Hypocapnia reduces the T wave of the electrocardiogram in normal human subjects

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Rutherford, J. J., T. H. Clutton-Brock, and M. J. Parkes. Hypocapnia reduces the T wave of the electrocardiogram in normal human subjects. Am J Physiol Regul Integr Comp Physiol 289: R148–R155, 2005. First published March 10, 2005; doi:10.1152/ajpregu.00085.2005.—During voluntary hyperventilation in unanesthetized humans, hypocapnia causes coronary vasoconstriction and decreased oxygen (O2) supply and availability to the heart. This can induce local epicardial coronary artery spasm in susceptible patients. Its diagnostic potential for detection of early heart disease is unclear. This is because such hypocapnia produces an inconsistent and irreproducible effect on electrocardiogram (ECG) in healthy subjects. To resolve this inconsistency, we have applied two new experimental techniques in normal, healthy subjects to measure the effects of hypocapnia on their ECG: mechanical hyperventilation and averaging of multiple ECG cycles. In 15 normal subjects, we show that hypocapnia (20 ± 1 mmHg) significantly reduced mean T wave amplitude by 0.1 ± 0.0 mV. Hypocapnia also increased mean heart rate by 4 beats/min without significantly altering blood pressure, ionized calcium or potassium levels, or the R wave or other features of the ECG. We therefore provide the first unequivocal demonstration that hypocapnia does consistently reduce T wave amplitude in normal, healthy subjects.

During voluntary hyperventilation in unanesthetized humans, hypocapnia causes coronary vasoconstriction and decreased oxygen (O2) supply and availability to the heart. Thus cardiac catheterization studies show that voluntary hyperventilation [to partial pressure levels of carbon dioxide in arterial blood (PaCO2) of 20 mmHg] increases coronary vascular resistance by 17% (47), decreases coronary blood flow by 30% (47), and increases the affinity of hemoglobin for O2 by 25% (35). During voluntary hyperventilation, hypocapnia can induce local epicardial coronary artery spasm in single or multiple vessels with associated ST displacement, both in susceptible patients with voluntary hyperventilation syndrome (but without symptoms of heart disease) (15, 24) and in the rare group of patients with Prinzmetal’s variant angina (29, 59).

It is unclear whether this effect has any diagnostic potential for early coronary heart disease. This is because numerous studies in healthy subjects report that hypocapnia produces only inconsistent decreases in the amplitude of the ECG T wave that are not reproducible in every subject (5, 6, 8, 16, 20, 22, 30, 49, 54, 58).

Such inconsistency is not surprising because of the methodological difficulties inherent with voluntary hyperventilation in the variability of inflation volumes achieved and of the duration, level, and stability of hypocapnia. Variability in movement of the body surface (and its attached electrodes) relative to the heart with each inflation introduces a crucial artifact that alone might explain this inconsistency. These difficulties are compounded by the lack of a standardized procedure for ECG analysis during hyperventilation. It is unclear precisely how many ECG complexes were measured, how they were selected, and what was their precise relationship to the inflation cycle (6, 16, 58, 60).

We have therefore applied two novel approaches to resolve this issue. First, we used rhythmic mechanical hyperventilation (9). This precisely controls inflation frequency and volume and achieves much lower (e.g., 20 ± 1 mmHg), more stable, and longer periods (e.g., 20 min) of hypocapnia than are achievable with voluntary hyperventilation. Second, we have standardized measurement of the ECG complex by averaging every heart beat in each 2-min experimental period (i.e., at least 100 consecutive heart beats) to obtain a more unbiased and representative measure of all T waves. Using these techniques, we have shown that hypocapnia does consistently and reproducibly decrease the amplitude of the T wave in normal, healthy subjects with no evidence of cardiovascular disease. We have shown, too, that much of the previous inconsistency can be explained by a chest movement artifact.

METHODS

Experiments were performed in the Wellcome Trust Clinical Research Facility at the Queen Elizabeth Hospital, University Hospital Birmingham National Health Service Trust, in accordance with the Declaration of Helsinki, with approval of the Local Ethics Committee, and with informed consent. Fifteen normal, healthy subjects (ages 19–41 yr) with normal ECGs and no known cardiovascular disease were studied.

Where hypocapnia is reported to affect the ECG, most studies have used limb leads and found representative changes when recorded from lead positions I-III (5, 6, 8, 16, 20, 49, 54). It was not the aim of this study to perform a detailed investigation of regional ischemia, and we placed ECG electrodes in the lead I position. Subjects were semirecumbent and did not move from their chosen position once experiments were started. Blood pressure was recorded using a finger plethysmograph (Finapres 2300). The ECG signal was amplified by 500–2,000 using Neurolog NL840 and NL104 amplifiers [frequency range direct current (DC) – 20 kHz] without filtering or DC couple. The ECG signal was sampled at 1,500 Hz and analyzed with Spike2 software (CED). End-tidal Pco2 (PETCO2) was measured by expiration through an in-line capnomograph (Hewlett-Packard 78354A). For experiments in which PCO2 was changed, a cannula was also placed in an antecubital vein to measure blood ionized calcium, potassium, and pH levels using a Rapid Lab 865 analyzer.

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Two minutes of ECG were recorded during spontaneous breathing. Subjects were then connected to a positive pressure ventilator (Engstrom Erica) via a face mask, as described by Cooper et al. (9), having previously been accustomed to mechanical ventilation. Because of its novelty, we expected subjects to remain awake during mechanical ventilation. We did not confirm this by monitoring arousal from electroencephalographic activity or eye movement. Subjects had their eyes open or closed and were not obviously asleep throughout, although we cannot exclude the possibility that when their eyes were closed they might sometimes have drifted in and out of light sleep. 

During rhythmic mechanical hyperventilation, we can choose either to maintain a constant inflation volume and induce hypocapnia by withholding CO2 from the inspirate or to maintain normocapnia (by adding CO2 to the inspired gas) and vary inflation volume systematically.

For measurement of the effects of hypocapnia, subjects were rhythmically and mechanically hyperventilated with air at a constant frequency (16 min	extsuperscript{-1}) and with a constant inflation volume (~1.3 liters), with the precise volume adjusted for each subject to reduce their PETCO2 to 20 mmHg. CO2 was added to maintain normocapnia or withheld to induce hypocapnia. PETCO2 was held at 40 or 20 mmHg for 10 min, and then 2 min of ECG data were recorded. Hyperoxia was induced during hypocapnia by replacing the air with O2, and after 8 min, a further 2 min of ECG data were recorded.

For measurement of the effects of increasing inflation volume in normocapnia, each subject was rhythmically mechanically hyperventilated in air at four inflation volumes (0.8, 1.0, 1.2, and 1.4 liters, or these volumes in reversed order). Inflation volumes <0.8 liter could not be applied because they caused dyspnea. Inflation frequency was constant (16 min	extsuperscript{-1}), and normocapnia was maintained at each inflation volume by addition of CO2 to the inspirate. Two minutes of ECG data were recorded at each inflation volume.

All ECG complexes within each 2-min period were averaged by identifying the peak of each R wave and averaging all waveforms from before each P wave until after the start of the next P wave. T and R wave amplitudes were always measured from the same point on the isoelectric line (the midpoint of the PR segment) with the use of interactive software and are expressed in millivolts.

Statistical analysis. Values are expressed as means with standard errors. Statistical analysis was performed using one-way repeated-measures analysis of variance (ANOVA) with application of the Huynh-Feldt correction for nonsphericity, as described previously (9). Separate ANOVA was applied to the experiments in which inflation volume was changed and to those in which PCO2 was changed.

When PCO2 was changed and three conditions were examined (normocapnia, hypocapnia, and hypocapnia in O2), there were significant F values for T wave amplitude (F = 6.9, P < 0.05), heart rate (F = 5, P < 0.05), pH (F = 55, P < 0.001), and potassium levels (F = 4.6, P < 0.05), but not for R wave amplitude, mean blood pressure, or ionized calcium levels. When inflation volume was changed and five conditions (eupnea and inflation volumes of 0.8, 1.0, 1.2, and 1.4 liters) were examined, there were significant F values within subjects for T wave (F = 9, P < 0.005) and R wave amplitude (F = 15, P < 0.001).

The sources of this significance when PCO2 was changed in two comparisons (normocapnia in air vs. hypocapnia in air, hypocapnia in air vs. hypocapnia in O2) or when inflation volume was changed in four comparisons (eupnea vs. 0.8 liter, 0.8 vs. 1.0 liter, 1.0 vs. 1.2 liters, 1.2 vs. 1.4 liters) were then investigated using Student’s paired t-tests. Correction for multiple comparisons is not applicable because, strictly, we are not considering a repetitive situation and testing whether the universal null hypothesis is true (9, 41). P < 0.05 was considered significant.

RESULTS

In eupnea, averaged mean blood pressure was 101 ± 5 mmHg and heart rate was 67 ± 3 beats/min. During mechanical hyperventilation in normocapnia, mean blood pressure was 105 ± 3 mmHg and heart rate was 61 ± 3 beats/min. Our group has shown previously that volunteers tolerate our mechanical hyperventilation regime well and that mechanical hyperventilation has no consistent effect on mean blood pressure, heart rate, or respiratory sinus arrhythmia (9).

Hypocapnia during rhythmic mechanical hyperventilation at constant inflation volume. Figure 1A shows that hypocapnia (lowering PETCO2 from 40 ± 1 mmHg to 20 ± 1 mmHg) significantly reduced the mean T wave by 0.1 ± 0.03 mV (P < 0.05) compared with normocapnia at the same inflation volume. Figure 2 shows this effect in subject 1. Apart from the T wave reduction, however, there was no other obvious change in the ECG. Figure 1B shows that hypocapnia did not significantly reduce the mean R wave, and there was no relationship between the T and R wave changes in hypocapnia (Fig. 3B).
Figure 4A shows that hypocapnia caused a significant increase in heart rate (4 ± 3 beats/min, P < 0.05) without significantly changing mean blood pressure (Fig. 4B). Hypocapnia had no significant effect on blood ionized calcium or potassium levels (Fig. 5, A and B) and raised venous blood pH from 7.40 ± 0.01 to 7.50 ± 0.01 (P < 0.001).

During hypocapnia, breathing 100% O2 at atmospheric pressure abolished the increase in heart rate (it fell again by 5 ± 3 beats/min, P < 0.01; see Fig. 4A), and mean potassium levels fell by 0.1 mM (P < 0.005; see Fig. 4B). Mean T wave height appears to have increased slightly (Fig. 1A) but remained significantly lower than in normocapnia.

During hypocapnic mechanical hyperventilation, individual ECG cycles were very stable. No T wave inversion, ST segment depression, or QT interval changes were visible in any cycle. During hypocapnia, one subject developed an intermittent nodal rhythm.

Increasing the inflation volume during rhythmic mechanical hyperventilation in normocapnia. To investigate whether increasing inflation volume could explain previous inconsistent effects of voluntary hyperventilation on the ECG, we measured the effects of increasing inflation volume during mechanical hyperventilation while maintaining the Pco2 at the normocapnic (eupneic) levels of 40 ± 1 mmHg. Compared with eupnea, mechanical hyperventilation at 0.8 liter had no effect on either T wave amplitude (Fig. 1A) or the overall ECG pattern. Figure 1A shows, however, that increasing inflation volume in normocapnia decreased mean T wave amplitude. Figure 6 shows that mean T wave decreased linearly by 0.2 mV/l as inflation volume increased from 0.8 to 1.4 liters at constant frequency and Petco2 levels. Figure 7 shows this effect in subject 1. However, individual ECG cycles were very stable when inflation volume was increased during normocapnic and rhythmic mechanical hyperventilation. No T wave inversion, ST segment depression, or QT interval changes were visible in any individual ECG cycles.

The simplest explanation for this effect is that the observed ECG changes as inflation moves the body surface electrodes relative to the heart. Thus, at each inflation volume, the mean T wave over the 2-min period represents the sum of the relatively unchanged deflation T waves and the T waves that decrease as inflation proceeds. Similarly, as inflation volume is increased from 0.8 to 1.4 liters, the deflation T waves remain unchanged but the inflation T waves decrease further, with the net effect being a progressive decrease of the mean T wave averaged over all inflation cycles.

Two factors confirm this interpretation. First, Figs. 1B, 3B, and 7 show similar decreases in the R wave (by 0.3 mV/l). Second, in the three subjects in which inflation produced the largest T wave reduction, we averaged separately the T waves occurring around peak inspiration from those around midexpiration. We measured whether the reduction with inflation persisted for inflation “only” T waves and was less for deflation “only” T waves. Although such separate averaging greatly reduces the number of T waves available, the mean reduction in inflation “only” T waves with increased inflation was the same as that for all T waves, whereas the mean reduction in deflation “only” T waves was much less. We also found that even at 0.8-liter inflation, the mean inflation “only” T wave was 0.03 mV smaller than the mean deflation “only” T wave.

Figure 6 also shows how previous voluntary hyperventilation studies could have observed T wave flattening or inversion in normocapnia. Extrapolation of the linear relationship between the T waves and mechanical inflation volume to the
horizontal intercept predicts that T wave inversion will be achieved at an inflation volume of 5 liters, a volume easily achievable with voluntary hyperventilation.

**DISCUSSION**

Our experiments provide the first unequivocal demonstration that hypocapnia itself does consistently reduce the amplitude of the T wave, when applied with mechanical hyperventilation and when ECG averaging techniques are used. **Mechanical hyperventilation.** Mechanical hyperventilation precisely controls inflation frequency and volume and provides much better conditions than voluntary hyperventilation for studying the effects of both hypocapnia and inflation volume on the ECG. Not only does it reduce the between breath variability during rhythmic chest inflation, but it also uses smaller increases in frequency and volume to achieve lower and more stable PaCO₂ levels. Indeed, the whole process is much more reproducible than with voluntary hyperventilation. Furthermore, whereas the act of voluntary hyperventilation increases metabolic rate, which opposes inducing hypocapnia, mechanical hyperventilation reduces metabolic rate and hence facilitates inducing hypocapnia.

Although healthy, unanesthetized, and awake subjects are not normally mechanically hyperventilated, this is well tolerated after familiarization (9, 11) and has not apparently been used previously to study ECG. Our subjects were relaxed, maintained a constant posture, made no other skeletal movements, and breathed with the ventilator (9). Their averaged mean blood pressure and heart rate during mechanical ventilation or hyperventilation were not consistently different from those in eupnea (9), as we have confirmed in the present study. We have shown, too, that mechanical ventilation in normocapnia has no detectable ECG with that effect (compare the ECG during eupnea) in normocapnia when an inflation volume of 0.8 liter is used.

**Electrolyte and cardiovascular changes during hypocapnia.** All subjects were mechanically hyperventilated to a PETCO₂ of 20 mmHg. This is the lowest hypocapnia that can normally be applied without inducing paresthesia (28). Subjects reported mild paresthesia only occasionally, and none had carpopedal spams. We maintained hypocapnia at 20 mmHg for at least 16 min in every subject and, therefore, lower and for longer than in any voluntary hyperventilation study.

We have confirmed and extended previous studies showing that hypocapnia has no effect on averaged mean blood pressure (9, 11, 23, 35, 42, 43, 53) or on blood ionized calcium or potassium levels (6). Whereas early studies suggested that hypocapnic voluntary hyperventilation might cause hypocalcemia, modern analysis techniques show that such hypocapnia produces either no hypocalcemia (6, 32, 48) or too small a reduction to explain adequately any ECG changes, paresthesia, or tetany (14, 52).

It is not clear from voluntary hyperventilation studies whether hypocapnia increases heart rate, because voluntary hyperventilation itself can increase heart rate in normocapnia by 7–90 beats/min (8, 19, 20, 56). We have shown that mechanically induced hypocapnia at 20 mmHg increases heart rate by 4 beats/min and does so without significantly affecting...
blood pressure. Because this increase in heart rate was absent during hypocapnia when subjects breathed O\textsubscript{2} [as we reported previously (9)], it appears to be caused by a reduced availability of O\textsubscript{2} rather than by withdrawal of any CO\textsubscript{2}-dependent tonic drive (50) or by the pH increase directly affecting the sinoatrial or atrioventricular nodes (1, 38).

This increase in heart rate resembles the chemoreflex increase in heart rate of \( \sim 8 \) beats/min (occurring also without a pressure rise) seen when unanesthetized humans breathe hypoxic gas mixtures (of 13\% or lower) in hypo- or isocapnia (18, 27, 44). In humans this chemoreflex is unaffected by carotid body denervation (18, 27) and, hence, may involve aortic and or pulmonary chemoreceptors (13). Aortic chemoreceptors are stimulated by decreases in O\textsubscript{2} availability at constant Pa\textsubscript{O\textsubscript{2}} (25), and their stimulation increases heart rate (21). Thus, in hypocapnia, aortic chemoreceptors could be stimulated by the reduced O\textsubscript{2} availability to cause a heart rate increase (12).

**Hypocapnia reduces the T wave during constant rhythmic mechanical hyperventilation.** Mechanically induced hypocapnia to 20 mmHg significantly reduced the mean T wave (by 0.1 \pm 0.0 mV). Reductions of 0.1 mV are considered to be of clinical importance (7), and a similar reduction occurs during hypocapnic mechanical hyperventilation under anesthesia (42).

This reduction cannot be an artifact of either mechanical ventilation itself or chest inflation (because chest inflation was the same in both normocapnia and hypocapnia), cannot be a time-dependent effect (because the order of the experiments was varied), and cannot be due to analysis biased by selection of single ECG cycles (because all ECG cycles were averaged). Hypocapnia caused this reduction, because it was absent during mechanical hyperventilation in normocapnia. This contrasts with the ECG changes seen during voluntary hyperventilation, which were sometimes abolished by 5\% CO\textsubscript{2} (5, 8, 16, 60) and sometimes not (6, 16, 49, 58, 60). Furthermore, our reduction was detected after 10 min of hypocapnia, whereas measurements during voluntary hyperventilation are sometimes made after only 60 s or less and without Pa\textsubscript{CO\textsubscript{2}} measurement (22, 26, 31, 58). This reduction occurred in 13 of 15 normal subjects and is therefore much more reproducible than any effect during voluntary hyperventilation (16, 20, 22, 58).

Our results also help to reveal the mechanisms by which hypocapnia reduces the T wave under these conditions. We can rule out any T wave reduction caused by hypocapnia changing the position of the heart in the chest following hypocapnic dilation (4) in the pulmonary vascular bed [hypocapnia to 30 mmHg increases pulmonary conductance 3-fold (45)], because a similar reduction would be expected in the R wave but was not observed (Figs. 1B and 4B). The T wave reduction also cannot be explained by changes in blood ionized calcium or potassium levels (6, 55), because these were absent (although we cannot exclude the possibility that hypocapnia has more subtle effects on intracardiac pump or channel kinetics for potassium or other ions). Strictly, we cannot distinguish whether the T wave reduction is caused by the decreased Pco\textsubscript{2} or the increased pH, and there is little published information available on the effects of increasing pH. Most studies appear to have examined only the effect on the ECG of decreasing pH (1, 38), rather than that of increasing it. There was no detectable change in atrioventricular conduction that might explain our results. Thus, although the shape of the chest surface T wave is believed to be governed by the relative timing of repolarization in each ventricle (1, 17, 36, 38, 57), no QT interval changes were apparent. Neither could the small increase in heart rate during hypocapnia have caused the T wave reduction, because we have shown that although breathing...
100% O₂ in hypocapnia abolished the increase in heart rate, the T wave reduction persisted.

Therefore, a more likely mechanism to explain hypocapnia reducing the T wave is as a result of the known effects of hypocapnia reducing O₂ availability to the heart muscle by causing both coronary vasoconstriction and reducing the release of O₂ from hemoglobin (35, 47). The conclusion of reduced O₂ availability is supported by the small heart rate rise during hypocapnia that was abolished by giving O₂ in hypocapnia. This reduced oxygen availability may be sufficient to alter myocardial contractility and ventricular repolarization (46) and, hence, reduce T wave amplitude. The fact that giving O₂ during hypocapnia failed to reverse the T wave reduction is itself inconclusive, because breathing O₂ only at atmospheric pressure could not completely counteract the reduced O₂ availability in hypocapnia.

The occurrence of hypocapnic coronary vasoconstriction is supported by the extensive literature describing the effects of hypocapnia (caused by voluntary hyperventilation) in the rare patients with Prinzmetal’s variant angina. In such cases, hypocapnia (PaCO₂ levels of ~20 mmHg) causes angiographically confirmed constriction or spasm in single or multiple coronary arteries (37, 59), with the effect prevented by voluntarily hyperventilating with a raised PCO₂ (3).

There is at present, however, no more direct evidence to establish that the T wave reduction is caused by hypocapnia reducing O₂ availability within the heart. Now that we have demonstrated how to apply hypocapnia to produce reproducible ECG changes in healthy subjects, it would be feasible to establish this with a combination of a full 12-lead ECG analysis to identify any T wave vector changes, with other measures of cardiac function and more direct measurements of coronary blood flow and O₂ availability.

Increased chest inflation reduces both T and R wave amplitudes in normocapnia. Even in normal healthy subjects, the amplitude of the T wave varies during eupnea (2). Using complex demodulation techniques to analyze T wave alternans in alternate beats (51), Nearing et al. (33, 34) found a 16 ± 2 μV beat-to-beat T wave variation in normal subjects, increasing to 37 ± 5 μV during treadmill exercise. Our averaging technique is fundamentally different from the alternans technique because it tends to average out such beat-to-beat differences, but we still found that the standard error of the mean for each subject’s T waves during eupnea was ~2 μV. The advantage of averaging all ECG cycles in a 2-min period (i.e., at least 100 consecutive heart beats) is that we obtain a much more representative measure of all cardiac cycles and eliminate the inevitable bias introduced when a few beats are arbitrarily selected.

The causes of such T wave variability when recording with chest surface ECG electrodes are complex (33, 51). One obvious contribution will be from a change in the relation of the body surface (and its attached electrodes) relative to the heart with each inflation. Even with the smallest inflation volumes used (0.8 liter), we still found that the T wave was 32 μV smaller during inflation than during deflation when inflation and deflation were averaged separately. This effect would not normally be noticeable by visually inspecting ECG records during eupnea, especially when using amplifiers with DC
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coupling that filter out low-frequency components of the ECG signal.

We have shown, however, that as we imposed a positional change, by systematically increasing inflation to 1.4 liters, the T wave reduced by 0.2 mV/l while PCO2 remained constant. The R wave also reduced [confirming and extending previous reports of voluntary hyperventilation sometimes reducing the R wave (8, 49)], and the T and R wave reductions appear to be proportionate. Furthermore, linear extrapolation predicts that the T wave in normocapnia would invert at an inflation volume of 5 liters, i.e., near vital capacity.

It is not surprising, therefore, that during voluntary hyperventilation and even in normocapnia, the occasional maximal lung inflation (perhaps combined with a change in posture that additionally rotates the heart within the chest) will result in T wave flattening or inversion in single cardiac cycles even in normocapnic subjects with perfectly normal hearts. Because previous studies of the ECG during voluntary hyperventilation do not indicate either how many ECG cycles were used for T wave measurement [even more recent studies (6, 16) indicate that only a maximum of ~5 consecutive cardiac cycles were used] or why particular ECG cycles were chosen for consideration, inadvertent selection of ECG cycles coinciding with maximal inflation could produce misleading results. Such inadvertent selection might also explain some of the reports of flattened or inverted T waves in patients with voluntary hyperventilation syndrome (10, 60), some of the false positive ECG responses to exercise tests (19, 26, 31), and some of the occasional and irreproducible T wave changes seen even in the resting ECG of otherwise healthy and symptomless subjects.

In conclusion, we have described the precise conditions under which hyperventilation reduces T wave amplitude in the limb lead ECG. Some of the effects appear to be present only if the inflation is combined with a change in posture of the head (and thus of the heart) in the thoracic cavity, and an increase in PCO2 of about 6 mm Hg. Asphyxia, hypoxia, isoproterenol infusion, and angina pectoris reduce T wave amplitude, and the response of T wave to PCO2 is even more sensitive in patients with these conditions. Further studies are clearly needed to determine the mechanisms underlying these changes in T wave amplitude and the clinical significance of the asphyxiated T wave response. It is also important to recognize that T wave changes can occur in the absence of hypoxia or acidosis, and therefore should not be interpreted as evidence of myocardial ischemia unless there are other clinical and laboratory signs of myocardial injury.

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