

## Heart Rate and QT Interval in Streptozotocin-induced Diabetic Rat

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### Abstract

*Aim:* Prolonged QT interval is a common finding in diabetic patients. The effects of streptozotocin (STZ) – induced diabetes on QT interval has been investigated by application of 4 standard QT correction algorithms.

*Methods:* The electrocardiogram was recorded in STZ-treated (60 mg/kg bodyweight, ip) and age-matched control rats with a biotelemetry system for the period of the study.

*Results:* Heart rate (HR) was significantly ( $P < 0.01$ ) reduced and QT interval was significantly ( $P < 0.05$ ) prolonged in diabetic rats compared to controls at 8, 10 and 12 weeks

after STZ treatment. At 8 weeks HR was  $260 \pm 16$  BPM ( $n=5$ ) in diabetic rats compared to  $333 \pm 25$  BPM ( $n=5$ ) in controls and QT interval was  $70 \pm 7$  ms ( $n=5$ ) in diabetic rats compared to  $59 \pm 6$  ms ( $n=5$ ) in controls. When QT interval was corrected for HR there was no longer any significant difference in QT interval between diabetic and control rats. The effects of different correction techniques have been compared and the consequences considered.

*Conclusion:* The rapid and dramatic reductions in HR observed after administration of STZ are associated with a prolongation of the QT interval. However, the magnitude of the difference of the QT interval between the STZ and control groups was not significant after QT interval correction for the difference in HR.

### Keywords

Correction factor; diabetes mellitus, heart rate, QT interval.

### Introduction

Cardiovascular disease is a major cause of morbidity and mortality in diabetic patients and hearts of diabetic patients are in a compromised condition<sup>1,2</sup>. Diabetic patients show a higher incidence of cardiac arrhythmias, including ventricular fibrillation and sudden death. The electrocardiogram (ECG) of diabetic patients may show several alterations from normal patterns, most of them related to the QT interval (duration of ventricular myocardial depolarisation and repolarisation) and T wave<sup>3-10</sup>. The prevalence of prolonged QT interval and increased QT dispersion (QTd) is higher in people with type 1 and type 2 diabetes compared to non-diabetic subjects<sup>5,6,8,11-16</sup>. The prevalence of QT prolongation has been reported to be as high as 16% in type 1 and 26% in type 2 diabetes<sup>8,12</sup>. Diabetic patients with more pronounced QT abnormalities tend

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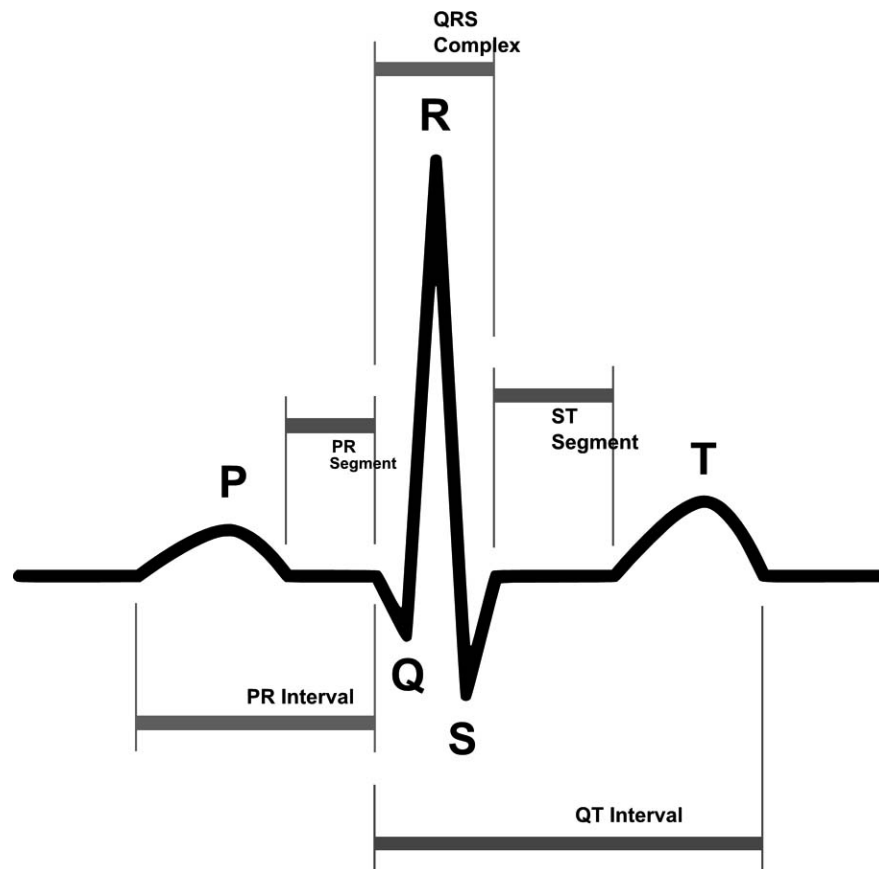


Fig. 1. Typical ECG signal with indicated P wave, QRS complex, T wave, and typical intervals.

to have higher age and blood pressure and tend to have cardiovascular complications<sup>8,11</sup>. Prolonged QT corrected for heart rate (QTc) and increased QTd are independent markers for coronary heart disease in type 1 and type 2 diabetes<sup>8,11</sup> and have been demonstrated as predictors of cardiac death even in newly diagnosed type 2 diabetes<sup>17,18</sup>. The aim of this study was to investigate the effects of streptozotocin (STZ) - induced diabetes on the QT interval and to compare the effects of various HR correction techniques on the QT interval.

### Methods

**Biotelemetry:** The electrocardiogram (ECG) was monitored on a continuous basis with a biotelemetry system (Data Sciences Int., St Paul, MN, USA) using previously described techniques<sup>19</sup>. The system was comprised of transmitter devices (TA11CTA-F40, Data Sciences Int., USA), receivers (RPC-1), a data exchange matrix (20CH) and a personal computer for system configuration, control, acquisi-

tion, and storage. The transmitter devices were surgically implanted in 14 male Wistar rats, 2 months of age, under general anesthesia (sodium pentobarbitone, 45 mg/kg, ip). The devices were inserted into the peritoneal cavity and electrodes from the transmitter were arranged in Einthoven bipolar – Lead II configuration (right foreleg and left hind leg). After recovery from surgery the transmitters were activated by use of a magnet switch. ECG data were collected 5 minutes per hour per animal, 24 hours per day, and 7 days per week for the duration of the study. After collection of baseline ECG data for a period of 1 week half the animals received STZ (60 mg/kg body-weight, ip) dissolved in citrate buffer whilst the other half received citrate buffer alone. Ethical approval for the project was obtained from the Faculty of Medicine & Health Sciences Ethics Committee for Animal Research.

HR and QT intervals were calculated from the ECG data. The HR was determined from the 5-

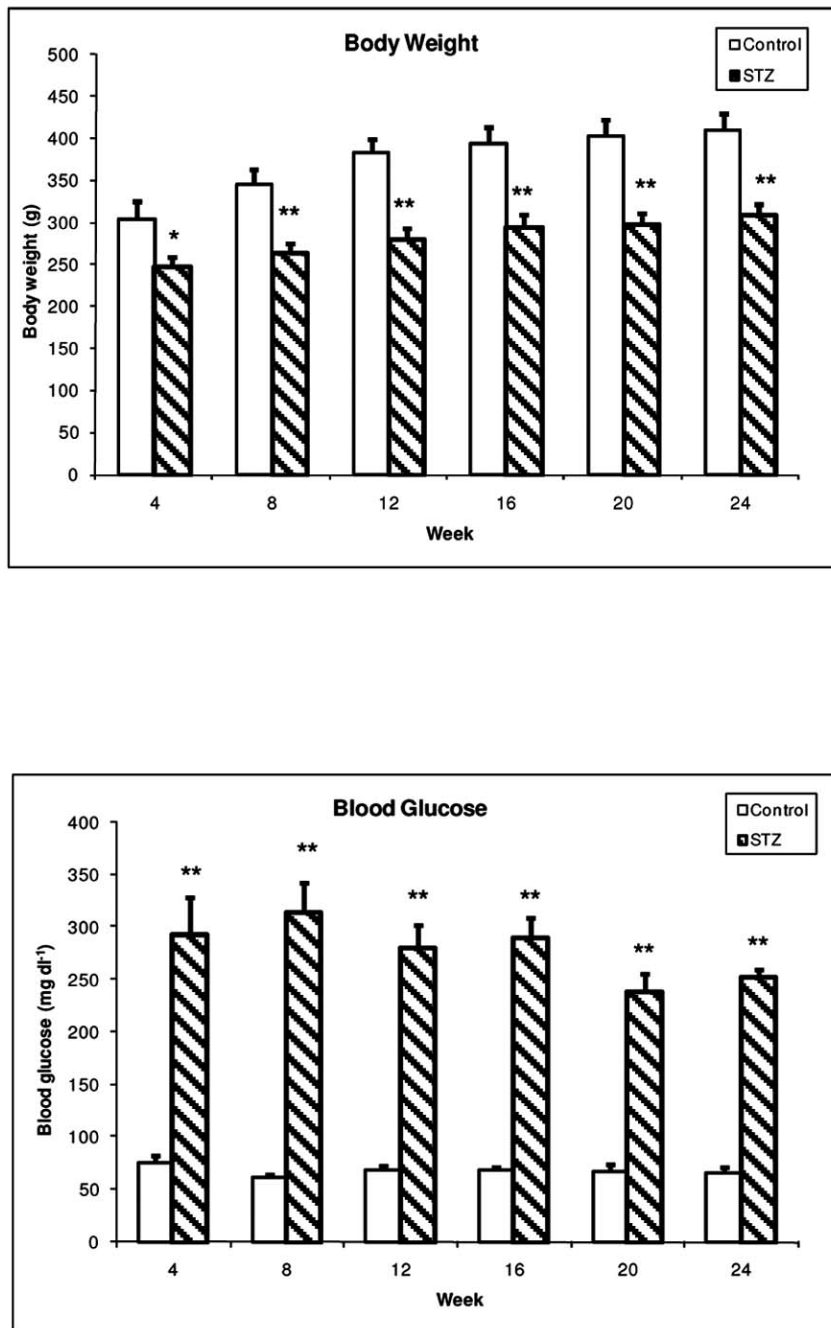


Fig. 2. Effects of STZ treatment on body weight (A) and blood glucose (B). Data are mean  $\pm$  S.E.M.,  $n = 5$ , \* $P < 0.05$ ; \*\* $P < 0.01$ .

minute average of all normal R-wave to R-wave intervals in the ECG. QT interval was measured as the time between Q and the end of the T-wave (Fig. 1). The QT interval was further processed to incorporate beat-to-beat changes in the heart rate using four different algorithms: Bazett, Hodges, Cube root, and Vanderwater.

The Bazett algorithm for HR correction of the QT interval is commonly used in clinical settings and consists of dividing the measured QT interval by the square root of the associated R-R interval (Table 1). Since a power factor of the RR interval is used, this algorithm is classified as a logarithmic correction<sup>20</sup>.

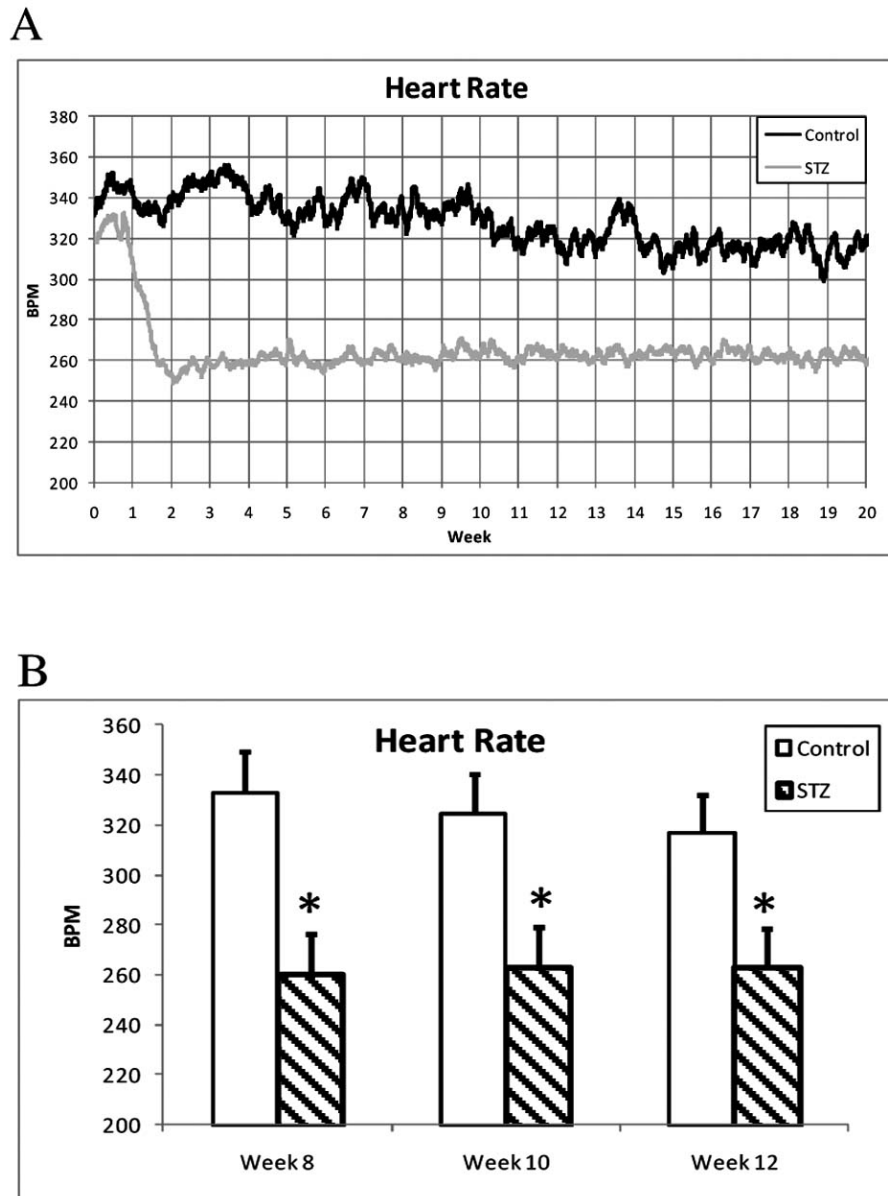


Fig. 3. Effects of STZ treatment on continuous heart rate (A) and mean heart rate at selected time points (B). Data are mean ± S.E.M., n = 5, \* P < 0.05.

The Cube Root correction, also called Fridericia's algorithm, is similar to the Bazett logarithmic algorithm but involves division by the cube root of the associated R-R interval instead of the square root (Table 1)<sup>20</sup>.

Hodge's and Vanderwater's algorithms are less standard, ad hoc corrections whereby the QT interval is proportionally adjusted by the associated RR interval (Table 1). These algorithms are classified as linear corrections of the QT interval since each involves the addition of a proportion (or inverse proportion) of the R-R

interval<sup>21</sup>, with consideration of typical human HR and QT interval.

Table 1. QT interval correction algorithms in seconds

Bazett	$QTcB = \frac{QT\ Interval}{\sqrt{RR}}$
Cube Root	$QTcC = \frac{QT\ Interval}{\sqrt[3]{RR}}$
Hodges	$QTcH = QT\ Interval + 1.75 (60RR^{-1} - 60)$
Vanderwater	$QTcV = QT\ Interval + 0.087 (1-RR)$

Each of the QT interval correction algorithms were developed for human use within a certain range of HR. Other species, such as rodents, have different physiological parameters and no standard correction algorithm. Thus, it is common to utilize these algorithms and employ group difference analysis.

Hypothesis testing was implemented by computing the probability associated with the two-sample, equal variance, student's t-test. P values less than 0.05 were considered significant.

### Results

The STZ-treated rats exhibited reduced body weight gain (*Fig. 2A*) and elevated blood glucose (*Fig. 2B*) compared to age-matched controls. At 8 weeks after STZ treatment blood glucose in diabetic rats was  $314 \pm 29$  mg/dl (n=5) compared to  $61 \pm 4$  mg/dl (n=5) in controls. The initial weight of the experimental animals prior to transmitter implantation was  $235 \pm 2$  g (n=10). The rate of body weight gain in diabetic rats was significantly less than in age-matched controls. At 8 weeks after STZ treatment the body weight in diabetic rats was  $264 \pm 12$  g (n=5) compared to  $345 \pm 18$  g (n=5) in controls.

The HR was determined from the 5-minute average of all normal R-wave to R-wave intervals in the ECG. The effects of STZ treatment on HR are shown in (*Fig. 3A*). HR fell rapidly and dramatically after administration of STZ (*Fig. 3A*). At 8 weeks after induction of diabetes, HR was  $260 \pm 16$  BPM (n=5) in STZ-treated rats compared to  $333 \pm 25$  BPM (n=5) in age-matched controls (*Fig. 3B*). Similarly, at 8 weeks after induction, the group average of the RR-interval was  $0.236 \pm 0.015$  sec (n=5) in STZ-treated rats compared to  $0.186 \pm 0.014$  sec (n=5) in age-matched controls.

The measured QT interval was longer in diabetic rats compared to controls at all measured time points between 4 and 20 weeks (*Fig. 4A*), with statistical significance computed at 8, 10, and 12 weeks (*Fig. 4B*). At 8 weeks after induction of diabetes, QT interval was  $70 \pm 7$

ms (n=5) in STZ-treated rats compared to  $59 \pm 6$  ms (n=5) in age-matched controls.

However, when corrected by the R-R interval, the difference between the diabetic and control rats no longer reached significance (*Figs. 4C-J*). At 8 weeks after STZ injection the group averages and standard error of the corrected QT intervals in diabetic and control rats respectively, were  $145 \pm 15$  vs.  $140 \pm 14$  ms using Bazett's formula;  $113 \pm 12$  vs.  $105 \pm 10$  ms using the Cube Root correction;  $419 \pm 30$  vs.  $534 \pm 46$  using Hodge's formula; and  $135 \pm 8$  vs.  $127 \pm 8$  ms using Vanderwater's linear correction. The Hodge correction displayed unusually large results due to use of the inverse RR interval and customization for humans. Even so, the group difference was not significant.

### Discussion

During the 24-week study body weight gain in diabetic rats was reduced and blood glucose was approximately 5-fold higher in diabetic rats compared to controls. There was a dramatic reduction in HR which began hours after administration of STZ and reached a new steady state, 1 week after STZ injection. The rapid effects of STZ on HR have been reported in some previous studies<sup>19,22</sup> and may be associated with the development of hyperglycemia, which also occurs within hours of STZ treatment, or it may be due, at least in part, to a direct action of STZ on the heart<sup>23</sup>. The mechanisms underlying the direct actions of STZ on HR remain to be elucidated but may be partly attributed to an effect of STZ on action potential and in particular on events of repolarization<sup>23</sup>.

Prolonged QT interval is a frequent finding in patients with either type 1 or type 2 diabetes 3 and has also been demonstrated in experimental models of diabetes<sup>19,24-26</sup>. In general QT was prolonged in diabetic rat heart compared to controls; however, correction of the QT interval for HR, using various approaches, appeared to remove the statistical significance of the results. *In vivo* Doppler and M-









wider gap between the two groups, but again, no significant difference since  $e^{\ln(0.070)^{-1/2} \ln(0.236)} = 0.113s$  and  $e^{\ln(0.059)^{-1/2} \ln(0.186)} = 0.104s$  which is less than an 8% difference.

As far as the linear corrections, Vanderwater produce similar results to the logarithmic correction algorithms with  $0.070s + 0.087(1-0.236s) = 136s$  and  $0.059s + 0.087(1-0.186s) = 130s$  for a less than 5% difference in values and again comparable to the group averages of the per animal QT interval corrections.

This linear correction algorithm was developed for use with human patients and utilizes an average HR of 60 BPM. In particular, the Vanderwater algorithm adjusts the QT interval by subtracting 8.7% of the difference of the associated R-R interval from 1 second (60 BPM). The average rat HR is much higher than 60 BPM, which accounts for the increased interval values produced by the algorithm, which is comparable to the over correction of the Bazett algorithm. Since this artifact affects both the STZ and control groups, its effect is removed in the comparison. Even so, adjusting the algorithm for an average rat HR lowers the overall, corrected interval values and the difference between the groups remains statistically insignificant with results similar to the cubic root correction algorithm.

### Conclusion

The rapid and dramatic reductions in HR observed after administration of STZ are associated with a prolongation of the QT interval. However, when corrected for the change in HR, there is no significant difference in QT interval after administration of STZ.

### Acknowledgements

This work was financially supported by a grant from Faculty of Medicine & Health Sciences.

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