Anthracycline-induced cardiotoxicity, a pathophysiology based approach for early detection and protective strategies

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CHAPTER 4

Increased Beat-to-Beat variation of the QT-interval in early-stage breast cancer patients treated with doxorubicin

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ABSTRACT

INTRODUCTION Diminished repolarization reserve is regarded as predictive for pro-arrhythmic events. Recently a new method for the evaluation of changes in QT-intervals, based on the dimensions of a Poincaré plot, has been developed to assess the repolarisation reserve. Further, it was recently discovered that doxorubicin, an antitumor drug with known cardiotoxic properties, influences cardiac repolarisation in rabbits. The aim of this study was to assess the effect of doxorubicin on cardiac repolarisation in humans using this new method.

PATIENTS AND METHODS In 39 patients treated with doxorubicin for early-stage breast cancer, 5-minute ECG recordings were obtained before, at 3 and 24 hr after the first and the last scheduled doxorubicin infusion. All ECG recordings were analyzed using fiducial fragment averaging, after which beat-to-beat QT variability was calculated. Data are shown as means and 95% confidence intervals (95%CI) and compared using analysis of variance.

RESULTS Mean short term QT-interval variability (STVmean) was 1.25 msec (95%CI: 1.08-1.42) at baseline of the first course and increased to 1.78 msec (1.48-2.08) and 1.81 msec (1.48-2.13) at 3 and 24 hrs after doxorubicin infusion respectively. During the last course a higher pre-dose STVmean of 1.72 msec (1.38-2.06) compared to the first course was observed. Also, the doxorubicin-induced increases were larger; STVmean increased to 2.45 msec (1.69-3.22) and 3.17 msec (2.35-3.99) at 3 and 24 hours post-administration respectively. Comparable changes in the normalized QTVI, as proposed by Berger, were observed.

DISCUSSION AND CONCLUSION We show that after doxorubicin infusion QT-variability increased, suggesting an effect of doxorubicin on the repolarisation reserve in humans. It remains to be elucidated whether these effects actually relate to an increased susceptibility for anthracycline induced cardiac failure.

INTRODUCTION

Prolongation of the QT/QTC interval is considered a risk factor for the development of arrhythmias, in particular Torsade de Pointes (TdP). Especially, drug-induced increases in QT/QTC-interval duration receive substantial scrutiny and has been an important reason for drugs to be taken off the market. To prevent these withdrawals it is obligatory that (almost) all drugs before receiving market authorization have to be evaluated for their potential to prolong the QT-interval.(1)

However, despite the wide-spread use of QT/QTC-prolongation as marker to assess pro-arrhythmic risk, there is increasing evidence that its ability to predict drug-induced arrhythmogenicity is limited.(2) Therefore, several other markers have been suggested, including T-wave morphology changes, increased spatial dispersion of repolarisation, and elevated lability of repolarisation also known as decreased repolarisation reserve.(3)

The latter can be measured using variation in T-wave morphology (eg T-wave alternans) and beat-to-beat QT-interval variations, such is the QT variability index as proposed by Berger.(4) Recently, another method for the assessment of short term beat-to-beat variations (STV) based on the dimensions of a Poincaré plot has been suggested.(5) Indeed, increased STV was predictive for the occurrence of TdP in animals (5-7) and also in humans increased STV was noted after administration of drugs with known arrhythmogenic potential such as sotalol.(8)

The cardiotoxicity of anthracyclines is well known and includes changes in repolarization (prolongation of QT-interval), arrhythmias, and congestive heart failure which develop years after exposure.(9) The mechanism of the arrhythmogenic potential of anthracyclines has never been fully explored. Recently it has been shown in animals that anthracyclines are able to diminish repolarization reserve, but is unclear if this also occurs in humans.(10)

We hypothesized that anthracyclines also reduce repolarisation reserve in humans at clinically employed doses. Therefore, serial 5-min ECG recordings obtained in female breast cancer patients treated with doxorubicin were analyzed for beat-to-beat QT variation and assessment of repolarization reserve.

METHODS

Patient population and study protocol

The patient population consisted of early-stage female breast cancer patients who underwent adjuvant treatment with a combination of cyclophosphamide and doxorubicin chemotherapy. Main exclusion criteria included pre-existing cardiovascular diseases, prior or concomitant use of drugs with known or suspected cardiotoxic effects, distant metastases, a history of other malignant disease, a life expectancy of less than one year, and elevated transaminases above 3 times the upper limit of normal. Eligible patients were scheduled for four or five (depending on the institutional guideline) three-weekly courses of doxorubicin 60mg/m2 and cyclophosphamide 600 mg/m2. Prior to every doxorubicin and cyclophosphamide administration all patients received anti-emetic therapy according to the institutional guideline. The medical ethical committee of Leiden University Medical Center (LUMC) approved the study protocol before inclusion of the first subject. All subjects gave written informed consent before participation.

ECG recordings and analysis

For each patient 5-minute ECG recordings (sampling rate 600/s, without filtering) were made at baseline, and at 4 and 24 hours after the start of the chemotherapy at the first and the last chemotherapy course, and 6 weeks after the last course. Recordings were made using the CardioPerfect device (Welch Allyn, Delft, The Netherlands). ECG recordings were analyzed for heart rate, QT-intervals and beat-to-beat QT-variability after fiducial segment averaging (FSA) (11) with the Intraval software package (Advanced Medical Systems, Maasdam, the Netherlands). FSA is based on the coherence of relative small segments within the QRS-complex from beat-to-beat. Fiducial points of each individual complex are first detected by the analysis software supplied with the ECG-recording device. The individual complexes were then cross-correlated in turn with the average of the remainder complexes until maximum correlation was attained. In a similar way the other trigger points were identified, after which a similar fine-adjustment procedure was followed. Two independent observers assessed whether the endT-segment was correctly cross-correlated, and if necessary correlation was manually adjusted until maximum correlation was attained.

QT variability parameters

Poincaré plots were constructed by plotting each QT value against the preceding value (figure 1). Short term QT variability (STV30) was calculated as proposed by Thomsen, [3] from the mean distance orthogonal to the diagonal between the points of the Poincaré 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 min data set. This results in the following parameters: mean short-term variability (STVmean) that is defined as the average of all STV values in the 5 minutes, the QT variability index over 30 consecutive QT intervals (QTVI30) as proposed by Berger, the average of all QTVI30 (QTVImean) values, and the normalized overall variability index (QTVIN) over the entire 5 min recording period.

Heart rate variability

Heart rate variability was assessed according to the most recent guidelines using validated HRV-analysis software (The Biomedical Signal Analysis Group, Kuopio, Finland).(12) The analyses were performed for the time domain and included the RR-interval (RR), standard deviation of the RR-interval (RRSD), the root-mean square of the difference of successive R-R intervals (RMSSD) and the percentage of intervals differing more than 50 msec (NN50) were calculated. After Fourier transformation was done analyses in the frequency were performed for the very low frequency power (0-0.04 Hz), low frequency power (0.04-0.15 Hz), high frequency power (0.15-0.4 Hz) and the ratio between LF and HF were calculated.

Statistics

All variables were analyzed using a mixed model analysis of variance with time, group and time by group as fixed factors and subject as random factor. The following contrasts were calculated within the model: for both the first and the last chemotherapy course the value obtained at baseline was compared to the values at 4 and 24 hrs after start of the chemotherapy, comparison of the baselines at the first and last chemotherapy course, and comparison of the baseline at the first course with the value obtained at 6 wks follow-up value. The effects were reported as the estimate of the difference, least square mean estimates, 95% confidence intervals and the p-value. All calculations were performed using SAS for windows V9.1.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

Thirty-nine patients were included in this study. The median age of the patients was 49 years (range 30-66 years) and the mean BMI was 25.3 kg/m2 (SD 4.4). Twenty-three and sixteen patients completed the scheduled 4 or 5 courses of chemotherapy respectively, which translates into a mean cumulative doxorubicin dose of 255 mg/m2 (SD 58).

QT interval and QT variability

Mean corrected (linear) QT interval was 424 msec at baseline and was prolonged at the 4 hrs time point by 13 msec (95%CI: 7-19msec), this prolongation was still present 24 hrs after administration. During the last chemotherapy course similar increments were observed (table 2).

The mean short term QT variability (STVmean) was 1.25 msec at baseline of the first course and increased to 1.78 msec ($p<0.0001$) and 1.81 msec ($p<0.0001$) at 4 and 24 hours after the start of the doxorubicin infusion respectively. The baseline STVmean value before the last chemotherapy course was with 1.72 msec higher than the baseline value before the first course ($p < 0.01$). During the last course larger increases compared to the effects after the first course were observed; STVmean was 2.45 msec ($p <0.02$) and 3.17 msec ($p <0.0001$) at 4 and 24 hours post-administration respectively.

The normalized QTV was -1.73 (-1.83 to -1.63) at baseline and increased to -1.46 (-1.57 to -1.34) and -1.55 (-1.66 to -1.43) at 3 and 24 hours post-chemotherapy. During the last course QTV was -1.47 (-1.61 to -1.34) at baseline and increased to -1.31 (-1.47 to -1.14), -1.18 (-1.37 to -0.99) at 3 and 24 hours post-chemotherapy respectively (figure 2).

Short term RR-variability and QT-dispersion did not change significantly during the courses.

Heart rate variabilty

Mean RR-interval did not change during the courses, but we observed changes in autonomic nervous system mediated regulation of the heart rate variability (table 2). This comprised of changes in the parasympathetic and sympathetic activity in both the time and frequency domain. The change in parasympathetic activity consisted of changes in RMSSD, NN50 and the high frequency component of the spectral analysis. For the sympathetic activity changes in RRSD and the low frequency component of the spectral analyses were noted. Consistent with these changes were the changes in LF/HF ratio, suggesting a shift in sympathetic/parasympathetic balance.

Comparable changes were observed after the first and the last chemotherapy course.

DISCUSSION

The main finding of the present study is that it in humans a combination of doxorubicin and cyclophosphamide at clinically relevant doses diminishes repolarization reserve. This was

evidenced by both an increase in beat-to-beat QT-variation and changes in the normalized QT-variation index. The changes in repolarisation reserve were accompanied by a change in the heart rate variability.

Repolarization reserve is a measure of the ability of the myocardial membrane to maintain its normal repolarisation behavior.(13) Important contributors to a stable repolarisation are the normal function of the delayed rectifier potassium currents Ikr and Iks. Several factors that may influence the repolarization reserve, such as gender, electrolyte imbalances, and congestive heart failure have been described. Importantly, it was recently described that in rabbits repolarisation reserve was reduced after administration of doxorubicin.(10) In these experiments the animals became more susceptible to erythromycin-induced TdP. Interestingly, erythromycin blocks the rapid component of the delayed rectifier potassium current, Ikr. This observation is in keeping with clinical reports showing that patients being treated with anthracyclines are more susceptible to TdP after receiving Ikr-blocking drugs.(9;14-17)

It is already known that anthracyclines can prolong of the QT-interval, but the underlying mechanism is unclear.(18) We suggest that the decreased repolarization reserve may play a role in the pro-arrhythmogenic properties of anthracyclines. Also beat-to-beat QT-variation is increased after exposure to doxorubicin, as shown by the increased short term variability and changes in the normalized QT-variation index.

The molecular or electrophysiological mechanisms underlying the finding are not immediately clear. Doxorubicin is not known to directly block Ikr/Iks channels. However, it may be possible that doxorubicin specific factors, including doxorubicin induced down-regulation of Ikr, increased interventricular and transmural heterogeneity by reduced cell-to-cell coupling, apoptosis of cardiomyocytes and the fact that the secondary alcohol metabolite of doxorubicin, doxorubicinol, influences several ion-pumps play a role.(13) It is also known that repolarisation reserve is influenced by the autonomic nervous system.(12;19) As we showed that both the parasympathetic and sympathetic activity were affected by the chemotherapy, altered nervous system tone could also have contributed to our observations.

There are several limitations in our experiment to unambiguously ascribe the observed effects to doxorubicin. First, the chemotherapy included both anthracyclines and cyclophosphamide rendering it theoretically possible that the observed effects are attributable to the administration of cyclophosphamide. However, we consider this unlikely as there is no evidence that cyclophosphamide has effects on cardiac conduction. Secondly, it might have been that general stress experienced by the patients caused by their clinical condition and the anticipation of treatment altered autonomic nervous system tone. We consider it unlikely that this causes the changes in repolarization reserve during the courses, as a constant "stress-level" can be assumed during a chemotherapy course.

Finally, our data conform with the findings after doxorubicin in animals.

In conclusion, we showed for the first time in humans that assessing beat-to-beat QT-variability in 5 min ECG recordings is a suitable approach to assess changes in repolarisation reserve. The results of the analysis suggest that doxorubicin decreases repolarization reserve in female breast cancer patients and confirms results in animals. We suggest that this method may possibly be suitable as a marker for anthracycline-induced arrhythmogenicity in humans.

It is tempting to speculate that STV could also be of use in drug-development programs to identify agents capable of inducing pro-arrhythmic events, but this has to be investigated further by exploring the effects of QT-prolonging agents with and without known association to TdP.

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Table 1

Baseline characteristics	**n = 39**
	MEAN ± SD
QT variability parameters	
QT (msec)	405 ± 27
QTC (msec)	424 ± 19
QTVI	-1.73 ± 0.29
STVi (msec)	1.24 ± 0.51
HRV analysis	
RR (msec)	881 ± 117
RRSD (msec)	33 ± 13
RMSSD (msec)	29.9 ± 15.3
NN50 (%)	11.0 ± 13.0
LF (n.u.)	53.3 ± 18.0
HF (n.u.)	46.7 ±18.0
LF / HF	1.52 ± 1.11

QTVI: QT-variation index; STVi: short term variation; QTd: QT dispersion; RR: RR-interval; RRSD: RR-interval; RMSSD: root-mean square of the difference of successive R-R intervals; NN50: percentage of intervals differing more the 50 msec; LF: low frequency component of HRV-spectral analysis, normalized units; HF: high frequency component of HRV-spectral analysis, normalized units.

Table 2

	1st course			last course			follow up
	pre-dose	4 hours	24 hours	pre-dose	4 hours	24 hours	
	LSM (95% - CI)	LSM (95% - CI)	LSM (95% - CI)	LSM (95% - CI)	LSM (95% - CI)	LSM (95% - CI)	LSM (95% - CI)
QT variability parameters							
QT (msec)	406 (397 TO 415)	415 (406 TO 423)	420 (412 TO 429)	404 (393 TO 415)	421 (410 TO 432)	427 (417 TO 438)	405 (395 TO 414)
QTC (msec)	424 (418 TO 431)	437 (431 TO 443)	436 (431 TO 441)	429 (422 TO 436)	447 (439 TO 454)	451 (443 TO 458)	427 (420 TO 434)
QTVI	-1.73 (-1.84 TO -1.61)	-1.43 (-1.57 TO -1.29)	-1.50 (-1.64 TO -1.36)	-1.40 (-1.60 TO -1.20)	-1.25 (-1.44 TO -1.06)	-1.08 (-1.30 TO -0.86)	-1.47 (-1.62-1.33)
STV (msec)	1.25 (1.08 TO 1.42)	1.78 (1.48 TO 2.08)	1.81 (1.48 TO 2.13)	1.72 (1.38 TO 2.06)	2.45 (1.69 TO 3.22)	3.17 (2.35 TO 3.99)	1.55 (1.33 TO 1.78)
HRV analysis							
RR (msec)	882 (843 TO 921)	854 (818 TO 891)	899 (857 TO 942)	839 (795 TO 882)	840 (805 TO 876)	848 (810 TO 886)	861 (812 TO 910)
RRSD (msec)	33.5 (29.1 TO 37.9)	28.8 (24.8 TO 32.8)	31.5 (27.4 TO 35.6)	28.1 (24.0 TO 32.2)	26.1 (22.6 TO 29.7)	29.3 (25.1 TO 33.4)	34.7 (27.6 TO 41.7)
RMSSD (msec)	30.1 (24.9 TO 35.3)	25.2 (20.5 TO 29.8)	32.3 (26.5 TO 38.1)	24.8 (20.1 TO 29.4)	21.8 (18.1 TO 25.5)	28.7 (23.2 TO 34.3)	32.3 (24.4 TO 40.2)
NN50 (%)	10.8 (6.4 TO 15.2)	6.1 (2.4 TO 9.8)	12.7 (7.4 TO 18.0)	8.2 (4.7 TO 11.8)	4.4 (1.8 TO 7.0)	8.9 (4.0 TO 13.9)	10.9 (5.5 TO 16.3)
LF (n.u.)	54 (47 TO 60)	56 (50 TO 62)	46 (39 TO 52)	58 (51 TO 66)	58 (52 TO 63)	49 (42 TO 56)	55 (47 TO 62)
HF (n.u.)	46 (40 TO 53)	44 (38 TO 50)	54 (48 TO 61)	42 (34 TO 49)	42 (37 TO 48)	51 (44 TO 58)	45 (38 TO 53)
LF / HF	1.5 (1.1 TO 1.9)	1.7 (1.2 TO 2.2)	1.2 (0.8 TO 1.6)	2.3 (1.3 TO 3.3)	1.8 (1.3 TO 2.4)	1.3 (0.8 TO 1.8)	2.0 (1.0 TO 3.0)

QTVI: QT-variation index; STVi: short term variation; QTd: QT dispersion; RR: RR-interval; RRSD: RR-interval; RMSSD: root-mean aquare of the difference of successive R-R intervals; NN50: percentage of intervals differing more the 50 msec; LF: low frequency component of HRV-spectral analysis, normalized units; HF: high frequency component of HRV-spectral analysis, normalized units.

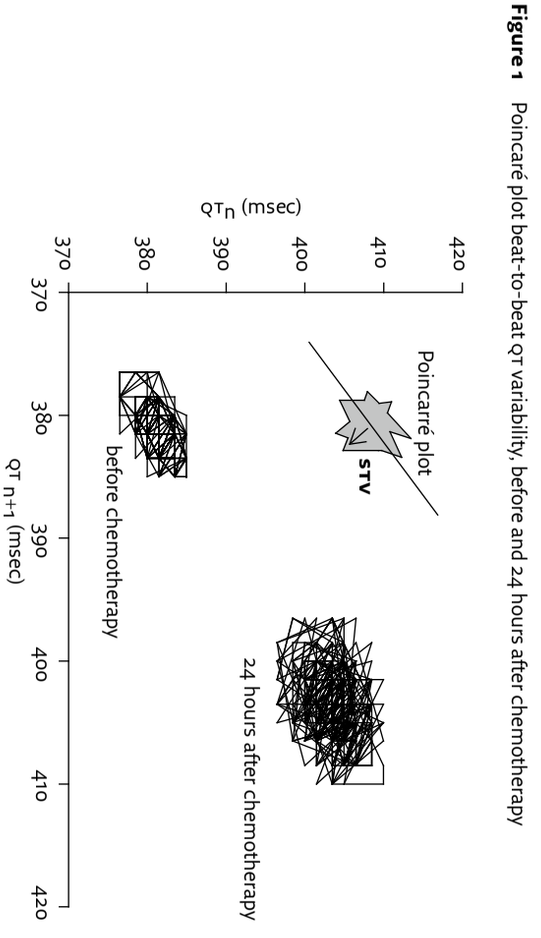

Figure 1 Poincaré plot beat-to-beat QT variability, before and 24 hours after chemotherapy

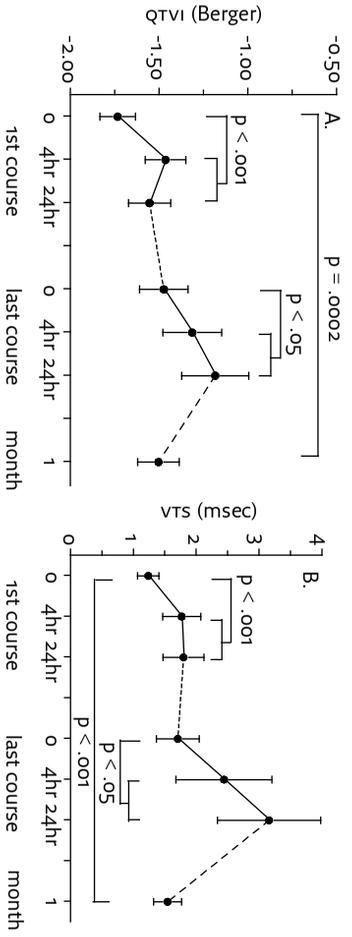

Figure 2 A: QT variation index, B: short term variability