

## QT Dispersion: a non-invasive predictor of cardiotoxicity in children treated with doxorubicin

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**Objective** : *To determine the diagnostic value of abnormal QT dispersion as a predictor of cardiac dysfunction by echocardiogram in children treated with doxorubicin.*

**Study design** : *Cross sectional study.*

**Patients population** : *Children aged 0 - 15 years who had been treated for malignancy with a cumulative dose of doxorubicin of more than 120 mg/m<sup>2</sup> were selected for this study. Patients with fever, hemoglobin less than 8 gm/dl, cardiac arrhythmia and heart block were excluded.*

**Intervention** : *Echocardiogram and 12 lead electrocardiogram at speed 50mm/sec were performed simultaneously. Systolic cardiac functions (ejection fraction and shortening fraction) were measured by a pediatric cardiologist. The QT dispersion was measured by an examiner who did not know the result of cardiac function. Sensitivity, specificity, positive predictive value and negative predictive value were used to determine the diagnostic value of abnormal QT dispersion.*

**Result** : *Fifty echocardiograms and electrocardiograms were examined in 38 children. Only one patient had clinical congestive heart failure. Abnormal QT dispersion (QT dispersion > 50 msec) and abnormal*

*systolic cardiac function (shortening fraction < 30 % and/or ejection fraction < 50 %) were found in 17 samples and 10 patients respectively. The sensitivity, specificity, positive predictive value and negative predictive value of QT dispersion > 50 msec to determine abnormal cardiac function were 90.0 %, 80.0 %, 52.5 % and 96.9 % respectively. In patients who received a cumulative dose of doxorubicin of more than 200 mg/m<sup>2</sup>, the specificity and positive predictive value of this method increased to 94.1% and 88.8% respectively.*

**Conclusion** : *Though abnormal QT dispersion cannot be used as a diagnostic test for cardiac dysfunction, it can be used as a screening test for referring patients for further diagnostic evaluation. The predictive value of abnormal QT dispersion is improved if patients have received a cumulative dose of doxorubicin of more than 200 mg/m<sup>2</sup>.*

**Key words** : *QT dispersion, Doxorubicin, Cardiotoxicity.*

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ระยะเวลา QT ในการบ่งชี้การเกิดภาวะหัวใจทำงานผิดปกติในเด็กที่ได้รับการรักษาด้วย  
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**วัตถุประสงค์** : เพื่อศึกษาถึงประโยชน์ของการใช้ค่า QT dispersion ในการใช้เป็นเครื่องมือใน  
การบ่งชี้การเกิดภาวะพิษต่อหัวใจ ในผู้ป่วยเด็กโรคมะเร็งที่ได้รับการรักษาด้วย  
ยา doxorubicin

**ประชากรที่ศึกษา** : ผู้ป่วยเด็กโรคมะเร็งที่มีอายุตั้งแต่แรกเกิดถึง 15 ปี และได้รับการรักษาด้วยยา  
doxorubicin ในขนาดของยาสะสมที่มากกว่า 120 mg/m<sup>2</sup>

**วิธีการศึกษา** : ผู้ป่วยที่ทำการศึกษาจะได้รับการตรวจคลื่นไฟฟ้าหัวใจด้วยเครื่องที่สามารถ  
บันทึกได้พร้อมกันทั้ง 12 leads ที่ความเร็ว 50 mm/sec ความสูง 1mV/10 mm  
และตรวจประสิทธิภาพการทำงานของหัวใจ (fractional shortening และ ejection  
fraction) ด้วย echocardiogram ในเวลาเดียวกัน การวัดค่า QT dispersion  
และการตรวจประสิทธิภาพการทำงานของหัวใจ ทำโดยผู้วิจัยที่ไม่ทราบผลการตรวจ  
ของแต่ละวิธี ในการศึกษาครั้งนี้ถือว่าค่า QT dispersion ที่มากกว่า 50 msec,  
fractional shortening < 30% และ/หรือ ejection fraction < 50 % เป็นค่าที่ผิดปกติ

**ผลการศึกษา** : ในผู้ป่วย 38 ราย ได้รับการตรวจคลื่นไฟฟ้าหัวใจและการทำงานของหัวใจ  
จำนวน 50 ครั้ง มีผู้ป่วยที่มีอาการของภาวะหัวใจล้มเหลว 1 ราย มีค่า QT  
dispersion ผิดปกติ 17 ราย และมีการทำงานของหัวใจผิดปกติ 10 ราย ค่า QT  
dispersion ที่ผิดปกติมีความไว ความจำเพาะ positive predictive value และ  
negative predictive value ในการวินิจฉัยความผิดปกติของประสิทธิภาพการ  
ทำงานหัวใจ ร้อยละ 90.0, 80.0, 52.9 และ 96.9 ตามลำดับ ในกรณีที่ผู้ป่วยได้  
รับยาในขนาดสะสมมากกว่า 200 mg/m<sup>2</sup> ค่า QT dispersion ที่ผิดปกติจะมีความ  
ไวและความจำเพาะเพิ่มขึ้นเป็นร้อยละ 94.0 และ 88.8 ตามลำดับ

**สรุป** : ค่า QT dispersion ที่มากกว่า 50 msec ถึงแม้ไม่สามารถใช้เป็นเครื่องมือใน  
การวินิจฉัยภาวะพิษต่อหัวใจจาก doxorubicin ได้ แต่ก็สามารถใช้เป็น screening  
test ในการส่งต่อผู้ป่วยเพื่อการตรวจวินิจฉัยที่จำเพาะต่อไป และค่า QT  
dispersion จะมีความจำเพาะเพิ่มขึ้นในผู้ป่วยที่ได้รับ doxorubicin มากกว่า  
200 mg/m<sup>2</sup>

Doxorubicin is a highly effective antineoplastic agent against various malignancies, but its therapeutic value is limited by myocardial toxicity. The cumulative dose of doxorubicin should be limited to 450 mg/m<sup>2</sup> body surface area,<sup>(1-3)</sup> although some patients have developed cardiomyopathy even at lower cumulative doses.<sup>(4)</sup> Patient at high risk must be detected, as the prognosis of this side effect depends on early diagnosis and discontinuation of the treatment before irreversible damage. Various monitoring methods had been advocated for early detection of abnormal cardiac function before clinical symptoms such as measurement of systolic and diastolic function by echocardiogram, radionuclide angiocardiogram, endomyocardial biopsy and indium-111-antimyosin monoclonal antibody.<sup>(5-9)</sup>

QT dispersion is defined as the difference between maximum and minimum QT interval from a 12 lead electrocardiogram. It reflects the variability of repolarization of cardiac myocytes, can be found as a normal variant, but also reflects the degree of ventricular function.<sup>(10-13)</sup> Doxorubicin causes specific ultrastructural changes in the myocardium. This effect can lead to scattering of cellular repolarization and cause dispersion of the QT interval. To determine whether QT dispersion can be used as a predictor for cardiac dysfunction in children treated with doxorubicin, a prospective study was performed using resting electrocardiogram and echocardiogram to evaluate systolic cardiac function.

#### Patients and methods

Thirty – eight children who had been treated with doxorubicin for childhood malignancies at cumulative dose of more than 120 mg/m<sup>2</sup> were studied.

In all patients, doxorubicin was part of a multiple drug regimen. No patient had mediastinal irradiation. At the time of this study, patients with a body temperature of more than 37.8° C, hemoglobin less than 8 gm/dl or abnormal cardiac rhythm were excluded. Electrocardiogram and echocardiogram were obtained simultaneously prior to subsequent courses of doxorubicin.

#### Measurement of QT dispersion

Standard electrocardiograms with simultaneous 12-lead acquisition were recorded at speed 50 mm/sec and amplitude 10 mV. A blinded observer measured the QT intervals manually with calipers from the onset of QRS complex to the end of the T wave. The end of T wave was defined visually as the point where T wave returned to the TP baseline. Where the T wave was interrupted by U wave before return to baseline, the QT interval was measured to nadir between the T and U waves. Leads where the T wave end could not be discerned were excluded from the analysis. Electrocardiograms with less than seven leads available for analysis were also excluded. The QT dispersion was defined as the difference between the maximum and minimum QT interval occurring in any of the 12 leads.<sup>(10,14)</sup> Five consecutive cardiac cycles were measured and mean QT dispersion was calculated.

#### Left ventricular function

Echocardiograms were performed with Aloka SSP 870 ultrasound imaging device with 3.5 and 5 MHz transducers. To eliminate inter-observer variability and bias, all echocardiograms were recorded by pediatric cardiologist, who did not know the result of

QT dispersion. The transducer was held in position for measurements. Five consecutive cardiac cycles were measured for left ventricular systolic cardiac function (ejection fraction and fractional shortening). An ejection fraction less than 50 % and/or fractional shortening less than 30 % and/or a decrease of cardiac function of more than 10 % as compared to a previous examination were considered abnormal systolic cardiac function.<sup>(15)</sup>

### Statistics

Sensitivity, specificity, positive predictive value and negative predictive value were used to determine the diagnostic value of abnormal QT dispersion.

### Results

Fifty electrocardiograms and echocardiograms were examined in 38 patients (27 male and 11 female).

Patients' age ranged from 2 to 15 years ( $7.6 \pm 4.3$  year). One third of cases had lymphoblastic leukemia and the remainder had a solid tumor. Concomitant other chemotherapeutic agents depended on the type of disease. Almost all patients were asymptomatic, only 1 patient had clinical symptoms of congestive heart failure. The cumulative dose of doxorubicin ranged from 120 - 450 mg/m<sup>2</sup> ( $313.6 \pm 95.6$  mg/m<sup>2</sup>). Five patients received a cumulative dose of doxorubicin of more than 400 mg/m<sup>2</sup>.

Abnormal cardiac function was found in 10 patients. All of these had abnormal fractional shortening, two had an abnormal ejection fraction, and a decreased ejection fraction of more than 10 % was found in three patients. (Table 1) Seventeen patients had QT dispersion of more than 50 msec., and the QT dispersion varied between 52 -120 msec ( $63.3 \pm 16.6$  msec).

**Table 1.** Cumulative dose of doxorubicin, ejection fraction (EF), shortening fraction (FS) and QT dispersion in 10 patients with abnormal systolic cardiac function.

No.	Dose(mg/m <sup>2</sup> )	EF (%)	FS (%)	QT dispersion
1	150	58	25	52.5
2	210	64	28	52.5
3	270	36	14	53.3
4	270	55	22	54.0
5	292	63	27	120.0
6	311	63	28	60.0
7	356	20	8	68.0
8	407	65	29	40.0
9	420	64	29	53.0
10	450	64	29	53.0

In these 50 samples, an increase in the dispersion of QT interval, was specific for predicting abnormal cardiac function in children who had received a cumulative dose of doxorubicin of more than 120 mg/m<sup>2</sup>. A QT dispersion of more than 50 msec had the highest sensitivity and specificity. (Table 2). The sensitivity, specificity, positive predictive value and negative predictive value of abnormal QT dispersion (> 50 msec) for predicted abnormal cardiac function were 90 %, 80 %, 52.5 % and 96.9 % respectively. The accuracy and likelihood ratio of this method were 82 % and 4.5 respectively. In patients who had received a cumulative dose of doxorubicin of more than 200 mg/m<sup>2</sup>, the sensitivity, specificity, positive predictive value and negative predictive value of abnormal QT dispersion increased to 88.8 %, 94.1 %, 88.8 % and 94.1 % respectively. The accuracy and likelihood ratio were increased to 92 % and 15.1 respectively.

## Discussion

Doxorubicin cardiotoxicity affects 2 – 20 % of patients receiving this drug and mortality rate of about 50 % of patients with clinical congestive heart failure. The amount of morphologic myocardial change

is indirect relationship to the amount of drug given, thus the cumulative dose of doxorubicin must be limited to 450 mg/m<sup>2</sup>.<sup>(10)</sup> Individual patients may have a lower threshold and develop left ventricular dysfunction at a lower dosage. If early left ventricular dysfunction is unrecognized and untreated, additional doxorubicin therapy may lead to irreversible severe congestive heart failure. This study found one patient with clinical congestive heart failure, and 10 of 38 patients (26 %) had evidence of cardiac dysfunction by echocardiogram. Five of these had cardiac dysfunction even after receiving a low cumulative dose (< 300 mg/m<sup>2</sup>) of doxorubicin. This demonstrates that serial cardiac monitoring is needed to insure cardiac dysfunction is detected early.<sup>(15-17)</sup>

Various monitoring methods had been advocated for early detection of abnormal cardiac function. Physical examination may miss over 50 % of early and reversible cardiac dysfunction and electrocardiography does not adequately predict congestive heart failure. Patterns such as a decrease in amplitude of QRS voltage in anterolateral pericardial leads have been reported, but these patterns appear too late and are not specific or sensitive enough to be a predictive monitor for doxorubicin cardio-

Table 2. The sensitivity and specificity at different QT dispersion.

QT dispersion (msec)	Sensitivity (%)	Specificity (%)
> 40	90	60
> 45	90	73
> 50	90	80
> 55	30	83
> 60	30	93

myopathy.<sup>(9,15)</sup> Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the cardiology committee of the children cancer study group recommended baseline cardiac evaluation with electrocardiogram, echocardiogram, and radionuclide angiocardigraphy. Subsequent echocardiogram was recommended before every other subsequent course of anthracycline below a cumulative dose of 300 mm/m<sup>2</sup> and before subsequent courses above 300 mg/m<sup>2</sup>. Radionuclide angiocardigraphy was recommended prior to additional cumulative dose of 400 mm/m<sup>2</sup>.<sup>(15)</sup> These serial measurements of left ventricular ejection fraction by echocardiogram and radionuclide angiocardigraphic determination were sensitive and specific for detection of early cardiac dysfunction<sup>(18-20)</sup> but their cost was moderately expensive.

This study found evidence of an increased dispersion of QT interval and impaired left ventricular function. A QT dispersion of more than 50 msec had high sensitivity and specificity to predict cardiac dysfunction in children who received cumulative dose of doxorubicin of more than 120 mg/m<sup>2</sup>, and specificity of this method increased to 94 % in patients who received cumulative dose of more than 200 mm/m<sup>2</sup>. This finding may be related to the phenomenon of cardiac toxicity of doxorubicin. The QT interval reflects complex and interrelated aspects of cardiac electrophysiology, cardiac geometry, tissue impedance, and biological signal processing. Regional changes in action potential duration and conduction play an important part in QT dispersion.<sup>(10,13,14)</sup> The cardiac toxicity of doxorubicin may be due to an alteration in calcium homeostasis,

augmentation of the slow calcium current and calcium influx, coronary artery vasoconstriction, induced myocardial edema or endomyocardial fibrosis.<sup>(10,17)</sup> All of the possible pathophysiologic changes may induce abnormality in repolarization and cause abnormal QT dispersion. Alternatively, QT dispersion could reflect indirectly the degree of left ventricular dysfunction. As QT dispersion increases, the specificity for prediction of abnormal systolic function is increased, but the QT dispersion of more than 50 msec had the highest sensitivity and specificity.

These results show that QT dispersion may be a non-invasive predictor of a patient's susceptibility to doxorubicin cardiomyopathy. There are problems in accurate measurement of the QT interval particularly in identifying the end of T wave. Careful selection of electrocardiogram with respect to T wave configuration and continued development of the method to analysis QT and QT dispersion by computerized electrocardiogram could improve the predictive accuracy of cardiac dysfunction prior to further measurement of cardiac function by echocardiogram and/or radionuclide angiocardigraphy with their attendant problems and cost.

## Conclusion

QT dispersion provides a potentially simple, cheap, non-invasive predictive monitor in patients susceptible to cardiac toxicity from doxorubicin. Serial measurement of QT dispersion may provide an important clinical benefit for detection and follow-up. As well as being an easy and relatively low cost procedure, it can be used as a screening test for referring patients to further diagnostic evaluation.

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