Vectorcardiographic diagnostic & prognostic information derived from the 12-lead electrocardiogram

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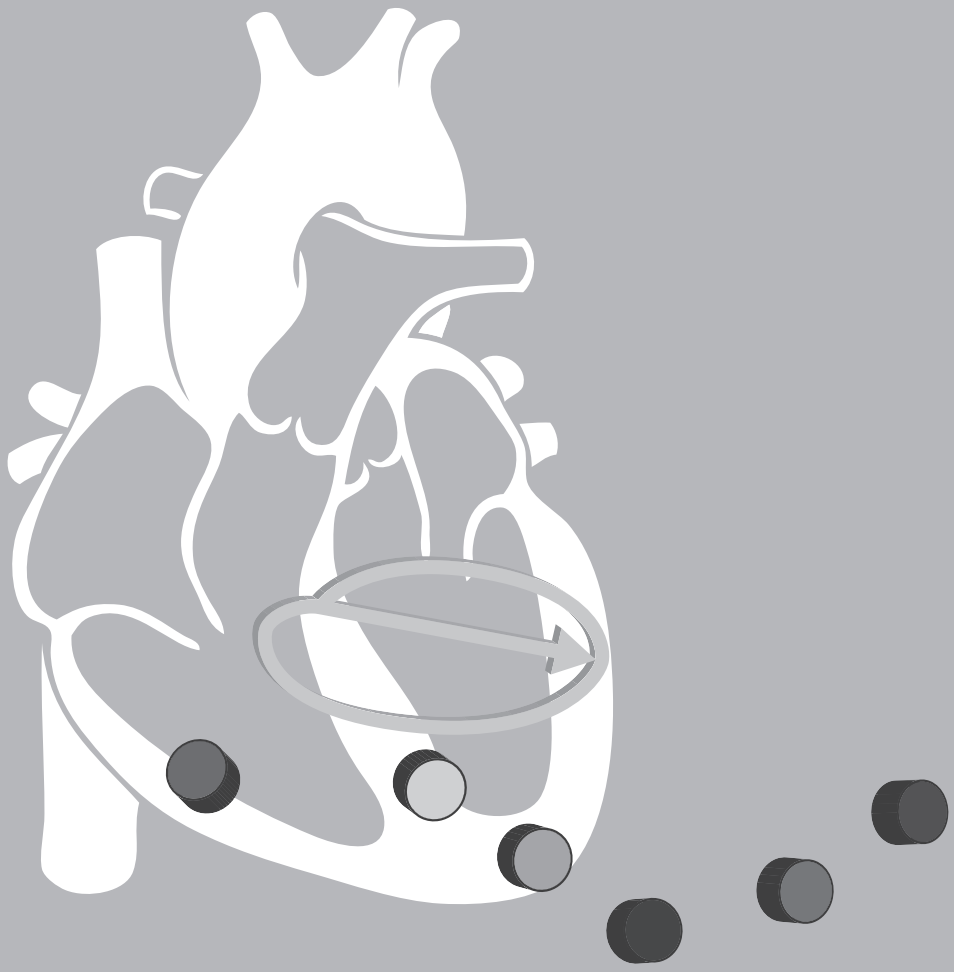

Chapter 11

Prediction of arrhythmias in primary prevention ICD patients: resting versus exercise electrocardiogram

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Abstract

Ejection fraction and microvolt T-wave alternans (mTWA) lack specificity to predict sudden cardiac death in heart failure (HF). We compared resting ECG variables (QRS duration, lead-dependent T-amplitudes and exercise-ECG-derived TWA variables (amplitude in the 12 leads, in the orthogonal X,Y,Z leads and in the vector magnitude) of 56 HF patients with an implanted cardioverter-defibrillator: cases and matched controls with/without antiarrhythmic therapy for VT/VF during follow up. Linear discriminant models, using resting and exercise ECG variables, were built in half of the study group, and were tested on the other half. QRS duration and TWA in lead Z discriminated best in the resting and exercise ECG, respectively, and had comparable diagnostic accuracy for VT/VF prediction.

Introduction

Implantable cardioverter-defibrillator (ICD) is a therapeutic option in heart failure patients, who have an increased risk for arrhythmic sudden cardiac death. Usually, the elevated risk of lethal arrhythmias is attributed to a reduced left ventricular ejection fraction (LVEF)[1]. Unfortunately, this risk criterion lacks specificity and it leads to a large number needed to treat[2], giving rise to unnecessary patient burden and to huge increases in the treatment cost. Therefore, continuing efforts are done to define extra, preferably noninvasive, predictors to better identify true candidates for ICD implantation for primary prevention. A potential predictor could be an increased QRS duration, that has been associated with sudden cardiac death[3]. Also, increased QT duration is associated with sudden cardiac death[4]. Furthermore, an increased spatial QRS-T angle has been associated with increased cardiac mortality risk in several studies[5;6]. Recently, we reported that a wide spatial QRS-T angle is a predictor for ICD therapy in primary prevention ICD patients[7]. Another potential predictor is the spatial ventricular gradient[8] (the vectorial sum of the integrals of the X, Y and Z components of the heart vector over the QT interval. This integral represents the action potential morphology gradients in the heart[9], as a consequence, any change in the gradient could be arrhythmogenic. In exercise ECG, the most promising candidate-predictor is microvolt T-wave alternans (mTWA) which is defined as every-other-beat changes in T wave morphology[10]. However, again because of a lack of specificity[11], more investigation is needed. As T-wave alternans is sometimes measured in all 12 leads[12], sometimes only in the precordial[13] or orthogonal[14] leads or in the vector magnitude[10], comparison of the results of these studies is impossible or very difficult, as the alternans phenomenon may be lead dependent. In this pilot study, we compared the predictive value of resting ECG variables and exercise ECG variables for ventricular arrhythmias in a population of heart failure patients with ICD implanted for primary prevention. Secondly, we investigated if the predictive value of the T wave in the resting and exercise ECG is lead dependent.

Methods

We selected heart failure patients with an ICD for primary prevention of sudden cardiac death, in whom a resting 10 second standard 12-lead ECG was made prior to the exercise test, in whom the exercise test had sufficient technical quality,

and in whom the baseline heart rate before exercise and the final recovery heart rate were below 95 bpm. We performed a case-control study with 56 patients. Patients were defined as cases if they had antiarrhyhtmic therapy for VT/VF during follow-up. Subsequently, cases were matched with 28 control patients on age, sex, aetiology, LVEF, and NYHA class who had no VT/VF during follow-up. Then, the resting ECGs were analyzed with our research program LEADS[15]. In brief, LEADS removes baseline wander, deselects noisy beats and defines the QRS onset, J point and end T for calculation of the ECG variables in the averaged beat. The following resting ECG variables were calculated: QRS duration, QTc using Bazett correction, the T-amplitude in every of the 12 leads, spatial QRS-T angle, the spatial ventricular gradient magnitude and its orientation (azimuth and elevation).

Exercise ECGs were analyzed by the heart-rate adaptive filter method[14] that results in a sinusoidal alternans signal. The exercise ECGs were analyzed in windows of 16 beats with a time step of 2 seconds. Beats that were 10% larger than the averaged interbeat interval were rejected, and replaced by an averaged beat. Windows were rejected if >1 beat was replaced. Alternans was calculated in each of the 12 standard ECG leads, mathematically synthesized orthogonal leads and in the

TABLE 1. Group characteristics

Group	**Cases**		**Controls**	
Set	Learning	Test	Learning	Test
N	14	14	14	14
Sex(Male/Female)	10/4	12/2	10/4	12/2
Age (y)	60±13	60±12	56±11	59±11
Height (cm)	173±9	178±6	177±10	177±7
Weight (kg)	79±15	85±18	87±14	80±12
BMI(kg/m2)	26±4	27±5	28±3	26±3
Device (ICD/CRT-D)	7/7	6/8	7/7	6/8
Follow-up (years)	4.3±1.3	4.9±2.1	3.8±1.9	4.1±1.8
Ischemic etiology	10	11	9	12
NYHA class				
I-II	9	12	12	10
III-IV	5	2	2	4
LVEF(%)	27±8	29±15	30±7	28±6

Data separated by a ± sign are mean ± SD. BMI = body mass index; NYHA = New York Heart Association; ICD = implantable cardioverter-defibrillator; CRT-D = cardiac resynchronization therapy with defibrillator; LVEF = left ventricular ejection fraction.

vector magnitude. The T-wave alternans was finally defined for each lead and for the vector magnitude as the averaged alternans over the valid windows.
Then, the case and control patients were randomly divided in an equal-sized learning and test set of 14 patients. The group characteristics of the learning and test set are shown in Table 1.

Statistical analysis

Patient characteristics of the learning and test sets were compared, when appropriate, with the paired t-test or chi-square test. Receiver operating characteristic (ROC) analyses were made to visualize and quantize the univariate diagnostic performance of the resting and exercise ECG variables. Then, stepwise linear discriminant analysis was performed. The discriminant model was built using Wilks' lambda method, with $P<0.05$ and $P>0.10$ as entry and removal criterion. Two models were built with the learning set: 1) the resting ECG variables, and 2) exercise ECG variables. The diagnostic performance of these models was tested on the test set. Finally, to get an impression of the model stability, a cross-validated

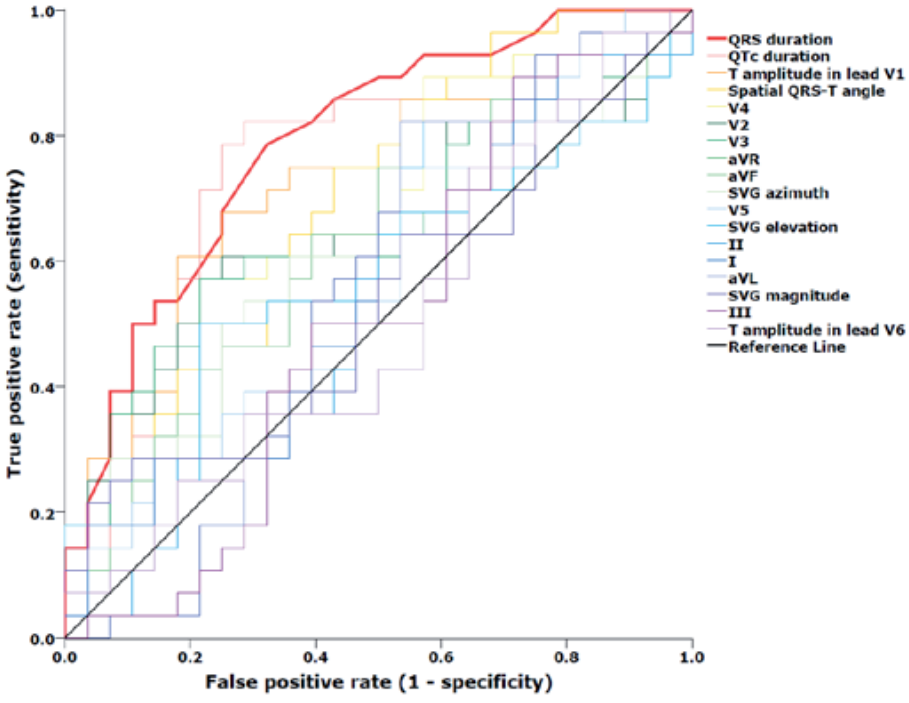

FIGURE 1. ROCs of resting ECG variables.

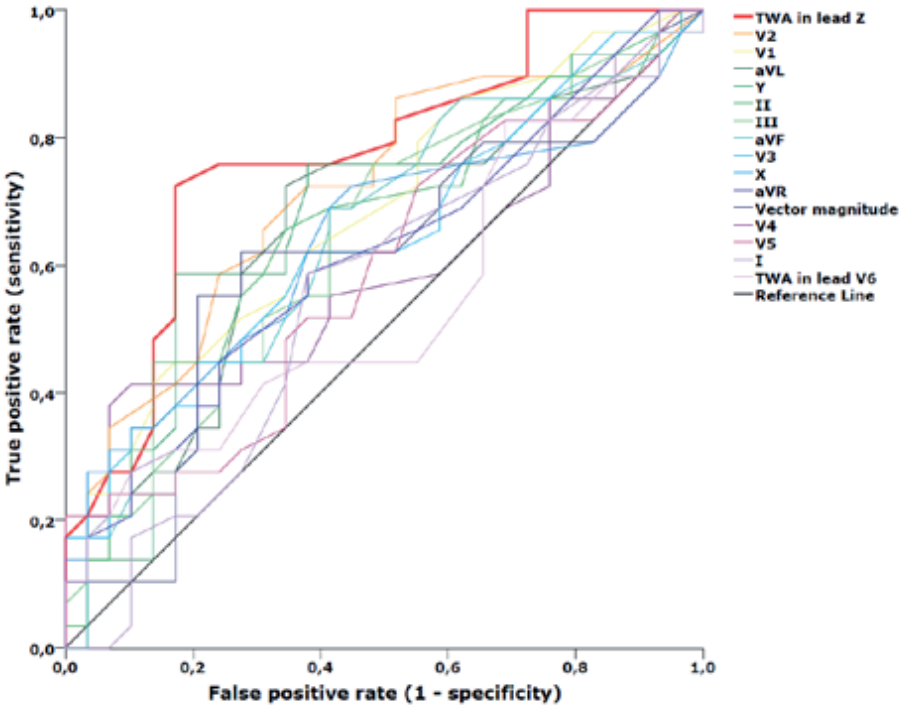

FIGURE 2. ROCs of exercise ECG variables.

(leave-one out classification) discriminant analysis of the whole study group (N=56) was done. Analyses were done in PASW Statistics (SPSS), version 18.0 (PASW Statistics; SPSS Inc).

Results

General patients' characteristics are given in Table 1 and were not statistically different between the learning and test sets within the case and control patients. Also, the resting and exercise ECG variables were not significantly different between the learning and test sets within the case and control patient groups (not shown).

To get an impression of the univariate predictive power for VT/VF, we made ROCs of the resting and exercise ECG variables, respectively (Figure 1-2). The ROC analyses showed that, in the resting ECG, QRS duration (area under the curve

TABLE 2. ROC analyses of resting ECG variables

Resting ECG variables	AUC	P
QRS duration	0.790	<0.001
QTc duration	0.746	0.002
Tamp in lead V1	0.710	0.007
Spatial QRS-T angle	0.698	0.01
Tamp in lead V4	0.670	0.03
Tamp in lead V2	0.662	0.04
Tamp in lead V3	0.648	0.06
Tamp in lead aVR	0.624	0.11
Tamp in lead aVF	0.624	0.11
SVG azimuth	0.602	0.19
Tamp in lead V5	0.583	0.29
SVG elevation	0.574	0.34
Tamp in lead II	0.557	0.46
Tamp in lead I	0.557	0.46
Tamp in lead aVL	0.555	0.48
SVG magnitude	0.537	0.64
Tamp in lead III	0.509	0.91
Tamp in lead V6	0.505	0.95

AUC= area under the curve, Tamp = T amplitude. SVG = spatial ventricular gradient. Results are sorted by increasing AUCs.

(AUC) 0.790, P<0.001), QTc duration (AUC=0.070, P=0.002), T amplitude in lead V1 (AUC=0.710, P=0.007), spatial QRS-T angle (AUC=0.698, P=0.01), T amplitude in lead V4 (AUC=0.670, P=0.03) and T amplitude in lead V2 (AUC=0.670, P=0.03) had significant discriminative power for VT/VF (Figure 1; Table 2). The ROC analyses of the exercise ECG variables showed that TWA in lead V3 (AUC 0.664, P=0.04), TWA in lead aVF (AUC 0.672, P=0.03), TWA in lead III (AUC 0.672, P=0.03), TWA in lead II (AUC 0.680, P=0.02), TWA in lead Y (AUC 0.684, P=0.02), TWA in lead aVL (AUC 0.695, P=0.01), TWA in lead V1 (AUC 0.713, P=0.006, TWA in lead V2 (AUC 0.746, P=0.002), and TWA in lead Z (AUC 0.807, P<0.0001) had significant discriminative power for VT/VF (Figure 2; Table 3).

Linear discriminant analysis in the learning set using resting ECG variables yielded the best performance with the QRS duration; other additional variables could not improve this result. The resting ECG model was: D=0.039 x QRS duration – 4.63 (D>0 predicts ventricular arrhythmia during follow-up (Table 4)). In the learning

TABLE 3. ROC analyses of exercise ECG variables

Exercise ECG variables	AUC	P
TWA in lead Z	0.807	<0.001
V2	0.746	0.002
V1	0.713	0.006
aVL	0.695	0.01
Y	0.684	0.02
II	0.680	0.02
III	0.672	0.03
aVF	0.672	0.03
V3	0.664	0.04
X	0.644	0.06
aVR	0.633	0.09
Vector magnitude	0.631	0.09
V4	0.607	0.17
V5	0.604	0.18
I	0.588	0.26
V6	0.545	0.56

AUC= area under the curve, TWA= T-wave alternans. Results are sorted by increasing AUCs.

TABLE 4. Performance of resting ECG discriminant model

Learning set N=14	Case	Control	
VT/VF+ (D>0)	10	4	PPV 71%
VT/VF– (D≤0)	4	10	NPV 71%
	Sensitivity 71%	Specificity 71%	Accuracy 71%
Test set N=14	**Case**	**Control**	
VT/VF+ (D>0)	8	3	PPV 73%
VT/VF– (D≤0)	6	11	NPV 65%
	Sensitivity 57%	Specificity 79%	Accuracy 68%

Model equation is D= 0.039*QRS duration – 4.63. If D>0, ventricular arrhythmia during follow-up is predicted (VT/VF+), while D≤0 predicts no arrhythmia (VT/VF–). PPV = positive predictive value; NPV = negative predictive value.

set, the diagnostic accuracy was 71%. When applied to the test set the performance was similar (68%; Table 4).

Discriminant analysis in the learning set using exercise ECG variables yielded the best performance with the TWA in lead Z; other additional variables could not improve this result. The exercise ECG model was: D=0.11 x TWA in lead

TABLE 5. Performance of discriminant models built using exercise ECG variables to predict ventricular arrhythmia in learning set and test set

Learning set N=14	**Case**	**Control**	
VT/VF+ (D>0)	8	2	PPV 80%
VT/VF– (D≤0)	6	12	NPV 67%
	Sensitivity 57%	Specificity 86%	Accuracy 71%
Test set N=14	**Case**	**Control**	
VT/VF+ (D>0)	7	2	PPV 78%
VT/VF– (D≤0)	7	12	NPV 63%
	Sensitivity 50%	Specificity 86%	Accuracy 68%

Model equation is D= 0.11*TWA in lead Z – 1.77. If D>0, ventricular arrhythmia during follow-up is predicted (VT/VF+), while D≤0 predicts no arrhythmia (VT/VF–). PPV = positive predictive value; NPV = negative predictive value.

Z – 1.77 (D>0 predicts ventricular arrhythmia during follow-up (Table 5)). In the learning set, the diagnostic accuracy was 71%, When applied to the test set the performance was similar (68%; Table 5). To get an impression of the stability of resting and exercise ECG discriminant models, leave-one-out classification (cross-validated) discriminant analyses were done using the whole study group of 56 patients: the resting ECG diagnostic accuracy was 75% and for the exercise ECG was 70%.

Discussion

In this pilot study, we have shown that the QRS duration in the resting ECG and lead Z alternans in the exercise ECG both have predictive power for ventricular arrhythmia. The derived models using QRS duration and lead Z TWA had similar diagnostic performance in the test set. Also, the cross validation analysis had comparable accuracy.

The remarkable differences in the AUC values of the T-wave amplitudes in the resting ECG (Figure 1) show clearly that the predictive value for VT/VF is lead dependent. The performance of the T-wave amplitude in some leads was quite good, however, QRS duration was superior (Figure 1; Table 2).

Similarly, for the exercise ECG, the discriminative power of TWA for VT/VF is lead dependent (Figure 2; Table 3). Alternans in lead Z was largest (Figure 2; Table 3), and appeared in the model. Of note, alternans in lead V2, which assumes, apart from an opposite sign, a similar direction as lead Z had comparable performance.

Conclusion

From this pilot study, we can conclude that the predictive values of the T-wave variables in the resting and exercise ECG models were lead dependent. The best resting ECG predictor is QRS duration and the best exercise ECG predictor is alternans in lead Z. Further studies are required to investigate why alternans in the Z direction is the best predictor.

Acknowledgements

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