Chapter 4

Increased dispersion of ventricular repolarization during recovery from exercise

Harmen H.M. Draisma
Bart Hooft van Huysduynen
Cees A. Swenne
Arie C. Maan
Martin J. Schalij
Ernst E. van der Wall
ABSTRACT

**Background.** T-wave morphology hysteresis between exercise and recovery from exercise has been reported. We investigated the possible impact of this hysteresis for dispersion of the repolarization during exercise and recovery.

**Methods and Results.** We studied 57 trained and untrained men of which the good health was ascertained by medical history, physical examination, echocardiography and a maximal oxygen consumption (V\textsubscript{O\textsubscript{2max}}) test. Baroreflex sensitivity (BRS) was noninvasively determined. Left ventricular mass (LVM) was assessed from the echocardiogram, and 10 unfit and 8 highly fit subjects were identified on the basis of their V\textsubscript{O\textsubscript{2max}}, LVM, BRS, and resting heart rate (HR). Every ECG made during the recovery phase of the V\textsubscript{O\textsubscript{2max}} tests was individually paired with a HR-matched ECG made during exercise. ECGs were characterized by QRS duration, QT\textsubscript{peak}, QT\textsubscript{end}, T-wave area symmetry ratio, maximal T-wave magnitude and ventricular gradient magnitude. These ECG parameters were binned for exercise and for recovery ECGs according to the corresponding % heart rate reserve (HRR) or recovery time since maximal exercise. QT\textsubscript{peak}, QT\textsubscript{end}, and T-wave area symmetry ratio were smaller, while maximal T-wave vector magnitude and ventricular gradient magnitude were larger during recovery than during exercise. For all parameters, the maximal recovery–exercise hysteresis was observed at 1 or 2 minutes recovery time and at 30-60% HRR. The highly fit subgroup had considerably larger exercise–recovery differences than the unfit subgroup.

**Conclusions.** The observed T-wave hysteresis, accentuated in highly fit subjects, signifies increased dispersion of ventricular repolarization due to increased action potential duration heterogeneity during recovery from exercise.
INTRODUCTION

There is a long-standing debate about the safety of exercise. Albert and associates found a slightly increased risk of sudden death immediately following strenuous exercise in male American physicians reportedly free of cardiovascular disease but concluded that the benefits of exercise outweigh this disadvantage.\(^1\) However, based on an observed increased risk for sudden cardiac death during or shortly after exercise in athletes,\(^2\) the European Society of Cardiology recently proposed ECG screening of young athletes before taking part in competitive sports.\(^3\) In athletes, arrhythmogenic right-ventricular dysplasia (ARVD) is a frequent post-mortem finding. Increased vulnerability of the substrate, in combination with ARVD-based triggering ectopic activity might, at least partly, provide an explanation for the increased risk.

The recovery phase after exercise deserves special attention. In a recent study, Frolkis and colleagues\(^4\) reported that ventricular ectopy occurring in the recovery phase of a maximal exercise test in a regular hospital population bears an independent mortality risk. Though the cause of death in this study remains unknown (all-cause mortality was the primary end point), it is conceivable that a number of deaths occurred after exercise, when abnormal automaticity (ectopy) met a more vulnerable substrate (increased dispersion of repolarization) to induce a lethal reentrant arrhythmia.\(^5\text{-}7\)

In the last decade, assessment of dispersion of the repolarization from the ECG has gained increasing interest.\(^8\text{-}9\) In the light of this development and the possible increased susceptibility to arrhythmias during recovery from exercise, we sought, in this study, to further establish the concept of the electrophysiological hysteresis\(^10\) in the setting of maximal exercise tests.
METHODS

The local Ethics Review Committee approved the protocol of this study. To include subjects spanning a large range of fitness, healthy male persons not intensively taking part in competitive sports, and male marathon skaters engaged in training on a daily basis for more than 5 years were recruited by advertisement in a local newspaper and by the Royal Dutch Skating Federation, respectively. All participants gave written informed consent. None of them used any medication. Good health of the participants was ascertained by medical history, physical examination, echocardiography and a maximal oxygen consumption ($VO_{2\text{max}}$) test. The study population (see Table 1) consisted of 57 individuals of an original cohort of 70 respondents who fulfilled the previously listed criteria.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Left ventricular mass (LVM) was estimated from the echocardiographic data following the area-length method according to the American Society of Echocardiography Committee on Standards, and normalized to body surface area as calculated using the formula of Mosteller. Baroreflex sensitivity (BRS) was assessed according to the protocol described by Frederiks et al.

Bicycle ergometry began with a load of 40 watts (W). This load was increased by 20W per minute until maximal exercise was reached. Ten-second ECG recordings (leads I, II, V1–V6; sampling rate 500 Hz) were obtained twice a minute with a Marquette Case 8000 exercise electrocardiograph (GE Healthcare, Milwaukee, WI, USA) during supine rest, exercise and recovery, up to 5 minutes after maximal exercise. Later, these ECGs were downloaded to a PC for analysis.
Exercise-recovery ECG comparison requires the selection of heart rate (HR)-matched exercise and recovery ECG pairs. In our healthy study group with a relatively rapid heart rate recovery, the number of ECGs recorded during the recovery phase is far less than the number of ECGs recorded during the exercise phase. Therefore, we selected the HR-matched exercise-recovery ECG pairs by finding for every recorded recovery ECG the best HR-matching exercise ECG. Exercise–recovery ECG pairs with a HR matching error >10 beats per minute (bpm) were excluded from analysis. Each thus selected ECG pair was characterized by its corresponding percentage of the heart rate reserve (HRR, the difference between the maximal HR

<table>
<thead>
<tr>
<th></th>
<th>All subjects (N = 57)</th>
<th>Unfit (N = 10)</th>
<th>Highly fit (N = 8)</th>
<th>P (H-U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>33.1 ± 11.3</td>
<td>35.9 ± 11.4</td>
<td>31.0 ± 10.5</td>
<td>20.4 – 54.0 NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>183 ± 6</td>
<td>181 ± 6</td>
<td>188 ± 5</td>
<td>178 – 193 .018</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.5 ± 10.9</td>
<td>80.6 ± 14.1</td>
<td>74.1 ± 5.8</td>
<td>64 – 83 NS</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>23.4 ± 3.2</td>
<td>24.8 ± 4.7</td>
<td>21.0 ± 7.8</td>
<td>19.9 – 22.3 NS</td>
</tr>
<tr>
<td>VO₂max (ml·kg⁻¹·min⁻¹)</td>
<td>52.9 ± 13.7</td>
<td>40.4 ± 8.3</td>
<td>66.8 ± 6.4</td>
<td>57.8 – 75.8 .000</td>
</tr>
<tr>
<td>LVM (g·m⁻²)</td>
<td>117.4 ± 19.9</td>
<td>100.9 ± 10.8</td>
<td>140.7 ± 11.3</td>
<td>123.2 – 155.6 .000</td>
</tr>
<tr>
<td>BRS (ms·mmHg⁻¹)</td>
<td>10.0 ± 5.0</td>
<td>6.8 ± 1.3</td>
<td>13.2 ± 3.8</td>
<td>9.6 – 21.1 .000</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>60 ± 8</td>
<td>65 ± 3</td>
<td>53 ± 6</td>
<td>39 – 59 .000</td>
</tr>
</tbody>
</table>

Table 1. Characteristics for all subjects, and for subgroups of low and high cardiorespiratory fitness. Abbreviations: BMI: body mass index; BRS: baroreflex sensitivity; H: highly fit; HR: heart rate; U: unfit; LVM: body surface area-corrected left ventricular mass; NS: nonsignificant; SD: standard deviation from the mean.
and HR during supine rest) and by the time instant after peak exercise at which the recovery ECG was recorded (recovery time, RCT). Figure 1 illustrates this procedure for a typical subject.

**Figure 1.** Symptom-limited exercise test in a normal subject. Triangles: exercise; squares: recovery. Each recovery ECG is heart-rate-matched with one exercise ECG. Thus selected exercise–recovery pairs are indicated by solid markers and connected by horizontal lines. The highlighted exercise–recovery ECG pair is shown in Figures 2 and 3. Abbreviations: HRmin, HRmax: resting heart rate (0% of the heart rate reserve) and maximal heart rate (100% of the heart rate reserve), in bpm.

We used LEADS to analyze the ECGs. After interactive beat selection and calculation of the averaged beat, LEADS sets the default end-of-QRS instant at the minimal heart vector between the QRS complex and the T wave, and the default end-of-T instant at the intercept with the baseline of the steepest tangent to the descending limb of the T wave in the vector magnitude signal. The latter prevents possible influences of fusion of the T wave with a U or a P wave — a problem arising at higher HRs. Finally, the operator adjusted the end-of-QRS instant by repositioning a vertical crosshair cursor in a display of the superimposed 12 ECG leads that can be magnified at will. In keeping with the Minnesota ECG coding
Increased dispersion of ventricular repolarization during recovery from exercise

protocol, end-of-QRS was set at the latest J point in any of the leads. In leads with two candidate J points the earliest J point was taken. All interactive procedures (beat selection for averaging; end-of-QRS adjustment) were done by one of the authors (H.H.M.D.).

Each ECG was characterized by six parameters: QRS duration, $QT_{\text{peak}}$, $QT_{\text{end}}$, T-wave area symmetry ratio ($SR_{\text{area}}$), maximal T-wave magnitude (maxT) and ventricular gradient magnitude (VG). $QT_{\text{peak}}$, $QT_{\text{end}}$, $SR_{\text{area}}$ and maxT were computed in the vector magnitude signal. $SR_{\text{area}}$ was calculated as the ratio of the early (from the end of the QRS complex to the apex of the T wave) to the late (from the apex of the T wave to its end) T-wave area. VG was computed by vectorially adding the QRST areas in the scalar X-Y-Z leads.

Exercise and recovery values of these six parameters were compared in the total study group (N = 57) and in two subgroups of unfit (N=10) and highly fit (N=8) subjects, respectively. Subjects were allocated to one of these subgroups on the basis of their $VO_{2\text{max}}$, BRS, LVM and resting HR values. Unfit subjects were those whose measured $VO_{2\text{max}}$, BRS, and LVM were below, and whose supine resting HR was above the median of the total study group. Highly fit subjects were those whose measured $VO_{2\text{max}}$, BRS, and LVM were above, and whose supine resting HR was below the median of the total study group. See Table 1.

Data was pooled in %HRR and in RCT bins, 10% and 1 minute wide, respectively. There was data in six RCT bins (centered around 0, 1, …, 5 minutes post peak-exercise) and in nine %HRR bins (centered around 20, 30, …, 100 %HRR). Presence of exercise–recovery hysteresis was tested in the total study group and in the unfit and highly fit subgroups by comparing the exercise and recovery contents of each %HRR and RCT bin, using paired t-tests at the 5% level. The amount of hysteresis in a given ECG parameter in a given bin was expressed as a fraction (difference between the recovery and exercise values, divided by the exercise value). Differences between the unfit and highly fit subgroups were tested in a similar way, this time using unpaired t-tests at the 5% significance level.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.
RESULTS

Exercise tests, including recovery, lasted $18 \pm 4$ minutes (mean $\pm$ SD). Subjects had a resting HR of $60 \pm 8$ bpm, reached a peak HR of $178 \pm 11$ bpm; after 5 minutes recovery HR was $101 \pm 18$ bpm ($36 \pm 11\%$ HRR).

Remarkable within-subject T-wave morphology differences were observed at equal heart rates during exercise and recovery (see Figures 2 and 3). The exercise–recovery ECG differences as depicted in Figures 2 and 3 are typical for what was observed in the whole study group: at similar heart rates, during recovery after maximal exercise, $QT_{\text{peak}}$, $QT_{\text{end}}$, and $SR_{\text{area}}$ were smaller, while maxT and VG were larger. QRS durations during exercise and recovery were not different.

Figure 2. Ten-second ECGs recorded at similar heart rates during exercise (panel A) and recovery (panel B) in a normal subject. ECGs were recorded at 55% of the heart rate reserve (in this subject 137 bpm, see also Figure 1). T-wave amplitude increases during recovery are most prominent in the left-precordial leads V2 and V3.
Figure 3. Vector magnitude signal of the averaged QRST complexes obtained from the heart-rate-matched ECGs displayed in Figure 2. In panel A the exercise ECG is displayed in black; the recovery ECG is displayed in grey for visual comparison. Panel B displays the recovery ECG in black, and the exercise ECG in grey. All parameter values in panel A relate to the exercise ECG, and in panel B to the recovery ECG. In the descending limb of the T wave the tangent to the steepest slope is drawn; the intercept of this tangent with the baseline is taken as the end of the T wave. Left hatched area: area under the curve between end-of-QRS and peak T. Right hatched area: area under the curve between peak T and end-of-T. Note that the differences between the QRS-T complexes concentrate in the T wave, the morphologies of the QRS complexes during exercise and recovery are strikingly similar. Abbreviations: HR: heart rate, maxT: maximal T-wave magnitude, SR area: T-wave area symmetry ratio, VG: ventricular gradient magnitude.

A summary of the exercise–recovery comparison in all subjects is given in Figures 4 (QT peak, QT end) and 5 (maxT, SR area, VG), and in Table 2. Significant exercise–recovery hysteresis was detectable for each T-wave ECG parameter, irrespective of whether the data were distributed over %HRR bins or over RCT bins. Maximal hysteresis in QT peak and in QT end occurred after 1 minute RCT or 20–60% HRR, recovery values differed about 5 to 9% from the exercise values. Maximal hysteresis in maxT and in VG occurred after 2 minutes RCT or 60% HRR, recovery values differed about 50 to 90% from the exercise values. Maximal hysteresis in SR area occurred after 1 minute RCT or at 30% HRR, recovery values differed about 20% from exercise values.
Figure 4. $QT_{\text{peak}}$ (upper panels) and $QT_{\text{end}}$ (lower panels) in heart-rate-matched ECGs recorded during exercise (triangles) and recovery (squares) in all subjects, ordered according to recovery time (left panels) and percentage HRR (right panels). Error bars indicate standard deviations from the mean. Significant differences between recovery and exercise are indicated by single ($P<0.05$) and double ($P<0.01$) asterisks.
Table 2. Maximal exercise-recovery hystereses in all participants, ordered according to recovery time (RCT, Panel A) and to percentage heart rate reserve (HRR, Panel B). Exercise-recovery changes are expressed with respect to the exercise values. Abbreviations: maxT: maximal T-wave vector magnitude; SR\textsubscript{area}: T-wave area symmetry ratio; VG: ventricular gradient magnitude.

Table 1 shows that age, weight and BMI did not differ in the unfit and highly fit subgroups. The highly fit subjects are a bit taller, though. Table 3 shows that, irrespective of RCT or %HRR binning, the amplitude of the hysteresis was larger in highly fit than in unfit subjects. VG and maxT roughly assumed the double value after 1 minute RCT or at 60% or 40% HRR, respectively.
### Panel A

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RCT (min)</th>
<th>Unfit hysteresis</th>
<th>Highly fit hysteresis</th>
<th>% Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT&lt;sub&gt;peak&lt;/sub&gt;</td>
<td>2</td>
<td>- 9.3 ms</td>
<td>- 24 ms</td>
<td>+ 160</td>
<td>.016</td>
</tr>
<tr>
<td>QT&lt;sub&gt;end&lt;/sub&gt;</td>
<td>1</td>
<td>- 7.5 ms</td>
<td>- 27 ms</td>
<td>+ 255</td>
<td>.020</td>
</tr>
<tr>
<td>maxT</td>
<td>1</td>
<td>+ 290 µV</td>
<td>+ 570 µV</td>
<td>+ 96</td>
<td>.000</td>
</tr>
<tr>
<td>SR&lt;sub&gt;area&lt;/sub&gt;</td>
<td>2</td>
<td>- 0.23</td>
<td>- 0.25</td>
<td>+ 8</td>
<td>NS</td>
</tr>
<tr>
<td>VG</td>
<td>1</td>
<td>+ 24 mV·ms</td>
<td>+ 41 mV·ms</td>
<td>+ 71</td>
<td>.007</td>
</tr>
</tbody>
</table>

### Panel B

<table>
<thead>
<tr>
<th>Parameter</th>
<th>%HRR</th>
<th>Unfit hysteresis</th>
<th>Highly fit hysteresis</th>
<th>% Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT&lt;sub&gt;peak&lt;/sub&gt;</td>
<td>60</td>
<td>- 9.7 ms</td>
<td>- 27 ms</td>
<td>+ 179</td>
<td>NS</td>
</tr>
<tr>
<td>QT&lt;sub&gt;end&lt;/sub&gt;</td>
<td>60</td>
<td>+ 0.6 ms</td>
<td>- 29 ms</td>
<td>- 5.2·10&lt;sup&gt;3&lt;/sup&gt;</td>
<td>NS</td>
</tr>
<tr>
<td>maxT</td>
<td>60</td>
<td>+ 283 µV</td>
<td>+ 669 µV</td>
<td>+ 136</td>
<td>.000</td>
</tr>
<tr>
<td>SR&lt;sub&gt;area&lt;/sub&gt;</td>
<td>80</td>
<td>- 0.15</td>
<td>+ 1.09</td>
<td>- 807</td>
<td>NS</td>
</tr>
<tr>
<td>VG</td>
<td>40</td>
<td>+ 15 mV·ms</td>
<td>+ 38 mV·ms</td>
<td>+ 153</td>
<td>.018</td>
</tr>
</tbody>
</table>

*Table 3.* Maximal exercise-recovery hysteresis differences between highly fit and unfit subjects, related to the unfit hysteresis value, and ordered according to recovery time (RCT, Panel A) and percentage heart rate reserve (%HRR, Panel B). Note the remarkably higher maximal T-wave vector (maxT) and ventricular gradient magnitude (VG) in highly fit subjects. Abbreviations: NS: nonsignificant; SR<sub>area</sub>: T-wave area symmetry ratio.
DISCUSSION

Our study demonstrates hysteresis in heart-rate-matched ECGs made during exercise and recovery, with the largest differences observed at 1–2 minutes after peak exercise or at 60% of the HRR. Highly fit subjects had more QT- and T-wave hysteresis than unfit subjects. In the following we interpret the ECG differences between exercise and recovery in the light of dispersion of the repolarization.

Dispersion of repolarization (DOR)

DOR in the ventricles is a physiological phenomenon that is caused by the added effect of heterogeneity in activation time and heterogeneity in action potential morphology. T-wave generation rests on DOR: when all myocytes would repolarize at the same time there would be no T wave at all. DOR is considered to facilitate reentrant activity. Tacitly assuming that DOR is closely linked to dispersion of refractoriness, an increase of DOR would widen the time window during which an extrasystole could initiate a tachyarrhythmia.

Evolving insight in exercise-recovery ECG hysteresis

Interest in ECG changes during recovery from maximal exercise arose about 35 years ago, when computerized exercise-ECG processing became available. Kitchin and Neilson showed that, after exercise, T-wave amplitude increased, and that the peak of the T wave occurred earlier in the cardiac cycle. The most striking changes occurred in the first minute after exercise. The study was conducted in untrained subjects who performed submaximal exercise, and only a single ECG lead was explored.

Simoons and Hugenholtz were the first to establish, in maximal exercise tests, differences in QT_{peak} and maxT at similar HR during exercise and during recovery from maximal exercise. They found shorter QT_{peak} and larger maxT values during recovery. Sarma and colleagues confirmed that QT_{peak} was shorter during recovery and measured, in addition, that QT_{end} intervals were shorter during recovery than during exercise. Chauhan and colleagues found higher QT_{end} hysteresis in healthy females than in healthy males. Heart-rate-matched exercise–recovery QT_{end} hysteresis is augmented in patients with long-QT syndrome; this phenomenon normalizes with beta-blockade.
Explanations for exercise–recovery hysteresis in T-wave morphology have ranged from sympathetic withdrawal, altered hemodynamic performance of the heart, residual sympatho-adrenal activity in the early post-exercise period and relatively slow QT-interval adaptation to rapid changes in the RR interval. More recently, Langley and colleagues published further quantitative data on altered T-wave symmetry during recovery from submaximal HR, and compared this with T-wave symmetry at rest. They attributed the lower symmetry ratio (more symmetric T wave) during recovery to increased DOR. However, this conclusion has a limited significance, as the heart rates in the resting and recovery states differed.

**ECG measures of dispersion of repolarization (DOR)**

In the past decades, multiple ECG indexes to quantify DOR have been proposed, like the QT interval, QT dispersion, the interval between the apex and end of the T wave (Tapex–end), T-wave complexity (Tcomplexity) estimated by singular value decomposition (SVD), T-wave amplitude, T-wave symmetry. In the current study, we used two of these parameters, T-wave amplitude and T-wave symmetry, to quantify DOR. We abandoned the other indexes for the following reasons:

- The QT interval does not specifically measure DOR, as a homogeneous APD increase that does not alter DOR can also prolong this interval.
- Although the dispersion in QT interval among ECG leads indeed is influenced by APD heterogeneity and by T-wave complexity, QT dispersion in the ECG does not necessarily represent DOR. Moreover, manual measurement of e.g. QT dispersion has been demonstrated to be subjective and error-prone.
- SVD is a mathematical method that indeed has been analytically demonstrated to quantify DOR from the T wave in the ECG. However, T-wave complexity estimated from singular values does not discriminate between higher values of DOR. Moreover, it is sensitive to noise (noise adds to the complexity), which renders it less suited for exercise electrocardiography.
- Tapex–end aims to measure the time window during which there is transmural DOR. This index was conceived on the basis of a wedge preparation of the left ventricular wall and two floating electrodes close to the epicar-
dium and the endocardium,\textsuperscript{26} which is an incomplete analogue of the intact heart in a torso. Moreover, mathematical simulation revealed that Tapex-end, though linearly related to transmural DOR, overestimates it.\textsuperscript{35}

The ventricular gradient The concept of the ventricular gradient was conceived by Wilson and co-workers.\textsuperscript{37,38} It has theoretically been demonstrated that the spatial ventricular gradient (the integral of the spatial QRST loop, $\vec{G} = \int \vec{H}(t) \cdot d$ in which $\vec{H}(t)$ the heart vector) is non-zero due to action potential morphology differences — most often thought of as differences in APD — and that it is independent of the order in which the ventricles are electrically activated.\textsuperscript{37-42} We have used the VG in our study as an extra parameter that helps to trace the cause of altered DOR (that necessarily has to be found in changes in the ventricular activation sequence and / or changes in APD heterogeneity).

**Augmented DOR during recovery from exercise**

Our study demonstrates that, in heart-rate-matched ECGs, QT\textsubscript{peak} and QT\textsubscript{end} intervals are briefer, the T wave is more symmetric, and the maximal T vector and the ventricular gradient are larger during recovery from exercise than during actual exercise. These ECG changes are consistent with the hypothesis that during recovery from exercise the repolarization heterogeneity is augmented due to increased APD heterogeneity. This can be concluded from the following four arguments:

1. **APD shortening during recovery.** The decreases in QT\textsubscript{peak} and QT\textsubscript{end} during recovery are suggestive for a generalized APD shortening shortly after exercise. This APD shortening could be caused by the increased adrenergic influences during recovery from exercise: norepinephrine and epinephrine levels, increasing during exercise, continue to increase further after exercise.\textsuperscript{43} Admittedly, parasympathetic outflow, which is very little during actual exercise, resumes during recovery,\textsuperscript{44} which creates a situation of both enhanced adrenergic and cholinergic influences during recovery from exercise in comparison to during actual exercise. However, the study by Inoue and Zipes\textsuperscript{45} has shown that, at identical heart rates, the ventricular effective refractory period (and, hence, likely, APD) is smaller under combined elevated sympathetic and parasympathetic stimulation.
Independent of autonomic influences on the myocardium, heart rate memory causes shorter APDs during recovery. At a given heart rate in the exercise phase, the recent history of slower heart rates tends to produce longer APDs than at the same heart rate in the recovery phase, where the recent history of higher heart rates tends to produce shorter APDs.

Both of the above mentioned effects may have accounted for the observed QT<sub>peak</sub> and QT<sub>end</sub> shortening during recovery.

2. Increased DOR. The more symmetrical T wave in combination with the increased T-wave amplitude during recovery from exercise indicate increased DOR<sup>17,32,35</sup> with respect to actual exercise.

3. Similar depolarization. The absence of exercise–recovery hysteresis in QRS duration suggests that ventricular depolarization did not dramatically change (compare panels A and B in Figures 2 and 3 for a visual impression). Therefore, it is not very likely that the observed T-wave changes were secondary changes (i.e., that these changes were caused by altered intraventricular conduction). This leaves primary changes (APD changes) as a plausible explanation of the modified T wave morphology.

4. Increased APD heterogeneity. The increase in VG during recovery signifies increased APD dispersion during recovery. This is likely to occur because APD alterations in response to a combination of sympathetic and parasympathetic stimulation, such as imposed upon the myocardium during recovery from exercise, differ regionally. E.g., at the endocardium, there is no independent parasympathetic effect on APD: parasympathetic stimulation mainly reduces sympathetically induced APD shortening.<sup>46</sup> However, stimulation of the epicardium by acetylcholine has an independent effect, and can slightly increase, but, at higher concentrations, also reduce APD.<sup>47</sup>

**Dynamics of exercise, fitness and hysteresis**

The marked electrocardiographic differences at matched heart rates during exercise and recovery signify a pronounced electrophysiological hysteresis. This hysteresis rests on the highly dynamic nature of a maximal exercise test, causing exercise–recovery contrasts in autonomic state and in recent heart rate history. The more extreme the exercise protocol, the more outspoken the hysteresis effect will be.

Our data demonstrate that T-wave symmetry, T-wave amplitude and VG magnitude
have a much larger hysteresis in highly fit than in unfit subjects. Possible cause is the stronger parasympathetic reactivation during recovery in highly fit subjects, as demonstrated by Imai and colleagues,\textsuperscript{48} in combination with the increased DOR as associated with hypertrophied hearts.\textsuperscript{49}

It has to be realized that the largest T-wave amplitudes and ventricular gradient magnitudes that occurred during recovery did not occur during any exercise stage (see Figure 5). Hence, a surge of intense exercise is possibly one of the most effective stimuli to create a situation with relatively large cardiac electrical heterogeneity.

**Clinical implications**

Our study provides suggestive evidence for the hypothesis that DOR is larger during recovery from exercise than during actual exercise, and that this effect is stronger in highly fit than in unfit persons. On itself, the very presence of a hysteresis phenomenon is not sufficient to create a situation of potential risk: the increased T-wave symmetry, larger T-wave amplitudes (markers for heterogeneity of the repolarization) and ventricular gradient magnitudes (a marker for APD heterogeneity) during recovery as compared to exercise might well be physiologically reasonable and, on itself, not arrhythmogenic. In fact, no arrhythmias were seen during the exercise tests.

*Figure 5. Maximal T-wave vector magnitude (upper panels), T-wave area symmetry ratio (middle panels) and ventricular gradient magnitude (lower panels) in heart-rate-matched ECGs recorded during exercise (triangles) and recovery (squares) in all subjects, ordered according to recovery time (left panels) and percentage heart rate reserve (right panels). Error bars indicate standard deviations from the mean. Significant differences between recovery and exercise are indicated by single (P<0.05) and double (P<0.01) asterisks.*
in our study population. It is conceivable, though, that increased DOR during recovery from exercise plays a facilitatory role in the development of reentrant tachyarrhythmias in persons having ambient arrhythmias during recovery from exercise that could serve as a trigger. However, conclusions about this hypothesis cannot be drawn from our study and require further investigation.

We acknowledge that in the general population, habitual sports activity improves several outcomes of overall health, including the risk of death caused by coronary artery disease. However, for example in those with increased automaticity due to undiagnosed structural heart disease, sports activity may set the stage for reentry type arrhythmias in a substrate which is transiently at increased vulnerability. Prevention strategies might aim at the detection of this subgroup. Furthermore, it might be useful to scan ECGs made during exercise tests on the changes as reported in our study. It must, however, be stressed that our study results were obtained in healthy individuals and that extrapolation to patients or to athletes with structural heart disease responsible for sudden death is highly speculative at this time. It remains to be proven that similar changes in dispersion of ventricular repolarization occur in such risk groups, and that increased dispersion of ventricular repolarization during recovery from exercise bears increased risk of sudden death in the setting of sports activity.

**Conclusion**

In conclusion, our study provides strong suggestive evidence for increased dispersion of repolarization during recovery from maximal exercise in normal male persons of any fitness level. Obviously, such an explicit exercise–recovery hysteresis will not exist to this extent at lower peak exercise intensity levels. We demonstrated also that, after maximal exercise, highly fit persons have a much larger hysteresis than unfit subjects. It should further be investigated if this effect renders individuals more susceptible to arrhythmia induction (e.g., by a triggering ventricular extrasystole) during recovery from exercise.
REFERENCES

15. Chauhan VS, Krahn AD, Walker BD, Klein GJ, Skanes AC, Yee R. Sex differences


35. Hooft van Huysduynen B, Swenne CA, Draisma HHM, Antoni ML, Van de
37. Wilson FN, MacLeod AG, Barker PS, Johnston FD. The determination and significance of the areas of the ventricular deflections of the electrocardiogram. Am Heart J. 1934;10:46-61.
38. Wilson FN, MacLeod AG, Barker PS. The T deflection of the electrocardiogram. Trans Assn Am Physicians. 1931;46.
45. Inoue H, Zipes DP. Changes in atrial and ventricular refractoriness and in atrioventricular nodal conduction produced by combinations of vagal and sympathetic stimulation that result in a constant spontaneous sinus cycle length. Circ Res. 1987;60:942-951.