QT Interval Analysis in Electrograms of Isolated Guinea Pig Hearts Treated with Haloperidol

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Abstract

The influence of antipsychotic drug haloperidol on repolarization defined by QTc interval was analyzed in electrograms of 8 isolated guinea pig hearts. Each experiment consisted of four phases: stabilization (S), first haloperidol administration (H1), washout (W), and second haloperidol administration (H2). QTc was computed according to three correction models: Bazett's, Fridericia's and dynamic model based on transfer function (TRF). Mean value and standard deviation of QTc were assigned from the interval of 2000 beats in the middle of all four experimental phases.

The inaccuracy of QTc given as STD/mean over all phases and experiments was 0.016±0.013, 0.015±0.010 and 0.0039±0.0024 for Bazett, Fridericia and TRF, respectively.

The QTc prolongation by haloperidol was confirmed by TRF model. Relative QTcT prolongation caused by haloperidol was (H2-W 0.0062±0.0054, P=0.07) and shortening (H1-W -0.0038±0.0037, P=0.07) caused by washout. The QTcB and QTcF changes were given more by RR changes than haloperidol influence. The dynamic, subject specific model of QT/RR coupling must be used in drugs analysis.

1. Introduction

Antipsychotic drug haloperidol is a butyrophenone derivative with serious cardiac side effects, including QT interval prolongation, as shown by Kijtawornrat et al. (2006). Sudden cardiac death is rarely seen, but repeatedly described [2]. In our region, haloperidol is widely used in the treatment of both acute (acute psychosis, delirium) and chronic (schizophrenia) mental disorders.

Repeated haloperidol treatment influence on QT interval in isolated guinea pig hearts was studied.

2. Methods

The experiments were performed on 10 male guinea pigs. Guinea pigs were divided into haloperidol-treated group (T, 8 animals) and control group (C, 2 animals). During 21 consecutive days, i.p. injection of either haloperidol or saline solution (1.33 ml/100 g of actual weight) was applied once a day. Group T was treated with haloperidol (2 mg/kg of actual weight), group C with physiological solution. One day after the last dose, guinea pigs were deeply anesthetized with inhalation of ether. The heart was excised, cannulated into the aorta and perfused according to Langendorff, at constant perfusion pressure (85mmHg), with K-H solution (NaCl, 118 mM; $NaHCO_3$, 24 mM; KCl, 4.2 mM; KH_2PO_4, 1.2 mM; $MgCl_2$, 1.2 mM; $CaCl_2$, 1.25 mM; glucose, 5.5 mM). The perfusion solution was continuously aerated with 95% O_2 and 5% CO_2. The heart was placed in a bath filled with K-H solution.

The experiment consisted of four 30 minutes lasting phases: stabilization (S), haloperidol 1 (H1), wash-out (W), and haloperidol 2 (H2). In each haloperidol phase, haloperidol at concentration of 10 nM was continuously applied. During the whole experiment three orthogonal ECG leads were continually recorded by the touch-free method, using USB PC card (National Instruments) with frequency of 2000 Hz and 12 bits resolution.

The R wave and the end of T wave were consequently automatically detected. The wavelet transform was used for R wave detection and the method of regression lines for detection of the end of T wave. The detected results were manually controlled. The QR interval was supposed to be constant and was given as mean level from manually detected QR

intervals from all phases of experiment.

The detected RR and QT intervals were used for evaluation of QTc interval according to three different models: Bazett's (QTcB=QT/√(RR)) [3], Fridericia's (QTcF=QT/^{3}√(RR)) [4] and dynamic model, based on transfer function (TRF) with three optimized parameters (QTcT) [5].

3. Analysis

Due to the small number of control experiments proper analysis of control hearts can not be done and hence only the haloperidol experiments were statistically processed.

The mean±STD were computed for RR, QT and different QTc in the window 2000 beats long in the middle of each phase. The inaccuracy of QTc was analyzed from normalized QTc variability in single intervals, given as STD/mean. The results over all phases in haloperidol experiments were 0.016±0.013, 0.015±0.010 and 0.0039±0.0024 for QTcB, QTcF and QTcT, respectively. The statistical significance of differences between inaccuracy of Bazett's and Fridiricia's corrections was 0.1, whereas the significance for differences between Bazett-TRF and Fridiricia-TRF was <0.0001.

The mean levels from above mentioned windows were used to analyze haloperidol influence. The mean levels and standard deviations over all experiments in different phases together with the normalized values, given as the quotient between value in given interval and mean level over all intervals in given experiment, are summarized in Tab 1. The differences between phases (absolute and normalized value) were used to test the haloperidol influence (Tab. 2, 3). The distribution of differences is shown in Fig. 2

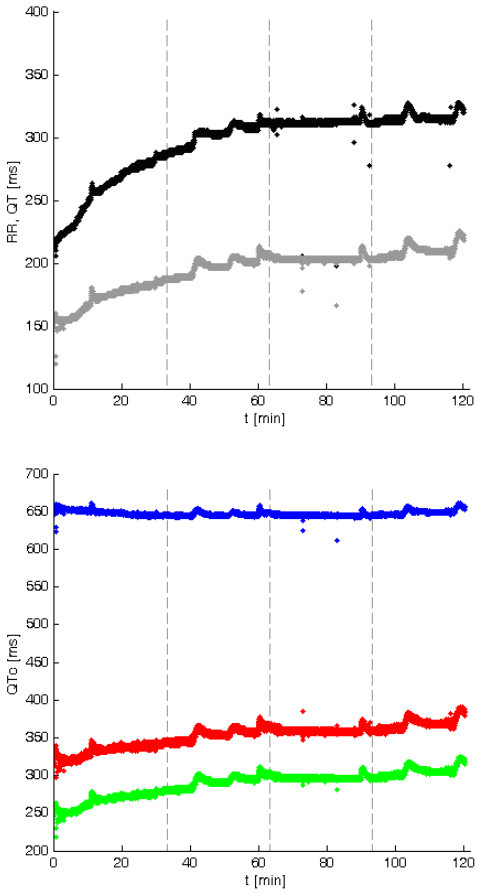

Figure 1. Examples of the time courses for a haloperidol experiment. Detected RR (black) and QT (gray) intervals. QTc according to different models Bazett's (red), Fridericia's (green) and TRF (blue). The gray dashed lines show the transitions between individual experiment phases (stabilization, haloperidol I, washout, haloperidol II).

Table 1. Mean ± STD over experiments for different phases of experiment (stabilization – S, haloperidol 1 – H1, washout – W, haloperidol 2 – H2). The absolute values in ms are in the left part and normalized values in the right part (values were normalized to mean value from all four phases of experiment).

Course	S Mean±Std	H1 Mean±Std	W Mean±Std	H2 Mean±Std	S Mean±Std	H1 Mean±Std	W Mean±Std	H2 Mean±Std
RR	280±13	321±21	330±23	333±23	0.886±0.037	1.016±0.015	1.044±0.016	1.054±0.025
QT	188±9	214±10	217±10	222±10	0.894±0.023	1.017±0.008	1.031±0.012	1.058±0.014
QTcB	350±13	372±14	372±13	381±14	0.949±0.007	1.010±0.004	1.010±0.006	1.032±0.008
QTcF	284±12	309±12	311±11	318±11	0.930±0.012	1.012±0.004	1.017±0.008	1.041±0.009
QTcT	614±66	616±64	613±64	617±66	0.998±0.003	1.001±0.003	0.997±0.003	1.004±0.003

Table 2. The interval differences [ms] between phases of experiment. Mean ± STD over experiments.

Course	H1-S		W-H1		H2-W		H2-H1	
	Mean±Std	P	Mean±Std	P	Mean±Std	P	Mean±Std	P
RR	41±16	0.008	9.1±7.4	0.07	2.9±6.6	0.29	11.9±9.8	0.07
QT	25.9±5.7	0.008	2.9±2.6	0.07	5.5±2.7	0.008	8.5±3.8	0.008
QTcB	22.6±2.9	0.008	-0.002±2.7	1.0	8.0±4.5	0.008	8.0±4.0	0.008
QTcF	25.3±3.9	0.008	1.4±2.3	0.29	7.1±3.6	0.008	8.6±3.6	0.008
QTcT	1.6±3.5	0.73	-2.3±2.3	0.07	4.0±3.2	0.07	1.6±3.0	0.73

Table 3. The interval differences between phases of experiment. Mean ± STD over experiments. Normalized values used.

Course	H1-S		W-H1		H2-W		H2-H1	
	Mean±Std	P	Mean±Std	P	Mean±Std	P	Mean±Std	P
RR	0.130±0.044	0.008	0.028±0.023	0.07	0.009±0.020	0.29	0.038±0.031	0.07
QT	0.123±0.026	0.008	0.014±0.012	0.07	0.026±0.014	0.008	0.040±0.019	0.008
QTcB	0.0613±0.0073	0.008	0.0001±0.0072	1.0	0.022±0.012	0.008	0.022±0.011	0.008
QTcF	0.083±0.013	0.008	0.0048±0.0074	0.29	0.023±0.012	0.008	0.028±0.012	0.008
QTcT	0.0029±0.0056	0.73	-0.0038±0.0037	0.07	0.0062±0.0054	0.07	0.0025±0.0047	0.73

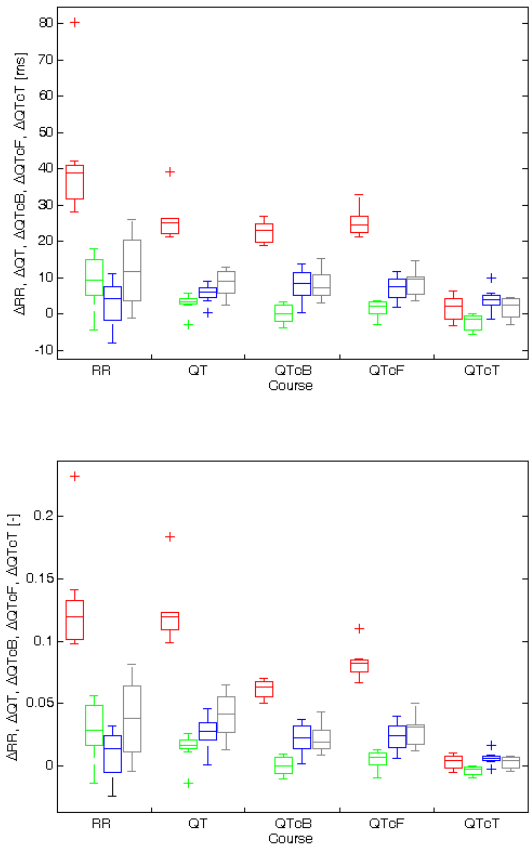

Figure 2. The differences between phases over all experiments. The upper graph shows absolute values whereas the bottom normalized values. The red boxes describe the differences between sections H1 and S (H1-S), green boxes (W-H1), blue boxes (H2-W) and the gray boxes (H2-H1).

4. Discussion

QTc calculation according to Bazett or Fridericia are still used in the drugs tests, although it is well known that only subject specific QTc model might eliminate the coupling between QT and RR. The QTc should be constant over steady part of phase [6]. Its relative variability, represented by STD/mean, defines the inaccuracy of QT correction method together with random QT variability and detections errors. The accuracy of QTcT is about 5 times better than accuracy of QTcB and QTcF. Accuracy of QTcB and QTcF is comparable. QTcT is given by subject specific, optimized model, with 3 optimized parameters and so its accuracy must be better than the accuracy of QTcB or QTcF that do not use optimization. The simplicity of QTcB and QTcF may be the reason of their applications, not looking on their worse accuracy. But the most important is the proper analysis of haloperidol influence.

QTcB and QTcF give nearly the same results. Significant increasing of QTc occur during H2 as compared to W, significant increasing exists during H1 compared to S, but no change (QTcB) or even decreasing (QTcF) appear during H1 compared to W. The shortening of QTc which would be caused by washout is apparent only in case of QTcF but it is insignificant (P=0.289). The difference QTcB between W and H1 is even positive that conversely symbolizes a

QTc prolongation. Moreover significant increasing exists during H2 relative to H1. Some differences may be given by known influence of haloperidol (H1-S, H2-W), but the strange relation between H1 and W can be hardly explained if we do not look on RR behavior. The RR intervals are increased over all experiment (Fig. 2, Tab. 1). Both QTcB and QTcF do not correct properly QTc for RR changes, and the results combine influence of RR changes and haloperidol effect. The influence of RR changes is dominant and the high statistical significance of QTcB and QTcF changes between H2 and W or S and H1 are given before all by RR changes. The analysis of haloperidol influence based on QTcB or QTcF may be inaccurate, if RR is changed during the experiment.

QTcT eliminates the RR influence and the differences H2-W and W-H1 simply confirm that QTc is prolonged by haloperidol as mentioned in [1] and shortened by washout (Fig. 2, Tab. 2, 3). The prolongation and shortening are not statistically significant (P=0.07); higher number of experiments must be included to achieve statistical significance. The inability to describe properly the haloperidol effect according to ΔQTcT between phases H1 and S is likely caused by the unstable RR course in phase of stabilization and by a small number of experiments.

The dynamic, subject-specific model of QT/RR coupling should be used in drugs tests. Such model preserves the valid results [7] even in case of changed heart rate. QTcB or QTcF do not correct QT hysteresis nor static properties of QT/RR coupling,

We analyzed the relative changes of QTc. The mean levels of QTcB, QTcF and QTcT are significantly different. The question is whether in animal experiments the QTc as 60-bpm equivalent of QT duration based on correction should be used, or the QT equivalent corresponding to basic heart rate of tested animal should be used.

Our experiments are limited by short stabilization phase. It should be at least twice longer. The RR intervals are going up over all experiment and limit the accuracy of analysis of haloperidol influence.

Although the small number of control experiments did not allow proper statistical, analysis and comparison of the partial results with results of haloperidol experiments showed different haloperidol effects. It seems that the first haloperidol administration evoked QT prolongation in control experiments which had much longer time constant than in case of haloperidol experiments. Moreover, the washout did not cause stopping of this effect. There are more experiments needed which might clarify haloperidol effect on the activity of the untreated hearts.

5. Conclusion

The results mentioned in discussion predicate that only a subject-specific model can be used for proper haloperidol effect analysis.

Analysis of ΔQTcT between individual phases of experiment revealed the QTc prolongation caused by haloperidol and QTc shortening caused by washout.

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