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Novel ECG Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy

By

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Short title: Novel ECG Criteria for ARVC

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Abstract

Background: In order to improve the electrocardiographic (ECG) diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC), we evaluated novel quantitative parameters of the QRS complex and the value of bipolar chest leads (CF leads) derived from the standard 12 leads.

Methods: We analysed digital 12-lead ECGs in 44 patients with ARVC, 276 healthy subjects including 44 who were age and sex-matched and 36 genotyped members of ARVC families. The duration, length and area of the QRS and terminal S waves in V1 to V3 were measured automatically. T wave negativity was assessed in V1 to V6 and in the CF leads computed from the standard 12 leads.

Results: The terminal S wave duration was longer whereas the length of the QRS and the terminal S wave were shorter in ARVC patients compared to matched controls. Among members of ARVC families, those with mutations (n=15) had shorter QRS length in lead V2 and V3 and smaller QRS area in lead V2 compared to those without mutations (n=20). In ARVC patients, diagnostic T wave negativity was significantly more common in the CF leads than in the unipolar precordial leads. Terminal S wave duration in V1 > 48 ms or major T wave negativity in the CF leads separated ARVC patients from matched controls with 90% sensitivity and 86% specificity.

Conclusions: The length and area of the QRS and terminal S wave in leads V1 to V3 and T wave negativity in the CF leads can improve the ECG diagnosis of ARVC.

Keywords: electrocardiography, arrhythmogenic right ventricular cardiomyopathy, terminal S wave, bipolar precordial leads, negative T wave

Background

The electrocardiographic (ECG) diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) is based upon changes in both ventricular depolarisation (QRS complex) as well as repolarisation (ST-T wave). Currently, the only depolarisation criteria derived from the standard 12-lead ECG that were endorsed by the 2010 Task Force Report on ARVC[1] are the "epsilon wave" and prolongation of the terminal part of the QRS (terminal S wave) ≥55 ms in leads V1 to V3.[2] The "epsilon wave" is a relatively rare, ill-defined and therefore subjective sign. In ARVC, the QRS in the right precordial leads often terminates with fractionated and low-amplitude signals which can render the accurate determination of the QRS end problematic for both human eye and computer algorithms. In addition, conduction abnormalities in ARVC can affect not only the terminal but also the initial and middle part of the QRS complex.[3] In an attempt to improve the diagnostic value of QRS changes in ARVC and to design parameters suitable for automatic ECG analysis, we analysed the duration, length and area of the QRS complex and of its terminal part (the S wave) in leads V1 to V3. The idea for these parameters evolved from frequent observation of a visible loss of area predominantly in the terminal part of the QRS area (like a "bite out") in the right precordial leads of patients with ARVC.

According to the 2010 Task Force Report[1] T wave inversion in leads V1 to V3 or beyond in the absence of complete right bundle branch block (RBBB) (QRS >120 ms) represents a major diagnostic criterion, whereas T wave inversion in leads V1 and V2 in the absence of complete RBBB or in leads V1 to V4 in the presence of complete RBBB is a minor diagnostic criterion. Based on our (unpublished) observations we hypothesised that bipolar precordial leads between the standard precordial electrodes (positive pole) and the left foot electrode (negative pole) could detect more sensitively the diagnostic T wave negativity in patients with ARVC than the conventional unipolar precordial leads. These leads can be computed easily from the standard 12-lead ECG provided the latter is available in a digital form.[4] The general shape of the ECG complexes in these leads is very similar to the one recorded with the unipolar precordial leads.[5,6,7]

In this study, we tested retrospectively the clinical utility of these novel diagnostic QRS and T wave parameters using digital resting ECG previously acquired in patients with: definite ARVC; healthy control subjects; and genotyped members of families in which a causative mutation for ARVC had been identified irrespective of clinical phenotype.

Methods

Patient population

The study group consisted of 44 patients diagnosed with ARVC according to the established criteria[1,8] who were investigated at St. George's Hospital between 2000 and 2011 (age, mean ± standard deviation (SD), 43.5±14.9 years, 32 men, 72.7%). Their clinical characteristics are presented in **Table 1**. Since the amplitude of the QRS waves varies with age,[9] they were compared with 44 age and sex-matched subjects with no apparent heart disease investigated at the Institute of Cardiovascular and Medical Sciences, University of Glasgow (control group A). Since the frequency of T wave negativity in the bipolar chest leads in healthy subjects (or, for that matter, in cardiac patients) is unknown, for the purpose of T wave analysis we also analysed the ECGs of another larger control group consisting of 232 healthy subjects (age 29.9±9.4 years, 106 men, 45.7%) previously investigated at St. George's Hospital (control group B).

In both control groups, heart disease was excluded on the basis of negative personal and family medical history and normal physical examination. None of the healthy subjects was involved in sport activity at professional level. Data in all patients and healthy controls were acquired as part of ethically approved research projects.

In order to investigate the genotype/ECG phenotype correlation of the new parameters we also analysed the ECGs of ARVC patients and 36 genotyped first degree relatives (age 45.6±17.6 years, 18 (50%) men) with limited or no phenotype expression of the disease investigated at the

Amsterdam Medical Centre (AMC), The Netherlands. They all were members of families in which mutations of the PKP2 gene have been identified. Of them, 15 were carriers of causative mutation for ARVC while 21 did not carry the causative mutation identified in their families.

ECG data

In all patients, healthy controls and genotyped family members, digital 12-lead resting ECGs were acquired at 500 samples/second and 5 μV/bit amplitude resolution either for 10 seconds (in ARVC patients, control group B and in the group of relatives) or for 8 seconds (in control group A). In each lead of each ECG, one representative P-QRS-T complex was created which was considerably less noisy than the original 10- or 8-second recording. In this study, all analyses were performed on the representative lead-specific ECG complexes instead of the original ECGs. All ECGs were exported into text files which later were analysed with a custom-developed software programme written in Matlab (The MathWorks Inc., Natick, Massachusetts, USA).

QRS analysis

The QRS onset and offset of the representative ECG complexes were determined manually from the earliest onset to the latest offset in any lead using electronic callipers with high magnification.

In each of leads V1, V2 and V3 the S wave nadir was determined automatically as the sample with a smallest (most negative) value within the QRS complex and the following parameters were calculated:

(1) S wave duration [ms] – from the nadir of the S wave in the respective lead to the common for all leads QRS offset (D_{SV1}, D_{SV2}, D_{SV3});

(2) Length of the curve of the total QRS (L_{QRSV1}, L_{QRSV2}, L_{QRSV3}) and of the S wave (L_{SV1}, L_{SV2}, L_{SV3}) in technical units. In each of the 3 leads, the length of the QRS curve was measured from the earliest QRS onset to the latest QRS offset in any lead whereas the length of the S wave was measured from the lead-specific S wave nadir to the common QRS offset.

(3) Area under the total QRS complex (A_{QRSV1}, A_{QRSV2}, A_{QRSV3}) and under the S wave (A_{SV1}, A_{SV2}, A_{SV3},) [seconds × millivolts] calculated as total area, i.e. areas above and below the isoelectric line were expressed as absolute values. The beginning and end of the QRS and S wave were defined as in (2).

T wave analysis

Bipolar precordial leads with the standard precordial electrodes serving as positive poles and the left foot electrode as a negative pole (labelled CF1, CF2,…, CF6 in accordance with accepted conventions[10]) were derived from the standard precordial and peripheral leads using the following formulae:[4]

- $CFn = Vn - 2 \times AVF/3$;

Since $AVF = (II+III)/2$, an alternative formula also can be used: $CFn = Vn - (II+III)/3$;

In the above formulae Vn (n=1,2,…,6) is the respective unipolar precordial lead (V1,V2,…,V6) and CFn is the bipolar precordial lead between the same precordial electrode and the left foot electrode.

In each patient or healthy control, the unipolar leads V1 to V6 and leads CF1 to CF6 were displayed on-screen with high magnification and the T waves were assessed and classified as positive, negative or flat (<0.05 mV). For the purpose of this study, biphasic T waves with a clear negative component (>0.05 mV) were reported as negative.

It is known that in healthy subjects that are not professional athletes, the negative T waves in the right precordial leads when present are usually not deep (less than 0.2 mV[11,12]). Therefore we also

compared the amplitude of the negative T wave, whenever present, in lead V1 between the different study groups.

Statistical analysis

Unpaired two-tailed t-test and Pearson's chi-square test were used for comparison of continuous parameters and proportions, respectively. Related samples McNemar chi-square test was used to compare the frequency of diagnostic T wave negativity between the unipolar and the bipolar precordial lead systems. P value of less than 0.05 was considered statistically significant. Values are expressed as mean ± standard deviation (SD) unless indicated otherwise. Microsoft Office Excel 2010 and IBM SPSS Statistics Version 19 (SPSS Inc., an IBM Company) were used for statistical analysis.

Results

*QRS analysis: ARVC patients vs matched healthy controls (group A) (**Table 2**)*

Four ARVC patients (3 with complete RBBB and one with permanent ventricular pacing) and one family member with complete RBBB were excluded from QRS analysis.

The QRS results for the remaining ARVC patients (n=40) and healthy controls of group A (n=44) are presented in **Table 2.** The QRS duration was considerably longer in ARVC patients compared to healthy controls of group A (p<0.0001). In accordance with previous publications,[2] the duration of terminal S wave in all 3 leads (D_{SV1}, D_{SV2}, D_{SV3}) also was considerably longer in the patient group A (P<0.0001 for all). On the other hand, the length of the curve of both the total QRS (L_{QRSV1} to L_{QRSV3}) as well as of its terminal part, the S wave (L_{SV1} to L_{SV3}) were considerably shorter in ARVC patients compared to healthy controls in all 3 leads. The area of the QRS and of the terminal S wave also was smaller in ARVC patients, but the difference was statistically significant only for lead V1 (P=0.003 for A_{QRSV1} and P=0.006 for A_{SV1}) (**Table 2**). Thus, there seem to be a typical QRS pattern in the right precordial leads of ARVC patients (most typically in lead V1) characterised by prolonged duration and decreased length and area of both the total QRS as well as of its terminal S wave (**Figure 1**).

*QRS analysis: Family members with and without causative mutations (**Table 3**)*

One family member with RBBB was excluded from analysis. The results of the remaining 35 genotyped family members are presented in Table 3. Those with causative mutations (n=15) had significantly shorter total QRS curve length in lead V2 (p=0.043) and V3 (p=0.029) and smaller total QRS area in V2 (p=0.047) compared to those without mutations (n=20). There were no significant differences in the terminal S wave parameters (duration, length or area) between the two groups or in the duration of the total QRS (**Table 3**).

*T wave negativity in the unipolar and bipolar precordial leads (**Table 4**)*

After excluding one patient with permanent ventricular pacing, 43 ARVC patients were analysed for presence of diagnostic T wave negativity in the standard unipolar and the bipolar precordial leads (**Table 4**). They were compared with all healthy controls (control groups A plus B, n=276). The ARVC patients were significantly older (43.0±14.7 years vs 32.1±12 years, p<0.0001) and included more men (32/43 (72.7%) vs 138/276 (50.0%), p=0.0008) than the healthy controls.

Among patients, T wave negativity both as a major diagnostic criterion as well as any diagnostic criterion (major or minor) was observed significantly more frequently in the bipolar than in the unipolar precordial leads (p=0.016 and p=0.008, respectively, **Table 4**). Importantly, in all cases in which the unipolar precordial leads demonstrated minor or major diagnostic T wave negativity, the

bipolar leads in the same patient also demonstrated negative T wave with the same or higher diagnostic significance (**Figure 2**), whereas the opposite was not the case.

Among the healthy controls (n=276), T wave negativity was significantly more common in lead CF1 than in lead V1 ($p<0.00001$, **Table 4**). However, T wave negativity beyond CF2 was seen only in one 13-year-old boy who had negative T waves in both V1 to V3 as well as in CF1 to CF3).Two 16-year-old healthy boys demonstrated negative T waves in both V1 and V2, as well as in CF1 and CF2, whereas one 24-year-old male demonstrated negative T waves in CF2 but not in V2.

As expected, a negative T wave in lead V1 was present more commonly (34/43 (79.1%) vs 110/276 (39.9%), $p<0.00001$) and was considerably deeper (0.21±0.12 mV vs 0.11±0.06 mV, $p<0.000001$) in ARVC patients than in healthy controls of group B (**Figure 2**). No healthy subject had a negative T wave in V1 deeper than 0.33 mV. A cut-off value of 0.3 mV discriminated healthy subjects from ARVC patients with 97% specificity but only 21% sensitivity.

Among family members of ARVC patients, there were no significant differences in the frequency of diagnostic T wave negativity (whether as a major or as either a major or minor diagnostic criterion) between individuals with and without causative mutations both with the standard unipolar as well as with the precordial bipolar CF leads (**Table 5**).

Diagnostic value of the QRS and T wave criteria

The QRS and T wave parameters (and combinations thereof) with best diagnostic value for ARVC are presented in **Table 6**. Length of the QRS curve in lead V1 < 2.3 (or combined length of the QRS curve in lead V1 and V2 < 5.7) separated ARVC patients without complete RBBB from matched healthy controls with sensitivity and specificity of 72.5% and 70.4%, respectively. The duration of the terminal S wave in lead V1 (alone or in combination with the QRS length in the same lead) slightly increased specificity to 86.3% and 90.9%, respectively, at the expense of some reduction in sensitivity (**Table 6**). The use of the CF leads instead of the standard unipolar precordial leads increased sensitivity for detection of major T wave negativity from the 42.5% to 60.0% with equal specificity of 100% (i.e. no major T wave inversion in the matched healthy control group with both systems).

The best separation between ARVC patients and controls was achieved by the combination of terminal S wave duration of more than 48 ms *or* major diagnostic negativity in the CF leads with a sensitivity of 90.0% and specificity of 86.4%.

Table 6 also presents the diagnostic value of QRS parameters for identifying mutation carriers among genotyped relatives of ARVC patients who had considerably milder phenotype expression of the disease. The best discrimination of individuals with and without mutations was achieved by the combined length of the QRS in leads V2 and V3 of less than 6.5 with a sensitivity and specificity of 73.3% and 70%, respectively. Importantly, none of the conventional parameters such as terminal S wave duration, major or major diagnostic T wave negativity was significantly different between mutation carriers and non-carriers.

Discussion

Our results confirmed the high diagnostic value in ARVC of prolonged terminal S wave duration in leads V1 to V3[2] and demonstrated that this value is preserved when the S wave duration is measured to a common for all 12 leads QRS end. This parameter is suitable for automatic ECG analysis since most modern algorithms for automatic QRS delineation determine a common for all leads QRS onset and offset[13] and the S wave nadir in each precordial lead can be determined automatically with high reliability.

There appears to be a typical QRS pattern in the right precordial leads (mainly V1 and V2) in ARVC characterised by terminal S wave prolongation and loss of S wave length/area. This pattern is often visible to the naked eye (**Figure 1**) but is also suitable for computerised ECG assessment.

The terminal loss of QRS potentials in ARVC probably reflects the replacement of right ventricular myocardium with electrophysiologically silent or damaged fibro-fatty tissue and is similar to the mid- or late QRS changes ("bite out") frequently observed in myocardial infarction.[14]

We obtained practically the same results (not reported above) when the length and area of the terminal S wave were calculated over a fixed 60 ms interval beginning from the S wave nadir instead of the variable interval from the S wave nadir to the QRS. The 60 ms duration was chosen arbitrarily. Such parameters would be even more suitable for automatic ECG processing since potential difficulties with the accurate automatic estimation of the QRS offset would be avoided. They will not, however, utilise the strong diagnostic power of the terminal S wave prolongation.

Importantly, there seem to be a decrease in the total QRS length and area (and not only of the terminal S wave) in the right precordial leads of patients with ARVC. This is logical since this disease can affect not only areas which are activated late (e.g. the right ventricular outflow tract) but also regions (of the right or left ventricle) which are activated during the inscription of the initial and mid part of the QRS complex. In this study, the length of the total QRS in leads V1 and V2 was at least as good as the QRS curve length in the same leads for distinguishing ARVC patients from healthy controls. The total QRS length in leads V2 and V3 and the QRS area in V2 were the only parameters that distinguished family members with and without causative mutations. This represents a potential benefit for the clinical diagnosis of relatives of index ARVC cases as they often demonstrate incompletely expressed or milder disease with little structural findings. The parameters may also represent a tool in the future for distinguishing disease-causing from non-disease-causing variants of unknown significance, a common problem in the cardiogenetic management of ARVC families.[15]

Bipolar chest leads

Bipolar chest leads with a positive electrode at one of the six conventional precordial positions and a negative electrode relatively away from the heart (e.g. right or left shoulder, right infra-clavicular fossa, etc.) are still used in exercise stress testing, ambulatory electrocardiography (comprehensively reviewed in[10]) or sometimes as a surrogate of the conventional unipolar precordial ones, when a 12-lead monitor is not available.[5] Such leads (with a negative electrode at the right arm, left arm or left ankle) were commonly used in standard resting electrocardiography before Frank Wilson introduced the "unipolar" precordial leads in the 1930's[16] with the idea of recording the variation of the ECG signal only in the vicinity of the exploring (precordial) electrode, since the potential of the other electrode (Wilson's central terminal – the average potential of the three peripheral electrodes) remained relatively constant throughout the cardiac cycle. The use of the bipolar chest leads in everyday resting electrocardiography was completely abandoned around the 1950's, probably following a recommendation of the British Cardiac Society from 1949.[17]

The real (or perceived) advantage of the unipolar precordial over their counterpart bipolar precordial leads, to our knowledge, has never been demonstrated in a comparative clinical trial. It seems intuitively likely that, even if the unipolar precordial leads are *generally* more useful in clinical electrocardiography, in some cases one or more bipolar precordial leads can offer information which is not directly or not so clearly visible in the counterpart unipolar lead (e.g. leads CF1, CL1 or CR1 vs lead V1).

In cardiac diseases with localised myocardial abnormalities such as, for example, myocardial infarction, ECG changes are observed not only in the lead with a positive electrode closest to the affected area but also in leads facing remote areas (e.g. reciprocal changes) or in the general shape of the QRS-T complex (e.g. axis deviation or changes in the vectorcardiographic loops). The increased T wave negativity in the bipolar CF leads in ARVC patients which we observed simply reflects that in this disease, lead AVF (or leads II and III, since lead AVF is simply the average of these two leads) also contains diagnostically useful information. This is in concert with a previous

study describing QRS abnormalities (epsilon potentials, QRS fragmentation) in both peripheral and precordial leads of patients with ARVC.[3]

Four years ago we reported that bipolar precordial leads with a positive pole at V2 and a negative at V4 or V5 (leads V2-4 and V2-5) that were derived electronically from the standard precordial leads detected more sensitively the diagnostic Brugada type 1 pattern than the unipolar lead V2.[18] Unlike the bipolar chest leads using one of the three peripheral electrodes as a negative pole (CF, CL or CR leads), however, the general shape of the QRS and ST-T wave in such "intra-precordial" (or "trans-precordial") bipolar leads often differs considerably from those in the unipolar precordial leads and hence is unfamiliar to the clinicians.

The inclusion of T wave negativity as the only repolarisation-related diagnostic sign[1] for ARVC is clearly an oversimplification which ignores the plethora of abnormal T wave shapes (flat, multiphasic, peaked, etc.) that can be observed in ARVC. In several cases in this study, a bipolar chest lead demonstrated a negative (and hence, diagnostic) T wave which in the counterpart unipolar lead had a clearly abnormal although not negative contour (and hence, did not meet the diagnostic criteria of the Task Force report[1]) (for example compare the T wave in lead V3 and lead CF3 in **Figure 2**).

In addition, the depth of a negative T wave in lead V1 also can have diagnostic significance (although probably not only for ARVC but rather for a general T wave abnormality). For example, in our study the negative T wave in V1 in ARVC patients was considerably deeper than that in healthy (not professional athletes) subjects (mean±standard deviation 0.21±0.12 vs 0.11± 0.06 mV, $p<0.0001$). In none of the healthy subject was the negative T wave deeper than 0.33 mV (3.3 mm at standard gain). Our figures for healthy subjects are similar to those reported by Macfarlane et al.[19] on 193 healthy women (average ± standard deviation, 96% range: -0.102 ± -0.063, -0.252 – 0.000 mV) and in 84 healthy men (-0.115 ± 0.082, -0.290 – 0.000 mV) aged 18 to 29 years. The figures for healthy men and women aged 30 to 39 years in their study[19] were very similar.

Limitations

We have not tested the proposed QRS and terminal S wave parameters in patients with complete RBBB. Due to the lack of sufficient data we also could not test their possible prognostic value. In this study, we used representative ECG complexes created from standard 10 or 8-second recordings. Such complexes, which are considerably less noisy than the standard "raw" ECG data are not always available in everyday clinical practice.

The total group of healthy controls (n=276) was significantly younger and included significantly more women than the group of ARVC patients which makes the comparison of T wave characteristics between the 2 groups (e.g. amplitude of the negative T wave in lead V1) formally incorrect. However, these differences likely can introduce only bias in favour of the null hypothesis since both younger age and female gender are related to higher frequency of T wave negativity in the right precordial leads.

Conclusions and practical implications

The duration and length of both the QRS complex and of its terminal S wave in leads V1 and V2 possess considerable diagnostic value in ARVC. These indices are suitable for computerised ECG analysis. The bipolar precordial leads with a negative electrode at the left foot (CF leads) detect more sensitively and with practically the same specificity the diagnostic T wave negativity. These new parameters or their combinations can increase the sensitivity and specificity of the standard ECG for the diagnosis of ARVC in index cases and their relatives even with minimal disease expression. This suggests a potential role for these new automatic measurements in future revision of the Taskforce criteria.

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Figure Legends

Figure 1: Comparison between terminal S wave parameters in leads V1 of 3 patients with ARVC (left column) and 3 healthy controls of the same sex and identical or very similar age (right column). All ECGs are displayed at 50 mm/s, 1 cm/mV. The vertical dotted lines indicate the interval from the S wave nadir to the QRS end. Note that in each pair, the terminal S wave of the ARVC patient is broader but has shorter length and smaller area than that of the healthy control.

Top panel: 44-year-old woman with ARVC (left) and a 44-year-old healthy woman (right). S wave duration: 73 vs 38 ms; length: 0.716 vs 1.358 and area: 0.013 vs 0.016 s×mV.

Middle panel: 59-year-old man with ARVC (left) and 57-year-olf man (right). S wave duration: 78 vs 40 ms; length: 0.709 vs 1.001 and area: 0.013 vs 0.021 s×mV.

Bottom panel: 32-year-old male patient with ARVC (left) and 32-year-old healthy man (right). S wave duration: 63 vs 42 ms; length 0.694 vs 1.270; area: 0.009 vs 0.025 s×mV.

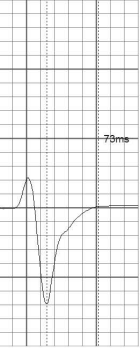
See the text for details.

Figure 2: Resting ECGs acquired in a 22-year-old woman with ARVC (top panels) and in a 26-year-old healthy woman (bottom panels). Only the precordial unipolar and derived bipolar leads are presented (25 mm/s, 1 cm/mV). In the ARVC patient, the unipolar leads demonstrate only a minor criterion for ARVC whereas the bipolar leads show a major diagnostic criterion.

For comparison, there is no T wave negativity beyond lead V1 with either lead system in the healthy subject.

Note also that in the ARVC patient, the T wave in lead V1 is deeper than 0.3 mV, which according to our results is a very specific marker of T wave abnormality.

See the text for details.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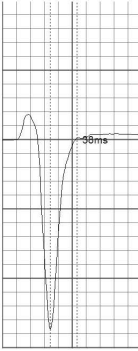
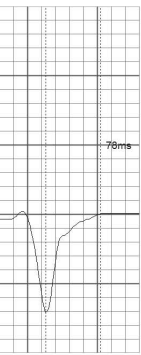
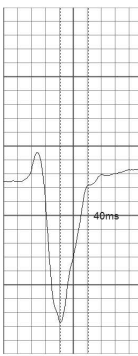
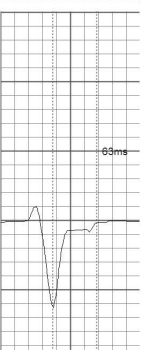
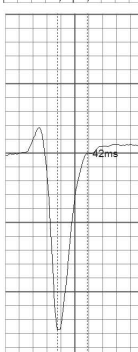
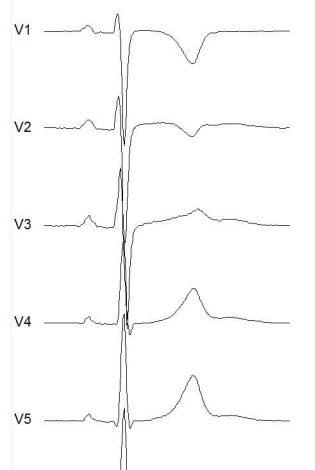

38ms


78ms


40ms


83ms


42ms


V1
V2
V3
V4
V5
V6
CF1
CF2
CF3
CF4
CF5
CF6

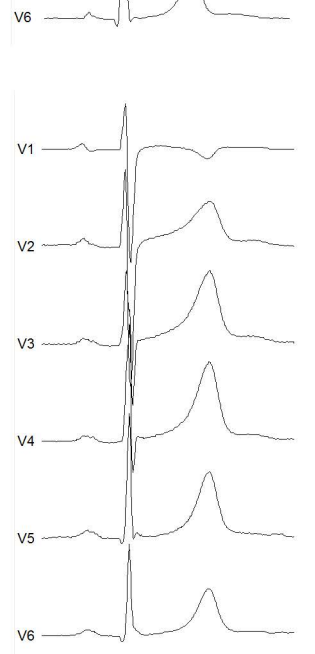

V1
V2
V3
V4
V5
V6
CF1
CF2
CF3
CF4
CF5
CF6

Table 1 Clinical characteristics of the ARVC patients (n=44) according to the 2010 Task Force criteria[1]

	Patients (n, %)
Family Hx of ARVC or premature SCD	33 (75.0)
Definite or probable pathogenic ARVC associated mutation (n = 17 tested)	8/17 (52.2)
ECG criteria (n=43)*	
• Repolarisation abnormalities	25 (58.1)
• Epsilon wave	3 (7)
• S wave ≥55 ms in leads V1, V2 or V3 in the absence of complete RBBB	20 (46.5)
• Abnormal SAECG	16/32 (50.0)
Global or regional dysfunction or structural alterations on echocardiography, MRI or RV angiography[f]	35 (79.5)
Arrhythmias	37 (84.1)

*=one patient was excluded because of permanent ventricular pacing;
[f]=endomyocardial biopsy has been performed in one patient with normal result

Table 2 QRS parameters in ARVC patients and healthy controls*

Parameter	ARVC (n=40)	Controls (n=44)	P value
Age (years)	42.2 ± 14.6	43.4 ± 14.7	0.71
Men (n, %)	32 (72.7)	28 (70.0)	0.78
Total QRS [ms]	109.2±13.7	90.0±10.5	<0.0001
D_{SV1} [ms]	53.9 ± 12.4	41.0 ± 9.7	<0.0001
D_{SV2} [ms]	49.5 ± 12.0	37.9 ± 8.0	<0.0001
D_{SV3} [ms]	44.8 ± 12.7	33.9 ± 11.4	<0.0001
L_{QRSV1} [mm]	1.99 ± 0.98	2.65 ± 0.87	0.001
L_{QRSV2} [mm]	3.05 ± 1.64	4.19 ± 1.57	0.002
L_{QRSV3} [mm]	2.83 ± 1.28	4.04 ± 1.45	0.0001
L_{SV1} [mm]	0.81 ± 0.39	1.08 ± 0.39	0.003
L_{SV2} [mm]	1.08 ± 0.60	1.51 ± 0.58	0.002
L_{SV3} [mm]	0.82 ± 0.49	1.11 ± 0.64	0.022
A_{QRSV1} [s × mV]	0.025 ± 0.012	0.033 ± 0.013	0.003
A_{QRSV2} [s × mV]	0.039 ± 0.022	0.048 ± 0.019	0.057
A_{QRSV3} [s × mV]	0.035 ± 0.018	0.043 ± 0.018	0.061
A_{SV1} [s × mV]	0.013 ± 0.007	0.018 ± 0.009	0.006
A_{SV2} [s × mV]	0.020 ± 0.014	0.023 ± 0.011	0.36
A_{SV3} [s × mV]	0.014 ± 0.012	0.015 ± 0.011	0.48

*Patients with complete RBBB were excluded

D_{SV1}, D_{SV2}, D_{SV3} = duration of the S wave (S wave nadir to the common QRS end);

L_{QRSV1}, L_{QRSV2}, L_{QRSV3}, L_{SV1}, L_{SV2}, L_{SV3} = length of the QRS and S wave curve in V1, V2 and V3, respectively;

A_{V1}, A_{V2}, A_{V3} AS_{V1}, AS_{V2}, AS_{V3} = area of the QRS and S wave in V1, V2 and V3, respectively.

Table 3 QRS parameters in relatives of ARVC patients with and without causative mutations*

Parameter	Mutation-carriers (n=15)	Without mutations (n=20)	P value
Age (years)	43.5 ± 19.2	46.2 ± 16.8	0.66
Men (n, %)	8 (57.1)	10 (50.0)	0.68
Total QRS [ms]*	103.2±9.2	105.0±10.9	0.61
DS_{V1} [ms]	54.0 ± 8.0	54.0 ± 8.6	1.00
DS_{V2} [ms]	45.2 ± 11.1	49.5 ± 8.6	0.21
DS_{V3} [ms]	40.9 ± 12.4	40.6 ± 11.1	0.93
L_{V1} [mm]	2.00 ± 0.90	1.96 ± 0.81	0.90
L_{V2} [mm]	2.99 ± 1.14	3.81 ± 1.15	0.043
L_{V3} [mm]	2.56 ± 1.09	3.47 ± 1.21	0.029
LS_{V1} [mm]	0.86 ± 0.45	0.86 ± 0.37	0.98
LS_{V2} [mm]	1.03 ± 0.55	1.32 ± 0.58	0.15
LS_{V3} [mm]	0.73 ± 0.53	0.81 ± 0.51	0.63
A_{V1} [s × mV]	0.025 ± 0.011	0.024 ± 0.010	0.79
A_{V2} [s × mV]	0.034 ± 0.015	0.046 ± 0.018	0.047
A_{V3} [s × mV]	0.031 ± 0.015	0.041 ± 0.018	0.072
AS_{V1} [s × mV]	0.013 ± 0.006	0.013 ± 0.005	0.80
AS_{V2} [s × mV]	0.015 ± 0.009	0.022 ± 0.012	0.082
AS_{V3} [s × mV]	0.011 ± 0.011	0.012 ± 0.010	0.81

Individuals with complete or incomplete RBBB were excluded

The abbreviations are the same as in Table 2.

Table 4 Incidence of T wave inversion in ARVC patients and healthy controls

Criterion \ Lead system	**V1 to V6**	**CF1 to CF6**	**P-value**
ARVC patients (n=43)			
• Major (n, %)	19 (44.2)	26 (60.5)	0.016
• Minor or major (n, %)	25 (58.1)	33 (76.7)	0.008
Healthy controls group A and B (n=276)			
• Negative T wave in V1 / CF1 (n, %)	110 (39.9)	224 (81.2)	<0.00001
• Negative T wave beyond V1 / CF1 (n, %)			
○ V1 & V2 (CF1 & CF2)	2 (0.7)*	3 (1.1)	0.99
○ Beyond V2 /CF2	1 (0.4)*f*	1 (0.4) *f*	

* = Both cases were 16-year old males in whom negative T waves were present in both V1 and V2, as well as in CF1 and CF2;

f = A 13-year-old boy with negative T wave both in V1 to V3 as well as in CF1 to CF3.

Table 5 Incidence of T wave inversion in family members of ARVC patients (n=36)

Criterion \ Lead system	**V1 to V6**	**CF1 to CF6**	***P-value***
Mutation carriers (n=15)			
• Major (n, %)*	4 (26.7)	4 (26.7)	*1.00*
• Minor or major (n, %)	5 (33.3)	6 (40.0)	*0.25*
Without mutations (n=21)			
• Major (n, %)	3 (20.0)	3 (20.0)	*1.00*
○ *P value vs mutation carriers*	*0.35*	*0.35*	
• Minor or major (n, %)	3 (20.0)	3 (20.0)	*1.00*
○ *P value vs mutation carriers*	*0.18*	*0.08*	

* = T wave inversion as a major criterion according to the 2010 Task Force Report
* = T wave inversion as either major or minor criterion according to the 2010 Task Force Report