the diagnosis of ARVC.

Reproducibility

Comparing TA for different ECGs of the same patient showed longitudinal reproducibility as the measured angle was not statistically different when evaluating subsequent ECGs for 37 patients (p-value: 0.331). Interobserver comparison indicated no significant variability between two different observers analyzing the same 20 ECGs (p-value: 1.0).

DISCUSSION

Benign RVOT ectopy and ARVC are two entities that can both manifest with PVCs originating from the right ventricle or right ventricular outflow tract, and VT with LBBB pattern and inferior axis (3). Since RVOT ectopy is not characterized by structural heart disease, it has a benign prognosis and requires a different treatment. In contrast to ARVC, RVOT ectopy is sensitive for medical treatment, and radiofrequency catheter ablation therapy has a more successful outcome (3, 14, 15). Hence differentiation between these two conditions on a simple 12-lead ECG would be very useful. To date, however, discrimination is based on specific electrophysiologic criteria (**Table 1**).

The concept of terminal QRS axis to evaluate the site of conduction delay on a 12-lead ECG, has previously been used to prove RV and/or RVOT conduction delay in CRBBB, IRBBB and BrS (Koopman et al, unpublished). Our present study aimed at using TA to distinguish two different conditions of right ventricular ectopy, particularly ARVC and benign RVOT ectopy, as opposed to normal ECGs. The study also attempted to use TA as a proof for RV conduction delay in ARVC patients.

TA was defined as the electrical axis of the QRS complex in the frontal plane at 20 ms before the end of the QRS. This point in time was chosen based on the total duration of the terminal activation in structurally normal hearts which has previously been measured to last 40 ms by average (16). At 20 ms before QRS termination, the electrical conduction is in the middle of the terminal activation. Leads I and aVF were chosen because of their perpendicular relationship which facilitates analysis. Furthermore, there is a good reproducibility of these electrograms due to the uniform placement of the limb electrodes on the patient.

Circular distribution of TA for the different study groups, assessed by the Rayleigh test, revealed some interesting results. ECGs of patients diagnosed with ARVC showed TA consistently directed to the right side, whereas TA in control patients and in patients with benign RVOT ectopy had no consequent direction but instead showed a uniform distribution. This phenomenon is also illustrated by the relatively large confidence intervals seen in the control (CI: [37.953; 143.252]) and RVOT ectopy (CI: [348.314; 103.953]) patient groups, reflecting the relatively low concentration of the data. This is in contrast with the smaller confidence interval and the larger value of kappa seen in ARVC patients (CI: [16.692; 42.129]; kappa-value: 1.015), which demonstrates the greater concentration of these data.

The random distribution of TA in the control group and the RVOT group might be due to subtle differences in conduction velocity for individuals with no apparent conduction disorder and no structural heart disease (17). These differences in conduction could be overridden by more dominant electrical alterations that have a major impact on TA angle. Therefore, the rightward deflection of TA in ARVC is suggestive for right ventricular conduction delay due to fibrosis, giving rise to a late vector of activation directing to the right ventricle.

In our study, 79% of ARVC patients have a right-sided TA. With a sensitivity of 79% together with a specificity of 37% this implicates that a right-sided TA is definitely a warning sign for the

diagnosis of ARVC, although not very specific. Low specificity is due to the fact that TA of control and RVOT ectopy patients is equally distributed on a circular diagram. Hence a right-sided TA is not uncommon in this group. Figures for sensitivity and specificity have to be interpreted with extreme caution, due to the high number of ARVC patients in our study as compared to control patients or patients with RVOT ectopy. Considering ARVC is a relatively rare disease, a TA oriented to the left will not totally exclude a positive diagnosis of ARVC, but will make it much less likely.

Because there is no significant difference between the mean direction of ARVC patients with or without a mutation, TA determination in this last group combined with the Task Force Criteria could positively reinforce a diagnosis of ARVC.

TA may be valuable as a diagnostic tool for ARVC although the power of this tool still remains to be determined in a global population. TA determination could nonetheless be a useful addition to the existing 2010 revised Task Force Criteria. Ideally TA could be used as a method to differentiate ARVC from RVOT ectopy without structural abnormalities.

LIMITATIONS

Because of the low prevalence of ARVC, the relatively small group of control and RVOT ectopy patients in our study is in disproportion with the larger sample of ARVC patients (2). Further multi-centre studies with a larger number of patients could be useful to overcome this limitation, and should include a larger group of patients with benign RVOT ectopy. The first phase of ARVC, namely the concealed phase, is often a non-symptomatic phase with subtle arrhythmias, which usually is unnoticeable (8, 18). These patients probably are underrepresented in our study.

Another restriction of this study consists of selecting patients with ARVC using the existing clinical diagnostic criteria, instead of selecting patients based on genetic diagnosis. Only about 22% of patients in our study had a confirmed pathogenic mutation related to ARVC, however this figure is in accordance with the worldwide expected percentage of gene-positive diagnoses (19). Furthermore, regardless of the presence of an underlying confirmed genetic cause, results for TA were consistent.

Specificity for TA directed to the right side of the heart is quite low, because TA of control patients is uniformly distributed. Due to this fact, TA of control patients can also be directed to the right side. TA could however be very useful in differentiating between benign RVOT ectopy and ARVC, as a leftward TA makes a diagnosis of ARVC less likely (21%).

As demonstrated by our database (**Table 1**), the analyzed ECGs could be influenced by the use of antiarrhythmic agents. Some of the most often used and effective pharmacological therapies for ARVC, consisting of the antiarrhythmic agents amiodarone and sotalol, can alter the QRS complex and could possibly influence TA (20). In this situation however, we expect a uniform effect on the cardiac conduction system, and not a preferential effect of delay in RV conduction only.

Directional statistics is beyond doubt the preferred method for analysis of angular data. Unfortunately, analyses are complex and not all statistical tests have a 'directional' counterpart. Values for sensitivity and specificity have to be regarded with extreme caution, as our study group proportions (large ARVC group) do not reflect proportions in real life.

CONCLUSION

The objective of this study was to validate a new method, using determination of terminal QRS axis, to distinguish ARVC from benign RVOT ectopy and normal ECGs, based on the level of conduction delay in the right ventricle. It is shown that TA of ARVC patients is significantly directed to the right side of the chest, pointing at the electro-anatomical location of the triangle of dysplasia in the right ventricle, thus corresponding with the pathophysiological mechanism of delayed activation in this region. In patients with benign RVOT ectopy, as in controls, TA was uniformly distributed in all directions, confirming lack of delayed activation or structural abnormalities of the right ventricle.

The new TA method is a valuable and easy-to-use clinical parameter that has the potential of discriminating between ARVC and non-ARVC ECG patterns on a simple 12-lead ECG.

ACKNOWLEDGEMENTS

The authors thank T. Neyens, MS (UHasselt) for his statistical assistance, and P. Volders, MD, PhD (MUMC+) for access to the MUMC+ patient database

CONFLICT OF INTEREST

The authors declared no conflict of interest.

REFERENCES

1. Saguner AM., Ganahl S., Kraus A., Baldinger SH., Akdis D., Saguner AR., et al., *Electrocardiographic features of disease progression in arrhythmogenic right ventricular cardiomyopathy/dysplasia*. BMC Cardiovasc Disord, 2015. **15**:p. 4.
2. Pinamonti B., Brun F., Mestroni L., Sinagra G., *Arrhythmogenic right ventricular cardiomyopathy: From genetics to diagnostic and therapeutic challenges.* World J Cardiol, 2014. **6**(12):1234-44.
3. Calvo N., Jongbloed M., Zeppenfeld K., *Radiofrequency catheter ablation of idiopathic right ventricular outflow tract arrhythmias.* Indian Pacing Electrophysiol J, 2013. **13**(1):14-33.
4. Emkanjoo Z., Mollazdeh R., Alizadeh A., Kheirkhah J., Mohammadi Z., Khalili M., et al., *Electrocardiographic (ECG) clues to differentiate idiopathic right ventricular outflow tract tachycardia (RVOTT) from arrhythmogenic right ventricular cardiomyopathy (ARVC).* Indian Heart J, 2014. **66**(6):607-11.
5. Srivathsan K., Lester SJ., Appleton CP., Scott LR., Munger TM., *Ventricular tachycardia in the absence of structural heart disease.* Indian Pacing Electrophysiol J, 2005. **5**(2):106-21.
6. Sen-Chowdhry S., Syrris P., Ward D., Asimaki A., Sevdalis E., McKenna WJ., *Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression.* Circulation, 2007. **115**: p. 1710-20.
7. Te Riele AS., Tandri H., Bluemke DA., A*rrhythmogenic right ventricular cardiomyopathy (ARVC): cardiovascular magnetic resonance update.* J Cardiovasc Magn Reson, 2014. **16**: p. 50.
8. Saguner AM., Brunckhorst C., Duru F., *Arrhythmogenic ventricular cardiomyopathy: A paradigm shift from right to biventricular disease.* World J Cardiol, 2014. **6**(4):154-74.
9. Bauce B., Rampazzo A., Basso C., Mazzotti E., Rigato I., Steriotis A., et al., *Clinical phenotype and diagnosis of arrhythmogenic right ventricular cardiomyopathy in pediatric patients carrying desmosomal gene mutations.* Heart Rhythm, 2011. **8**: p. 1686-95.
10. Marcus FI., Edson S., Towbin JA., *Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians*. J Am Coll Cardiol, 2013. **61**(19):1945-8.
11. Marcus FI., McKenna WJ., Sherrill D., Basso C., Bauce B., Bluemke DA., et al., *Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria.* Eur Heart J, 2010. **31**: p. 806-14.
12. Cox MG., van der Smagt JJ., Noorman M., Wiesfeld AC., Volders PG., van Langen IM., et al., *Arrhythmogenic right ventricular dysplasia/cardiomyopathy diagnostic task force criteria: impact of new task force criteria.* Circ Arrhythm Electrophysiol, 2010. **3**: p. 126-33.
13. Kamath GS., Zareba W., Delaney J., Koneru JN., McKenna W., Gear K., et al., *Value of the signal-averaged electrocardiogram in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart Rhythm.* Heart Rhythm Society, 2011. **8**: p. 256-62.
14. Cox MG., Nelen MR., Wilde AA., Wiesfeld AC., van der Smagt JJ., Loh P., et al., *Activation delay and VT parameters in arrhythmogenic right ventricular dysplasia/cardiomyopathy: toward improvement of diagnostic ECG criteria.* J Cardiovasc Electrophysiol, 2008. **19**: p. 775-81.
15. Francis J., Fontaine G., *Role of catheter ablation in arrhythmogenic right ventricular dysplasia*. Indian Pacing Electrophysiol J, 2005. **5**(2):81-5.
16. Dalal D., Jain R., Tandri H., Dong J., Eid SM., Prakasa K., et al., *Long-term efficacy of*

catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol, 2007. **50**: p. 432-40.

17. Craft N., Schwartz JB., *Effects of age on intrinsic heart rate, heart rate variability, and AV conduction in healthy humans,* Am J Physiol, 1995. **268**(4 Pt 2):H1441-52.

18. Gemayel C., Pelliccia A., Thompson PD., *Arrhythmogenic right ventricular cardiomyopathy*. J Am Coll Cardiol, 2001. **38**: p. 1773-81.

19. Hamilton RM., Farhan M., Baskin B., Ray PN., Scherer SW., *The Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): Evaluation of New Criteria in a Young Gene-tested Population.* Circulation, 2010. **122**(21).

20. Marcus GM., Glidden DV., Polonsky B., Zareba W., Smith LM., Cannom DS., et al., *Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry.* J Am Coll Cardiol, 2009. **54**: p. 609-15.

Table 1: Patients characteristics

	Patients with ARVC (n=170)	Patients with RVOT ectopy (n=26)	Control patients (n=50)	p-value
Male gender	116 (68.2%)	13 (46.4%)	20 (40%)	**0.002**
Age (years)	53.0 (±15.3)	51.8 (±12.8)	55.8 (±17.6)	0.456
Family history of SCD	55 (32.4%)	3 (11.5%)	2 (4%)	**<0.0001**
Genetic diagnosis	54 (31.8%)	0 (0%)	0 (0%)	**<0.0001**
Syncope	49 (28.9%)	7 (27%)	8 (16%)	**<0.0001**
Age (symptomatic)	47.4 (±15.9)	47.2 (±13.3)	/	0.527
Ablation	28 (16.5%)	25 (96.2%)	12 (24%)	**<0.0001**
Structural heart disease				
RV hypertrophy	2 (1.2%)	2 (7.7%)	0 (0%)	**<0.0001**
RV aneurysm	16 (9.4%)	0 (0%)	0 (0%)	**<0.0001**
RV dilatation	43 (25.3%)	2 (7.7%)	0 (0%)	**<0.0001**
SAECG				
positive	33 (19.4%)	2 (7.7%)	0 (0%)	**<0.0001**
Negative	7 (4,1%)	0 (0%)	1 (2%)	**<0.0001**
Not measured	131 (77,6%)	24 (92,3%)	50 (100%)	**<0.0001**
Device				
ICD	59 (34.7%)	1 (3.8%)	7 (14%)	**<0.0001**
Pacemaker	2 (1.2%)	0 (0%)	0 (0%)	**<0.0001**
ECG				
Frequency (bpm)	67.4 (±15.6)	74.9 (±19.4)	69.6 (±18.3)	0.092
QRS (ms)	103.7 (±22.0)	100.5 (±27.5)	94.7 (±11.8)	**0.030**
Epsilon waves	22 (12.9%)	0 (0%)	0 (0%)	**<0.0001**
T-wave inversion	39 (22.9%)	1 (3.8%)	3 (6%)	**<0.0001**
Arrythmia				
Atrial fibrillation	15 (8.8%)	0 (0%)	2 (4%)	**<0.0001**
Ventricular extrasystole	76 (44.7%)	24 (92.3%)	23 (46%)	0.849
Ventricular tachycardia	81 (47.6%)	11 (42.3%)	14 (28%)	**0.027**
Ventricular fibrillation	15 (8.8%)	0 (0%)	0 (0%)	**<0.0001**
Medication				
ATII-antagonist	6 (3.5%)	0 (0%)	13 (26%)	**<0.0001**
β-blocker	67 (39.4%)	9 (34.6%)	29 (58%)	**0.019**
Statine	18 (10.6%)	7 (26.9%)	11 (22%)	**<0.0001**
antithrombotic	24 (14.1%)	15 (53.6%)	26 (52%)	**<0.0001**
α-blocker	2 (1.2%)	0 (0%)	2 (4%)	**<0.0001**
ACE-I	15 (8.8%)	7 (25%)	13 (26%)	**<0.0001**
K-channel blocker	5 (2.9%)	0 (0%)	3 (6%)	**<0.0001**
Na-channel blocker	12 (7.1%)	4 (15.4%)	4 (8%)	**<0.0001**
Comorbidities				
ATH	13 (7.6%)	5 (19.2%)	15 (28.8%)	**<0.0001**
Diabetes	4 (2.4%)	2 (7.7%)	4 (7.7%)	**<0.0001**
Hypercholesterolemia	11 (6.5%)	10 (38.5%)	16 (30.8%)	**<0.0001**
atheromatosis	2 (1.2%)	1 (3.8%)	0 (0%)	**<0.0001**

SCD, sudden cardiac death; RV, right ventricle; RVEF, right ventricular ejection fraction; SAECG, signal averaged electrocardiogram; ICD, implantable cardioverter defibrillator; RBBB, right bundle branch block; LBBB, left bundle branch block; ACE-I, angiotensin-converting-enzyme inhibitor; ATH, antihypertensive. Data are expressed as mean±standard deviation, number of patients and percentage (%).

Figure 1: Flowchart of patient selection

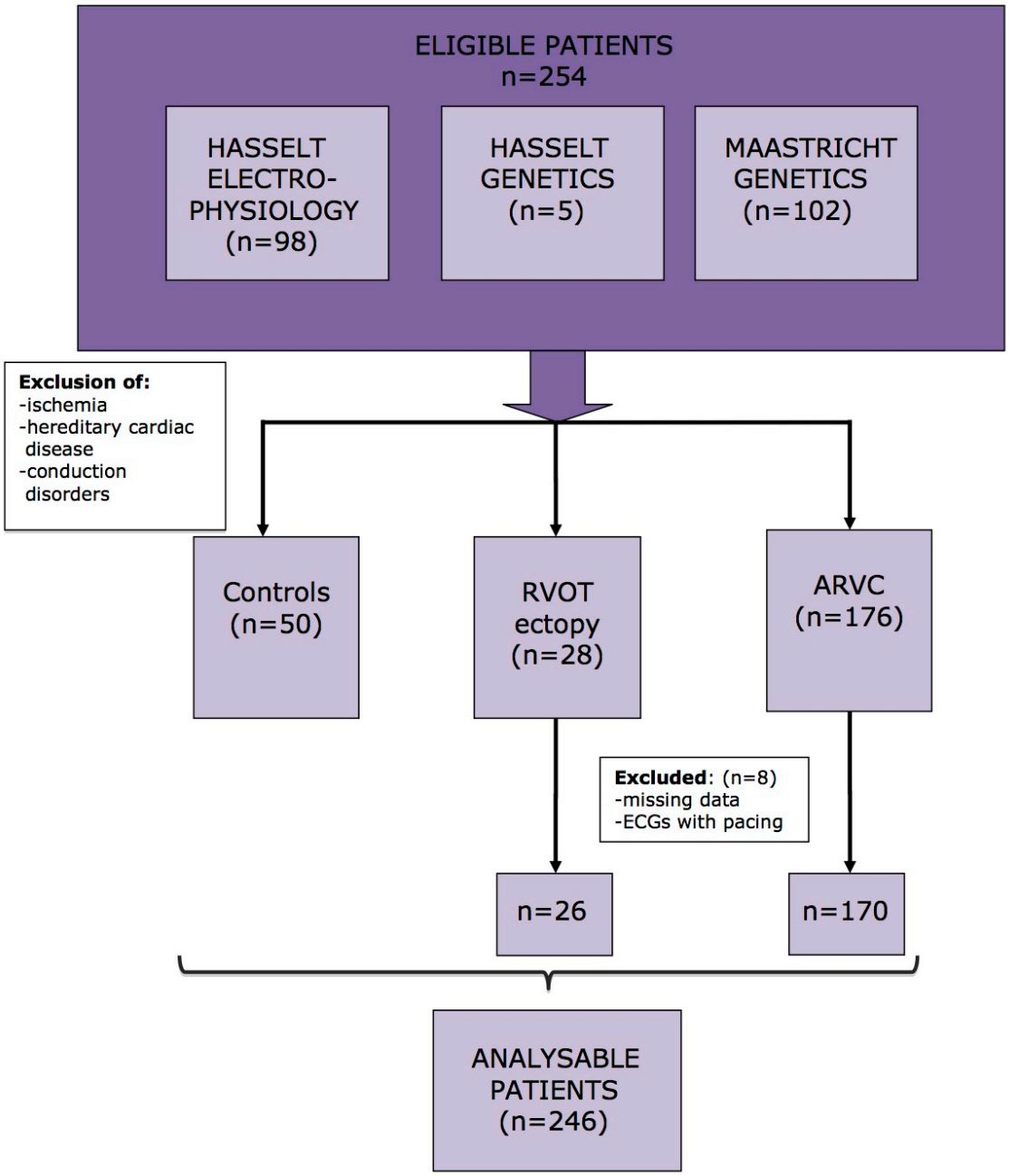

Figure 2: Determination of TA

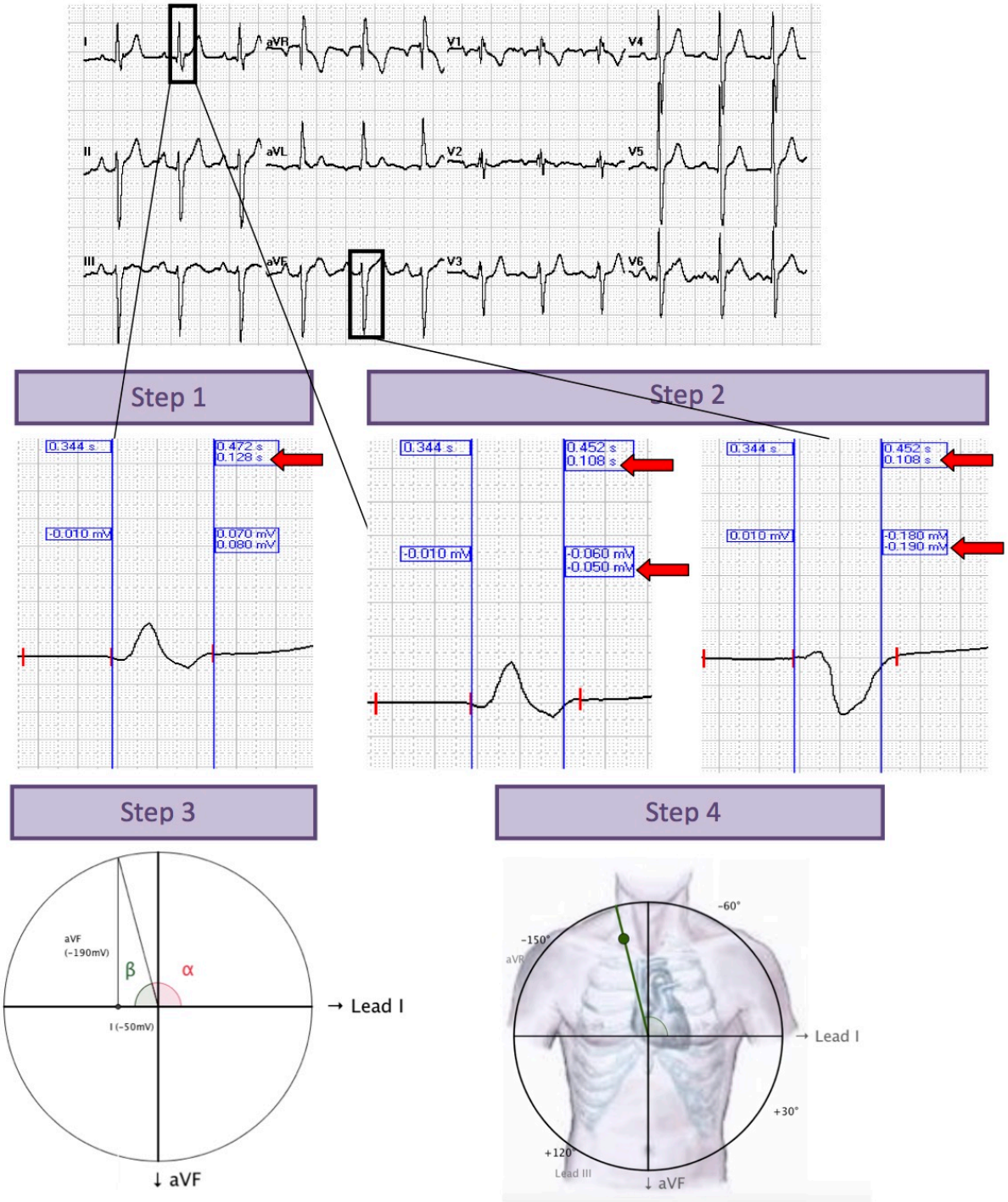

Figure 2 Step 1: Measurement of the QRS duration. Step 2: Measurement of the amplitude at 20 ms before the end of the QRS in leads I and aVF. Step 3: Calculation of the TA angle. Step 4: Visualization of the TA on a circular diagram.

Figure 3: Visualization of TA

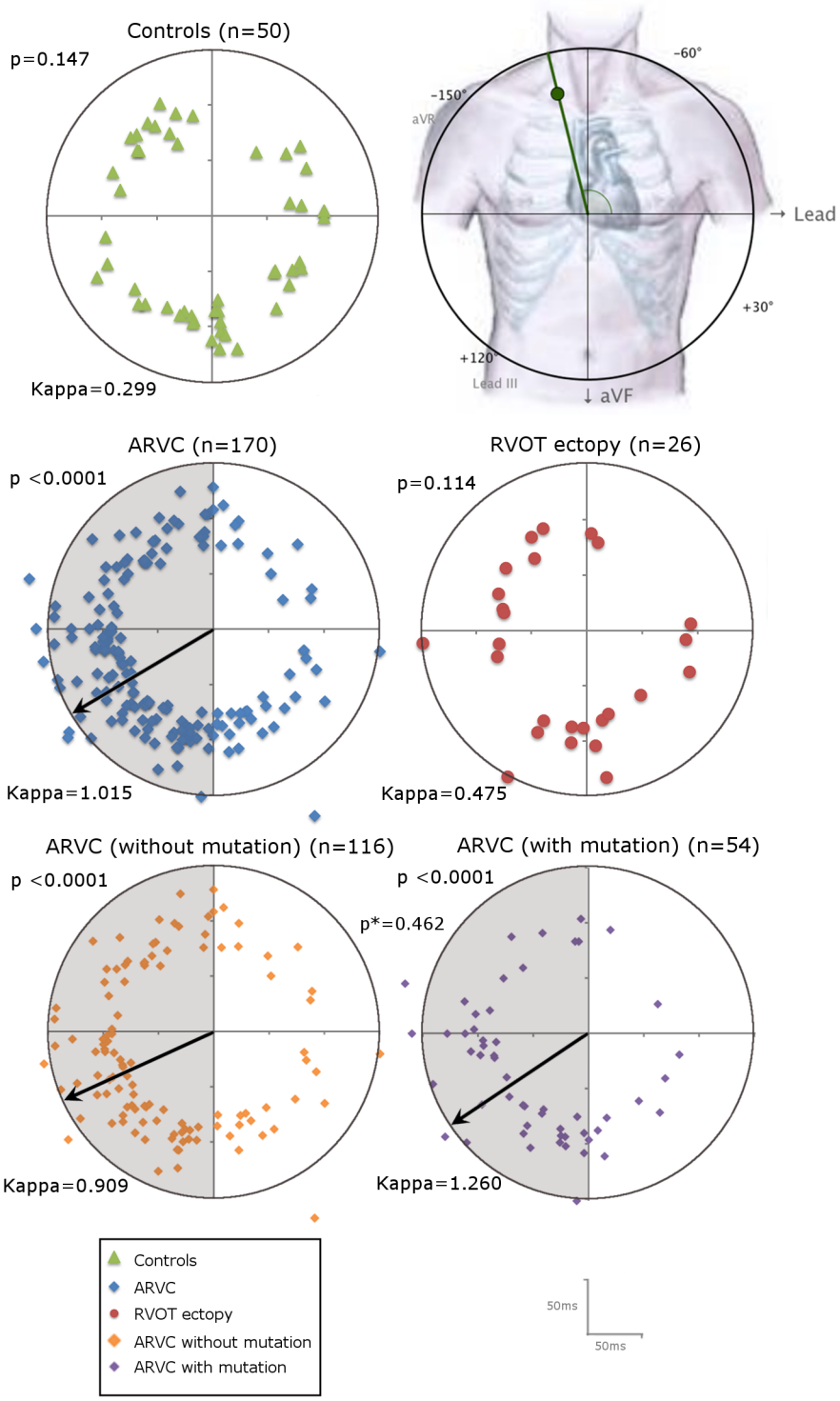

Figure 3. Visualization of the terminal QRS axis as if it would be projected on the patient's chest. Each dot represents a measurement for one patient. The angle of TA corresponds to the location of the dot on the circle. The distance from the dot to the center of the circle is function of the QRS duration. TA is displayed for controls, ARVC and RVOT ectopy patients. P-values according to Rayleigh's test for uniformity. (*) P-value for comparison of mean direction of TA between ARVC patients with and without a mutation.