

## Alterations in QT dispersion in medicated schizophrenia patients following electroconvulsive therapy

Eitan Nahshoni<sup>a,d,\*</sup>, Nira Manor<sup>b,d</sup>, Faina Bar<sup>b,d</sup>, Rafael Stryjer<sup>b,d</sup>, Gil Zalsman<sup>a,d</sup>,  
Abaraham Weizman<sup>a,c,d</sup>

<sup>a</sup>Geha Mental Health Center, Campus Beilinson, Petach Tikva, Israel

<sup>b</sup>Beer Yaakov Mental Health Center, Beer Yaakov, Israel

<sup>c</sup>Felsenstein Medical Research Center, Rabin Medical Center, Petach Tikva, Israel

<sup>d</sup>Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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### Abstract

QT dispersion (QTd) is a measure of interlead variations of the surface 12-lead electrocardiogram (ECG). Increased QTd, found in various cardiac diseases, reflects cardiac instability and is associated with increased risk for cardiac death. Research suggests a link between antipsychotics, ECG abnormalities (QT prolongation) and increased sudden cardiac mortality rates. However, QTd analysis has been scarcely investigated in schizophrenia patients. We calculated QTd in 20 medicated psychotic inpatients with schizophrenia, before and 3 days after electroconvulsive therapy (ECT), concomitantly with Brief Psychiatric Rating Scale (BPRS) assessment. QT interval and the rate-corrected QT (QTc) were abnormally prolonged before ECT. However, although QT was significantly shortened, QTc showed only a marginal decrease after ECT. QTd, the rate-corrected QTd, as well as BPRS, showed a significant decrease after ECT. Further large-scale studies are warranted to determine if QTd can serve as a marker for response to ECT, and if it is a risk factor for sudden cardiac death in schizophrenia patients.

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### 1. Introduction

It is well established that patients with schizophrenia demonstrate altered autonomic nervous system (ANS) activity. Skin conductance and heart rate reactivity were demonstrated to be abnormal and determined relatively more by endogenous factors than by external stimuli (Zahn et al., 1981). Inspiratory and positional challenge tests point towards hyperexcitability in both arms of the ANS: the sympathetic nervous system and the parasympathetic nervous system (Nielsen et al., 1988). Tonic and phasic electrodermal measures, which have been widely used to detect ANS abnormalities in schizophrenia, also appeared as state and vulnerability markers (Dawson et al., 1994). Recent measures of cardiovascular ANS reactivity, using

standardized autonomic test batteries in medicated schizophrenia patients, have pointed out that a greater heart rate variability (HRV) in responders might be due to an early decrease in parasympathetic activity (Agelink et al., 1998). However, recently, measures of HRV, assessing the relation between psychotic states in schizophrenia and the different arms of the cardiac ANS, indicated that in patients who changed in psychotic state, the parasympathetic activity was significantly decreased without significant changes in the sympathetic activity (Toichi et al., 1999). It was suggested that psychotic states suppress the parasympathetic function without affecting the sympathetic function. Moreover, in another study, diminished cardiovagal tone was associated with brain laterality and clinical features in schizophrenia (Malaspina et al., 1997).

Day et al. (1990) suggested that the maximal interlead difference in QT intervals in the surface 12-lead electrocardiogram (ECG), the QT dispersion (QTd), may serve as a measure of myocardial repolarization inhomogeneity. Data from recent studies suggest that QTd usually measures 20–

\*Corresponding author. Present address: Geha Psychiatric Hospital, POB 102, 1 Helsingy St., Petach Tikva 49100, Israel. Tel.: +972-3-925-8258; fax: +972-3-924-1041.

E-mail address: enahshoni@clalit.org.il (E. Nahshoni).

50 ms in normal subjects and 60–80 ms in patients with cardiac disease (Barr et al., 1994; Higham and Campbell, 1994; Statters et al., 1994; van de Loo et al., 1994; Roukema et al., 1998). Several researches have therefore postulated that it may be a predisposing factor for arrhythmic events and sudden death (Manttari et al., 1997). According to experimental and clinical studies, the ANS modulates both the duration of cardiac ventricular repolarization, by conditioning ventricular repolarization to alterations in heart rate, and the spatial heterogeneity of repolarization (Davidowski and Wolf, 1984). Ishida et al. (1997) correlated the circadian variation of QTd with HRV in normal subjects, using 24-h ECG recordings. Recently, Nakagawa et al. (1999) used the head-up tilt test to evaluate the influence of the ANS on HRV and QTd. QTd was positively correlated with HRV measures, indicating increased sympathetic tone and/or decreased vagal tone. Furthermore, plasma norepinephrine concentrations correlated positively with QTd.

The use of QTd in psychiatry was first reported in the context of electroconvulsive therapy, in order to depict patient vulnerability to arrhythmic events immediately after treatment (Guler et al., 1998). Indeed, the results paralleled the sequence of change in autonomic modulation: a vagal discharge followed by a sympathetic surge (Gaines and Rees, 1992). Recently, Nahshoni et al. (2000) found that physically healthy patients with major depression have significantly higher values of QTd than normal controls. This observation supports the hypothesis of reduced vagal modulation in major depression, an alteration which maybe a risk factor for sudden death in depressed patients. Increased QTd was also reported for social anxiety disorder, pointing towards cardiac ANS imbalance (Nahshoni et al., 2003).

A series of case reports have associated antipsychotic treatment with the risk for serious ventricular arrhythmias and sudden cardiac death (Glassman and Bigger, 2001). Cohort studies of schizophrenic patients maintained on various antipsychotic agents have reported excess cardiovascular disease-related mortality (Ray et al., 2001). Both clinical and animal studies of antipsychotic drugs point toward ECG abnormalities, including QTc prolongation, which is thought to increase the risk for serious ventricular arrhythmias (Zarate and Patel, 2001). QTd analysis has been only recently implemented in an effort to evaluate the cardiotoxic effects of neuroleptics. Two reports have detected QT interval prolongation without a significant effect on QTd (Hartigan-Go et al., 1996; Warner et al., 1996), while a later report detected both increased QTc and QTc dispersion (Kitayama et al., 1999) in schizophrenic patients maintained on long-term antipsychotic drug regimen.

Since schizophrenia, neuroleptic treatment and ECT are associated with possible cardiac autonomic imbalance, the present study was designed to assess, for the first time, QTd, as a measure of cardiac ANS activity and repolarization heterogeneity, in relation to short-term clinical response of

schizophrenic inpatients to ECT. In order to minimize the effect of the medications and the immediate effects of ECT on cardiac autonomic activity, we evaluated the alteration in QTd in patients maintained on stable drug treatment, before and 72 h after the last ECT. It was hypothesized that ECT course will be associated with increased parasympathetic modulation, as was reported by us previously in major depressed patients (Nahshoni et al., 2001).

## 2. Experimental procedures

### 2.1. Subjects

The study population included 20 psychotic inpatients (nine women, 11 men; age  $43.5 \pm 13.3$  years), with schizophrenia, paranoid type, diagnosed using the Structured Clinical Interview for DSM-IV (SCID-I/P 2.0) (First et al., 1996). Physical examination, ECG and routine blood tests were within normal limits and no history of any physical illness was obtained. The average duration of schizophrenia in our cohort was  $13.8 \pm 10.8$  years. Three patients had their first hospital admission and six had a family history of mental disorders. The study was approved by the Institutional Review Board of Beer Yaakov Mental Health Center. All patients provided written informed consent, after the nature of the study was fully explained to them.

### 2.2. Drugs

All patients were maintained on antipsychotic medications: haloperidol (5–20 mg/day,  $n=4$ ), perphenazine (8–16 mg/day,  $n=3$ ), levomepromazine (150–600 mg/day,  $n=3$ ), zuclopenthixol (150 mg/day,  $n=1$ ), risperidone (2–5 mg/day,  $n=4$ ), olanzapine (15–20 mg/day,  $n=3$ ), fluphenazine decanoate (25 mg,  $n=1$ ), and fluphenazine (10 mg/day,  $n=1$ ). Two patients were also maintained on biperiden hydrochloride (4–6 mg/day), two on promethazine (100–150 mg/day), one on procyclidine hydrochloride (10 mg/day), and one on amantadine (200 mg/day). Over the course of the study the drug regimen was not changed. The study population was neither on vasoactive or anxiolytic agents, except those mentioned above, nor were they smokers or drug or alcohol consumers.

### 2.3. ECT

The patients were subjected to ECT because of non-response to pharmacotherapy trials or because it was indicated by the urgency of the patient's declining psychiatric status. Premedication consisted of atropine (0.5 mg) and the anesthetic medications administered were methohexital sodium (1.0 mg/kg) and succinylcholine (0.5 mg/kg), which were adjusted on the basis of the response after the first ECT treatment. The electrical dose was titrated to seizure threshold during the first treatment (Sackeim et al., 1987). Seizure

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