Hypertensive stress increases dispersion of repolarization

Bart Hooft van Huysduynen
Cees A. Swenne
Henk J. Ritsema van Eck
Jan A. Kors
Anna L. Schoneveld
Hedde van de Vooren
Piet Schiereck
Martin J. Schalij
Ernst E. van der Wall

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**ABSTRACT**

**Purpose.** Several electrocardiographic indices for repolarization heterogeneity have been proposed previously. We studied the behavior of these indices under two different stressors at the same heart rate: *i.e.*, normotensive gravitational stress, and hypertensive isometric stress.

**Methods.** In 56 healthy males ECG and blood pressure were recorded during rest (sitting with horizontal legs), hypertensive stress (performing handgrip) and normotensive stress (sitting with lowered legs). During both stressors, heart rates differed less than 10 % in 41 subjects, who constituted the final study group.

**Results.** Heart rate increased from 63 ± 9 bpm at rest to 71 ± 11 bpm during normotensive and to 71 ± 10 bpm during hypertensive stress (*P*<0.001). Systolic blood pressure was 122 ± 15 mmHg at rest and 121 ± 15 mmHg during normotensive stress, and increased to 151 ± 17 mmHg during hypertensive stress (*P*<0.001). The QT interval was larger during hypertensive (405 ± 27) than during normotensive stress (389 ± 26, *P*<0.001). QT dispersion did not differ significantly between the two stressors. The mean Tapex-Tend interval of the midprecordial leads was larger during hypertensive (121 ± 17 ms) than during normotensive stress (116 ± 15 ms, *P*<0.001). The singular value decomposition T wave index was larger during hypertensive (0.144 ± 0.071) than during normotensive stress (0.089 ± 0.053, *P*<0.001).

**Conclusion.** Most indices of repolarization heterogeneity were larger during hypertensive stress than during normotensive stress. Hypertensive stressors are associated with arrhythmogeneity in vulnerable hearts. This may in part be explained by the induction of repolarization heterogeneity by hypertensive stress.
INTRODUCTION

Increased dispersion of the repolarization in the myocardium, also called heterogeneity of repolarization, increases the sensitivity of the substrate to reentry-based arrhythmias such as torsade de pointes. A number of studies involving mathematical simulation models\textsuperscript{1-4}, animal experiments\textsuperscript{5} and observations in humans\textsuperscript{6} have provided evidence for the facilitory role of dispersion of the repolarization in arrhythmogenesis. During repolarization (phase 3 of the monophasic action potential), cardiac cells return from the refractory to the excitable state. As cardiac cells have different repolarization times, there is a time window during which a mix of refractory and excitable cells is present, roughly corresponding to the terminal part of the T wave in the electrocardiogram (ECG). Within this dispersion time-window, the conduction pathway of electrical extrastimuli is functionally determined by the distribution of excitable and non-excitable tissue. It is conceivable that hearts with larger dispersion time windows are more vulnerable to reentrant arrhythmias; obviously an additional triggering mechanism is needed to initiate such an arrhythmia.

Apart from the patchy, local changes of the electrophysiological properties of the myocardium, resulting from ischemia\textsuperscript{7,8}, infarction\textsuperscript{9}, and inflammation\textsuperscript{10}, which we will not consider here, primary electrical heart disease\textsuperscript{11}, hypertrophy\textsuperscript{12}, medication\textsuperscript{6}, heart rate\textsuperscript{13}, and autonomic nervous system influences\textsuperscript{14} have been mentioned as causes of increased dispersion of repolarization. All these conditions may amplify the intrinsic differences in action potential durations as normally found within the myocardium, e.g. between the right and the left ventricle, between the apex and the base, and between the epicardium, mid-myocardium and endocardium\textsuperscript{15}.

As the concept of dispersion of repolarization evolved, multiple electrocardiographic indices for its quantitative assessment have been proposed, such as the QT interval, QT dispersion, the Tapex-Tend interval in the precordial leads and singular value decomposition of the T wave. These measures are based on different electrophysiological and electrocardiographic concepts and have therefore different theoretical and practical strengths and weaknesses with respect to the nature of the dispersion reflected and the arrhythmogenic risk. To a certain extent they may, however, carry similar information.
In this study we exposed normal subjects to two stressors, gravitational and isometric stress, while taking care that each subject attained the same heart rate under both stressors\textsuperscript{16}. In a previous study\textsuperscript{14}, we have shown that this experimental setup results in intra-individual repolarization differences, despite the identical heart rate. Thus, this experiment facilitates the studying of the dynamic behavior of all indices by intra-individual comparison during normotensive and hypertensive stress with minimal errors introduced by heart rate adjustment. In the current study we sought to answer two questions: 1) Will the above mentioned indices for repolarization heterogeneity all change in the same direction when gravitational and isometric stress are compared? 2) What can be said about differences of repolarization heterogeneity under gravitational and isometric stress?
SUBJECTS AND METHODS

The Leiden University Medical Center Ethics Review Committee approved the protocol of this study. To include subjects with a large range of fitness, healthy male subjects, 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 Union, respectively. All participants gave written informed consent. The subjects were instructed to restrict, on the day preceding the measurements, their caffeine and alcohol consumption to respectively 6 and 2 beverages (the alcoholic drinks not later than 8 PM). On the day of the measurements, subjects were instructed not to smoke and not to drink alcohol or caffeine containing beverages. Furthermore, any exertional activity preceding the measurements had to be avoided. None of the participants used any medication. At recruitment, the good health of the participant was ascertained by medical history, physical examination, echocardiography, and a maximal oxygen consumption test was performed after the measurement session described below.

Measurement session

Instrumentation. Ten electrodes were attached to derive a standard 12-lead ECG. The finger cuff of a noninvasive continuous blood pressure measurement device (Finometer Medical systems, Arnhem, The Netherlands) was attached to the middle finger of the non-dominant hand. After the Finometer was switched on, the device was allowed to adapt to the conditions in the finger. If no satisfactory continuous blood pressure signal was attained, the cuff was wrapped around the ring finger of the same hand. The eight ECG signals I, II, V1-V6 were digitally stored together with the blood pressure signal on a ST Surveyor monitoring device (Mortara Rangoni Europe, S. Giorgio di Piano, Italy; sampling rate 500 Hz).

Setting. The measurements were done in a quiet air-conditioned room (approximately 22°C). One investigator performed the measurements. No other personnel was allowed to enter the room during the measurement session, and speaking during the measurements was minimized. The subjects were placed on a tilt bed with foot support and an adjustable backrest that was always kept at a 70° angle with respect to the horizontal plane. Thus, the subjects were always “sitting”, with a constant position of the thorax throughout the experiment (Figure 1).
Figure 1. Experimental conditions, from left to right: rest (sitting with horizontal legs), isometric stress (sitting during handgrip), gravitational stress (leg lowering at 4 different angles).

Rest measurement. The rest measurements were performed with the legs in horizontal position as shown in Figure 1. For stabilization purposes, the subjects rested during 20 minutes in this position prior to the actual 5-minute measurement.

Isometric stress: handgrip. Still with the legs in horizontal position, the maximal grip force of the dominant hand was measured with a handgrip device (Jamar, Bolingbrook, IL, USA). Subsequently, the subject performed a standard handgrip maneuver (30% maximal grip force during three minutes).

Gravitational stress: leg lowering. After a rest of 5 minutes, a number of recordings were made at various leg lowering angles (tilt bed angles 30º, 45º, 60º, and 70º; the angle of the backrest was always kept at 70º with the horizontal plane) as shown in Figure 1. Each angle was maintained for five minutes.

Analysis

Rest, gravitational stress, isometric stress. We evaluated the data as obtained under three different loading conditions: rest (sitting with horizontal legs), the state with isometric stress (handgrip) and a selected state of gravitational stress (leg lowering). For each volunteer, a leg-lowering angle was sought at which the heart rate was closest to the heart rate during handgrip (maximal tolerated difference = 10 %). The ECG and blood pressure recorded during the last minute of these measurements were used for further analysis.

QT interval. The QT interval is defined as the time between the earliest visible de-
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Flextion from the isoelectric line between the P wave and the QRS complex in any of the twelve leads of the ECG until the last visible T wave activity in any of the leads. For the processing of the data the ECG computer program MEANS (Modular ECG Analysis System) was used. MEANS determines common QRS onset and T offset for all 12 leads on one representative averaged beat, using template matching techniques. Bazett’s formula was used for the computation of the heart rate adjusted QT intervals.

**QT dispersion.** The QT dispersion is defined as the difference between the longest and the shortest QT intervals in any of the leads. Starting from the overall end of T measurement, MEANS also determined lead-dependent T offsets, from which QT dispersion was derived as the difference between the longest and the shortest QT interval in any lead.

**Tapex-Tend interval.** These ECG measures were determined by means of a recently developed interactive ECG measurement computer program. The end of T was manually set at the TU nadir of the precordial leads. The apex of the T wave was automatically determined. One observer initially did all analyses after which a second observer reviewed and when necessary adapted the results. Analyst and reviewer were blinded to the subject and state under consideration. Afterwards, the mean Tapex-Tend interval of the precordial leads closest to the heart, V2, V3 and V4, were averaged. Bazett’s formula was used for the computation of the heart rate adjusted Tapex-Tend intervals.

**Repolarization complexity.** Singular value decomposition of the T wave is a method that calculates eight new orthogonal ECG derivations that represent the original ECG. The first derivation contains most energy; the second contains most energy orthogonal to the first derivation, the third most energy orthogonal to the first two derivations, etc. The first three derivations contain the dipolar signal of the ECG; they correspond to the long and the short axis of the spatial T loop and to its non-planar component, respectively. The next 5 derivations (in which the amplitudes become progressively smaller) reflect non-dipolar components. As an index of dispersion of the repolarization we computed the singular-value-decomposition-based T wave complexity, expressed as the quotient of the second and the first singular values. Singular value decomposition was performed in the terminal 10 seconds of the selected one-minute ECG episodes. Singular value decomposition algorithms were implemented in Matlab 6.5 (The MathWorks, Natick, USA). After computation of an averaged beat, the singular value decomposition was computed over an interval.
of 250 ms, from –100 ms to +150 ms around the peak of the T wave.

Statistics
To detect intra-individual differences between the dispersion parameters in the control state, under gravitational stress and under isometric stress, paired two-tailed t-tests were done at a significance level of 0.05.
RESULTS

Study group
Measurements were initially performed in 56 subjects. In 41 subjects a leg-lowering angle could be found during which the heart rate differed less than 10% from the heart rate during handgrip. These 41 subjects constituted the study group (mean ± SD age 32.6 ± 11.2 years). The 15 subjects excluded from this analysis all had maximal leg lowering heart rates below the heart rate during handgrip. Obviously, prolonged tilting could have increased heart rate further, but we restricted the duration of our gravitational stress protocol to prevent orthostatic complications.

Heart rate and systolic blood pressure responses to gravitational and isometric stress.
Heart rates during gravitational (71 ± 11 bpm) and isometric stress (71 ± 10 bpm) were significantly higher than at rest (63 ± 9 bpm, \( P < 0.001 \)). The average individual matching percentage for the heart rates under gravitational and isometric stress was \(-0.07 \pm 3.14\%\), without any significant difference between the heart rates (\( P = 0.948 \)).

Systolic blood pressure was 122 ± 15 mmHg at rest, remained 121 ± 15 mmHg during gravitational stress, and increased to 151 ± 17 mmHg during isometric stress (\( P < 0.001 \)). Compared to rest, the gravitational stress was normotensive and the isometric stressor was hypertensive. The rate-pressure product increased progressively from rest (7684 ± 1438 bpm·mmHg) via gravitational (8638 ± 1605 bpm·mmHg) to isometric stress (10826 ± 2296 bpm·mmHg, \( P < 0.001 \) for all conditions).

QT interval differences between gravitational and isometric stress
The QT interval of the two stress states differed significantly. The QT interval during isometric stress (405 ± 27 ms) was longer than the QT interval during gravitational stress (390 ± 26 ms, \( P < 0.001 \)). The QT interval during rest (408 ± 27 ms) was only significantly different from the QT interval during gravitational stress (\( P < 0.001 \)). When corrected for heart rate, the QTc interval during both stressors differed significantly from rest (414 ± 18 ms), and the isometric stress QTc interval (433 ± 17 ms) was larger than the gravitational stress QTc interval (421 ± 18 ms, \( P < 0.001 \)). Values of the QTc intervals are depicted in Figure 2.
QT dispersion differences between gravitational and isometric stress
The QT dispersion was $48 \pm 22$ ms during rest, $45 \pm 22$ ms during gravitational stress and $51 \pm 26$ ms during isometric stress, which was not significantly different during any condition.

Tapex-Tend interval differences between gravitational and isometric stress.
The averaged Tapex-Tend interval from the midprecordial leads V2, V3 and V4 was significantly larger during isometric stress than during gravitational stress, $121 \pm 17$ ms vs. $116 \pm 15$ ms, respectively ($P < 0.001$). The Tapex-Tend interval during rest ($123 \pm 16$ ms) was only significantly different from the interval during gravitational stress ($P < 0.001$). When corrected for heart rate, Tapex-Tend during isometric stress ($129 \pm 15$ ms) was significantly larger than during rest ($126 \pm 12$ ms, $P = 0.003$) and during gravitational stress ($125 \pm 14$ ms, $P < 0.001$). The heart rate corrected Tapex-Tend intervals are depicted in Figure 3.

Singular value decomposition differences between gravitational and isometric stress.
T wave complexity as computed with the singular value decomposition technique is depicted in Figure 4. All differences were significant; the complexity values under
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isometric stress were larger than under gravitational stress, (0.144 ± 0.071 vs. 0.089 ± 0.053, \( P < 0.001 \)).

**Figure 3.** Bazett-corrected mean Tapex-Tend interval of V2, V3 and V4.

**Figure 4.** Singular value decomposition of the T wave, S2/S1 ratio.
DISCUSSION

Our experimental set-up made intra-individual ECG comparisons possible at two different levels of blood pressure with minimal errors introduced by heart rate adjustment. Gravitational stress only increased heart rate, while isometric stress increased blood pressure as well. The rate-pressure product indicated that the stress levels increased from rest via leg-lowering to handgrip.

We measured a number of parameters that have been put forward as indices for dispersion of repolarization. Most indices suggested that isometric stress is associated with increased dispersion of repolarization. The QTc interval increased under hypertensive stress, suggesting a lengthened repolarization time. The Tapex-Tend interval in the midprecordial leads was small but significantly longer under isometric stress, denoting increased transmural dispersion of the repolarization. The ratio of the second and first singular values of the singular value decomposition, a measure of T-wave complexity, was also significantly larger during isometric stress, implying increased global dispersion of the repolarization.

QT dispersion differences between gravitational and isometric stress remained inconclusive. However, according to current insight, the physiological basis of this index is questionable.

Although prolongation of the QT interval has proven to be predictive of sudden cardiac death, arrhythmias and all-cause mortality, not only in populations with diseased hearts but also in seemingly healthy subjects, the duration of the QT interval is mainly determined by the longest action potentials, rather than by APD differences.

QT dispersion was believed to measure the spatial dispersion of the repolarization of the ventricle. In a healthy population but also in patients with left ventricular dysfunction, QT dispersion is associated with increased susceptibility to ventricular arrhythmias. However, the theoretical foundation of this index has come under severe criticism. If the last part of the T vector is perpendicular to one of the 12 leads, this will result in the shortest QT interval in that lead. Thus, QT dispersion depends not only on the repolarization process itself, but also on the projection of the repolarization vector on the twelve ECG lead vectors.
The interval between the *apex and the end of the T wave* (Tapex-Tend) in the precordial leads was proposed as a measure reflecting the transmural dispersion of repolarization in the region of the heart immediately under the electrode\(^{34}\). (Sub)endocardial cells have longer action potentials and repolarize later than the epicardial myocytes. In this concept the peak of the T wave corresponds to the end of the epicardial action potential while the end of the T wave corresponds to the end of the longest action potential. The experiments underlying this theory have been done in the laboratory, the ECG being derived from two electrodes placed at a short distance from the epicardium and endocardium in a wedge preparation of the ventricular wall\(^{15,35}\).

Mathematical elaboration has shown that with increasing dispersion the relative contributions of derivations two and higher of the *singular value decomposition* increase\(^{36}\). So far, the clinical focus has been on the relative contribution of derivation two\(^{37}\) and on the non-dipolar components, four and higher\(^{38,39}\). The great advantage of singular value decomposition is its objectiveness in contrast to the usual phenomenological approach of the ECG.

As mentioned above, all measured parameters have typical flaws and rely on different notions of dispersion. However, they all showed to be predictive for sudden cardiac death. The singular value decomposition and the Tapex-Tend interval provided the strongest physiological link with dispersion of the repolarization, because they are based on mathematical modelling\(^{40}\) and laboratory measurements\(^{15,34}\), respectively.

The underlying mechanisms of the altered T-wave morphology under stress are the differences of the electrophysiological properties of the ventricular myocardium due to differences in sympathetic and parasympathetic tone and wall stress. With respect to the normotensive stressor, the hypertensive stressor encompasses increased wall stress due to increased cardiac afterload, elevated sympathetic tone due to chemoreceptor firing from muscles involved in the handgrip maneuver, and baroreflex-mediated elevated para-sympathetic tone\(^{14}\).

Our study regards a physiological phenomenon in the general population. The stressors that were applied (leg lowering, that increased heart rate with 8 bpm, and handgrip, that additionally increased blood pressure with 30 mmHg) are comparable with the many physical and mental stressors that are met in daily life\(^{41}\). Our finding that
hypertensive stress increases dispersion of the repolarization has potential clinical implications. In normal subjects, stress is associated with increased ventricular ectopy\textsuperscript{42}. In this way hypertensive stress could provide the trigger (ectopy) plus the substrate (increased dispersion of the repolarization) needed to initiate serious arrhythmias. Although the chances are small, this still might be an important arrhythmogenic scenario as it applies to a large number of individuals (\textit{i.e.}, the general population). In patients with primary electrical disease, like long QT syndrome\textsuperscript{43}, the increase in dispersion of the repolarization and incidence of ectopic beats caused by hypertensive stress may be exaggerated. Similarly, this scenario might explain why anger and mild exercise often precede serious arrhythmias in patients with internal defibrillators\textsuperscript{44}.

We conclude that hypertensive stress increases dispersion of the repolarization in the myocardium in healthy male subjects. This conclusion mainly relies on the increases of the Tapex-Tend interval and of the quotient of averaged absolute values of the second and first singular value decompositions of the T-wave. The increase of the QT interval may denote similar changes. Hypertensive stressors (physical and mental) are associated with arrhythmogeneity. These stressors may well increase dispersion of the repolarization, thus setting the stage for serious reentrant arrhythmias in vulnerable subjects.
REFERENCES
