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# Short-term effect of percutaneous recanalization of chronic total occlusions on QT dispersion and heart rate variability parameters

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**Background:** QT dispersion (QTd), which is a measure of inhomogeneity of myocardial repolarization, increases following impaired myocardial perfusion. Its prolongation may provide a suitable substrate for life-threatening ventricular arrhythmias. We investigated the changes in QTd and heart rate variability (HRV) parameters after successful coronary artery revascularization in a patient with chronic total occlusions (CTO).


**Material/Methods:** This study included 139 successfully revascularized CTO patients (118 men, 21 women, mean age 58.3±9.6 years). QTd was measured from a 12-lead electrocardiogram and was defined as the difference between maximum and minimum QT interval. HRV analyses of all subjects were obtained. Frequency domain (LF: HF) and time domain (SDNN, pNN50, and rMSSD) parameters were analyzed. QT intervals were also corrected for heart rate using Bazett's formula, and the corrected QT interval dispersion (QTcd) was then calculated. All measurements were made before and after percutaneous coronary intervention (PCI).

**Results:** Both QTd and QTcd showed significant improvement following successful revascularization of CTO (55.83±14.79 to 38.87±11.69;  $p < 0.001$  and 61.02±16.28 to 42.92±13.41;  $p < 0.001$ ). The revascularization of LAD (n=38), Cx (n=28) and RCA (n=73) resulted in decrease in HRV indices, including SDDN, rMSSD, and pNN50, but none of the variables reached statistical significance.

**Conclusions:** Successful revascularization of CTO may result in improvement in regional heterogeneity of myocardial repolarization, evidenced as decreased QTcd after the PCI. The revascularization in CTO lesions does not seem to have a significant impact on HRV.

**Key words:** chronic total occlusions • percutaneous coronary intervention • QT dispersion • heart rate variability

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## Background

Chronic total occlusion of coronary arteries (CTO) is observed in 35%–50% of patients with significant coronary artery disease (CAD) undergoing diagnostic angiography [1,2]. Percutaneous coronary intervention (PCI) for CTO has become a widely accepted treatment strategy and accounts for up to 20% of all PCIs [3–6]. Successful PCI of CTO has been associated with improved left ventricular (LV) systolic function, reduced anginal symptoms, increased exercise capacity, decreased need for bypass surgery, and, most importantly, an increase in survival [7,8].

QT dispersion (QTd), first introduced by Campbell et al., is the maximum inter-lead variation between the longest and shortest QT intervals recorded in the standard 12-lead electrocardiogram (ECG) [9]. Ventricular contraction and recovery are recorded as QT interval in ECG; hence, QTd represents the regional heterogeneity of ventricular repolarization duration in the 3-dimensional structure of ventricular myocardium [10–12]. It has been previously demonstrated by many studies that the defect in myocardial microvascular perfusion was presented as an increase in QTd [13–15] and the QTd was decreased following successful revascularization [16,17].

Heart rate variability (HRV) has been shown to be a reliable non-invasive technique for the quantitative analysis of the activity of the components of the autonomic nervous system [18]. Analysis of HRV consists of a series of measurements of successive RR interval variations of sinus origin, which provide information about autonomic tone [19]. Increased sympathetic tone may increase the incidence and severity of arrhythmias in the setting of ischemia. However, a decrease in vagal tone may also increase the frequency of arrhythmias [20,21]. The significance of autonomic factors for arrhythmogenesis following early reperfusion of CTOs has not yet been well established.

The myocardial defect and/or ongoing myocardial ischemia in CTO patients may lead to impairment in ventricular repolarization. The change in autonomic tone in these patients may also be related to ventricular arrhythmias. The aim of this study was to assess short-term changes in QTd and HRV parameters after successful PCI of CTO patients.

## Material and Methods

In this prospective, observational study, conducted from April 2011 to February 2013, we enrolled 139 successfully revascularized patients with CTO. All patients underwent physical examination, chest X-Ray, ECG, and transthoracic echocardiographic evaluation. CTO was defined as the lumen compromise resulting in either Thrombolysis In Myocardial Infarction

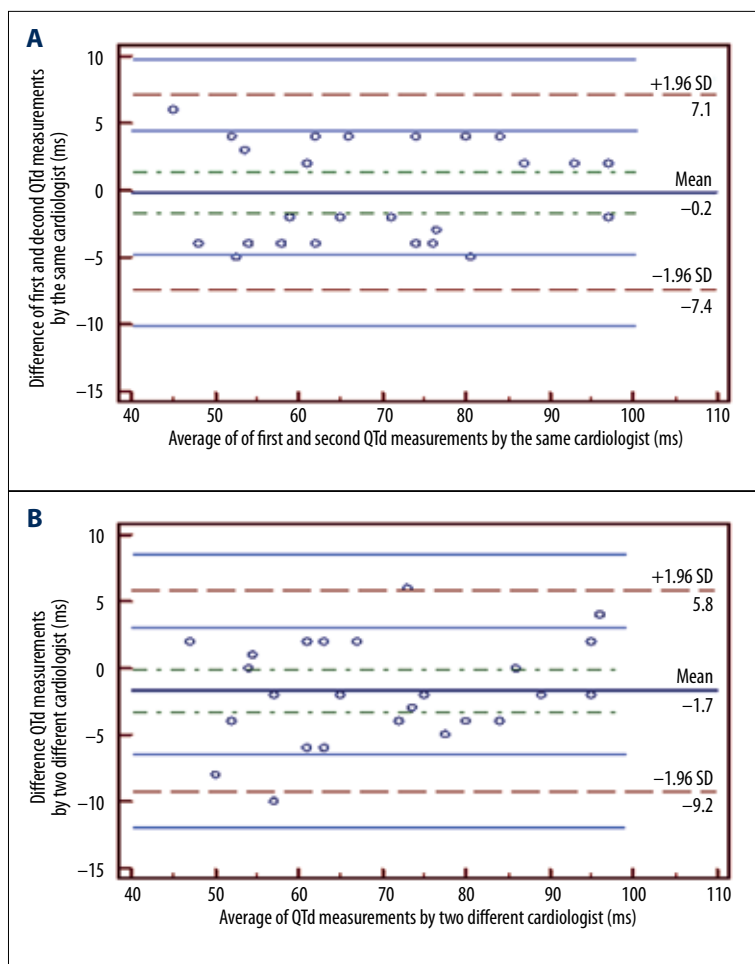
(TIMI) flow grade 0 or 1, with a likely duration of >3 months [22]. All patients included had a native vessel occlusion estimated to be of at least 3-month duration on the basis of a history of sudden chest pain, a previous myocardial infarction (MI) in the same target vessel territory, or the time between diagnosis made on coronary angiography and PCI. All patients had symptomatic angina and/or a positive functional ischemia study. We excluded patients with MI within the previous 6 months, second or third-degree atrioventricular conduction disturbances, atrial fibrillation or flutter, frequent (>10/min) ventricular extrasystoles, sinus node disease, LV hypertrophy, permanent ST changes on ECG, permanent cardiac pacemaker, abnormal serum electrolyte levels, congenital long-QT syndrome, an ECG with more than 6 missing leads, and patients taking drugs that modify the QT interval. The PCI and stent implantation were performed in a standard manner. Drug-eluting stents were used in all angioplasty procedures. After PCI, all patients were prescribed lifelong aspirin; in addition, clopidogrel was prescribed for at least 12 months in all participating sites. Patients were followed prospectively by telephone interview or outpatient visit after 30 days. Procedural success was defined as successful recanalization and dilation of at least 1 CTO per patient with or without stent implantation, residual stenosis of < 50%, and TIMI flow >2.

The study protocol was approved by the institutional ethics committee, and all patients provided written informed consent.

### Electrocardiographic and QT dispersion analysis

The QT intervals and QTd were measured manually from the standard ECGs available before and after PCI. Standard 12-lead ECG was recorded at a 25 mm/s paper speed and a gain of 10 mm/mV (Montara Instrument EU 250 Electrocardiograph, Milwaukee, WI, USA). All ECGs were scanned at a 600 dpi resolution and computer-based analysis was performed by 2 independent cardiologists who were blind to the timing of the ECGs and patients data. To measure QTd, QT interval was defined as the interval between beginnings of QRS complex to the point the T wave returned to isoelectric line and for each lead the mean of QT interval in 4 consecutive beats was measured. When the U wave was present, the end of the T wave was defined as the nadir of the curve between the T and the U waves. Dispersion of the QT interval was measured as the difference between the maximum and minimum mean QT intervals recorded in any of the 12 leads of the standard ECG. For each patient, QTd was measured twice; once 6–12 hours before, and once 6 hours after PCI. Both the QT interval and QTd were rate-corrected with a modification of Bazett's formula (corrected QT interval – QT/square root of the RR interval) (QTcd) [23].

After completing the computer-based measurements, QTd was tested to identify intra-observer variability in 25 randomly



**Figure 1.** Bland-Altman plots demonstrating the 95% limits of agreement between (A) the repeated measurements of QTd by the same observer and (B) between the measurement of QTd by 2 different observers, in 25 randomly selected patients.

selected patients using the Bland-Altman method. The 95% limit of agreement for QTd was acceptable ( $-7.4$  and  $7.1$  ms, respectively) (Figure 1A). The same ECGs were measured by another cardiologist to ascertain inter-observer variability. The 95% limit of agreement for QTd was  $-9.2$  and  $5.8$  ms, respectively (Figure 1B).

### Heart rate variability

HRV was analyzed using data from Holter recordings (Synetec™ version 1.10, Ela Medical, Montrouge, France), which were started on hospital admission. R-R data from Holter recordings were assessed using power spectral analysis before and within 24 hours after PCI. HRV was assessed in 2 ways: time- and frequency-domain analyses. We calculated time-domain HRV indices of standard deviations of the normal-to-normal QRS intervals (SDNN), square roots of the mean squared differences of successive N-N intervals (rMSSD), and percentage of consecutive RR differences  $>50$  ms (pNN50). For frequency domain HRV indices, we used the Fourier transform method for the spectral measurements, and the heart rate spectrum between 0.003 and 0.40 Hz was defined as total energy ( $\text{ms}^2$ ).

This energy was divided into 2 components: low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.16–0.40 Hz).

### Statistical analysis

Continuous variables are reported as mean  $\pm$  standard deviations (SD) and categorical variables are expressed as percentages. Comparison of categorical and continuous variables between the 2 groups was performed using the  $\chi^2$  test and unpaired t-test, respectively. A value of  $p < 0.05$  was considered statistically significant. SPSS 15.0 for Windows statistical software package program was used for statistical analysis.

### Results

Baseline patient characteristics are shown in Table 1. The mean patient age was  $58.3 \pm 9.6$  years, 118 (84%) were male and 59 (42%) had diabetes mellitus. The cohort included 47 patients (34%) with prior MI and 14 patients (10%) with a history of congestive heart failure. At the baseline, most of the patients were on aspirin ( $n=139$ , 100%),

**Table 1.** Baseline demographic and angiographic characteristics of the patients (n=139).

Age (years)	58.3±9.6
Men (n/%)	118 (84%)
Prior MI (n/%)	47 (34%)
History of CHF (n/%)	14 (10%)
Hypertension (n/%)	122 (87%)
Diabetes mellitus (n/%)	59 (42%)
Hyperlipidemia (n/%)	118 (84%)
Smoking (n/%)	46 (30%)
LVEF (%)	58.9±7.7
<b>Lesion location</b>	
LAD (n/%)	38 (27%)
Cx (n/%)	28 (20%)
RCA (n/%)	73 (53%)
<b>Medications</b>	
Acetylsalicylic acid (n/%)	139 (100%)
Beta-blockers (n/%)	124 (89%)
Clopidogrel (n/%)	139 (100%)
Nitrate (n/%)	29 (20%)
ACE inhibitors (n/%)	98 (70%)
Angiotensin receptor blockers (n/%)	34 (24%)
Calcium channel blockers (n/%)	23 (16%)
Statin (n/%)	113 (81%)

ACE – angiotensin-converting enzyme; CHF – congestive heart failure; Cx – circumflex artery; LAD – left anterior descending artery; LVEF – left ventricular ejection fraction; MI – myocardial infarction; RCA – right coronary artery.

angiotensin-converting enzyme (ACE) inhibitors (n=98, 70%), lipid-lowering medications (n=113, 81%), and  $\beta$ -blockers (n=124, 89%). However, use of nitrate (n=29, 20%), calcium channel blockers (n=23, 16%), and angiotensin receptor blockers (n=34, 24%) was limited.

**Table 2.** Comparison of QT dispersion before and after percutaneous coronary intervention.

	Pre-PCI	After-PCI	p
QTd (ms)	55.83±14.79	38.87±11.69	<0.001
QTcd (ms)	61.02±16.28	42.92±13.41	<0.001

QTd – QT dispersion; QTcd – heart rate corrected QT dispersion.

The results of QTcd analysis are summarized in Table 2. Both QTd and QTcd showed significant improvement following successful revascularization of CTO (55.83±14.79 vs. 38.87±11.69;  $p<0.001$  and 61.02±16.28 vs. 42.92±13.41;  $p<0.001$ , respectively).

Regarding HRV parameters, the revascularization of the left coronary artery (LAD) (n=38) resulted in a decrease in HRV indices, including SDDN, rMSSD, and pNN50, but none of them reached statistical significance. Similar findings were observed after revascularization of the circumflex branch of the left coronary artery (Cx) (n=28) and right coronary artery (RCA) (n=73) lesions (Table 3).

## Discussion

We investigated changes in QTcd and HRV parameters in CTO patients undergoing successful percutaneous revascularization. The major findings of this study are: (1) successful revascularization may improve QTcd in patients with CTO, (2) the revascularization in CTO lesions does not seem to have a significant impact on HRV, and (3) the impact on HRV does not change with the intervention to the LAD, Cx, or RCA.

Myocardial necrosis and reversible myocardial ischemia both impact QTd. A direct relationship between the prolongation of the QT interval and myocardial ischemia has been reported by Roukema et al., who observed increased QTd in patients with exercise-induced myocardial ischemia [24]. In experimental animal studies and in human studies it has been shown that the QT interval shortened in acutely hypoperfused areas, whereas in infarcted myocardium there was a prolonged repolarization time associated with QT prolongation on the ECG [25]. The heterogeneity of the ventricular excitability was presumed to increase the propensity for arrhythmic manifestations and arrhythmic death, especially in patients with previous MI or history of CAD [10]. Perkimki et al. reported that increased QTd is related to susceptibility to reentry ventricular tachyarrhythmias, independent of degree of LV dysfunction or clinical characteristics of the patient, suggesting that the simple, noninvasive measurement of this interval from a standard 12-lead ECG significantly contributes to identifying patients at risk for life-threatening arrhythmias after a previous

**Table 3.** Changes of the heart rate variability parameters indices following percutaneous coronary intervention of the left coronary artery (LAD), circumflex branch of the left coronary artery (Cx) and right coronary artery (RCA).

	Pre-PCI	After-PCI	p
<b>LAD (n=38)</b>			
SDNN (ms)	81±32	71±26	0.2
rMSSD (ms)	29±17	24±11	0.1
pNN50 (%)	8.9±10.2	6.7±7.9	0.1
LF: HF	3.27±1.98	3.49±3.15	0.7
<b>Cx (n=28)</b>			
SDNN (ms)	73±25	64±25	0.4
rMSSD (ms)	30±13	27±11	0.4
pNN50 (%)	9.8±9.7	7.6±7.8	0.4
LF: HF	3.43±1.38	2.95±0.8	0.2
<b>RCA (n=73)</b>			
SDNN (ms)	93±51	81±42	0.2
rMSSD (ms)	30±13	27±11	0.1
pNN50 (%)	10.4±10.6	7.7±7.6	0.1
LF: HF	3.72±2.1	3.44±2.45	0.5

LF: HF ratio – low to high frequency ratio; PCI – percutaneous coronary intervention; pNN50 – percentage of consecutive RR differences >50 ms; QTcd – heart rate-corrected QT dispersion; rMSSD – square root of the mean of the squared successive differences in R–R intervals; SDNN – standard deviation of all normal R–R intervals.

MI [26]. The Strong Heart Study of assessment of QT interval and QTd for prediction of all-cause cardiovascular (CV) mortality showed that QTcd was a strong predictor of all-cause mortality and a weaker predictor of CV mortality, and that QTd is a significant predictor of CV mortality [27]. In the present study we showed that successful revascularization of CTOs resulted in significant decrease in QTd and QTcd. Our results are consistent with data reported by Yunus et al., who assessed QTd in patients with ischemia due to 1-vessel CAD without prior MI and who underwent successful PCI [28]. However, our patient population included patients with only CTOs and demonstrated the improvement in QTd in this challenging group. We suggest that the electrophysiological mechanism of action is based on a decrease in ischemia-induced prolongation of conduction and in dispersion of conduction times. The improvement in QTd with PCI in may suggest a role for revascularization in achieving more homogenous repolarization and, perhaps, greater clinical stability in CTO patients.

HRV analysis is a safe and convenient method for the evaluation of the function of the autonomic nervous system activity in accordance with guidelines for standardization [18]. Significant decrease in autonomic tone has been shown to be

an independent predictor of mortality in patients with CAD [18]. It has been shown that HRV indices decreased following coronary revascularizations [29]. In our study, although there was a trend in decrease in some HRV parameters following PCI of CTO, none of the parameters reached statistical significance. These findings were in accordance with the results reported by Tseng et al., who also showed a decrease in HRV following recanalization of CTO lesions [30]. Similar results were also reported by Szwoch et al., but they repeated the HRV analysis after 3 months and observed improvement in most of the parameters [31]. We speculate that the decrease in HRV parameters in early periods following recanalization of CTOs could be transient and might be associated with acute endothelial injury during the procedure or microembolization to the vascular bed that was previously protected from ischemia by collateral support. Consistent with the results of a previous study, localization of totally occluded coronary arteries in this study did not have significant impact on HRV results after the revascularization procedure [32]. Because the sinus node blood supply primarily comes from this artery, a significant change in HRV following successful PCI to RCA might be expected. The reason may not only be the incomplete disclosed mechanisms of HRV, but also a common

impact of each artery on the sinus node artery or other mechanisms that might be responsible from HRV changes in addition to changes in blood supply.

The main limitations of our study were lack of long-term follow-up and heterogeneous patient population with concomitant diseases. Nearly half of our patients (42%) had diabetes. Diabetes itself may be associated with depressed HRV due to diabetic autonomic neuropathy and may result in reduced HRV, inducing hemodynamic changes that involve adrenergic activation and vagal tone reduction [33]. However, our patient group may not be representative of the overall patient population with CAD. Changes in respiratory rate are known to have an effect on HRV [18]. We analyzed HRV parameters before and after PCI, but we did not measure respiratory rate. In addition, because HRV was affected by various factors such as

age of the patient and the use of ACE inhibitors and  $\beta$ -blockers, these factors might have affected our results [34–36].

## Conclusions

In conclusion, successful PCI of CTO patients may improve ventricular repolarization abnormalities, and thus may reduce the incidence of ventricular arrhythmias. Early assessment of HRV parameters does not seem to be changed following recanalization of CTO lesions.

## Declaration of interest

All authors declare that there are no conflicts of interest.

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