Short-Term QT Variability: A Marker for Reduced Repolarization Reserve in Anthracyclin Therapy

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Abstract

Using Fiducial Sgment Averaging we measured the individual QT intervals in 5 minute recordings of patients on anthracyclin therapy. These intervals are used to calculate the short term QT-variability. The effect of anthracyclin therapy is seen in an increased variability together with an increased QTc interval both signifying a reduced repolarization reserve.

1.   Introduction

The QT interval of the human electrocardiogram (ECG) reflects the duration of the ventriculair repolarization. Prolongation of the QT interval is considered a risk for the development of arrhythmias, in particular Torsade de Points (TdP). It occurs as a congenital condition but may also be caused by pharmacological agents. Hence, in the assessment of drug safety the measurement of the QT interval plays an important role. The standard methodology prescribes that the QT interval be measured on a minimum of 3-5 complexes, usually in standard lead II and/or one of the precordial leads. The mean value of the measured QT intervals is corrected for the prevailing heart rate and is rendered as QTc.

The cardiotoxicity of anthracyclines is well known. It may cause potentially life-threatening arrhythmias and/or inflict damage on the myocardium with chronic heart failure as the late sequel. The arrhythmogenic potential of these anticancer agents is attributed to their effect on cardiac repolarization. Either alone or in combination with other medication they cause in particular a reduction in the delayed rectifier current (I_{Kr}). This leads to a diminished repolarization reserve. We hypothesized that a reduced repolarization reserve will be expressed not only in a prolonged QT interval but also in an increased beat-to-beat QT-interval variation. In the standard measurement procedure, in which the average is taken over 3-5 beats, the beat-to-beat variation remains obscure. In the present study beat-to-beat variability was measured by a special technique and was studied as a marker for reduced repolarization reserve.

2.   Methods

Patients

We examined 39 patients treated with anthracyclin-based chemotherapy (Doxorubicin, DXR) as treatment for early-stage breast cancer. DXR infusions were administered in 4 courses at least one month apart. They were part of a study in which biomarkers for cardiotoxicity of anthracyclin-base chemotherapy were evaluated [1].

ECG recording

For each course, recordings were obtained before and at 4 and 24 hours after DXR infusion. Recordings were made at rest in the supine position using the Cardio Perfect system (Welch-Allyn CardioControl, Delft, The Netherlands). The sampling rate was 600/s without filtering. The duration of the recordings was 5 minutes.

ECG measurement

We have developed a technique that makes it possible to measure with a high degree of precision the QT interval of each individual complex in the recording. The timing of the T waves is determined from 5-minute continuous standard 12-lead ECGs, using the "fiducial segment averaging" (FSA) technique [2]. FSA uses the beat-to-beat coherence of relatively small segments around the T fiducial point. The segment of each individual complex is in turn cross-correlated with the average segment of the remaining complexes and shifted till maximal correlation is achieved. This iterative process continues until no further improvement can be made. The individual QT intervals obtained in this way are then used for beat-to-beat QT variability calculations.

QT variability parameters

Poincaré plots were drawn by plotting each QT value against the preceding value (fig 1).

Short term QT variability (STV_{30}) is calculated (as proposed by Thomsen, [3]) from the mean distance orthogonal to the diagonal between the points of a Pointcaré plot in a window of 30 consecutive QT intervals. This window is moved over the total length of the recording, tracking the STV value over the full 5-

minutes. Mean short-term variability (STV_{mean}) is the average of all STV values in the 5 minutes.

The QT variability index ($QTVI_{30}$) as proposed by Berger (ref 4) is calculated over 30 consecutive QT intervals. $QTVI_{mean}$ is the average of all $QTVI_{30}$ values in the 5 minutes. The overall normalized variability index ($QTVI_N$) is calculated as above over the full 5 minutes.
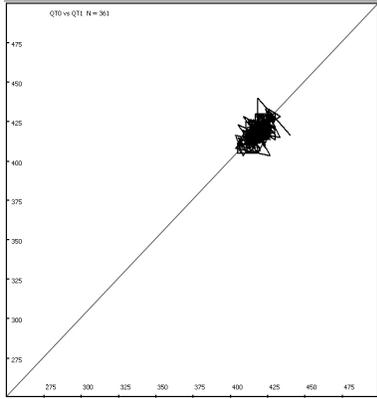
Figure 1 (Poincaré plot)

3.   Results

Mean short-term variability (STV_{mean}) was 1.25 ms (95% CI 1.08-1.42) at baseline of the first course and increased to 1.78 ms (95% CI 1.48-2.08) and 1.81 ms (95% CI 1.48-2.13) at 4 and 24 hours after DXR infusion, respectively. During the last course even larger increases were observed: at baseline STV_{mean} was 1.72 ms (95% CI 1.38-2.06), which increased to 2.45 ms (95% CI 1.69-3.22) and 3.17 ms (95% CI 2.35-3.99) at 4 and 24 hours post-administration, respectively. Table 1 summarizes the findings for first and last course and follow up.

The observed heart rate changes are all not significant different from each other. There is a small overall increase from first to last course.

Comparable changes in normalized QTVi were observed. Changes in STV_{mean} and $QTVI_N$ across de courses are depicted in fig 2 and 3.
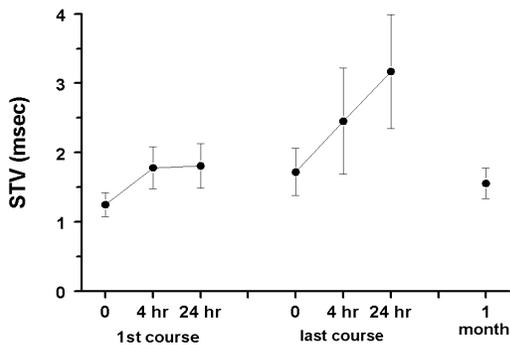
Figure 2 STV_{mean}
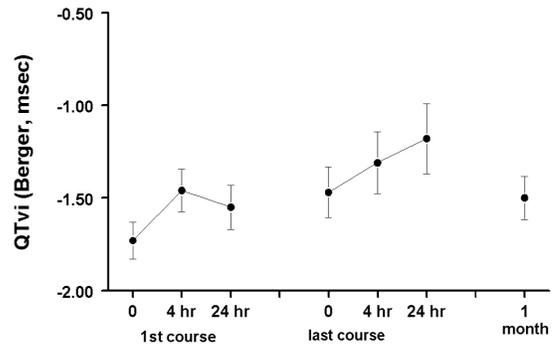
Figure 3 $QTVI_N$

Trend of STV_{30} and $QTVI_{30}$ over 5 minutes occasionally showed a substantial range of values.

QTc increased by 9.56 ms (P<0.001) at 4 hours and by 11.48 ms (P<0.0001) at 24 hours at course one. At the last course the increments were even bigger. At 4 hours 17.22 ms (P<0.0001) and 21.34 ms (P<0.0001) at 24 hours.
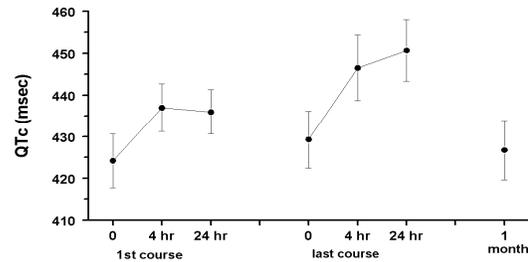
Fig 4 QTc

There were no serious arrhythmias observed during the trial period.

4.   Discussion and conclusions

Prolongation of the QT interval is a known risk factor for the occurrence of ventricular arrhythmias. It has been established that an increased QT or QTc interval aggravates the risk for sudden cardiac death in a population of the elderly [5]. Similarly, widening of the spatial angle QRS-T predicts cardiac death in a general population [6]. Treatment with anthracyclines was shown to increase QTc and to be associated with the occurrence of TdP even late after the treatment [7].

More recently the beat-to-beat variability of the QT interval has received attention as an independent marker of myocardial vulnerability.

Tabel 1	1st course					
	pre dose		4 hrs		24 hrs	
	LSM	95% - CI	LSM	95% - CI	LSM	95% - CI
RR (msec)	882	843 to 921	854	818 to 891	899	857 to 942
HR (bpm)	69	66 to 72	71	68 to 74	68	65 to 71
QT (msec)	406	397 to 415	415	406 to 423	420	412 to 429
QTc (msec)	424	418 to 431	437	431 to 443	436	431 to 441
QTvi	-1.73	-1.84 to -1.61	-1.43	-1.57 to -1.29	-1.50	-1.64 to -1.36
STV (msec)	1.25	1.08 to 1.42	1.78	1.48 to 2.08	1.81	1.48 to 2.13
last course						
RR (msec)	839	795 to 882	840	805 to 876	848	810 to 886
HR (bpm)	73	70 to 77	73	70 to 76	72	69 to 75
QT (msec)	404	393 to 415	421	410 to 432	427	417 to 438
QTc (msec)	429	422 to 436	447	439 to 454	451	443 to 458
QTvi	-1.40	-1.60 to -1.20	-1.25	-1.44 to -1.06	-1.08	-1.30 to -0.86
STV (msec)	1.72	1.38 to 2.06	2.45	1.69 to 3.22	3.17	2.35 to 3.99

	follow up	
	LSM	95% - CI
RR (msec)	861	812 to 910
HR (bpm)	72	68 to 76
QT (msec)	405	395 to 414
QTc (msec)	427	420 to 434
QTvi	-1.47	-1.62-1.33
STV (msec)	1.55	1.33 to 1.78

Thomsen et al [3] showed that an increased STV_{30}, the short term QT variability over 30 consecutive intervals, predicts d-Sotalol-induced TdP's in dogs.

Berger et al [4] had already pointed out that beat-to-beat variability in patients with dilated cardiomyopathy increases with worsening functional class, independent of ejection fraction.

Milberg et al [8] introduced the term "repolarization reserve" to indicate the ability of the myocardial membrane to maintain its normal repolarization behaviour and drew attention to the effect of anthracycline therapy in relation to I_{Kr} blockers.

We showed that after DXR infusion QT-variability increased suggesting an effect of DXR on the repolarization reserve in humans. The absence of serious arrhythmias can be explained by the relative modest dosing and concomitant modest increase in STV and QTc-linear.

It remains to be elucidated whether these effects actually relate to an increased susceptibility for anthracyclin-induced heart failure.

References

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