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Electrocardiographic changes after successful recanalization of a chronic total coronary occlusion. A systematic review and meta-analysis☆,☆☆

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ABSTRACT

Background: Observational studies suggest that in patients with a CTO successful recanalization is associated with better clinical outcome. This could be related to a reduction in the occurrence of arrhythmias, which may result from modifications of the hibernating myocardium in a CTO region.
Methods and results: We aimed to evaluate the effect of CTO PCI on electrophysiological parameters, and conducted a systematic review and meta-analysis according to the PRISMA guidelines. MEDLINE and EMBASE were searched. Titles and abstracts identified by the search strategy were independently screened by two investigators. Data were extracted and used for meta-analyses where possible.
In total, eight studies incorporating 467 patients were included in this review, evaluating the effect of successful CTO PCI on various ECG parameters. Three studies showed a significant decrease in mean QT dispersion of 17.46 ms [95% CI 10.62–24.30] after successful CTO PCI. QTc dispersion also decreased significantly, with a mean decrease of 18.74 ms [95% CI 11.53–25.94]. In one trial a significant decrease in Tp-e interval in leads V2 and V5, and a significant decrease in Tp-e/QT ratio in leads V2 and V5 post-CTO PCI were observed.
Conclusions: This first systematic review and meta-analysis suggests that successful CTO PCI is associated with an immediate decrease in ECG parameters that reflect heterogeneity in depolarization and repolarization, which could lead to a reduction in the risk for ventricular arrhythmias and sudden cardiac death. We raise the hypothesis that hibernating myocardium in a CTO region may not be as deeply "in sleep" as one would assume.

Contents

1. Introduction

Chronic total occlusions (CTOs) affect approximately 15% of patients with clinically significant coronary artery disease (CAD) [1,2]. Observational studies strongly suggest that successful elective percutaneous coronary intervention for CTO (CTO PCI) is associated with better left ventricular function (LVF), higher quality of life and improved survival,

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compared to failed CTO PCI or no CTO PCI [1,3–6]. Improvement in LVF results from restoring of coronary flow, and may hypothetically be the strongest in patients with hibernating myocardium. Sudden cardiac death (SCD) also appears to occur five times more frequent in medically treated patients with a CTO, compared to patients undergoing successful CTO PCI [6]. Nevertheless, little is known about the etiology of the worse clinical outcomes and related mechanisms (arrhythmic or non-arrhythmic death) in untreated CTO patients [4,5].

Fractional flow reserve (FFR) measurements during successful CTO PCI procedures and positron emission tomography (PET) imaging in resting condition in CTO patients have shown that almost all CTO patients have areas of hypo-perfusion, without any signs of necrosis [7,8]. Intracoronary Doppler measurements during stress testing with adenosine have confirmed these findings [9]. Arrhythmias may originate from these hypo-perfused and/or intermittently ischemic areas, and in the presence of damaged parasympathetic and sympathetic nerves the arrhythmogenic vulnerability may be even higher [10,11]. In both the *Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary)* and the *Impact of Chronic Total Coronary OcclusiononRecurrence of Ventricular Arrhythmias in Ischemic Secondary Prevention Implantable Cardioverter-Defibrillator Recipients (VACTO Secondary Study)* studies (n = 162 and 425, respectively), presence of a CTO was significantly associated with higher rates of ventricular arrhythmias and mortality compared to patients without a CTO [12,13].

These findings add to the concept that a CTO may have an important effect on the electrophysiological properties of the myocardium, resulting in an increase of ventricular arrhythmias. Thus far, research on the association between CTOs and conduction and repolarization deficits and the effects of successful revascularization on these electrophysiological phenomena has been limited.

The aim of this systematic review was to systematically examine all available evidence on the effect of CTO PCI on electrophysiological parameters and the possible correlation with ventricular arrhythmias, and to identify which electrophysiological parameters could best be used for future research.

2. Methods

PRISMA guidelines for reporting items for systematic reviews and meta-analysis [14] were used. An experienced information specialist (JL) conducted a systematic search in OVID MEDLINE and OVID EMBASE from inception to May 29th 2017. No restrictions were applied. The search consisted of controlled terms (i.e. MeSH) and many synonyms in title, abstract and author keywords. We searched for PCI (and revascularization in general) and combined this with either 1) terms for CTO and a broad search for electrophysiological parameters/autonomic regulation or 2) a broad coronary occlusion search and a narrow search for electrophysiological parameters/autonomic regulation. The latter approach served to find papers not mentioning complete occlusion in title and abstract, but in the full text. Reference lists and citations of relevant studies were crosschecked for additional publications. ENDNOTE X7.5 (Thomson Reuters) was used to manage, de-duplicate and screen the references.

The identified publications were reviewed by two investigators (JE and ID) with the use of Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). If papers were considered eligible, the quality was carefully assessed using the *Newcastle Ottawa Quality Assessment* scale (NOS).

The eligibility criteria were chosen using the research question of this review, and consisted of:

1) Investigation of CTOs;
2) Electrophysiological parameter testing before and after revascularization.

Data were extracted by two authors (JE and ID), using the eligibility criteria. Data on study- and patient characteristics, electrophysiological parameters and follow-up (i.e. survival, arrhythmic events) were collected, where available.

Binary and categorical variables are reported as percentages; continuous variables as mean ± SD or median (IQR). Meta-analyses were performed if three or more studies reported on the same electrophysiological parameter. The data regarding these parameters were entered into ReviewManager (Version 5.3. Copenhagen, the Cochrane Collaboration, 2014) to create forest plots and calculate Z-scores for overall effect using random effects models. P-levels <0.05 were considered statistically significant. I^2 was calculated as a measure of heterogeneity of the results, and 25%, 50% and 75% represented mild, moderate and severe heterogeneity, respectively.

3. Results

The search identified 1273 publications. After screening, nine observational studies describing electrocardiographic (ECG) parameters for ventricular depolarization and repolarization [15–23] were eligible for inclusion. One trial also investigated the correlation between successful CTO PCI and the occurrence of arrhythmic death 5 years after the procedure [21]. Fig. 1 depicts the PRISMA flow diagram, and in the supplementary files the full MEDLINE search is shown. Two papers were written in Polish, and the required information was extracted by a native Polish-speaking nurse.

The following types of treatment were investigated (Supplementary Table 1):

1) Successful CTO PCI only (n = 6);
2) Successful versus failed CTO PCI (n = 1);
3) Successful balloon versus stent PCI (n = 1);
4) Successful CTO PCI versus successful Coronary Artery Bypass Grafting (CABG) (n = 1).

According to the criteria of the NOS, the overall quality of the studies was moderate to poor (Supplementary Table 2). In total, 504 patients were studied and 449 underwent successful CTO PCI. In most studies follow-up was short (ranging from 12 to 48 h post-CTO PCI, up to 6 months after PCI). Study populations varied and characteristics were not always fully described (Supplementary Tables 3 and 4). The pooled mean age was 59 SD 14 years, 79% of patients were male, 46% had had previous myocardial infarction (MI) and baseline mean left ventricular ejection fraction (LVEF) was 56 SD 9%. Definitions for successful CTO PCI and techniques for ECG parameter analysis differed between studies (Supplementary Table 5).

A variety of ECG parameters that have been investigated in the papers are included in this review (Table 1). Four trials investigated QT and/or QTc dispersion (QTd, QTcd) at similar time points, so meta-analyses could be performed with these trials (Fig. 2) [15–18]. For heart rate variability (HRV) and baroreceptor sensitivity (BRS) parameters this was not possible, because these studies used different subgroups and timeframes (Table 1). Of the HRV parameters, we considered SDNN(ms) the most relevant because it is one of the four parameters recommended by the task force of the ESC + NASPE [24]. The I^2 for heterogeneity in the two meta-analyses on QTd and QTcd were high (61% and 88%, respectively) (Fig. 2).

1) QTd and QTcd (Fig. 2): successful CTO PCI was associated with a significant decrease in QTd within 1 day post-PCI, with a mean decrease of 17.46 ms [95% CI 10.62–24.30], p < 0.001. QTcd showed a significant decrease within 1 day post successful CTO PCI, with a mean decrease of 18.74 ms [95% CI 11.53–25.94], p < 0.001 (Fig. 2). Pristipino et al. reported no change in QTd and QTcd values at 1, 3 and 6 months follow-up of patients in the unsuccessful CTO PCI group (Table 1). Successful CABG was also associated with a significant reduction in QTd (78 SD

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