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Original Article

Within-subject electrocardiographic differences at equal heart rates: role of the autonomic nervous system

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Abstract. Various combinations of sympathetic and vagal tone can yield the same heart rate, while ventricular electrophysiology differs. To demonstrate this in humans, we studied healthy volunteers in the sitting position with horizontal legs. First, heart rate was increased by lowering the legs to 60° and back. Thereafter, heart rate was increased by handgrip. In each subject, a leg-lowering angle was selected at which heart rate matched best with heart rate in the third handgrip minute. Thirteen subjects had a heart rate match better than 1%. Heart rate (control: 65.2±9.0 bpm) increased to 72.1±8.7 (leg lowering) and to 72.1±8.8 (handgrip) bpm. QRS azimuth, QRS duration, maximal T vector, T azimuth, T elevation, ST duration, QRS-T angle and QT interval differed significantly (P<0.05) between leg lowering and handgrip (QT interval 418±15 versus 435±21 ms). Also, septal dispersion of repolarization, assessed as the time difference between the apex and the end of the T wave in the V2 and V3 leads, differed significantly (V2: 96.7±19.3 versus 110.0±23.3 ms, P<0.01; V3: 88.7±19.3 versus 97.3±23.3 ms; P<0.01). Hence, leg lowering and handgrip cause different ventricular depolarization and repolarization. The hypertensive handgrip manoeuvre entails a longer QT interval and probably an increased septal dispersion of repolarization.

Keywords. Autonomic nervous system - Baroreceptors - Electrocardiology - Heart rate - QT-intervals

Introduction

Classic models of sympathovagal interaction at the sinus node [*24*, *31*, *38*] adhere to the concept that sympathetic and vagal effects contrast (sympathetic *acceleration* and vagal *deceleration*) and compensate each other partly when occurring at the same time. More recent work [*19*, *20*, *36*] confirms this view. Basically, this insight implies that various combinations of sympathetic and vagal tone can yield identical heart rates.

In the laboratory, Inoue and Zipes [*17*] demonstrated ventricular effective refractory period changes in the dog under various combinations of artificial autonomic cardiac stimulation that yielded identical heart rates. The described how sympathovagal interaction at the level of the sinus node and in the ventricular myocardium makes it likely that different combinations of vagal and sympathetic tone may produce identical heart rates, but, at the same time, entail a different ventricular electrophysiology. This would allow for individual dissociation of heart rate and the electrocardiographic (ECG) waveform.

Two studies have attempted to demonstrate this at the level of the surface ECG. Browne et al. [*12*] demonstrated that there are within-subject day-night differences in QT time at equal heart rates. Bexton et al. [*7*] reported within-subject diurnal differences in individually normalized corrected QT intervals (not necessarily at equal heart rates). Both studies accounted for the observed changes merely by the varying activity of the autonomic nervous system. However, there are several deficiencies in these measurements carried out to date in humans. They were not made using a full ECG (only with 1- or 2-lead Holter ECGs), they were made from patients rather than healthy controls (patients may be abnormal in terms of autonomic response), posture was not controlled (which may have considerable influence on QT intervals measured in 1- and 2-lead ECGs), activity was not controlled and also the body temperature will have fluctuated during the 24-h observation periods (this considerably influences the intrinsic heart rate, thus hampering interpretation of the autonomic components of the actual sinus rate).

The current work aims to unequivocally demonstrate, within healthy subjects, differences in the ECG waveform (QRS-complex morphology, T-wave morphology, QT interval) at the same heart rate, and to assess the role of the autonomic nervous system in these changes. To minimize difficulties in ECG interpretation, the thoracic orientation was fixed throughout the measurements and, in addition to measurements made using separate ECG leads, vectorcardiographic analyses were carried out. In contrast to earlier ambulatory studies, our measurements were made under laboratory conditions. Natural, all-day life stimuli (normotensive, gravitational stress in the form of leg lowering, and hypertensive, isometric stress in the form of handgrip) were used to attain equal heart rates with different combinations of sympathetic and vagal tone.

Subjects and methods

Subjects

The Leiden University Medical Center Ethics Review Committee approved the protocol of this study. Healthy male and female students were invited to participate. All subjects gave signed informed consent. Subjects were apparently healthy according to their medical history, physical examination, and a 12-lead diagnostic ECG. The subjects were instructed to restrict, on the day preceding the measurements, their caffeine and alcohol consumption to respectively six and two beverages (the

alcoholic drinks not later than 20:00 hours), and, on the day of the measurements, not to smoke or drink alcohol or caffeine-containing beverages.

Instrumentation

The armcuff of an automatic sphygmomanometer (Accutorr, Datascope, Montvale, USA) was attached to the subject's dominant arm. The fingercuff of a non-invasive continuous blood pressure measurement device (Finapres, Ohmeda, Englewood, USA) was attached to the middle finger of the non-dominant hand. If this did not give a good signal, the cuff was placed on a different finger of the non-dominant hand. The ECG was obtained with a Marquette Case-12 electrocardiograph (Marquette Electronics, Milwaukee, USA). The signals were AD converted (sampling rate 500 Hz, resolution 16 bits) and digitally stored.

Protocol

The measurements were made in a quiet, air-conditioned room (approximately 22°C), and started between 12:00 and 18:00 hours, at least 2 h after the subjects' last meal. Two people, one of whom was a physician, performed the measurements. No other personnel were allowed to enter the room during the measurement session. The subjects were placed on a tilt bed with foot support and a backrest with adjustable inclination. Regardless of the bed's tilt angle, the backrest was always kept at a 70° angle with respect to the horizontal plane. Thus, the subjects were always "sitting", with their thorax in the same position throughout the experiment. The sitting position with horizontal legs was taken as the reference position. From this control state, gravitational or isometric stress could be applied by lowering the legs or by performing a handgrip (see Fig. 1).

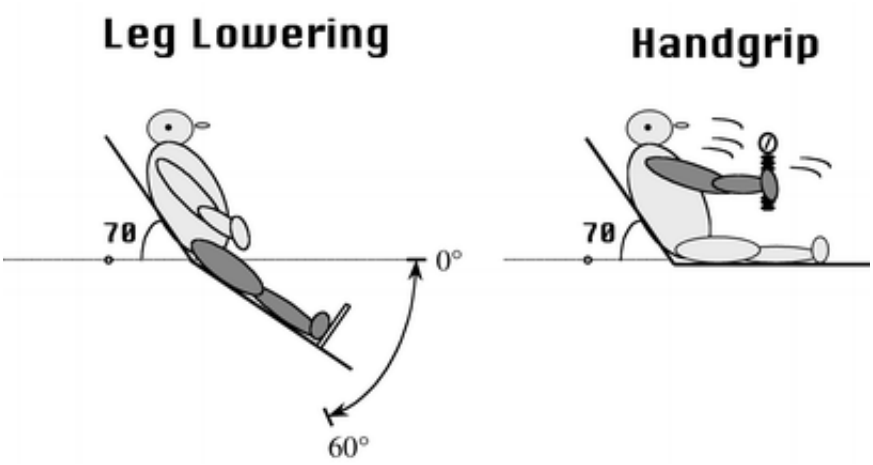

Fig. 1. Experimental set-up. Subjects were always seated during the experiment, with the thorax in a 70° position. This was realized by an adjustable backrest that was placed on a tilt bed. The leg-lowering-induced gravitational load (*left*) was accomplished by inclining the tilt bed, while the angle of the backrest was simultaneously adjusted to keep the position of the thorax fixed. During handgrip (*right*), the legs were horizontal

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To assess baroreflex sensitivity, and to prevent breath-holding during handgrip, the subjects were asked to perform metronome breathing during specific episodes described below. An indicator of metronome breathing was made visible on a computer monitor. The subjects were instructed before the measurements how to breathe comfortably at a fixed rate of 15 breaths per minute (0.25 Hz), at a freely chosen tidal volume. Also, the handgrip manoeuvre was rehearsed in advance.

After these instructions, the subjects rested (sitting, with their legs in the horizontal position) for 30 min to attain a stable control state. Then, a slow incremental leg-lowering sweep was performed (duration 85 min), followed by a handgrip manoeuvre.

Leg lowering

The incremental leg lowering sweep was symmetrical around 60°. There were seven intermediate leg-lowering angles between 0° and 60°, namely 10°, 20°, 30°, 40°, 45°, 50° and 55°. Taken together, this protocol comprised 17 situations: 0°, seven intermediate angles; 60°, seven mirrored intermediate angles; and 0° again. Each angle was maintained for 5 min. At each angle, the subjects performed 15 breaths/min (0.25 Hz) metronome breathing for 1 min. An arm-cuff blood pressure measurement reading was performed after metronome breathing. During later off-line processing of the data, one of the 17 metronome breathing episodes was selected for final analysis on the basis of the best heart rate match between leg lowering and handgrip (see below).

Handgrip

During the handgrip manoeuvre, the legs were in the horizontal position. Before the handgrip manoeuvre was executed, an arm-cuff blood pressure measurement was taken, to calibrate the Finapres pressures. Handgrip was applied at 30% of the maximal force (this maximal force was determined before the onset of the measurements) for 3 min. During the first 2 min, breathing rate was free, whereas during the third minute metronome breathing at 15 breaths/min (0.25 Hz) was done. We analysed the data collected in the third minute.

Heart rate matching

Heart rates were computed for all 1-min metronome breathing episodes (17 episodes during leg lowering, plus the third minute of handgrip). For each subject, the leg-lowering heart rate that was closest to (smallest absolute difference) the handgrip heart rate was selected. We only compared the handgrip and leg-lowering episodes for those subjects who had a smaller than 1% difference in heart rate between handgrip and the best matching leg-lowering angle. We chose 1% as a cut-off point to avoid the risk of bias: with higher tolerated differences, subjects would be included whose handgrip heart rate was greater than the maximally reached heart rate with leg lowering.

ECG/VCG analysis

The ECG leads were linearly transformed to three orthogonal vectorcardiographic (VCG) leads using a set of weighing factors. For the purpose of this study, the VCG was considered the most convenient representation of the heart's electrical activity: the three leads X, Y and Z and their phase relationships shown in vector loops allow a general characterization of the heart's electrical activity in a limited number of parameters. The transformation coefficients were derived by linear regression from an independent set of simultaneously obtained ECGs and VCGs according to Frank, which were collected in the project Common Standards for Quantitative Electrocardiography [*39*]. The reconstructed VCGs were further processed by the Modular ECG Analysis System (MEANS) [*5*]. MEANS computes a representative averaged QRS-T complex for each of the three leads, X, Y and Z. From these complexes the vectorcardiographic loops in the frontal (XY), transversal (XZ) and sagittal (YZ) planes are constructed.

The mean QRS axis and T axis were obtained by vectorially adding the instantaneous heart vectors during the QRS loop and the T loop, respectively. Axis directions were expressed in azimuth (angle between the axis projection on the horizontal plane and the X axis) and elevation (angle between the axis and the horizontal plane). The QRS-T angle was defined as the spatial angle between the QRS axis and the T axis. Maximal QRS and T amplitudes were taken as the magnitude of the largest instantaneous vector in the QRS and T loops, respectively. The timing of the largest instantaneous T-loop vector was taken as the instant of the spatial apex of the T wave.

MEANS determines common QRS onset and offset as well as T offset for all three leads together on the averaged beat, using template-matching techniques [*6*]. From these time instants, the QRS duration, the QT interval and their difference, the ST-T duration, were computed and adjusted for heart rate with Bazett's formula [*3*].

In precordial leads V2-V6, the timing of the apex and the end of the T wave were manually measured (the MEANS software does not address this analysis) as follows. The ECGs were magnified by writing them out at 300 mm/mV, 1500 mm/s. The steepest tangent to the down-sloping part of the T wave was drawn, the intersection of this tangent with the baseline constitutes the end of the T wave. Then, the apex-to-end-of-T distance was measured with a caliper rule in millimetres, converted to milliseconds, and corrected for heart rate with Bazett's formula.

Baroreflex sensitivity

In the 15 breaths/min (0.25 Hz) metronome breathing episodes, non-invasive baroreflex sensitivity (BRS) was assessed from the ECG-derived heart rate variability (HRV) and from the Finapres-signal-derived blood pressure variability (BPV). The analysis algorithm is described in detail by Frederiks et al. [*16*].

Statistical analysis

For the statistical comparisons between the control state, leg lowering and handgrip, a one-factor ANOVA analysis was done (significance level 5%) with a Newman-Keuls post hoc test. For paired data, statistical comparisons were made by paired *t*-test and differences were considered statistically significant at $P<0.05$.

Results

Twenty subjects participated in the study. As the heart rate responses to leg lowering and handgrip differ considerable between individuals, not all subjects met the 1% criterion for a heart rate match of leg lowering and handgrip. After application of this criterion 13 subjects (5 male, 8 female, mean ±SD age 25.3±2.8 years) were left for further analysis.

Table 1 shows mean heart rate, systolic and diastolic blood pressure and baroreflex sensitivity in the control state (legs horizontal), during the third minute of handgrip (legs horizontal), and during the individually heart-rate-matched leg-lowering state. There was no difference between heart rates measured during leg lowering and during handgrip, but leg lowering and handgrip significantly increased heart rate with respect to control. Systolic blood pressure did not change with leg lowering, but significantly increased with handgrip. Diastolic blood pressure increased significantly with leg lowering and with handgrip, while there was a small, but not significant difference between leg lowering and handgrip. There were no significant changes in baroreflex sensitivity during leg lowering and during handgrip with respect to the control state.

Table 1. Heart rate, blood pressure and baroreflex sensitivity during control, leg lowering and handgrip. Mean ±SD values of heart rate, systolic and diastolic blood pressure, and baroreflex sensitivity in the control state (legs horizontal), during leg lowering (legs sloping down), and handgrip (legs horizontal). Statistical comparisons were done with a one-factor ANOVA analysis (significance level 5%) with a Newman-Keuls post hoc test. (*BRS* Baroreflex sensitivity, *DBP* diastolic blood pressure, *HR* heart rate, *NS* non-significant, *SBP* systolic blood pressure)

	Control	Leg lowering	Handgrip	Control versus leg lowering	Control versus handgrip	Leg lowering versus handgrip
HR (bpm)	65.2±9.0	72.1±8.7	72.1±8.8	$P<0.05$	$P<0.05$	NS
SBP (mmHg)	113.2±10.2	113.3±12.2	132.5±15.2	NS	$P<0.05$	$P<0.05$
DBP (mmHg)	68.0±6.0	80.6±11.6	86.8±11.8	$P<0.05$	$P<0.05$	NS
BRS ($ms \cdot mmHg^{-1}$)	11.6±4.9	9.3±5.8	9.9±4.6	NS	NS	NS

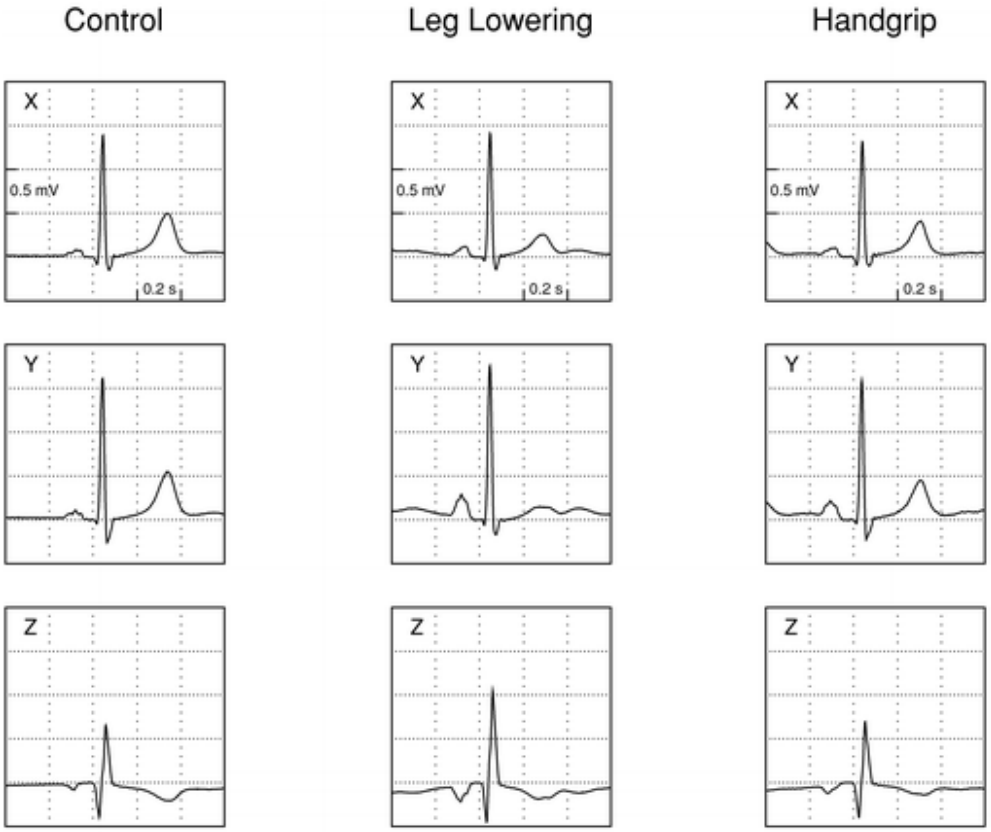
The QRS parameters as measured in the control state, during leg lowering and during handgrip are listed in Table 2. The last column of Table 2 lists the results of statistical comparison of leg-lowering and handgrip data. QRS azimuth and QRS duration differed significantly; however, the relative difference (quotient of absolute difference and average) in the QRS duration was small (3.8% increase with handgrip). The effects were more pronounced in the T wave, where all parameters differed significantly (Table 2). Also the spatial orientation of the T wave with respect to the QRS complex differed significantly (Table 2), and the corrected QT interval was significantly (17 ms or 4.1%) longer with handgrip. The corrected QT intervals with leg lowering did not differ from control (418±15

versus 418±24 ms); corrected QT intervals with handgrip were larger than control (435±21 versus 418±24 ms, $P<0.05$).

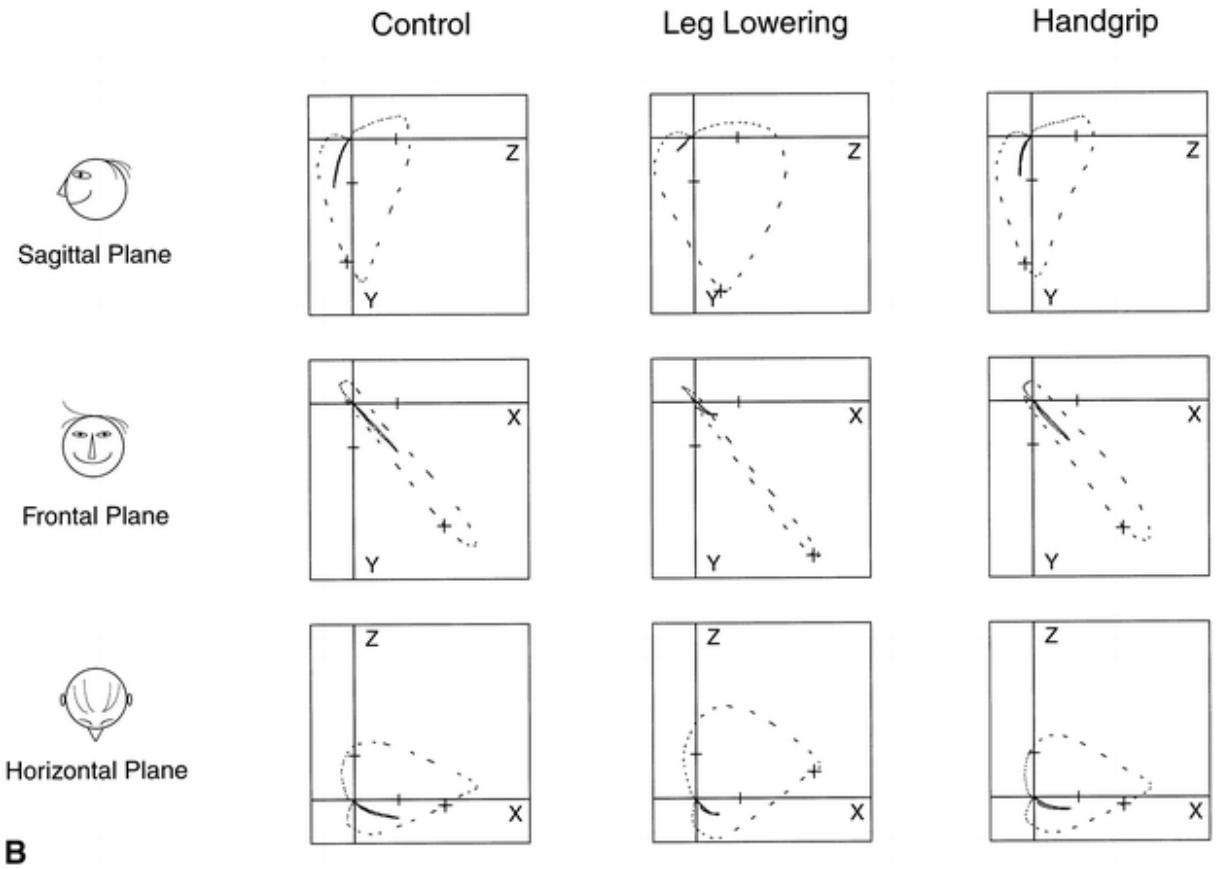
Table 2. ECG parameters during control, leg lowering and handgrip. Mean ±SD values of maximal amplitude, azimuth, elevation and duration of the QRS complex and the T wave, during leg lowering and handgrip. Also, the QRS-T angle and QT interval during leg lowering and handgrip are given. Statistical comparisons (between handgrip and leg lowering) were done with paired *t*-tests, the *P* values for which are listed. Durations and intervals are normalized for heart rate according to Bazett's formula

	Control	Leg lowering	Handgrip	*P* value (leg lowering versus handgrip)
QRS parameters				
Maximal amplitude (μV)	2346±467	2477±612	2395±500	0.11
Azimuth (°)	-23.1±21.0	-33.5±15.0	-22.4±22.5	<0.01
Elevation (°)	48.8±16.2	47.7±16.8	48.0±16.5	0.84
Duration (ms)	104±14	103±10	107±13	0.04
T wave parameters				
Maximal amplitude (μV)	705±193	646±200	703±184	0.03
Azimuth (°)	40.9±13.5	45.3±14.5	38.6±13.6	<0.01
Elevation (°)	42.4±6.1	39.5±9.5	43.9±6.7	0.03
ST-T duration (ms)	314±18	315±14	329±18	<0.01
QRS-T parameters				
QRS-T angle (°)	46.9±21.4	57.5±27.1	44.5±22.4	<0.01
QT interval (ms)	418±24	418±15	435±21	<0.01

An example of the morphological differences between control, leg-lowering and handgrip is given in Fig. 2. Figure 2A gives the scalar X, Y and Z components of the VCG (subject no. 17). Particularly noteworthy are the differences in T-wave morphology between leg lowering (middle panels) and handgrip (right panels); for example, with handgrip the T-wave amplitudes in the X and Y directions are much larger. The ECG of this subject was selected as an example because it has a distinct U wave during leg lowering (in the other 12 of the 13 subjects selected no clear U waves were seen, but two had bifurcated T waves). Figure 2B shows the vector loops that illustrate the time relationships between the scalar X, Y and Z components. Differences in the QRS and T loops in all planes are readily apparent.


Control
Leg Lowering
Handgrip
X
Y
Z
0.5 mV
0.2 s

A


Control
Leg Lowering
Handgrip
Sagittal Plane
Frontal Plane
Horizontal Plane
Z
Y
X

B

Fig. 2. A Scalar vectorcardiographic X, Y and Z leads of subject 17 in the control state (*left panels*), during leg lowering (*middle panels*) and during handgrip (*right panels*). T-wave morphology differences between leg lowering and handgrip are striking, and a prominent U-wave is seen with leg lowering. **B** Planar vectorcardiograms (from *top* to *bottom*: sagittal, frontal and horizontal planes) of subject 17 in the control state (*left panels*), during leg lowering (*middle panels*) and during handgrip (*right panels*). The depicted vector loops are constructed from the scalar vectorcardiographic leads shown in **A**. Except for T-loop differences, the QRS-loop differences between leg lowering and handgrip are obvious in the vectorcardiographic representation. *One dash* in the vectorcardiographic loops represents 2 ms in time

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The difference in QT interval between handgrip and leg lowering was 17±10 ms (the 1 ms difference in numbers in Table 2 is due to rounding). This prolongation of the QT interval with handgrip as compared to leg lowering is partly due to QRS prolongation and partly to ST-T prolongation. We compared, within individuals, the differences in QRS duration and in ST-T duration between leg lowering and handgrip. Average differences were 4±6 ms and 14±7 ms, respectively (see also Table 2). As compared to leg lowering, the handgrip-induced prolongation of the ST-T duration was significantly (P<0.01) larger than the prolongation of the QRS duration.

Three subjects (including no. 17, whose ECG is depicted in Figs 2A, B) had bifurcated T waves or U waves [*40*] which made it impossible to establish the apex and the end of the T wave with the geometrical method (this problem is typical for the lead-dependent end of T determination; in contrast, spatial determination of the end of repolarization in the vectorcardiogram is not hampered by such electrocardiographic patterns). Of the remaining ten subjects, the apex-to-end T-wave intervals as measured in leads V2-V6 and corrected for heart rate are graphed in Fig. 3. There were significant (P<0.01) differences in the V2 (leg lowering: 96.7±19.3 ms; handgrip: 110.0±23.3 ms) and in the V3 (leg lowering: 88.7±19.3 ms; handgrip: 97.3±23.3 ms) leads.

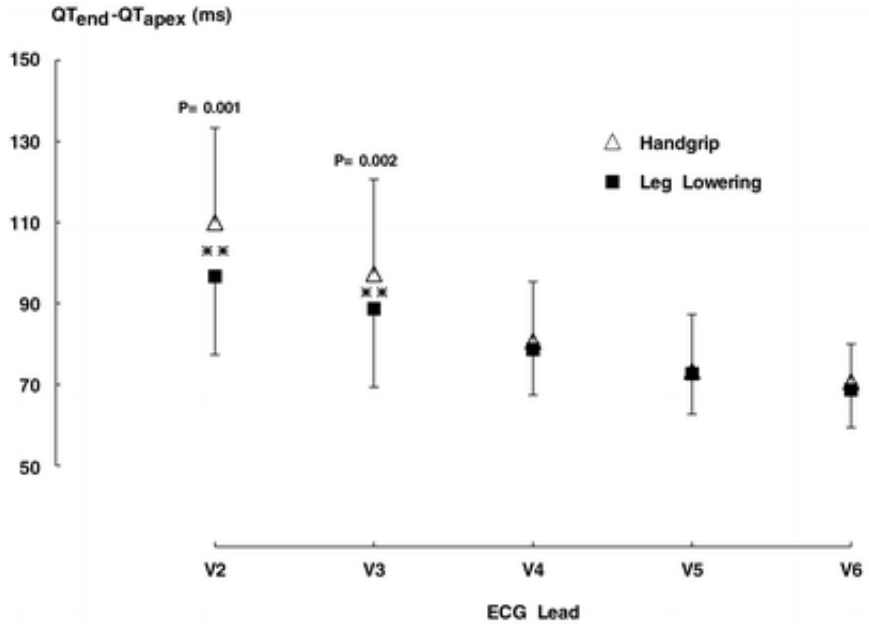

Fig. 3. Intervals between apex and the end of the T-wave. Heart-rate-corrected intervals between the apex and the end of the T-wave in leads V2, V3, V4, V5 and V6, in 10 of the 13 studied subjects. (*Open triangles* Handgrip, *solid squares* leg lowering.) Handgrip and leg lowering values differed significantly in leads V2 and V3

Discussion

This study demonstrates the existence of within-subject ECG differences between two distinct autonomic states with equal heart rates (Table 1). With an incremental leg-lowering procedure, 13/20 subjects had one leg-lowering angle at which their heart rate differed less than 1% from that measured during the third minute of handgrip (Table 1). In these 13 subjects, several ECG parameters related to ventricular depolarization and repolarization differed significantly between leg lowering and handgrip (Table 2). Amongst others, the QT interval was larger with handgrip (Table 2). In 10/13 subjects with monophasic T waves in leads V2-V6, handgrip was associated with a greater interval between the apex and the end of the T wave, as compared with leg lowering (Fig. 3).

Our study was fully non-invasive. This prevents the instrumentation itself from being the cause of autonomic changes [*10*]. In the following text, the physiological and electrophysiological interpretation of our observations is discussed. By applying the results of studies done by others, often focusing on a single specific effect or phenomenon, we hold a qualitative discussion that enables us to interpret the results of our own study, which is essentially focused on integrated physiology.

Autonomic and haemodynamic differences between leg lowering and handgrip

Any stressor invokes circulatory adaptations. Neural mechanisms constitute an essential part of the response. Much is known about how healthy individuals react to gravitational stress (e.g. tilt, leg lowering) and isometric stress (e.g. knee extension, handgrip). Our measurements (Table 1) are completely consistent with these scenarios: leg lowering is normotensive, while handgrip is hypertensive and the arterial baroreflex remains fully functional under these stressors [*1, 35*] (Table 1).

During gravitational stress (tilt, leg lowering), blood pools in the lower extremities, thus reducing central venous pressure and cardiac output [*21*]. Cardiopulmonary baroreceptor deactivation induces a reciprocal sympathovagal response: an increase in sympathetic outflow, and a decrease in vagal outflow [*22*]. In most healthy individuals, the resulting alpha-adrenergically induced increase in peripheral resistance helps to keep arterial blood pressure just normotensive (the gross response consists of an increase in diastolic pressure while systolic pressure remains about constant). As a result, the arterial baroreceptors are not specifically activated or deactivated during gravitational stress.

Isometric stress, like handgrip, increases sympathetic outflow [*28, 33*]. This is a reflex response to the associated stimulation of the mechano- and chemoreceptors in the working muscle and to central command. This increased sympathetic tone alpha-adrenergically increases peripheral resistance. This increases arterial blood pressure (systolic and diastolic), which, in turn, entails arterial baroreceptor activation. The arterial baroreflex blunts the sympathetic response, while increasing vagal outflow [*29, 32*], and this limits the rise in heart rate and blood pressure [*37*]. Central venous pressure remains unchanged in healthy persons, and the cardiopulmonary baroreceptors are not specifically activated or deactivated during isometric stress [*32*].

Sympathetic, vagal and mechanical influences on the sinus node

The classic [*18*] Rosenblueth-Simeone model [*31*] is often cited in the form of: $HR=mnHR_0$. In this formula, HR is the actual heart rate, *m* a factor representing sympathetic acceleration ($m \geq 1$), *n* a factor representing vagal deceleration ($n \leq 1$), and HR_0 the intrinsic heart rate. The factors *m* and *n* may be thought of as the sympathetic and vagal tone, respectively, while the product *mn* may be thought of as the sympathovagal balance [*11, 27, 34*]. In supine resting healthy young male persons typical values of *m*, *n* and HR_0 are around 1.15, 0.60 and 90 bpm, respectively [*9*]. In our current study, intrinsic heart rate, sympathetic tone and vagal tone are all dynamic; the Rosenblueth-Simeone model helps our understanding of the combined effect.

It is important to emphasize the role that mechanical factors play in the observed responses in our current study. During handgrip, central venous pressure and right atrial pressure are not notably different from values in the resting state [*32*], but these pressures are known to decrease with gravitational stress [*21*]. When atrial stretch decreases, HR_0 decreases too (a 6% change in rate per mmHg pressure change in the in vivo rabbit atrium has been reported [*8*]). A possible drop of 3 mmHg [*21*] in central venous pressure upon leg lowering would thus cause a 18% decrease in HR_0. In our study group we measured a 7 bpm (11%) heart rate increase upon handgrip or leg lowering (Table 1). Hence, roughly estimated, in our study the increase in sympathovagal balance (the product *mn*) with handgrip was 11%, while it was 11%+18%=29% with leg lowering.

Sympathetic, vagal and mechanical influences on the ventricular myocardium

We found prominent electrocardiographic differences between leg lowering and handgrip in the QRS complex and in the T wave (Table 2; Fig. 2A, B). The differences in QRS duration, ST-T duration, QT interval, QRS amplitude (though not significant), T amplitude and QRS-T angle straightforwardly signal different electrical activity. Differences in QRS and T azimuth and elevation (Table 2) are difficult to interpret, as these parameters are also sensitive to possible rotation of the heart. The difference in ST-T duration is larger than the difference in QRS duration; hence, the effect on the action potential duration (APD) predominates over the effect on intraventricular conduction. Here, we

concentrate on how, in our study, autonomic and mechanical factors may have differentially influenced the cardiac action potential duration during handgrip and during leg lowering.

On the basis of mechanical effects alone, APDs during isometric stress are likely to be smaller than APDs during gravitational stress at the same heart rate. This is caused by the difference in ventricular dimensions: during isometric stress [*23, 32*] the heart is larger than during gravitational stress [*4, 21*]. When cardiac tissue is stretched, APD shortens via mechano-electrical transduction [*13*]. In contrast, we observed in our study APD prolongation during handgrip, instead of shortening. This leads to the conclusions that:

1. The autonomic effects must directly oppose (APD prolongation, see also the next section on dispersion of repolarization) the mechanical effects (APD shortening);

2. The autonomic effects predominate the mechanical effects.

Recent research has shed more light upon the separate and combined vagal and sympathetic effects on ventricular tissue [*25, 26*]. It appears that the autonomic effects are not uniformly distributed over the ventricular myocardium. But, in the setting of a coexisting sympathetic tone, increased vagal involvement always entails an APD increase, no matter whether there is an independent vagal effect (e.g. in dogs in the epicardium [*25*]) or not (e.g. in dogs and in cats in the endocardium [*25, 26*]), and regardless of the regional sensitivity to vagal stimulation. Hence, increased vagal involvement is the most likely explanation of the observed prolongation of, amongst others, the QT interval (Table 2) during handgrip, as opposed to leg lowering.

Dispersion of repolarization

Experimental transmural ECGs made at a short distance from a wedge preparation of left-ventricular tissue suggest that the apex of the T wave corresponds to the termination of repolarization of the epicardial tissue, while the end of the T wave corresponds to the termination of repolarization of midmyocardial tissue [*40*]. The time between the apex and the end of the T wave would then correspond to an episode during which ventricular repolarization is incomplete, and might represent a measure of such dispersion.

In our study, we observed a significant prolongation of dispersion in leads V2 and V3 (see Fig. 3). This suggests that, with respect to epicardial cells, midmyocardial ventricular cells repolarize later with handgrip than with leg lowering, thus increasing ventricular dispersion of repolarization with handgrip. The absence of significant differences in leads V4, V5 and V6 may be explained by the relatively large distance between these electrodes and the left ventricle, as a consequence of which overall electrical activity will be picked up. Alternatively, it suggests that the increase in the dispersion of repolarization is stronger in the septum than in the left ventricular free wall. Of course, such an interpretation is subject to the multiple constraints opposed by the differences between the laboratory experiment and real-life observation [*40*].

The autonomic nervous system governs the differential circulatory responses between gravitational and isometric stress, and our study demonstrates that it also predominates the electrophysiological cardiac response. Most likely, M-cell APD prolongation is the main cause of the prolonged QT interval during handgrip. Our measurements suggest that handgrip increases septal transmural dispersion of repolarization, and this would render the heart a more onerous substrate for arrhythmias during hypertensive isometric stress.

The autonomic effects of handgrip are not different from those of mental stress: both stressors elicit primarily sympathetic (and, hence, hypertensive) responses [*2*]. The arterial baroreflex remains operational during mental stress [*14*, *30*] and during handgrip (Table 1). If this comparison between isometric stress and mental stress is valid, our study might be a clue to certain arrhythmias that are known to be bound to mental stress, rather than to heart rate, e.g. in the long-QT syndrome [*15*]. Increased arrhythmogeneity might be the result of the sympathetic excitation plus the baroreflex-mediated enhancement of vagal tone that occur with a hypertensive stressor. This differs from the autonomic state during rest, where there is much less sympathetic outflow, and the vagus may even exert a protective influence. Also, the regional differences in the way the tissue reacts to combined sympathetic and vagal stimulation may functionally become more important when both autonomic branches are considerably active at the same time (during hypertensive stress). This might then explain the increase in the dispersion of repolarization that we surmise on the basis of the observed terminal T-wave changes.

Conclusion

Our study demonstrates that, in Man, with fixed posture, dissociation of heart rate and ventricular depolarization/repolarization exists. Unlike previous work by others [*7*, *12*] our study excludes the possibility that these differences are posture-related artefacts: they occur as a result of different autonomic responses to different stressors. The stimuli of leg lowering and handgrip that we used to manipulate autonomic nervous system activity were natural, and relatively weak. It is, hence, likely that similar or larger autonomic differences will also occur in daily life. Relative prolongation, during handgrip, not only of the QT interval but also of the apex-to-end-T interval in V2 and V3 may signal increased septal dispersion of repolarization, a pro-arrhythmic condition.

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