Original Article

Beat-to-beat Analysis of the Relation between RT and RR Intervals in Newborns

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OBJECTIVE:

To evaluate the dynamic RT (QRS apex-end of T wave) rate dependence in newborns.

STUDY DESIGN:

A Digital Holter ECG was acquired on day 15 in nine full-term and eight preterm infants. Ten-minute periods were recorded during wakefulness and sleep. The accuracy of fit with RT–RR pairs was individually assessed by 14 regression formulas (r coefficient, Akaike score, residual analysis). The medians of RT and Bazett's RT correction were calculated for each 10 milliseconds of RR.

RESULTS:

The mean RR and RT were 429 ± 51 and 263 ± 18 milliseconds. None of the prediction formulas were sufficiently accurate to describe RT over the whole range of RR ($r < 0.56$). The Bazett correction produced differences of more than 50 milliseconds at different RR. Prematurity, sleep state and heart rate variability did not influence RT–RR relation.

CONCLUSION:

None of the parametric formulas were found to be accurate in describing RT rate dependence in newborns.

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INTRODUCTION

The measurement of the QT interval on electrocardiogram (ECG) represents a marker of global ventricular repolarisation in vivo.[1,2] An accurate measurement of the QT interval is of great importance, particularly in view of increasing evidence that a number of drugs produce a QT prolongation and that the QT prolongation may cause ventricular arrhythmias and even sudden death.

The heart rate and particularly the duration of the preceding cardiac cycles are the primary source of QT changes, but the QT interval duration is also known to be sensitive to various factors (electrolyte disorders, drugs, gender and autonomic nervous system).[1–8] Age-related differences in QT duration have also been reported in humans, they justify the need for specific references in the neonatal period.[9–13] Bazett's formula ($QT_c = QT/RR^{1/2}$) is widely used to correct QT interval for heart rate in humans, but this normalisation of QT to the value that it would have had if the heart rate were 60 beats per minute (b.p.m) has been reported to be inaccurate for the range of heart rate observed during the neonatal period.[1] This correction of QT interval duration has been used in most of the neonatal studies performed,[13–17] but remains insufficiently evaluated. Numerous other formulas that have been proposed to correct the QT for heart rate have not been tested in newborn infants. Most of them are derived from empirical regression analyses of QT versus RR plots using various equations, which were often obtained retrospectively and applied without being prospectively validated.[1,18–24] In general, QT and RR data upon which these corrections are based have been obtained from averaged or nonaveraged standard ECGs without testing the validity of applying them in different clinical or physiological situations. In several studies Holter monitoring, which allows the study of a large range of heart rate in different conditions, was used to assess the QT rate dependence and the dynamic response of QT interval to changes in heart rate in newborns and infants.[25,26] The results obtained in newborns with this method have suggested that the correlation between QT and cardiac cycle length can vary among infants.[26]

In the present study, RT was used as the surrogate for QT interval.[26,27] We prospectively investigated the relation between RT and RR intervals in newborns under physiological conditions by measurement of these intervals on ambulatory Holter ECGs and reviewed the acceptability of 14 QT prediction formulas.[1,18–24]

METHODS

Subjects

Electrocardiographic recordings with a Holter recorder were performed on day 15 on 17 newborns (nine normal full-term infants and eight preterm infants). The postnatal age was chosen to avoid the transient QT prolongation observed during the first days after birth.[28,29] The sleep state and the analysis of heart rate variability were used to evaluate the influence of changes in sympathovagal balance on RT rate dependence. Infants with congenital heart disease, electrolyte disorders, myocardial or neurological pathologies or receiving drugs were excluded. The protocol of the study was approved by the institutional ethics committee of the Rennes' teaching hospital and informed consent was obtained from the parents.

Data Acquisition

Electrocardiographic data were recorded with a digital ambulatory Holter ECG recorder (Burdick PC card recorder 6632; Burdick Inc., Milton, WI, USA) while the newborn was lying in a supine position. Lead II obtained from adhesive electrodes (Red Dot™, 3M health care, Borken, Germany) was used for ECG analysis.

Study Design

Ten-minute periods were successively recorded, one when the newborns were awake and two when they were asleep (10 minutes during quiet sleep, and 10 minutes during combined active+indeterminate sleep). Each 10-minute period was defined on a clinical basis during the recording by the same investigator. The sleep state was determined looking at eye movements and agitation. The newborns were considered to be in quiet sleep state when the respiratory rate was regular in the absence of any movement.

ECG Processing

ECG recordings were acquired with a digital recorder at the sampling frequency of 1000 Hz and amplitude resolution of 12 bits. The ECG signal (stored on a removable hard disk PCMCIA card) was transferred to a standard personal computer. Beat-to-beat analysis of ECG was performed with an algorithm developed and validated in the Holter Laboratory of Lariboisiere Hospital as previously described in detail.[27,30] The algorithm executes the following series of beat-to-beat steps: detection of QRS complex, estimation of a dynamic isoelectric line that was removed from the measured ECG, low-pass ECG data filtration, detection of the end of T wave. On the basis of all cursors automatically detected, the algorithms provided beat-to-beat time series of RR intervals (from QRS apex to next QRS apex) and RT interval (from QRS apex to end of T wave) as a surrogate of QT interval.[26] The mean QRS duration was measured at 60 milliseconds with a standard deviation of 8 milliseconds in the newborns studied and was not correlated to RR interval duration. The peak of the R wave was located between 40 and 60% of the QRS period in agreement with the standard description of the normal sequence of waves constituting the QRS complex.[31] Thus, QT duration can reasonably be estimated by adding 30 milliseconds to the RT measurement. All ECG tracings and relative fiducial points were visually inspected and all misplaced cursors were rejected (leading to missing data in the beat-to-beat sequences).

The analysis of heart rate variability (HRV) has been performed with a classical time domain analysis method. Mean RR, standard deviation (SD) and root-mean-square successive differences (RMSSD), which represents the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals, were calculated. SD reflects global HRV and depends upon the influence of both sympathetic and parasympathetic drives. RMSSD reflects the respiratory sinus arrhythmia that depends principally upon parasympathetic input.[32]

Data Analysis

This was conducted on the softwares Statistica (Statistica for Windows. StatSoft Inc. Tulsa, OK, USA) and Matlab (The Mathworks Inc, Natick, USA). The relations between the RT and preceding RR intervals were plotted (Figure 1). The accuracy of fits was tested in pooling the three RT − RR series obtained when the newborns were awake and when they were asleep. The RT − RR relation was evaluated by one regression line analysis with linear or nonlinear fitting. The constant values of each formula were calculated by least-mean-square method. The relative accuracy of fit to RT − RR pairs by regression analysis was assessed according to the minimum Akaike information criteria (AIC): $AIC = N\ Ln(SSR) + 2P$, where N is the number of observations (RT − RR pairs), Ln is the natural logarithm, SSR is the sum of squares residual, and P is the number of parameters in the equation. The equation with minimum AIC and maximum r correlation coefficient (least-mean-square method) was regarded as the best representation of a given plot data and was assigned the best rank in the analysis.[33] Since AIC is directly dependent on the number of observations (N) we only used AIC to assess the relative intraindividual accuracy of equations. The accuracy of fit with RT − RR pair of data for the individual newborns was assessed by

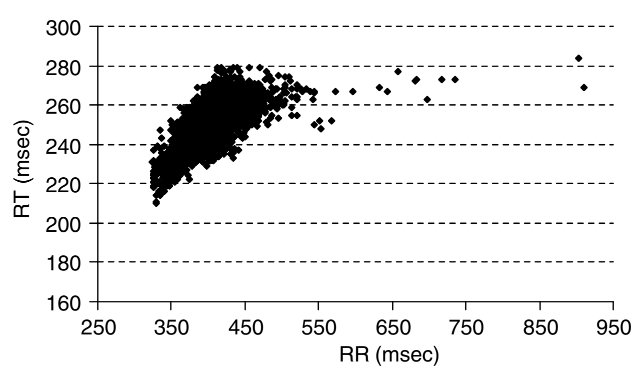

Figure 1. Plot of the relations between the RT and preceding RR intervals ($n = 2100$ beats) in a normal full-term infant.

Table 1 *r* Coefficient values (±SD) and Performances Ranks for QT Prediction Formulas by Individual Data Analysis

	r Coefficient	Rank *r*	Rank AIC
Linear analysis by one parameter (a) formulas with X-axis transformation			
F1: RT=a RR	0.531±0.173	14	14
F2: RT=a $RR^{1/2}$	0.538±0.173	11	11
F3: RT=a $RR^{1/3}$	0.540±0.173	8	9
F4: RT=a $RR^{1/4}$	0.541±0.173	6	10
F5: RT=a log RR	0.543±0.173	4	12
Linear analysis by two parameters (a, b) formulas with X-axis transformation			
F6: RT=a RR+b	0.531±0.173	13	8
F7: RT=a $RR^{1/2}$+b	0.538±0.173	12	7
F8: RT=a $RR^{1/3}$+b	0.540±0.173	9	6
F9: RT=a $RR^{1/4}$+b	0.541±0.173	7	4
F10: RT=a log RR+b	0.543±0.173	5	3
F11: RT=a/RR+b	0.551±0.173	1	2
Non linear analysis by two parameters (a, b) formulas with X-axis transformation			
F12: RT=a RR^{b}	0.539±0.173	10	5
F13: RT=a $(1\text{-}e^{bRR})$	0.551±0.175	2	1
F14: RT=a arctang (b RR)	0.549±0.174	3	13

The constant values of regression parameters (a and b) were individually calculated by least-mean-square method. F1 is the linear regression formula; F2 is Bazett's[1] square root formula; F3 is Fridericia's[19] cubic root formula; F4 is the fourth root formula proposed by Kawataki et al.[18]; F5 is the logarithmic formula. F6 – F11 are two parameters formulas. F6 is the linear regression formula proposed by Adams;[20]; F7 – F9 are roots formulas including a constant as the second parameter to F2 – F4; F10 is Ashman's[21] logarithmic formula; and F11 is Kovacs' inverse RR formula (1985). F12 – F13 are exponential formulas: F12 is a generalised power function of RR; F13 is the two-parameter exponential formula of Carmeliet.[22] F14 is an arctang formula.

the 14 formulas (F1 – F14) listed in Table 1. The individual RT – RR relations were also studied using nonparametric statistical analysis. The median and the fifth and 95th centiles of RT duration and Bazett's RT correction were calculated for each 10-millisecond interval of RR duration. A summary presentation of Median, fifth and 95th centiles data curves were calculated using individual median and fifth and 95th centiles of RT duration as summary measure and considering the individual as the basic unit.[34]

The influences of prematurity, heart rate variability (SD, RMSSD) and sleep state on RT duration was assessed using Spearman correlation test. $p<0.05$ was considered to be statistically significant. The results are expressed as mean (SD).

RESULTS

Patients

A total of nine normal full-term newborns (gestational age: 39(1.4) weeks, birthweight: 3020 (380) g) and eight preterm infants (gestational age: 31 (2.8) weeks , birthweight: 1625 (438) g) were studied on a beat-to-beat basis. For the whole population, the mean RR was 429 (51) milliseconds with an SD of 34 (14) milliseconds and an RMSSD of 8 (5) milliseconds. The mean RT duration was 263 (18) milliseconds with an SD of 12 (4) milliseconds. Individual RT – RR relations are presented in Figure 2a.

Accuracy of QT Prediction Formulas (Table 1)

The accuracy of fits was low with *r* correlation coefficient below 0.56 for all the prediction formulas tested on the beat-to-beat RT – RR series. Bazett's correction formula produced differences of more than 50 milliseconds in the estimation of corrected RT duration at different RR intervals (Figure 3). The first ranks were achieved by F11 and F13. These functions gave a relatively good fit for data obtained at RR intervals between 375 and 475 milliseconds (meaning 126 to 160 b.p.m), whereas a poor fit was found below and above this RR interval range (example given in Figure 4).

Non parametric Analysis

The results of the individual nonparametric analysis obtained from the beat-to-beat RT – RR series are shown in Figure 2a and a summary presentation of median, fifth and 95th centiles in Figure 2b. We did not find any significant difference in RT – RR relation between preterm and full-term newborn infants nor between wakefulness, quiet sleep and active or indeterminate sleep states. We did not find any significant correlation between the RT duration and the indices of HRV (RMSSD or SD).

DISCUSSION

We have investigated the dynamic relation between RT and RR intervals in full-term and preterm newborns by automatically measuring the individual RT and preceding RR intervals on a beat-to-beat basis in order to include a wide range of RT and RR intervals in our analysis. The main results of the present study based on Holter monitoring are: (i) none of the parametric correction formulas used were sufficiently accurate to describe QT duration over the range of cardiac cycle length observed in the same individual during the neonatal period and (ii) prematurity, sleep state and time domain indices of HRV did not influence QT duration.

The QT correction formulas are not adapted to the neonatal period because QT interval is usually corrected for heart rate of 60 or 100 b.p.m, which does not reflect the normal neonatal heart rate (140 bpm in our study). None of the RT correction formula tested was sufficiently accurate to describe RT duration over the whole range of cardiac cycle lengths, especially in the extremes. Furthermore, we observed that the correlation coefficients were relatively low and did not dramatically change between the regression formulas tested suggesting that none of them was really superior for the population studied. The low *r* coefficients seen could be explained in part by the dispersion of the RT values

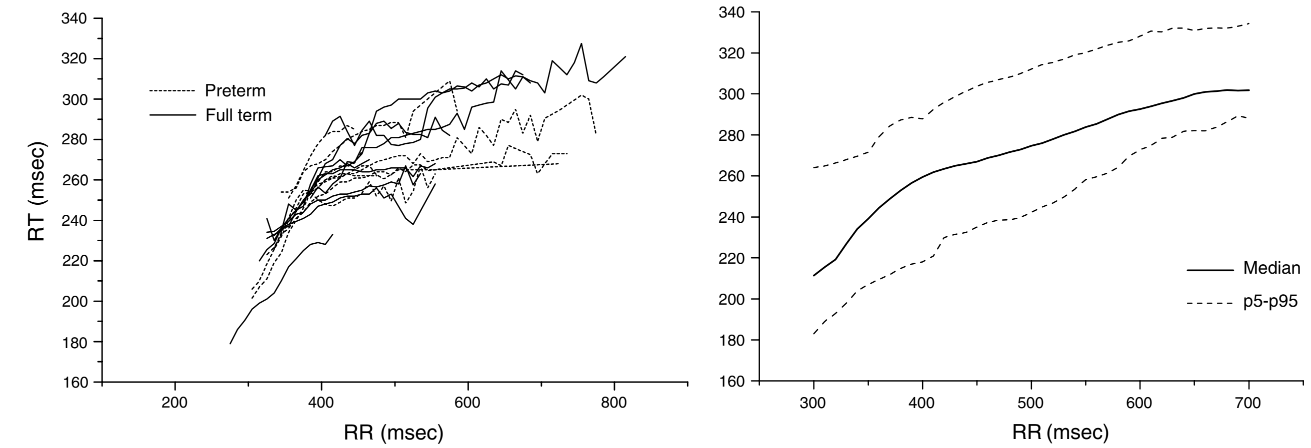

Figure 2. Beat-to-beat analysis of RT – RR relations. (Left) Each line represents individual median values of RT. There was no significant difference between full-term and preterm infants. (Right) Summary presentation of RT median, fifth and 95th centiles data curves (QT duration can be estimated by adding 30 milliseconds to the RT measurement).

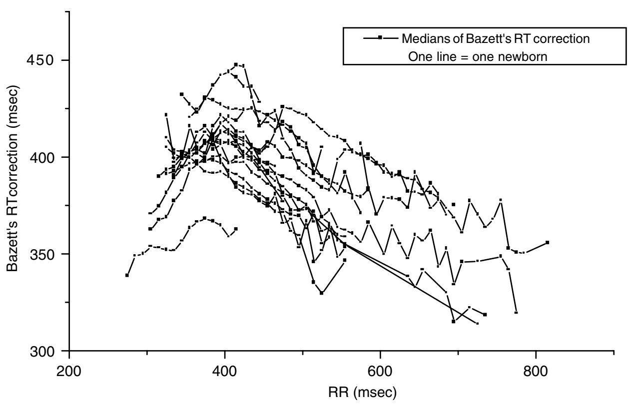

Figure 3. RT – RR relations: Each line represents individual median values of RT corrected with Bazett formula (RT = QT – 30 milliseconds). We can observe that Bazett formula was inadequate to correct RT interval for heart rate in the newborns studied.

induced by the beat to beat analysis, but appear also to depend largely on the fact that none of the formulas was able to fit with the RT values obtained for RR intervals outside the 375 to 475-millisecond interval. This has led to an increase in the sum of squared distances between the points and the regression line and consequently to an alteration in the r correlation coefficient. Nonetheless, it is to be noted that our approach was based on individually calculated regression parameters, which is known to induce better results than when group-based regression parameters are applied to individuals.[35,36] We think that these limitations of QT correction formulas could lead to erroneous assessments concerning the effect of different interventions on QT interval duration and to misdiagnosis of QT prolongation. These results argue for an expression of QT or RT in centiles, as it has been performed in the study of Schwartz et al.,[17] rather than in QT_c or RT_c values. Another approach could be to measure QT or RT at a predetermined heart rate (e.g., 135 b.p.m for the newborns) since this would avoid the drawbacks due to the small sample sizes at the extremes of heart rate.

The relation between QT and RR is known to be altered by various conditions such as electrolyte disorders, drugs, gender (not in newborns, only after puberty),[16,37] myocardial or neurological pathologies. The autonomic nervous system (ANS), which can act directly at the cellular level or indirectly through heart rate modulation, is also an important source of QT changes.[27] This influence is involved in the prolongation of QT interval duration independent of heart rate observed in adults during the sleep.[38,39] This effect was not apparent in our study since we did not observe any consistent influence of sleep state or heart rate variability on RT – RR relation in newborns. These developmental differences between newborns and adults argue for an ongoing maturation of the repolarisation rate dependence after birth. This process could depend on the modifications of cardiac channels expression that are associated with an age-related increase in QRS duration (+20 milliseconds in humans) or on the functional maturation of the autonomic nervous system.[40,41]

When comparing our results with the results of Schwartz et al.[17] who have studied standard ECGs obtained in a large cohort of different newborns, we can observed significant differences in the reference values at different heart rates (from 0 to 30 milliseconds). This is concordant with the previous reports that underline that the method used for ECG recording and ECG analysis is another possible limitation to the interpretation of QT measurements.[42] There are several technical or mathematical artefacts that could easily modify the estimate of QT duration. In the present study, we have used a validated computerised beat-to-beat analysis; however, other methods of ECG processing have been used in the neonatal period (e.g., averaged ECG analysis or manual single beats measurements of QT interval). It is generally considered that each of these quantification procedures can be used reliably in clinical practice, but it is also well-known that they are not totally

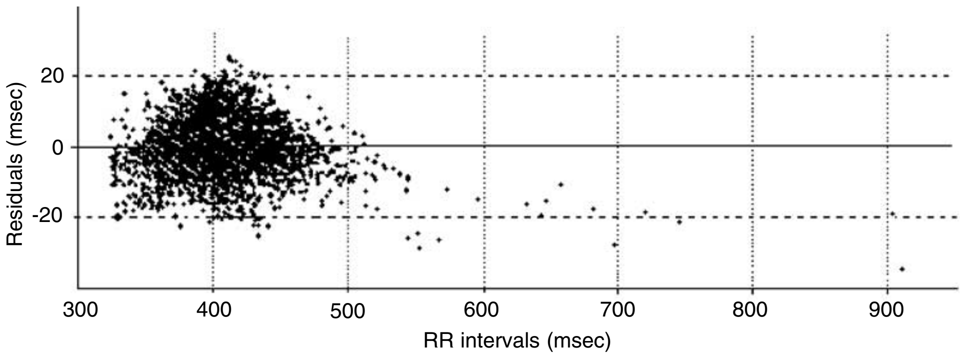

Figure 4. Representative example of the results of residual analysis in one newborn. In this case, the RT − RR relation was tested using the F11 regression formula (first rank of *r* coefficient classification). We observed that the distribution of the residuals was not homogeneous for the range of RR intervals studied and was therefore inadequate to describe the whole range of RR intervals.

equivalent. We have also observed that the comparison between the methods cited above can produce differences of more than 20 milliseconds in the QT values measured at the same heart rate for the newborns we studied (data not shown). These considerations are important when comparing individual QT measurements with specific references.

The prediction of the upper limits of normal QT by Bazett's correction has to be used with caution and we have shown that the QT − RR relation over a wide range of heart rates does not permit the use of one single adjustment equation in newborn infants. A good way to avoid conflicting results could be Holter recording method since it permits evaluation of QT duration at different heart rates and avoids the need of correction. The measurement of QT on standard ECG can be expressed in centile taking account of the ECG processing used and should be repeated at different heart rates in avoiding low and high heart rates (out of the range of 125 to 160 b.p.m.) before using the information in clinical setting.

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