Exercise-Recovery Hysteresis in the Ventricular Gradient Predicts Antiarrhythmic Therapy in Primary Prevention ICD Patients

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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 analyzed exercise tests of 34 HF pts with an implanted cardioverter-defibrillator – cases and matched controls with/without antiarrhythmic therapy for VT/VF during follow up –, computing the individual relative exercise-recovery hysteresis, ΔSVG%, in the spatial ventricular gradient (SVG, a measure for action potential morphology heterogeneity) in the 95-110 bpm heart rate range. ΔSVG% differed significantly between cases (-18.1±25.6%) and controls (1.2±28.1%, P=0.003). ROC analysis (AUC=0.737, P=0.02) revealed that ΔSVG% < 14.8% discriminated cases and controls with 94.1% sensitivity and 41.2% specificity; hazard ratio was 3.03 (1.03-8.96). These results can compete with the performance of mTWA analysis. We conclude that ΔSVG% is a promising additional predictor for lethal arrhythmias in HF pts.

1. Introduction

Worldwide, more than 150000 heart failure patients have an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death. According to the guidelines, the elevated risk of lethal arrhythmias is mainly attributed to a reduced left ventricular ejection fraction (LVEF) [1]. Unfortunately, this selection criterion lacks specificity, which leads to a large number needed to treat [2], giving rise to much extra 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. One of these candidate noninvasive predictors is microvolt T-wave alternans (mTWA) [3]. However, according to the guidelines, mTWA has but a Class IIa indication, again because of a lack of specificity [1], and because of conflicting results of several studies [4,5].

As mTWA typically occurs at elevated heart rates, it is oftentimes measured in exercise tests, during the exercise phase, in the 95-110 bpm heart rate range [6]. Usually, the recovery phase remains unexplored. The recovery phase may, however, contain important independent prognostic information. This is, e.g., illustrated by the study by Frolkis et al., who found that, amongst others in heart failure patients, frequent ventricular ectopy during recovery from exercise is a stronger predictor for all-cause mortality than the occurrence of ventricular ectopy during the exercise phase [7]. Indeed, in the recovery phase of an exercise test, cardiac electrophysiology differs dramatically from that in the exercise phase at similar heart rates [8]. This hysteresis phenomenon is due to increased levels of circulating catecholamines and to increased parasympathetic tone in the recovery phase as compared to the exercise phase. In a previous study we demonstrated the existence of exercise-recovery hysteresis in the spatial ventricular gradient (SVG) of normal subjects. 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.

In our current study, we investigate if exercise-recovery SVG hysteresis has predictive value for lethal arrhythmias in a population of heart failure patients with ICDs implanted for primary prevention.

2. Methods

From our database of exercise ECGs, that became into existence in 2006, we selected exercise tests made in primary prevention ICD patients with heart failure that were of sufficient technical quality, without abundant arrhythmias, with a 95-110 bpm heart rate zone in the exercise phase that lasted at least 1 minute, and with a recovery phase in which heart rate decreased again to values <95 bpm. None of the exercise tests were made with the purpose to stratify the patients for ICD implantation. Patients were divided into cases – with appropriate antiarrhythmic therapy (AT) for

VT/VF during follow up – and controls – no VT/VF during follow up. Here, we report about the first 17 cases and their matching controls (matching was done on age, sex, etiology, left ventricular ejection fraction, NYHA class). Exercise tests in case patients were excluded when a major cardiac event (infarction, VT ablation, CABG) occurred between the exercise test and the moment of VT/VF. When, in case patients, more than one exercise test was available for analysis, the exercise test the closest in time before or after the moment of VT/VF was selected. In control patients with more than one suitable exercise test, the earliest available exercise test was selected, however, without a major cardiac even during follow up. Table 1 lists the general characteristics of our study group.

	Case(N=17)	Control(N=17)
Sex (male/female)	14/3	14/3
Etiology:		
• **Ischemic**	14	14
• **Non-ischemic**	3	3
Age (years)	57.2 ± 12.1	57.2 ± 11.9
NYHA class	2.2 ± 0.6	1.9 ± 0.7
LVEF (%)	27.9 ± 12.8	29.9 ± 7.4
Follow-up (years)	4.0 ± 1.6	4.4 ± 1.9

Table 1. Patient characteristics of the study group. Abbreviations: NYHA = New York Heart Association; LVEF = Left Ventricle Ejection Fraction. No significant differences existed between the case and control groups.

Exercise ECGs were analyzed with our interactive research oriented ECG analysis program BEATS [11] to identify all sinus beats with sufficient signal quality and the landmarks in time required for SVG calculation (onset QRS and end of T). Subsequently we computed, in a vectorcardiographic representation of the ECG recording synthesized by using the matrix according to Kors [12], the SVG of each beat, and calculated the mean SVG (mV·ms) in the exercise and recovery phases in the 95-110 bpm heart rate ranges. The hysteresis was individually normalized on the exercise SVG value: $\Delta SVG\% = (SVG_{recovery} - SVG_{exercise}) / SVG_{exercise}$.

Differences in ΔSVG% between the matched cases and controls were statistically tested by a paired t test at the 5% significance level. ROC analysis was performed to determine the area-under-the-curve, and to define the optimal cut-off point of ΔSVG% 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. A hazard ratio (HR) with 95% confidence interval was calculated for ΔSVG%. All statistical analyses were performed using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego California USA).

3. Results

Age, NYHA class, left ventricular ejection fraction and follow-up period did not differ significantly between cases and controls (Table 1). Heart failure had an ischemic origin in the majority (83%) of the patients.

The individual exercise-recovery SVG hysteresis values are depicted in Figure 1. Apparently, the case-control matching strategy made sense, because in 14 out of the 17 case-control pairs, the hysteresis value in the case patient turned out to be smaller than the hysteresis value in the matched control patient. The mean SVG exercise-recovery hysteresis differed significantly between cases (-18.2 ± 25.6%) and controls (1.2 ± 28.1%, P=0.003).

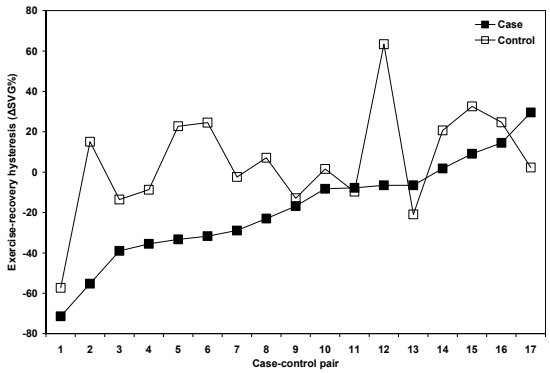

Figure 1. Exercise-recovery hysteresis in 17 case-control pairs. For visual clarity, connecting lines were added and the case-control pairs were sorted on ascending values of the exercise-recovery SVG hysteresis in the cases.

ROC analysis results are depicted in Figures 2 (ROC curve) and 3 (sensitivity and specificity versus criterion value). Figure 2 shows that the SVG exercise-recovery hysteresis indeed discriminates cases and controls: the area under the curve, 0.737, is significantly larger than 0.5 (P=0.02). For our current study we adopted a discrimination threshold that yields a comparable sensitivity as adopted/reported in several mTWA studies [13] (range 78.6-100%). When patients with ΔSVG% < 14.8% are considered high-risk, the sensitivity in our study group is 94.1%. It appears that the specificity of the SVG exercise-recovery hysteresis at this cut-off value is 41.2%, which is better than the range of values (28.9-37.1%) reported in several mTWA studies [13].

Kaplan-Meier analysis on the basis of the exercise-recovery SVG hysteresis cut-off value of 14.8% is shown in Figure 4. The curves depicting the event-free patient fractions for the "at risk" patients (N=26) and the "not at risk" patients (N=8) differ significantly (P<0.05). The hazard ratio of "at risk" patients is 3.03 (95% confidence interval = 1.03 to 8.96).

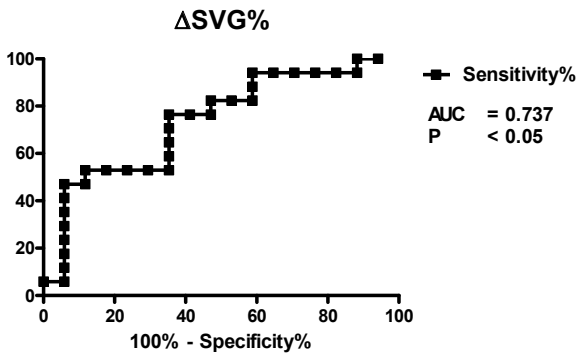

Figure 2. ROC analysis for lethal arrhythmia prediction based upon exercise-recovery SVG hysteresis.

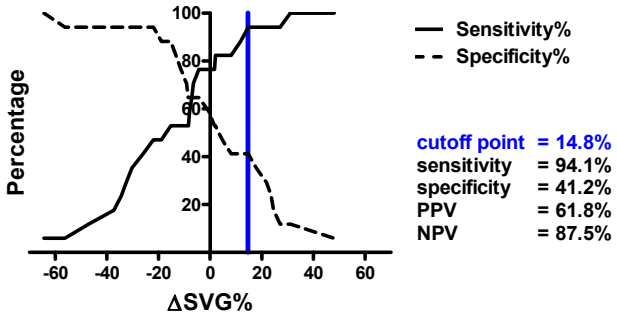

Figure 3. Sensitivity and specificity versus criterion value, and cut-off point for discrimination of high-risk patients. PPV= positive predictive value; NPV= negative predictive value.`

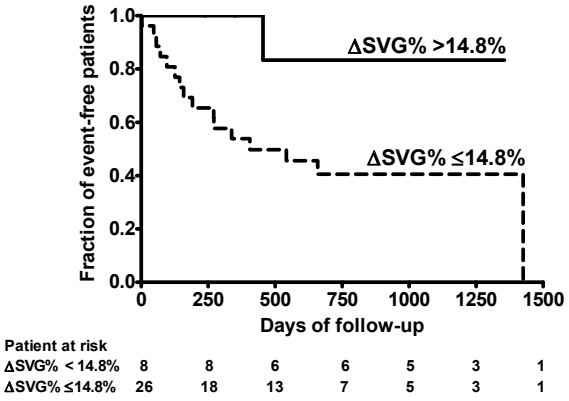

Figure 4. Cumulative event-free fractions of patients using the ΔSVG% cut-off point of 14.8%; $P<0.05$.

4. Discussion

We demonstrated that in exercise tests of heart failure patients who were selected for ICD implantation, the exercise-recovery hysteresis in the SVG within the 95-110 bpm heart rate range discriminates for an arrhythmic event (VT/VF) in the follow-up period. The performance of this SVG hysteresis criterion was comparable with the performance of mTWA in detecting high-risk patients. Obviously, we have presented here a relatively small study group; currently, we are analyzing a group of around 100 cases to corroborate our findings.

The phenomenon of electrocardiographic exercise-recovery hysteresis is known, and has a physiologic cause. During standard clinical maximal exercise tests, equal heart rates during the exercise and recovery period are attained under greatly different autonomic influences. During the incremental exercise phase, heart rate is elevated due to parasympathetic withdrawal and by direct (i.e., neural, and not as much humoral) sympathetic influences on the sinus node; while heart rate during recovery is determined by elevated circulating catecholamines combined with elevated parasympathetic efferent activity. Though resulting in equal sinus rates, these distinct neurohumoral influences during exercise and recovery are not at all indifferent for the electrophysiological properties of the myocardium. As a result, exercise-recovery differences in the action potential morphology and distribution over the whole heart occur[8].

In normal subjects, the SVG during a maximal exercise test assumes average values around 70 mV·ms in the 95-110 bpm heart rate range during exercise, and around 100 mV·ms in the 95-110 bpm heart range during recovery [8]. This would yield an estimated 40-50% SVG hysteresis in normal subjects.

The patients in our current study had a much smaller exercise-recovery hysteresis in their SVG than normal subjects (see Figure 1), most of them had even a negative hysteresis: in other words, the SVG during recovery was smaller than the SVG during exercise. This is true for the cases and the controls in our study, but the phenomenon of a small or even negative exercise-recovery SVG hysteresis is stronger in the cases, what enables us to discriminate cases and controls by their amount of exercise-recovery SVG hysteresis.

Multiple factors may have caused the smaller or even negative exercise-recovery SVG hysteresis in our studied heart failure patients, compared to normal subjects. The maximal effort (Wmax) of heart failure patients is less than that of healthy subjects; and in this respect, one would expect weaker hysteresis effects during exercise tests. At the same time, heart failure patients have abnormal and damaged hearts, in which the action potentials and action potential distribution have already undergone considerable modification in respect to healthy persons. This has a direct impact on the ventricular gradient (which is the integral of the gradients in action potential morphology over the whole heart) and on the dynamics in the ventricular gradient, e.g., during exercise. In addition, there is the unknown

influence of various forms of medication on the ventricular gradient. Finally, the possibility exists that the decreased or even negative hysteresis is caused by abnormal functioning of the autonomic nervous system rather than by abnormal reactivity of cardiac myocytes.

Even while we cannot fully explain the observed effects, it is important to realize that decreased or even negative exercise-recovery SVG hysteresis denotes abnormal action potential distribution adaptations to exercise. Abnormal action potential distribution in the heart is potentially linked to abnormal dispersion of the refractoriness, which may be arrhythmogenic.

5. Conclusion

Our study demonstrates that, in addition to the well-known predictive value of mTWA, which measures beat-to-beat electrophysiological instability in the heart, there is more predictive information in exercise tests, e.g., related to a possibly several minutes long instable condition – amongst others characterized by a decreased SVG – during recovery from exercise. If this situation would represent a condition of increased dispersion of the repolarization, ectopic activity during such periods might more easily trigger lethal arrhythmias. Of course, this is but a speculation in the setting of our current study. However, the strong predictive value that can be attributed to a lowered or negative exercise-recovery SVG hysteresis deserves further exploration of this hypothesis.

Acknowledgements

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