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

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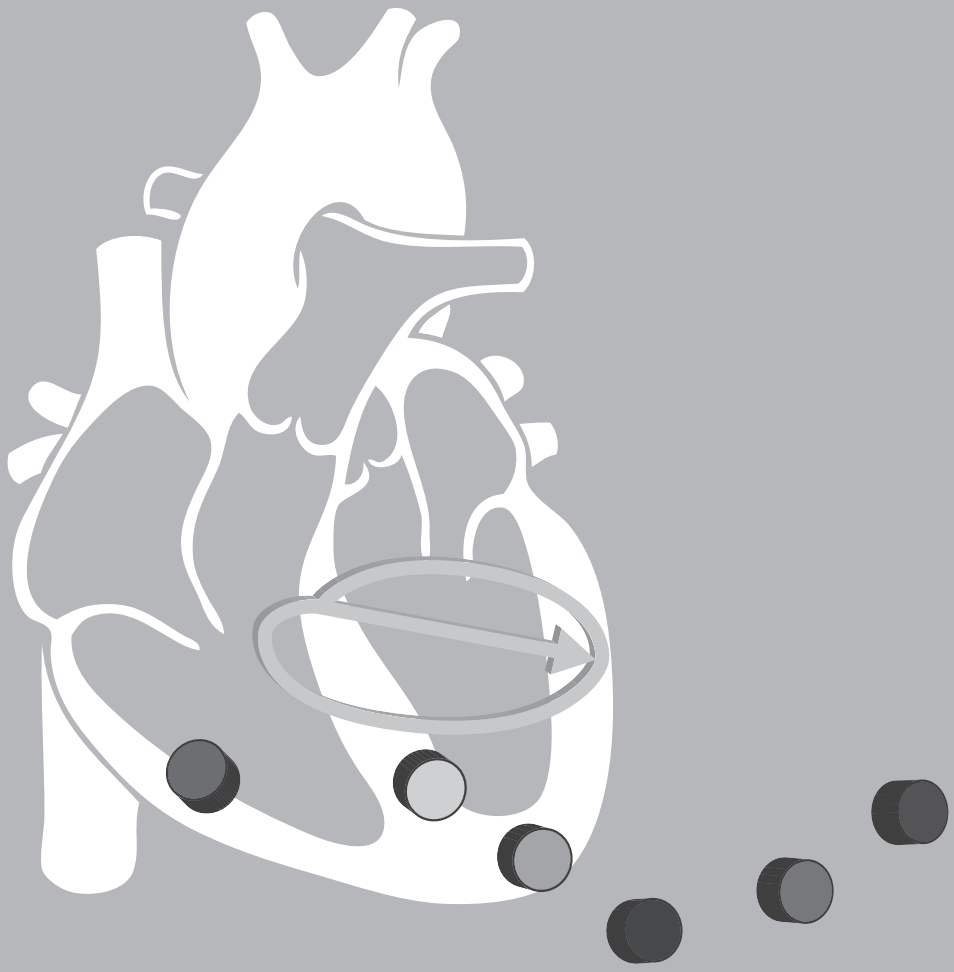

Chapter 10

Predictive power of T-wave alternans and of ventricular gradient hysteresis for the occurrence of ventricular arrhythmias in primary prevention cardioverter-defibrillator patients

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Abstract

Background

Left ventricular ejection fraction lacks specificity to predict sudden cardiac death in heart failure. T-wave alternans (TWA; beat-to-beat T-wave instability, often measured during exercise) is deemed a promising noninvasive predictor of major cardiac arrhythmic event. Recently, it was demonstrated that TWA during recovery from exercise has additional predictive value. Another mechanism that potentially contributes to arrhythmogeneity is exercise-recovery hysteresis in action potential morphology distribution, which becomes apparent in the spatial ventricular gradient (SVG). In the current study, we investigated the performance of TWA amplitude (TWAA) during a complete exercise test and of exercise-recovery SVG hysteresis (SVGH) as predictors for lethal arrhythmias in a population of heart failure patients with cardioverter-defibrillators (ICDs) implanted for primary prevention.

Methods

We performed a case-control study with 34 primary prevention ICD patients, wherein 17 patients (cases) had, and 17 patients (controls) had no ventricular arrhythmia during follow-up. We computed, in electrocardiograms (ECGs) recorded during exercise tests, TWAA (maximum over the complete test) and the exercise-recovery hysteresis in the SVG. Statistical analyses were done by using the Student t-test, Spearman's rank correlation analysis, receiver operating characteristics (ROC) analysis and Kaplan-Meier analysis. Significant level was set at 5%.

Results

SVGH and TWAA differed significantly ($P<0.05$) between cases (mean ± SD SVGH -18±26%, TWAA 80±46 μV) and controls (SVGH 5±26%, TWAA 49±20 μV). TWAA and SVGH values showed no significant correlation in cases ($r=-0.16$, $P=0.56$) and in controls ($r=-0.28$, $P=0.27$). Receiver operating characteristics of SVGH (area under the curve = 0.734, $P=0.020$) revealed that SVGH <14.8% discriminated cases and controls with 94.1% sensitivity and 41.2% specificity; hazard ratio was 3.34 (1.17-9.55). Receiver operating characteristics of TWA (area under the curve = 0.699, $P=0.048$) revealed that TWAA >32.5 μV discriminated cases and controls with 93.8% sensitivity and 23.5% specificity; hazard ratio was 2.07 (0.54-7.91).

Discussion and conclusion

SVGH bears predictive potential for arrhythmias in heart failure patients with an ICD for primary prevention, while TWA analysis seems to have lesser predictive value in our pilot group. SVGH is relatively robust for noise, and, as it rests on different electrophysiological properties than TWA, it may convey additional information. Hence, joint analysis of TWA and SVGH may, possibly, improve the noninvasive identification of high-risk patients. Further research, in a large group of patients, is required and currently carried out by our group.

Introduction

Currently, a reduced left ventricular ejection fraction (LVEF[1]) is the major criterion to select patients for primary prevention cardioverter-defibrillator (ICD) implantation. Many primary prevention ICD patients do not develop ventricular arrhythmia during follow-up[2], hence, this criterion lacks specificity. Therefore, continuing efforts are done to define extra, preferably noninvasive, predictors to better identify true candidate patients for primary prevention ICD implantation. T-wave alternans (TWA) was deemed such a promising predictor[3], but appears also to lack specificity; conflicting results of several studies[4;5] render TWA to have a Class IIa indication in the Guidelines[1],

Diagnostic significant (maximal) TWA is often measured in the exercise phase of an exercise test[6]. The recovery phase of exercise tests remains often unutilized, but may contain important independent prognostic information. In a recent study, combined analysis of TWA during exercise and recovery[7] increased the estimated relative risk.

In the recovery phase, cardiac electrophysiology differs dramatically from that at similar heart rates in the exercise phase (hysteresis[8]). This is due to increased levels of circulating catecholamines and parasympathetic tone in the recovery phase as compared to the exercise phase. When the shape of action potentials at similar heart rates during exercise and recovery differ, the electrocardiogram (ECG) differs too. It has been demonstrated that exercise-recovery hysteresis in the spatial ventricular gradient (SVG) exists in normal subjects[8]. According to Burger[9], the SVG is the integral of the action potential morphology gradients in the heart, and, as a consequence, any change in the SVG denotes a change in the action potential morphology distribution[10] and may thus be arrhythmogenic.

Hence, both TWA (measured during exercise and during recovery) and exercise-recovery SVG hysteresis (SVGH) signify instability, TWA signifies beat-to-beat instability, while SVGH signifies sensitivity of cardiac electrophysiology to alterations in neurohumoral modulation during exercise and recovery. As this relates to different aspects of cardiac electrophysiology, TWA and SVGH are likely to yield different information about cardiac arrhythmogeneity. In this study, we investigate if the performance of SVGH to predict lethal arrhythmias is superior to TWA in primary prevention ICD patients.

Methods

Study cohort and exercise tests

This retrospective case-control study consisted of primary prevention ICD patients with heart failure, and in whom a bicycle exercise test was done for other than ICD stratification reasons. Patients were divided into cases (if, during follow-up patients had appropriate antiarrhythmic therapy for ventricular tachycardia or fibrillation (VT/VF)), and controls (no VT/VF during follow up). Here, we report about the initial 17 case-control patient pairs. Controls were matched to cases on the following confounding factors: age, sex, etiology, LVEF and NYHA class. All patients used heart failure medication (*e.g.* amiodarone and beta blockers).Table 1 lists the general characteristics of our study group.

Exercise ECGs (xECGs) were collected since 2006, and obtained using a CASE 8000 stress test recorder (GE Healthcare, Freiburg, Germany) with a sampling frequency of 500 Hz and a resolution of 4.88 μV/LSB (least significant bit). All patients had a depressed LVEF (≤ 35%), an exercise test of sufficient technical quality and without abundant arrhythmias, with at least 1 minute in the 95-110 beat per minute (bpm) heart rate zone in the exercise phase, and with a recovery phase in which heart rate decreased below 95 bpm. The exercise protocol was tailored to the patients expected maximal exercise capacity by applying load-increments of 10% of the expected maximal exercise capacity per minute, thus aiming at a 10-minute duration of the exercise phase.

Major cardiac events (myocardial infarction, VT ablation, coronary artery bypass surgery) affect the electrophysiological properties of the heart, thus weakening the association between the xECG and the occurrence of ICD therapy for VT/VF (cases) or the absence of ICD therapy during follow-up (controls). Hence, for the cases only xECGs were selected for which there was no major cardiac event between the exercise test and the ICD therapy, preferably with the smallest time difference between the exercise test and ICD therapy. For the controls the earliest available exercise test was selected after which no major cardiac event occurred during follow-up.

TABLE 1. General characteristics of the study group

	Cases	Controls
Patients (N)	17	17
Age (years)	56±13	58±10
Sex (male)	13(77)	13(77)
Height (cm)	175±9	176±8
Weight (kg)	83±15	80±11
CRT-D	9(53)	9(53)
LVEF (%)	27±4	28±6
Etiology		
Ischemic	14(82)	14(82)
Non-ischemic	3(18)	3(18)
NYHA functional class		
I-II	13(77)	14(82)
III-IV	4(23)	3(18)
Follow-up (years)	4.4±1.7	4.4±2.1
Medication at exercise test		
Beta blocker	15(88)	15(88)
ACE inhibitor / AT antagonist	16(94)	17(100)
Diuretics for CHF	13(77)	14(82)
Statins	14(82)	13(77)
Amiodarone	3(18)	2(12)
ECG parameters		
SVGH (%)	-18±26	5±26*
TWAA (μV)	80±46	49±20*

Data between parentheses are percentages. Data separated by a ± sign are mean ± SD. Cases are patients with arrhythmia during follow-up. Controls are patients without arrhythmia during follow-up. CRT-D indicates cardiac resynchronization therapy with defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ACE = angiotensin converting enzyme; AT = angiotensin; CHF = congestive heart failure; SVGH = exercise-recovery spatial ventricular gradient hysteresis; TWAA = T-wave alternans amplitude. *P<0.05; compared with patients with appropriate ICD therapy during follow-up.

Measurement of exercise-recovery spatial ventricular gradient hysteresis (SVGH)

Exercise ECGs were analyzed with our interactive research-oriented ECG analysis program BEATS (beat editing and tracking software[11]). In brief, BEATS performs baseline correction, identifies all sinus beats with sufficient signal quality and the landmarks in time required for SVG calculation (onset QRS and T offset). Beats and landmarks with a correlation <90% with the previous ten beats or with the average time of the markers were rejected from analysis, respectively. Subsequently,

the SVG (mV·ms) of each sinus beat was computed in a vectorcardiographic representation of the xECG, synthesized by using the matrix according to Kors[12], by taking the spatial integral of the area formed by the moving spatial heart vector during the QRST interval (vectorial QRST integral). The mean SVG in the exercise ($SVG_{exercise}$) and recovery ($SVG_{recovery}$) phases in the 95 to 110 bpm heart rate range was calculated, respectively, and followed by the computation of the SVGH (%) wherein the resulted value is normalized on the exercise SVG value:

$$SVGH\ (\%) = (SVG_{recovery} - SVG_{exercise}) / SVG_{exercise}$$

Measurement of T-wave alternans (TWA)

TWA was measured using the heart-rate adaptive-match-filter (AMF) method[13-17]. TWA is, by definition, characterized by a frequency (f_{TWA}) equal to half the heart rate. To account for physiological variations of the interbeat interval, a narrow frequency band, instead of a single frequency, was assumed to characterize TWA accordingly. On this basis, our AMF was implemented as a 6th order bidirectional Butterworth band-pass filter, with its passing band centered at a frequency (f_{TWA}) and 0.12 Hz wide (value experimentally found), constituted by a cascade of a low-pass filter (LPF; cut-off frequency $f_{LPF}=f_{TWA}+df_{TWA}$, $df_{TWA}=0.06$ Hz) and a high-pass filter (HPF; cut-off frequency $f_{HPF}=f_{TWA}-df_{TWA}$). The squared module of the AMF transfer function is expressed by the following equation[15;16]:

$$\left|H_{AMF}(\omega)\right|^2 = \left|H_{LPF}(\omega)\right|^2 \cdot \left|H_{HPF}(\omega)\right|^2 = \frac{1}{1+\left(\frac{\omega}{\omega_{LPF}}\right)^{2n}} \cdot \frac{\left(\frac{\omega}{\omega_{HPF}}\right)^{2n}}{1+\left(\frac{\omega}{\omega_{HPF}}\right)^{2n}}$$

where n=3 (half of AMF order), $\omega_{LPF}=2\pi f_{LPF}$, and $\omega_{HPF}=2\pi f_{HPF}$. Being the AMF applied in a bidirectional fashion, no phase delay occurs. Thus, the AMF filters out signal components (including those related to noise, baseline and respiration) but remaining the TWA-typical one and provides, as an output, the TWA sinusoidal signal, eventually amplitude modulated, whose maxima and minima have to occur in correspondence of the T waves for pertaining to TWA and not to other kinds of

alternations (phase constraint). The TWA signal amplitude, in correspondence of the T-waves, provides a local (i.e. relative to a specific beat) estimate of the TWA amplitude (A_{TWA} , μV), so that an A_{TWA} value is computed for each beat in a tracing. In the absence of TWA, the sinusoid reduces to a zero constant. An example of the TWA analysis is shown in Figure 1. The case-patient ECG tracing is affected by respiratory modulation (with an approximate period of 4-5 beats) but also by TWA. Indeed, the up and down trend is still perceptible, even though corrupted by the superimposition of respiratory modulation. Conform to expectation, the TWA-signal peaks nicely aligned with the T waves (contrarily to what will happen if the alternation was due to noise or QRS alternans). The estimated A_{TWA} is around 100 μV, over the recording resolution (4.88 μV/LSB), while the control subject appeared to not have significant TWA.

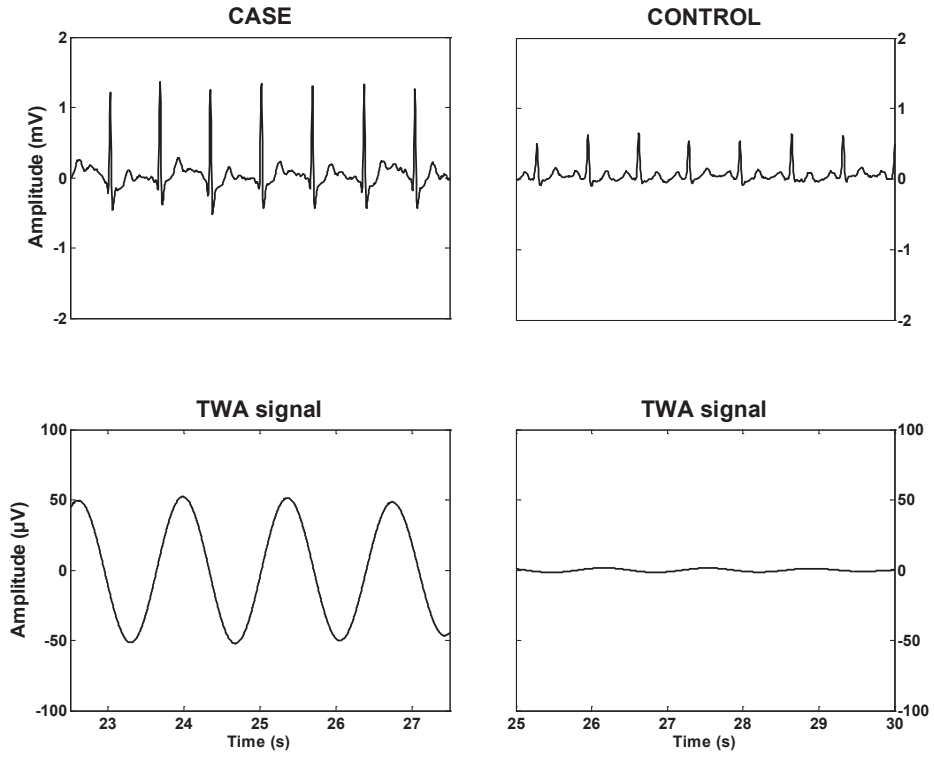

FIGURE 1. Example of T-wave alternans analysis in a case-control patient pair. Upper panels: ECG lead V4 for the case patient (left); ECG lead V6 for the control patient (right). Lower panels: T-wave alternans signal for the case patient (left) and the control patient (right). In the case patient T-wave alternans amplitude was around 100 μV (twice the T-wave alternans signal amplitude), and control patient had less than 5 μV T-wave alternans.

In this study, the AMF was applied to windows consisting of 64 (instead of 128[16]), consecutive beats moving over the entire xECG recording (hence, over both the exercise and recovery phase) in steps of 2 seconds. To avoid signals where TWA could be driven by heart-rate variability, windows were rejected if the standard deviation of the interbeat intervals was >10% of the average interbeat interval. To avoid cases in which TWA could be driven by arrhythmias or artifacts, these were, if appropriate, replaced by interpolated average beats. Windows with more than 5 replaced beats were rejected. Windows that were rejected after application of the above mentioned validity criteria were not taken into account for the TWA calculation. Instead, for each accepted ECG window, the AMF based technique provided 64 A_{TWA} values, one for each beat, which were then averaged for a comprehensive evaluation of TWA amplitude (mean_A_{TWA}) in a single window.

All ECG leads I, II, V1-V6, were analyzed independently. Per lead, the maximal mean_A_{TWA} was computed over all valid windows. Finally, the three largest maximal lead-dependent mean_A_{TWA} values were averaged, and taken as the resulting TWA amplitude (TWAA) for the exercise test.

Statistical analysis

Comparison of data was performed with the Student t-test for paired or unpaired data and Chi-square tests when appropriate. Data are expressed in mean ± SD or in numbers and percentages. The relationship between SVGH and TWAA was assessed by Spearman's rank correlation analysis, in cases and in control patients. Receiver operating characteristics (ROC) analysis was performed to determine the area under the curve (AUC), and to define the optimal cut-off point of SVGH and TWAA for the prediction of lethal arrhythmias. Kaplan–Meier analysis was done to compare the cumulative event-free rates between patients above and below the cut-off point. Hazard ratios (HRs) with 95% confidence interval were calculated for TWAA and SVGH. Statistical analyses were performed using GraphPad Prism v5.01 for Windows (GraphPad Software Inc., San Diego, CA, USA), except for the analysis of the statistical difference between the SVGH and the TWA ROCs, that was done by using the ROC comparison module in MedCalc v11.4.4.0 (MedCalc Software, Mariakerke, Belgium). Significant level was set at 5%.

Results

The general characteristics of the study group (medication at exercise test, height, weight, follow-up time) did not differ significantly between cases and controls (Table 1). In the ECG variables differences between cases and controls were present for SVGH (cases mean ± SD -18 ± 26% vs. controls 5 ± 26%, P=0.004), as well as for TWAA (cases 80 μV ± 46 μV vs. controls 49 μV ± 20 μV, P=0.03).

TWA and SVGH values of case and control patients are shown in Figure 2. TWAA and SVGH yielded no significant correlation in cases (r=-0.16, P=0.56) and in control patients (r=-0.28, P=0.27).

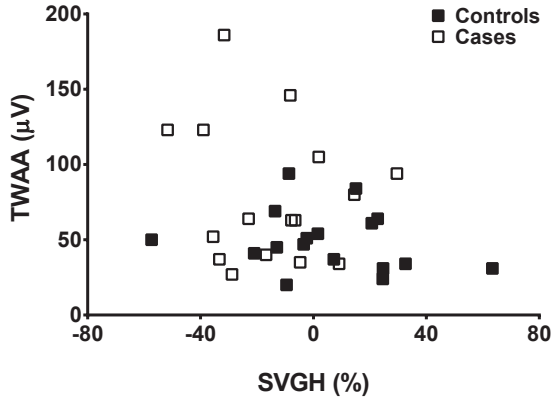

FIGURE 2. Scatter plot of T-wave alternans amplitude and SVGH values in case patients and in control patients. Spearman's rank correlation analysis yielded no significant association, neither in cases (r=-0.16, P=0.56) nor in control patients (r=-0.28, P=0.27).

The individual SVGH values are depicted in Figure 3. For this Figure, the case-control pairs were sorted on increasing hysteresis values in the cases. The SVGH turned out to be significant smaller in case patients than the hysteresis value in the matched control patient in 14 out of the 17 case-control patient pairs (P< 0.05).

The individual TWAA values are depicted in Figure 4. For this Figure, the case-control pairs were sorted on increasing TWAA values in the cases (hence, differently ordered than in Figure 3). Also here, there was a significant difference between case and control patients (P<0.05). The TWAA value in the case patient turned out to be significant larger than in the matched control patient in 11 out of the 17 case-control pairs. There was one missing value (the case patient of case-control pair 1 in this Figure), case-control pair 3 had equal values, and in the remaining 4 case-control pairs, TWAA in the control patients was larger than TWAA in the case patients.

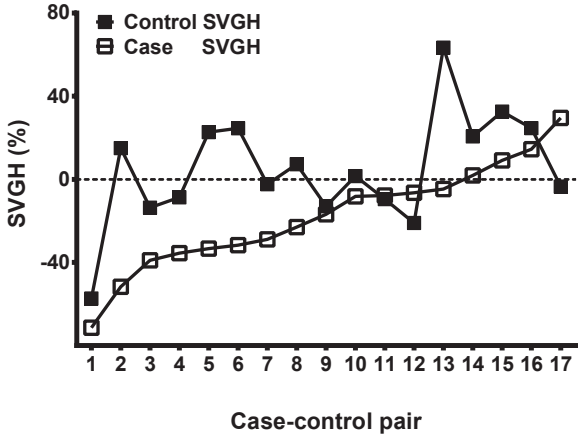

FIGURE 3. SVGH in 17 case-control patient pairs. For visual clarity, connecting lines were added and the case-control pairs were sorted on ascending values of SVGH in the cases.

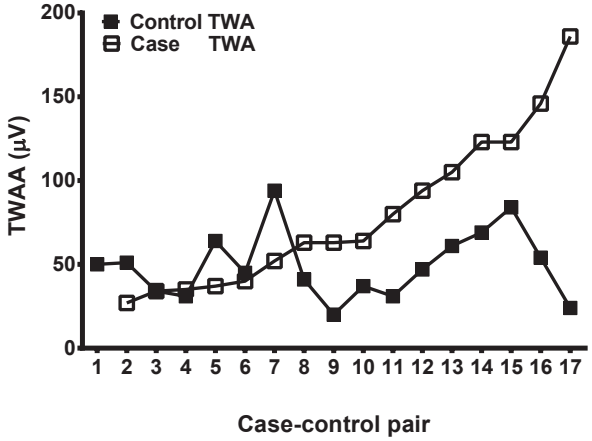

FIGURE 4. T-wave alternans amplitude in 17 case-control patient pairs. For visual clarity, connecting lines were added and the case-control pairs were sorted on ascending values of the T-wave alternans amplitude in the cases.

Results of the ROC analyses of case-control discrimination on SVGH and on TWA are displayed in Figure 5. The AUC-SVGH and the AUC-TWA were 0.734 and 0.699, respectively, both significantly larger than 0.5 (P=0.020 and P=0.048, respectively). Statistical comparison of ROC-SVGH and ROC-TWA yielded no significant difference (P=0.89).

For the current study we adopted a discrimination threshold, which was determined from the ROC analysis, and yields a comparable sensitivity as adopted/reported in several TWA studies[18] (range, 78.6%–100%). The highest sensitivity of 94.1% was chosen from the ROC curve, which resulted in a cut-off value of 14.8%. Patients with SVGH < 14.8% are considered at high risk to develop VT/VF during follow-up. It appears that the specificity of the SVGH at this cut-off value is

41.2%, which is somewhat better than the range of values (28.9–37.1%) reported in several TWA studies[18]. Similarly, patients with TWAA > 32.5 μV are considered at high risk to develop VT/VF during follow up. The cut-off value resulted from a chosen high sensitivity of 93.8% determined from the ROC analysis. It appears that the specificity of the TWAA at this cut-off value is 23.5%, which is somewhat inferior to the range of values (28.9–37.1%) reported in several TWA studies[18].

Kaplan-Meier analyses on the basis of the exercise-recovery SVG hysteresis cut-off value of 14.8% and TWAA cut-off value of 32.5 μV is shown in Figure 6. The curves depicting the event-free patient fractions for the "at risk" patients and the "not at risk" patients differ significantly for SVGH (P=0.024) but not for TWAA (P=0.29). The hazard ratio of "at risk" patients is (95% confidence interval, 1.17–9.55) for SVGH and 2.07 (95% confidence interval, 0.54–7.91) for TWAA, respectively.

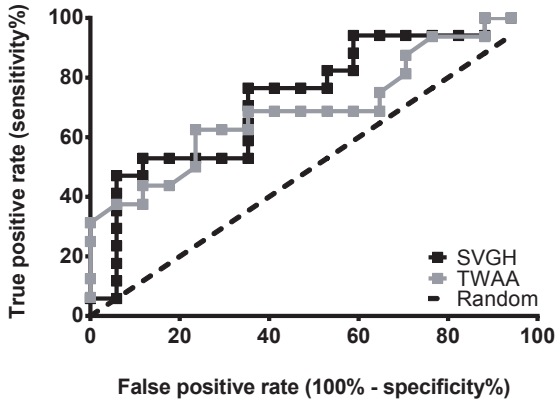

FIGURE 5. Receiver operating characteristics analyses for lethal arrhythmia prediction based on SVGH and on TWAA.

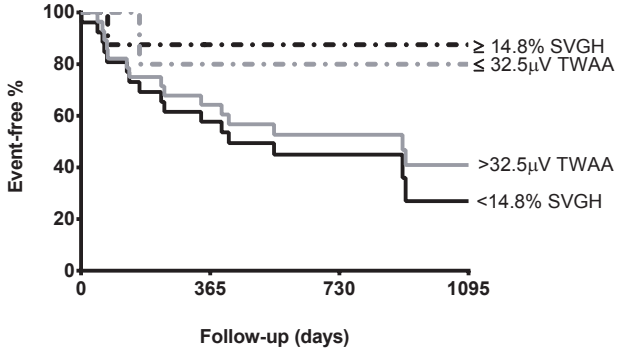

FIGURE 6. Kaplan-Meier analyses of the complete study group using the SVGH cut-off point of 14.8%, and the TWAA cut-off point of 32.5 μV.

Discussion

This study represents the first attempt to compare TWA vs. SVGH performances in predicting ventricular arrhythmias in primary prevention ICD patients. TWA was analyzed here by means of the AMF method, an automatic technique widely tested in both simulated and clinical settings[13-17]. Compared to the several others present in the literature[3;19-21] the AMF has the major advantages of being able to identify stationary as well as transient TWA[14], and of being particularly robust to several interferences (such as noise, respiratory modulation, and heart-rate variability), often affecting real ECG recordings[17].
Specifically, the AMF method proved to be suitable for TWA detection and quantification in the presence of an alternans signal whose amplitude and phase vary with time[14;17], situation which likely occurs in real cases, as indicated in Janusek *et al.*[19]. Instead, SVGH was expressed as the mean difference of the SVG during recovery and exercise, normalized on the mean SVG exercise value. The SVG equals the vectorial approach of the QRST integral, which should be robust to noise**.**

In our study group, both TWAA and SVGH differed significantly between the case and control patients. Both AUCs of the ROCs were significantly larger than 0.5, although the significance level of the AUC of the ROC of TWA was marginal. Although the AUC of SVGH (0.734) was larger than the AUC of TWA (0.699), this difference did not reach statistical significance. Kaplan-Meier analysis yielded a significant result for SVGH<14.8% with a relative risk of 3.34, while this analysis was not significant for TWAA >32.5 μV (with a relative risk of 2.09).

The electrophysiological basis of TWA rests on the electrical restitution properties of cardiac myocytes, of which the metabolism and membrane properties are seriously affected in heart failure[22;23]. This can give rise to beat-to-beat instability of action potentials, and finally lead to arrhythmias due to exaggerated fluctuations in action potential shapes, excitability and conduction in certain regions of the heart, possibly in combination with ectopic activity[24], hence temporal dispersion of action potential duration changes.

The electrophysiological basis of SVGH rests on autonomic derangement and altered sensitivity of myocardial cells to autonomic stimuli, which may give rise to large contrasts in electrophysiological properties during exercise and recovery.

Therefore, it is based on spatial dispersion of action potential duration changes. It has to be stressed that in normal hearts the ventricular gradient has substantial exercise-recovery hysteresis, due to the fact that it increases during recovery. In normal subjects, the SVG during a maximal exercise test assumes average values around 70 mV·ms in the 95 to 110 bpm heart rate range during exercise, and around 100 mV·ms in the 95 to 110 bpm heart range during recovery[8]. This would yield an estimated 40 to 50% SVG hysteresis in normal subjects. Diminished or nearly absent SVGH hence denotes abnormal behavior. No or little change in the ventricular gradient is not necessarily no or little change in the action potential morphology distribution in the heart. It may well be, that, due to cancellation effects, substantial dynamic exercise-recovery changes remain hidden. This may be the cause in the control patients. Our case patients appear to have, during recovery, even a smaller SVG than during exercise, which is simply an aggravation of the effect seen in the control patients. Further interpretation of these changes in terms of arrhythmogenic mechanisms is not possible on the basis of this research, because despite a small number of experimental studies, the physiologic explanations for the ventricular gradient are still somewhat theoretical. There are only a limited amount of studies about the mechanism of SVG under different circumstances of the heart (*e.g.* heart failure, infarction). We can only demonstrate here that there is an abnormal behavior of SVGH in the case patients with respect to the control patients, and with respect to a normal group. This study is one of the examples that investigate the behavior of SVG under certain conditions (here: heart failure and depressed LVEF).

Because TWA and SVGH probe different aspects of electrophysiological instability, it is likely that these variables contain, at least partly, uncorrelated information. This concept is supported by Spearman's rank correlation analysis that yielded low and statistically not significant correlation coefficients between TWAA and SVGH in cases and in control patients (Figure 2).

TWA analysis seems to be somewhat less powerful than SVGH analysis in our pilot group. This may be inherent to the electrophysiological basis of these variables, however, it may also be due to the fact that we analyzed normal routine exercise ECGs, in which no special provision was taken to enhance the signal quality (like the procedures around the Cambridge Heart system[6] and with regard to the

exercise protocol[6;7]. The advantage of the SVGH with respect to TWAA is that the SVGH is calculated over the averaged values of SVG during exercise and recovery, and not measuring beat-to-beat instability, therefore is SVGH by definition, less sensitive to noise.

Limitations

The group included for this study consisted of small number of patients. Given that, Kaplan Meier analysis was performed to acquire an impression of the predictive value of SVGH and TWA for ICD therapy. The TWAA defined in our study was an average of three leads that had the largest TWA. This choice to select the best segment and the maximal TWA of all leads might not be the optimal one, however there is limited evidence that one ECG lead should be the best to detect TWA. Determination of the best leads to identify TWA is beyond the scope of this study, but investigation of the best lead(s) is currently carrying out by our group. Further (prospective) research on TWA and SVG is also necessary, including combined evaluation of both variables with a larger number of patients to confirm the predictive values of SVGH and TWA. Also, the case and control patients should be divided in a learning and training set to find the best cutoff point, and to validate these points.

Conclusion

In conclusion, our study suggests that exercise-recovery hysteresis in the ventricular gradients bears predictive potential for lethal arrhythmias in heart failure patients with an ICD implanted for primary prevention. This ECG variable is relatively robust for noise, and, as it rests on different electrophysiological properties than TWA (exercise-recovery instability, rather than beat-to-beat instability), it may convey additional information. Hence, joint analysis of TWA and SVGH may, possibly, improve the noninvasive identification of high-risk patients. Further research, in a large group of patients, is required and currently carried out by our group.

Acknowledgements

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References

1. Zipes, D. P., Camm, A. J., Borggrefe, M., *et al.* ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation* 2006;114:e385.
2. Camm, J., Klein, H., and Nisam, S. The cost of implantable defibrillators: perceptions and reality. *Eur Heart J* 2007;28:392.
3. Rosenbaum, D. S., Jackson, L. E., Smith, J. M., *et al.* Electrical alternans and vulnerability to ventricular arrhythmias. *N Engl J Med* 1994;330:235.
4. Chow, T., Kereiakes, D. J., Onufer, J., *et al.* Does microvolt T-wave alternans testing predict ventricular tachyarrhythmias in patients with ischemic cardiomyopathy and prophylactic defibrillators? The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial. *J Am Coll Cardiol* 2008;52:1607.
5. Gold, M. R., Ip, J. H., Costantini, O., *et al.* Role of microvolt T-wave alternans in assessment of arrhythmia vulnerability among patients with heart failure and systolic dysfunction: primary results from the T-wave alternans sudden cardiac death in heart failure trial substudy. *Circulation* 2008;118:2022.
6. Bloomfield, D. M., Hohnloser, S. H., and Cohen, R. J. Interpretation and classification of microvolt T wave alternans tests. *J Cardiovasc Electrophysiol* 2002;13:502.
7. Leino, J., Minkkinen, M., Nieminen, T., *et al.* Combined assessment of heart rate recovery and T-wave alternans during routine exercise testing improves prediction of total and cardiovascular mortality: the Finnish Cardiovascular Study. *Heart Rhythm* 2009;6:1765.
8. Draisma, H. H., Hooft van Huysduynen, B, Swenne, C. A., *et al.* Increased Dispersion of Ventricular Repolarization during Recovery from Exercise. *Computing in Cardiology* 2005;32:85.
9. Burger, H. C. A theoretical elucidation of the notion ventricular gradient. *Am Heart J* 1957;53:240.
10. Draisma, H. H., Schalij, M. J., van der Wall, E. E., *et al.* Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. *Heart Rhythm* 2006;3:1092.
11. Man.S., Maan, A. C., van der Wall, E. E., *et al.* BEATS: An Interactive Research Oriented Extended ECG Analysis System. *Computing in Cardiology* 2010;37:1007.
12. Kors, J. A., van, Herpen G., Sittig, A. C., *et al.* Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J* 1990;11:1083.
13. Burattini, L., Zareba, W., and Burattini, R. Assessment of physiological amplitude, duration, and magnitude of ECG T-wave alternans. *Ann Noninvasive Electrocardiol* 2009;14:366.
14. Burattini, L., Bini, S., and Burattini, R. Comparative analysis of methods for automatic detection and quantification of microvolt T-wave alternans. *Med Eng Phys* 2009;31:1290.
15. Burattini, L., Zareba, W., and Burattini, R. Automatic detection of microvolt T-wave alternans in Holter recordings: Effect of baseline wandering. *Biomedical Signal Processing and Control* 2006;1:162.

16. Burattini, L., Zareba, W., and Burattini, R. Adaptive match filter based method for time vs. amplitude characterization of microvolt ECG T-wave alternans. *Ann Biomed Eng* 2008;36:1558.
17. Burattini, L., Bini, S., and Burattini, R. Automatic microvolt T-wave alternans identification in relation to ECG interferences surviving preprocessing. *Med Eng Phys* 2011;33:17.
18. van der Avoort, C. J., Filion, K. B., Dendukuri, N., *et al.* Microvolt T-wave alternans as a predictor of mortality and severe arrhythmias in patients with left-ventricular dysfunction: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2009;9:5.
19. Janusek, D., Pawlowski, Z., and Maniewski, R. Evaluation of the T-wave alternans detection methods: a simulation study. *Anadolu Kardiyol Derg* 2007;7 Suppl 1:116.
20. Martinez, J. P. and Olmos, S. Methodological principles of T wave alternans analysis: a unified framework. *IEEE Trans Biomed Eng* 2005;52:599.
21. Nearing, B. D., Huang, A. H., and Verrier, R. L. Dynamic tracking of cardiac vulnerability by complex demodulation of the T wave. *Science* 1991;252:437.
22. Walker, M. L. and Rosenbaum, D. S. Cellular alternans as mechanism of cardiac arrhythmogenesis. *Heart Rhythm* 2005;2:1383.
23. Watanabe, M. A. and Koller, M. L. Mathematical analysis of dynamics of cardiac memory and accommodation: theory and experiment. *Am J Physiol Heart Circ Physiol* 2002;282:H1534
24. Cutler, M. J. and Rosenbaum, D. S. Explaining the clinical manifestations of T wave alternans in patients at risk for sudden cardiac death. *Heart Rhythm* 2009;6:S22.