RESEARCH PAPER

The effect of changes in core body temperature on the QT interval in beagle dogs: a previously ignored phenomenon, with a method for correction

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Background and purpose: Body core temperature (Tc) changes affect the QT interval, but correction for this has not been systematically investigated. It may be important to correct QT intervals for drug-induced changes in Tc.

Experimental approach: Anaesthetized beagle dogs were artificially cooled (34.2 ± 0.1°C) or warmed (42.1 ± 0.1°C). The relationship between corrected QT intervals (QTcV; QT interval corrected according to the Van de Water formula) and Tc was analysed. This relationship was also examined in conscious dogs where Tc was increased by exercise.

Key results: When QTcV intervals were plotted against changes in Tc, linear correlations were observed in all individual dogs. The slopes did not significantly differ between cooling (−14.85 ± 2.08°C) or heating (−13.12 ± 3.46°C) protocols. We propose a correction formula to compensate for the influence of Tc changes and standardize the QTcV duration to 37.5 ± 0.1°C: QTcVcT (QTcV corrected for changes in core temperature) = QTcV − 14 (37.5 − Tc). Furthermore, cooled dogs were re-warmed (from 34.2 to 40.0 ± 0.1°C) and marked QTcV shortening (−29%) was induced. After Tc correction, using the above formula, this decrease was abolished. In these re-warmed dogs, we observed significant increases in T-wave amplitude and in serum [K+] levels. No arrhythmias or increase in pro-arrhythmic biomarkers were observed. In exercising dogs, the above formula completely compensated QTcV for the temperature increase.

Conclusions and implications: This study shows the importance of correcting QTcV intervals for changes in Tc, to avoid misleading interpretations of apparent QTcV interval changes. We recommend that all ICH S7A, conscious animal safety studies should routinely measure core body temperature and correct QTcV appropriately, if body temperature and heart rate changes are observed.

Keywords: hyperthermia; hypothermia; QT interval; dog; correction formula; hyperkalaemia; hypokalaemia; drug-induced temperature changes

Abbreviations: ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; QTcV, QT interval corrected according to the Van de Water formula; QTcVcT, QTcV corrected for changes in core temperature

Introduction

The QT interval of the ECG is an indirect measurement of the time taken for the ventricles to depolarize and repolarize. Assessment of the QT interval is of clinical importance because prolongation of repolarization is often associated with conditions such as electrical instability and sudden cardiac death (Algra et al., 1991), but can also be indicative of the pro-arrhythmic activity for new chemical entities (De Clerck et al., 2002). As the QT interval is dependent on the length of the cardiac cycle, this interval has to be corrected for changes in heart rate (HR) (Fridericia, 1920; Van De Water et al., 1989). In addition to HR, changes in core temperature (Tc) can also influence the ventricular repolarization time (Alhaddad et al., 2000). However, Tc is rarely measured in Good Laboratory Practice safety studies, even though most radio-telemetry devices used in such studies have a temperature measurement function, and a method for correcting this phenomenon is currently lacking. Tc is normally maintained within narrow well-defined limits, but under certain circumstances, it can be increased, for example, by pharmacological agents (White and Simpson, 1984; Nimmo et al., 1993; serotonin syndrome, see...
www.fda.gov/cder/drug/advisory/SSRI_SS200607.htm), by fever or by malignant hyperthermia, and can be decreased, for example, during surgery, postoperative recovery and illness. If the QTc interval is used to diagnose prolongation of repolarization during hypo- or hyperthermic situations within drug safety evaluations, then the sole use of a standard QT correction formula may be inadequate and thus misleading. Over-correction or under-correction may lead to artificial results, when body temperature is changed. Although the underlying mechanisms of QT interval changes associated with hypo- and hyperthermia are not fully understood, it is known that serum potassium concentrations can increase during hyperthermia in different species (Spurr and Barlow, 1959; Sprung et al., 1991), and during malignant hyperthermia in humans (Wappler et al., 2000). However, what role these electrolyte alterations have on cardiac repolarization during temperature change is also unknown, as action potential durations are also increased in in vitro studies—using tissue from guinea-pigs (Lathrop et al., 1998), rabbits (unpublished data) and pigs (Roscher et al., 2001), where electrolyte levels are controlled through perfusion of physiological salt solutions. The aim of the present study was to explore the changes of QT interval (QTcV interval; QT interval corrected according to the Van de Water formula), under controlled hypothermic and hyperthermic conditions in anaesthetized dogs, and to propose a mathematical formula to correct the QTcV interval for changes in body temperature. The formula was tested in the same group of dogs, to mimic clinical situations, such as re-warming (analogous to procedures for postoperative or cooled patients) and re-cooling (procedures for heat stroke or fever). Furthermore, we have challenged this formula during exercise tests in conscious telemetered beagle dogs and during malignant hyperthermia in humans (Wappler et al., 2000). However, what role these electrolyte alterations have on cardiac repolarization during exercise tests is also unknown, as action potential durations are also increased in in vitro studies—using tissue from guinea-pigs (Lathrop et al., 1998), rabbits (unpublished data) and pigs (Roscher et al., 2001), where electrolyte levels are controlled through perfusion of physiological salt solutions. The aim of the present study was to explore the changes of QT interval (QTcV interval; QT interval corrected according to the Van de Water formula), under controlled hypothermic and hyperthermic conditions in anaesthetized dogs, and to propose a mathematical formula to correct the QTcV interval for changes in body temperature. The formula was tested in the same group of dogs, to mimic clinical situations, such as re-warming (analogous to procedures for postoperative or cooled patients) and re-cooling (procedures for heat stroke or fever). Furthermore, we have challenged this formula during exercise tests in conscious telemetered beagle dogs, as exercise also increases body temperature (Febbraio et al., 1996) and none of the existing formulae correct the QT interval properly during exercise (Aytemir et al., 1999; Benatar and Decraene, 2001; Newbold et al., 2007). The applicability of the formula in dogs and humans under different circumstances was further investigated by a review of published data.

Methods

This investigation was conducted in accordance with ‘the provision of the European Convention’ on the protection of vertebrate animals, which are used for experimental and other scientific purposes, and with ‘the Appendices A and B’, made at Strasbourg on 18 March 1986 (Belgian Act of 18 October 1991).

Animals

Sixteen adult beagle dogs (eight males and eight females) were used in this study, their body weight averaging 11.9 kg (range: 9.8–13.8 kg) and their age averaging 12 months (range: 10–17 months). All dogs were examined before use and found to be healthy and active. Food (but not water) was withheld for at least 12 h prior to anaesthesia and cardiovascular experimentation.

Anaesthesia and measured parameters

Briefly, under total intravenous anaesthesia induced by 0.075 mg kg$^{-1}$ lofentanil, 0.0015 mg kg$^{-1}$ scopolamine (Janssen Pharmaceutica, Johnson & Johnson Pharmaceutical R&D (J&J PRD), Beerse, Belgium) and 1.0 mg kg$^{-1}$ succinylcholine (Myoplegine; Christiaens NV, Brussels, Belgium) and maintained by infusion of etomidate 1.5 mg kg$^{-1}$ h$^{-1}$ (J&J PRD), dogs were ventilated with 30% oxygen in pressurized air to normocapnia (PaCO$_2$ between 30 and 50 mm Hg). The ECG (ECG lead II limb leads; Emka, Paris, France) was continuously monitored (sampling frequency, 1000 Hz) and an open lumen catheter was placed into the femoral artery and positioned close to the heart to obtain blood samples for blood gas analysis (ABL700; Radiometer, Brønshøj, Denmark), to monitor stability of the preparation over the course of the experiment.

Heart rate (b.p.m.) was calculated from the pressure signal and the QT interval (measured from the onset of the QRS to the end of the T wave; ms) was taken from the lead II ECG, from which the T-wave morphology was also examined. Furthermore, the QT intervals were corrected for changes in HR according to the Van de Water formula (QTcV; ms, Van de Water et al., 1989). Body Tc (°C) was measured continuously from within the right ventricle of the heart and all signals and parameters were automatically analysed (Notocord-Hem 3.3; Croissy, France) and represented in an Excel file as median values over 1 min.

Study protocol

Eight dogs (five males and three females) were observed during controlled changes of Tc and were divided into two subgroups to investigate a decrease and an increase in Tc. Four dogs were cooled to 34 °C by a blanket of ice and a cold air fan, and another group of four dogs was warmed to 42 °C using a heating plate in combination with a heating lamp. At the end of the study, the results from each group were pooled, to achieve data over a range of temperatures, from normothermia to hypothermia (from 37.5 to 34 °C), and from normothermia to hyperthermia (from 37.5 to 42 °C). Both groups were compared with a set of eight control dogs (three males and five females), evaluated with a constant Tc of approximately 37.5 °C over the same time period. The cooled dogs were thereafter slowly re-warmed to 40 °C by a heating plate in combination with a heating lamp and the heated dogs were slowly re-cooled to 37 °C by turning off all heating equipment. During the re-warming and re-cooling procedures, special attention was given to T-wave morphology, and arterial blood samples were obtained every 15 min in both groups to determine the plasma concentration of potassium.

Calculation of the correction formula

To calculate the temperature correction formula, we plotted the QTcV intervals against Tc (median value of every minute) of all individual cooled (from 37.7 to 34.2 °C) and heated (from 37.3 to 42.1 °C) dogs. As the relationship between the parameters appeared to be linear (Figure 1a) for both groups, and the $R^2$ for a linear relationship was highly significant in all dogs (Table 2), the mean slope of the linear relationship of both parameters in all dogs was used to derive the formula. To validate the formula, we corrected the QTcV intervals for
correlation over all dogs (slope heated (closed circles). Regression analysis showed a good linear
\( QTcVcT \) of all individual dogs (n (264

The changes in Tc (\( QTcVcT \)) were calculated. In addition, we conducted a
literature survey to investigate published changes in Tc and QTc in dogs and man. To achieve comparable slopes we
we correced the QT interval, where necessary, in the dog studies
by the de Van de Water formula, and by the Fridericia
formula in human studies.

Statistical analysis
Pooled data were expressed as mean ± standard deviation. Intergroup comparisons were made with ANOVA Dunnett’s
test on repeated measures (WINKS SDA Software, Cedar Hill,
USA). Comparisons within a group were made with a paired t-test (Microsoft Excel 2000). Linear regression and correlation
analysis were made using Pearson’s correlation coeffi-
cient (WINKS SDA Software, Cedar Hill, USA). A two-tailed
\( P<0.05 \) was considered statistically significant.

Results
In this study, we used two groups of dogs, eight dogs that
were cooled (n = 4) or heated (n = 4) and eight dogs, which
were kept at basal Tc, as a time control group. There were no
notable differences between both treated and control groups
in gender (male/female = 5/3 versus 3/5, respectively), body
weight (11.7 ± 1.4 versus 11.9 ± 1.0 kg, respectively), age
(12 ± 2 versus 12 ± 1 months, respectively), basal Tc
(37.5 ± 1.3 versus 37.8 ± 1.2°C, respectively), basal HR
(88 ± 33 versus 72 ± 13 b.p.m., respectively), basal QT
(240 ± 19 versus 257 ± 22 ms, respectively) and basalQTcV
(264 ± 4 versus 261 ± 18 ms, respectively).

In the pooled averaged data (Table 1) from the cooled
dogs, the decrease of Tc (\( P = 0.003 \)) within 63 ± 13 min
induced a decrease in HR (\( P = 0.014 \)), prolongation of QT
interval (\( P = 0.007 \)) and QTcV interval (\( P = 0.002 \). Table 1
also shows that in pooled averaged data from the heated
dogs, the increase of Tc (\( P = 0.004 \)) induced an inconsistent
increase in HR (\( P = 0.137 \)), but a clear shortening of QT
(\( P = 0.005 \)) and QTcV intervals (\( P = 0.006 \). Neither the
prolongation of QTcV on cooling nor the shortening on
warming were associated with arrhythmias or pro-arrhythmic
biomarkers, such as extrasystoles, early after depolarisations
or enhanced J waves (data not shown). The values of Tc, QT
and QTcV of the treated dogs were significantly different
from the control group over the same time frame. During
this time course, no significantly different changes of Tc, HR,
QT or QTcV from baseline (time = 0) were evident in the
control group (Table 1).

To investigate the relationship between the duration of the
QTcV interval and the Tc, the slope and the correlation
coefficient (\( R^2 \)) of the relationship between QTcV interval
and Tc, of all individual dogs (cooled and heated), were
examined (Table 2). Over the range of temperatures exam-
in (34.2–42.1°C), the relation between QTcV and Tc
appeared to be linear (Figure 1a); therefore, linear regression
was therefore used. No significant difference (\( P = 0.242 \)) was
observed between the slopes in the two procedures: cooling
the dogs resulted in a slope of \(-14.85 ± 2.08 \) with an \( R^2 \) of

Validation of the correction formula
To validate and check the applicability of the correction
formula, it was used in the same dogs after re-warming and
re-cooling. Furthermore, we checked the formula in freely
moving telemetered beagle dogs before and after an exercise
test. In this study, 36 female dogs were telemetered (ITS
(International Telemetry Systems, Dexter, MI, USA) T27F-11)
to measure ECG and Tc, at rest and during a speed-increasing
protocol of 40 min (from walking to running against
15 km h\(^{-1}\)) on a roller band treadmill. During the study, Tc,
HR and QT were monitored and after the study QTcV and
QTcVcT were calculated. In addition, we conducted a
literature survey to investigate published changes in Tc and QTc in dogs and man. To achieve comparable slopes we
we corrected the QT interval, where necessary, in the dog studies
by the de Van de Water formula, and by the Fridericia
formula in human studies.
0.90 ± 0.01 and heating the dogs resulted in a slope of −13.12 ± 3.46 with an R² of 0.97 ± 0.01. This gave an average slope for cooling and heating of −14.0, that is, a decrease or increase in Tc of 1 °C induced an increase or decrease in the QTcV interval of 14 ms.

Table 1  Core body temperature (Tc), heart rate (HR), QT interval (QT) and QTcV interval (QTcV) in cooled dogs (n = 4), heated dogs (n = 4) and control dogs (n = 8)

| Time (min) | Tc (°C) | HR (b.p.m.) | QT (ms) | QTcV (ms) |
|------------|---------|-------------|---------|-----------|
| Cooled     |         |             |         |           |
| 0          | 37.7 ± 0.8 | 96 ± 24 | 241 ± 12 | 269 ± 9 |
| 63 ± 13    | 34.2 ± 0.3 | 61 ± 13 | 323 ± 35 | 321 ± 19 |
| Heated     |         |             |         |           |
| 0          | 37.3 ± 1.0 | 80 ± 24 | 239 ± 13 | 259 ± 9 |
| 148 ± 41   | 42.1 ± 0.8 | 132 ± 71 | 171 ± 27 | 208 ± 11 |
| Control    |         |             |         |           |
| 0          | 37.5 ± 0.9 | 71 ± 11 | 256 ± 17 | 262 ± 20 |
| 60         | 37.6 ± 1.1 | 76 ± 12 | 252 ± 18 | 265 ± 10 |
| 150        | 37.5 ± 0.9 | 71 ± 11 | 256 ± 17 | 262 ± 20 |

Values are expressed as mean ± s.d.
Comparisons within a group: p-value < 0.05; t-test (two sided, paired).
Intergroup comparisons: p-value < 0.05; ANOVA/Dunnett’s test (two sided, unpaired).

Table 2  ΔTc, ΔQTcV, slopes and R² values of all individual dogs; cooled (n = 4) and heated (n = 4)

| Dog | Gender | ΔTc (°C) | ΔQTcV (ms) | Slope | R²  |
|-----|--------|----------|------------|-------|-----|
| C   |         |          |            |       |     |
| 1   | Male   | −3.2     | + 66       | −16.33 | 0.91|
| 2   | Male   | −2.5     | + 56       | −16.53 | 0.90|
| 3   | Male   | −3.8     | + 49       | −14.47 | 0.89|
| 4   | Female | −4.2     | + 40       | −12.06 | 0.88|
| H   |         |          |            |       |     |
| 5   | Male   | + 6.5    | −65        | −9.71  | 0.95|
| 6   | Female | + 4.8    | −34        | −17.11 | 0.96|
| 7   | Male   | + 3.8    | −45        | −10.82 | 0.97|
| 8   | Female | + 4.4    | −61        | −14.85 | 0.98|

To correct the duration of the QTcV interval for changes in Tc to a temperature of 37.5 °C (normal body temperature in conscious telemetered dogs), the following formula was derived:

\[ \text{QTcV}_{\text{C}} = \text{QTcV} - 14(37.5 - \text{Tc}) \]

Plotting QTcV values against Tc (Figure 1b) produced a horizontal regression line with a slope of −0.06 and without any correlation (R² = 0.0001, P = 0.758).

The four cooled dogs were re-warmed (from 34 to 40 °C; Table 3, rows A) and showed not only a clear decrease in QT interval (P < 0.002) and QTcV (P < 0.002) without significant changes in HR (P = 0.684) or QTcV (P = 0.326), but we observed an increase of the small T wave in the cooled dog to a tall, narrow based, peaked and symmetrical (‘tented’) T wave (see Webster et al., 2002) at a high Tc (from 0.09 ± 0.08 to 0.52 ± 0.21 mV, P = 0.024; Figure 2). Furthermore, an increase in serum potassium concentrations (from 3.1 ± 0.3 to 4.3 ± 0.2 mmol L⁻¹, P = 0.004) was noted throughout this temperature range. The slope and the correlation coefficient (R²) of the linear relationship (P < 0.001) between QTcV time and Tc of pooled data in this group are shown in Figure 3a.

The four heated dogs were then cooled (Table 3, rows B), but now showed inconsistent changes in QT interval (P = 0.141) and QTcV (P = 0.071), and the increased HR (P = 0.770) did not return to normothermic baseline values. Furthermore, the increased serum potassium concentrations did not return to baseline values (P = 0.724), only the T-wave amplitude was slightly decreased (P = 0.269). The slope and the correlation coefficient (R²) of the relationship between QTcV time and Tc of pooled data in this group after re-cooling from 42 °C were now much lower (Figure 3b). Indeed, after re-cooling these four warmed dogs to normal Tc, two of them showed a further increase in serum potassium concentration (from 4.9 and 4.7 to 6.7 and 5.1 mmol L⁻¹, respectively), and QTcV did not return to baseline values (from 206 and 208 ms to 205 and 239 ms; slopes: −1.31 and −0.02 and R²; 0.4 and 0.15, respectively). The other two dogs showed only partial decreases in serum potassium concentrations (from 5.3 and 4.4 mmol L⁻¹ to 4.6 and 3.8 mmol L⁻¹, respectively)
In the normothermic control group, as expected, no significant changes were measured in HR, QT, QTcV, etc., during a constant Tc of 37.7 to 37.5°C over the same time period as the cooling and warming experiments reported above (Table 3, rows C). In addition, experiments with atrially paced normothermic dogs showed that QTcV was not significantly altered at rates up to 120 b.p.m. (unpublished data).

In freely moving telemetered dogs (Table 4), the exercise procedure (from walking to running over 40 min) induced a small increase in Tc ($P<0.05$) and HR ($P<0.05$), and a decrease in QT ($P<0.05$). The rate-correcting formula by Van de Water did not fully correct for HR: exercise induced a decrease in QTcV ($P<0.05$) and showed a slope of $-15.7$. Using our Tc correction formula, we calculated a fully HR- and body temperature-independent parameter, QTcVcT of 244 ± 11 ms ($P=0.824$).

Estimated slopes of changes in Tc and QTc in dogs and humans, extracted from already published data showed similar results compared to our own data (Table 5). Cooling, heating, re-warming or fever induced changes in Tc, but all studies showed after calculation (ΔQTc/ΔTc) an estimated slope between −11.0 and −17.1.

### Table 4

| Tc (°C) | HR (b.p.m.) | QT (ms) | QTcV (ms) | QTcVcT (ms) |
|---------|-------------|---------|-----------|-------------|
| Rest    | 37.6 ± 0.6  | 109 ± 23| 206 ± 16  | 244 ± 14    |
| Exercise| 38.3 ± 0.8  | 152 ± 22| 181 ± 14  | 233 ± 10    |

Values are expressed as mean ± s.d.

Table 4 Core temperature (Tc), heart rate (HR), QT interval (QT) and QTcV interval (QTcV), temperature corrected QTcV (QTcVcT), in freely moving telemetered beagle dogs ($n=36$) at rest and after exercise.

$P$-value $<0.05$; *t*-test (two sided, paired).

**Discussion and conclusions**

In this study, we were able to cool the Tc of anaesthetized dogs to 34.2°C (hypothermic conditions), and to warm the Tc to 42.1°C (hyperthermic conditions) with only minor changes in HR. Hypothermia prolonged the QT interval and conversely, hyperthermia shortened the QT interval, both without obvious pro-arrhythmic signs. The reliable Van de Water formula (King et al., 2006), often used in dog studies, did not properly correct these large changes in QT intervals. The prolongation of the QT interval in hypothermic conditions has been previously described before in dogs (Beyda et al., 1960) and humans (Mattu et al., 2002; Aslam et al., 2006), but the shortening of the QT interval in hyperthermic conditions has been poorly studied (Geller et al., 1952). The relationship between QTcV and Tc over the temperature range investigated, cooling (from 37.7 to 34.2°C) and heating (from 37.3 to 42.1°C) in this study was linear for all individual dogs ($R^2$ between 0.88 and 0.98), and a slope was calculated, showing an average decrease of 14 ms per degree change. The correction formula for the Tc was calculated and validated for different circumstances (re-warming, re-cooling and exercise), for different models.
re-warmed Human 31.7–35.8 250–460
Cooled Infant 37.0–30.0 388–508
Fever Human 37.2–39.4 388–508
Re-warmed Human 25.6–30.7 609–522
Cooled Human 36.0–29.0 460–570

are probably caused by the very high body temperatures
through perfused physiological salt solutions. (Roscher
et al., 2002). Other investigators have noted that enhancement of
amplitude and induces QT prolongation (Slovis and Jenkins,
1987; Lathrop et al., 1998), rabbits
in vitro
in
anaesthetized and telemetered dogs) and from cases in the
literature (dogs and humans).

The mechanisms of temperature change on the ECG in
general, and on the QT interval in particular, are almost
certainly multi-factorial. Metabolic rate varies with body
temperature in both homeothersms and poikilotherms, and
affects most bodily processes. Biologists are familiar with
the marked changes in contractility and spontaneous activity in
isolated organs produced by different bath temperatures (for
example, Smith et al., 1951). However, under such conditions
in vitro, extracellular ionic concentrations are constant.
In whole animals, however, other factors may also be
involved. It has been reported that hypothermia is accom-
panied by hypokalaemia, a shift of potassium from extra-
cellular to intracellular or extra-vascular spaces (Koht et al.,
1983). Hypokalaemia causes a decrease in the resting
membrane potential in ventricular cells, reduces the T-wave
amplitude and induces QT prolongation (Slovis and Jenkins,
2002). Other investigators have noted that enhancement of
the body temperature, induced by exercise-dependent
malignant hyperthermia (Wappler et al., 2000), or by
artificially induced hyperthermia in dogs (Spurr and Barlow,
1959), can lead to an increase in serum potassium concen-
trations. Hyperkalaemic states have an effect on the ECG, and
the early signs are tall, narrow based, peaked and
symmetric T waves (so called 'tented' T waves), and the QT
interval is decreased (Webster et al., 2002). In our study, we
found increases in Tc to be associated with increases in
T-wave amplitudes and in serum potassium concentration in
re-warmed dogs. As such, changes in serum potassium
concentrations could be considered to contribute towards
the effects on QTcV reported here. However, it is important
to note that the changes in serum potassium concentrations
do not affect the QTcV/Tc slope in our anaesthetized dogs,
and the proposed formula fully corrected the QTcV interval
for the increase in Tc. Indeed, action potential durations have
also been shown to be markedly altered in vitro in
guinea-pigs (Duker et al., 1987; Lathrop et al., 1998), rabbits
(unpublished data from Langendorff hearts) and pigs
(Roscher et al., 2001), where electrolyte levels are controlled
through perfused physiological salt solutions.

The small slopes and lack of linearity between Tc and QTc
in dogs warmed to over 42°C and then re-cooled to 36.8°C
are probably caused by the very high body temperatures
induced in these dogs. Indeed, it was noted that when the
body temperature was raised to over 42°C, the return to
normothermia was associated with lower QT intervals, and
higher HRs, serum potassium concentration and T waves in
these dogs. The critical thermal maximum (CTM) in dogs is
between 43.0 and 44.5°C, and in heatstroke models dogs die
after CTM has been reached for a longer period (Bynum et al.,
1977), so these temperatures are by themselves pathological.
In our study, four dogs were increased to a Tc close to the
CTM. During re-cooling to normal Tc, two of them showed
only a partial decrease in serum potassium concentrations,
and QTcV did not fully increase to baseline values. The other
two dogs showed a further increase in serum potassium
concentrations, and the increases in QTcV were even smaller
than those seen in the two dogs whose potassium concen-
trations decreased.

It should be emphasized that these apparently pathologi-
cal influences of high temperature on serum potassium
concentrations and on QTcV intervals (Table 3 (rows B) and
Figure 3b) were obtained subsequent to the data shown in
Tables 1 and 2, which were used to derive the proposed
correction factor.

As mentioned above, the effects of drug-induced tempera-
ture changes on QT (QTc) have been poorly studied, and to
our knowledge, have not been systematically examined
within cardiovascular safety studies. However, there are
many existing drugs that are known to affect body
temperature. Indeed, it can easily appear to prolong QTc interval, simply by a
decrease in body temperature. Conversely, the effects of a
new chemical entity, with a direct blocking effect on IKr
(HERG) can easily appear to prolong QTc interval, simply by a
decrease in body temperature. Therefore, any drug that affects
Tc can be expected to have temperature effects on QTc (~14 ms per degree) whether or not
the drug has actual direct effects on cardiac repolarization. Thus in a CV safety
study, a new chemical entity with no effect on IKr (HERG) can easily appear to prolong QTc interval, simply by a
decrease in body temperature. Conversely, the effects of a
new chemical entity, with a direct blocking effect on IKr
could be masked by the shortening of QTcV intervals resulting
from an increase in body temperature.
Drugs may also affect locomotor activity, which itself can affect $T_c$ (Tontodonati et al., 2007). In conscious animal safety studies, modern technology (for example, ITS systems) now allows accurate online measurement of $T_c$ and locomotor activity in addition to cardiovascular parameters, but the former parameters are rarely examined in conventional study protocols. Our study in conscious, exercising dogs showed an apparent shortening of QTcV by 11 ms (4.5%), which was fully compensated by taking the $T_c$ rise into account. This emphasizes the importance of investigating possible drug-induced effects on locomotor activity as well as on $T_c$, both to examine a new drug’s safety profile, and to distinguish between direct and indirect changes on $T_c$.

Limitations
First, the results were achieved in the anaesthetized animal, so may not be directly applicable to the conscious state using a similar method. However, both the exercise study with freely moving telemetered dogs showed a complete correction for HR and temperature by the proposed correction formula, and the results recalculated from literature studies tabulated in this study are qualitatively supportive of the results reported—in animals and in humans—in cases of both hypo- and hyperthermia.

Second, we have investigated this relationship over an adequate range for drug- or exercise-induced changes in $T_c$ (–34–42°C), but it may not be valid for lower temperatures. The apparently pathological body changes (for example, massive increase in serum potassium concentrations, irreversible effects on ECG) seen in some dogs warmed to near the CTM of ~43°C, should be taken into account and avoided in further studies.

Lastly, although this correction formula has been obtained in anaesthetized dogs, and validated in one example in freely moving exercising dogs, it may not be appropriate for other species (including humans) and circumstances. Further studies will be required to check and/or improve this formula. In conclusion, this study has demonstrated a marked dependence of the QT interval (QTc) on temperature correction for temperature changes on the QT interval systems) now allows accurate online measurement of $T_c$ and locomotor activity in addition to cardiovascular parameters, but the former parameters are rarely examined in conventional study protocols. Our study in conscious, exercising dogs showed an apparent shortening of QTcV by 11 ms (4.5%), which was fully compensated by taking the $T_c$ rise into account. This emphasizes the importance of investigating possible drug-induced effects on locomotor activity as well as on $T_c$, both to examine a new drug’s safety profile, and to distinguish between direct and indirect changes on $T_c$.

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First, the results were achieved in the anaesthetized animal, so may not be directly applicable to the conscious state using a similar method. However, both the exercise study with freely moving telemetered dogs showed a complete correction for HR and temperature by the proposed correction formula, and the results recalculated from literature studies tabulated in this study are qualitatively supportive of the results reported—in animals and in humans—in cases of both hypo- and hyperthermia.

Second, we have investigated this relationship over an adequate range for drug- or exercise-induced changes in $T_c$ (–34–42°C), but it may not be valid for lower temperatures. The apparently pathological body changes (for example, massive increase in serum potassium concentrations, irreversible effects on ECG) seen in some dogs warmed to near the CTM of ~43°C, should be taken into account and avoided in further studies.

Lastly, although this correction formula has been obtained in anaesthetized dogs, and validated in one example in freely moving exercising dogs, it may not be appropriate for other species (including humans) and circumstances. Further studies will be required to check and/or improve this formula. In conclusion, this study has demonstrated a marked dependence of the QT interval (QTc) on temperature correction for temperature changes on the QT interval systems) now allows accurate online measurement of $T_c$ and locomotor activity in addition to cardiovascular parameters, but the former parameters are rarely examined in conventional study protocols. Our study in conscious, exercising dogs showed an apparent shortening of QTcV by 11 ms (4.5%), which was fully compensated by taking the $T_c$ rise into account. This emphasizes the importance of investigating possible drug-induced effects on locomotor activity as well as on $T_c$, both to examine a new drug’s safety profile, and to distinguish between direct and indirect changes on $T_c$.

(1) Some drugs may be incorrectly classified as having direct effects on repolarization (QT) if they also change body temperature by direct or indirect (for example, by changing locomotor activity) mechanisms;

(2) Conversely, direct QT effects may be missed when testing drugs that change body temperature;

(3) Altered plasma potassium levels are found in association with the phenomena reported, and

(4) Identification or classification of patients (for example, long QT syndrome) by exercise tests may be improved by using a more accurate correction formula.

We recommend that all ICH S7A, conscious animal, safety studies should routinely measure body $T_c$ and locomotor activity (which may indirectly influence $T_c$), and correct QTc using an appropriate formula if body temperature changes are detected. This will help to avoid generating misleading data and to explain false-positive or-negative results. Indeed, correction for temperature changes on the QT interval should also be considered in human trials, especially where stress testing is incorporated into the design, and repeated-dose large animal toxicological studies.

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Conflict of interest
The authors state no conflict of interest.

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