Infarct-related chronic total coronary occlusion and the risk of ventricular tachyarrhythmic events in out-of-hospital cardiac arrest survivors

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Abstract

Introduction Chronic total coronary occlusion (CTO) has been identified as a risk factor for ventricular arrhythmias, especially a CTO in an infarct-related artery (IRA). This study aimed to evaluate the effect of an IRA-CTO on the occurrence of ventricular tachyarrhythmic events (VTEs) in out-of-hospital cardiac arrest survivors without ST-segment elevation.

Methods We conducted a post hoc analysis of the COACT trial, a multicentre randomised controlled trial. Patients were included when they survived index hospitalisation after cardiac arrest and demonstrated coronary artery disease on coronary angiography. The primary endpoint was the occurrence of a VTE, defined as appropriate implantable cardioverter-defibrillator (ICD) therapy, sustained ventricular tachyarrhythmia or sudden cardiac death.

Results A total of 163 patients from ten centres were included. Unrevascularised IRA-CTO in a main vessel was present in 43 patients (26%). Overall, 61% of the study population received an ICD for secondary prevention. During a follow-up of 1 year, 12 patients (7.4%) experienced at least one VTE. The cumulative incidence rate of VTEs was higher in patients with an IRA-CTO compared to patients without an IRA-CTO (17.4% vs 5.6%, log-rank $p = 0.03$). However, multivariable analysis only identified left ventricular ejection fraction <35% as an independent factor associated with VTEs (adjusted hazard ratio 8.7, 95% confidence interval 2.2–35.4). A subanalysis focusing on CTO, with or without an infarct in the CTO territory, did not change the results.

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Conclusion In out-of-hospital cardiac arrest survivors with coronary artery disease without ST-segment elevation, an IRA-CTO was not an independent factor associated with VTEs in the 1st year after the index event.

Keywords Chronic total occlusion · Ventricular tachycardia · Out-of-hospital cardiac arrest · Implantable cardioverter-defibrillator

Introduction

Chronic total coronary occlusion (CTO) is common (approximately 20%) in patients presenting for diagnostic coronary angiography [1, 2]. A CTO is associated with chronic hibernating myocardium in the CTO territory, which can lead to electrical instability and may increase the risk of ventricular arrhythmias [3–5]. The exact role of a CTO in the pathophysiological mechanism of ventricular arrhythmias is not fully understood. Several studies in patients who received an implantable cardioverter-defibrillator (ICD) for primary or secondary prevention demonstrated a higher risk of appropriate ICD therapy and all-cause mortality in patients with a CTO [6–11]. A recent single-centre study demonstrated that the presence of a CTO is an independent predictor of appropriate ICD therapy in out-of-hospital cardiac arrest (OHCA) survivors with coronary artery disease who received an ICD for secondary prevention [11]. However, studies have suggested that a CTO in an infarct-related artery (IRA) is a better predictor of ventricular arrhythmias than a CTO in a non-IRA [9, 10]. The aim of the current study is to investigate the impact of an IRA-CTO on the incidence of ventricular arrhythmias in OHCA survivors with coronary artery disease who present without ST-segment elevation.

Methods

Study population

The present study is a post hoc analysis of the COACT (Coronary Angiography after Cardiac Arrest) trial, a multicentre randomised controlled trial that was conducted in 19 Dutch hospitals [12, 13]. Patients were included in the period between January 2015 and July 2018. Overall, 552 OHCA patients without ST-segment elevation were included, who were randomly assigned to undergo immediate coronary angiography or coronary angiography after neurological recovery. The COACT trial demonstrated that a strategy of immediate angiography was superior to a strategy of delayed angiography with respect to survival at 90 days [13]. The 11 centres with the highest enrolment rates were approached, of which 10 centres participated in this study. Our study population included patients who survived their index hospitalisation and displayed coronary artery disease on their coronary angiogram.

Study endpoints

In this study, a CTO was defined as a total coronary occlusion in a major epicardial coronary artery with Thrombolysis in Myocardial Infarction (TIMI) 0 flow and an estimated occlusion duration of ≥3 months [9]. Previously chronic occluded vessels that were surgically or percutaneous revascularised were not defined as CTO in this study. An IRA-CTO was defined as a CTO associated with a previous myocardial infarction in the territory of the coronary artery. Previous myocardial infarction had to be documented by Q waves on electrocardiography (ECG) and/or evidence of scar on imaging, such as regional wall motion abnormalities on echocardiography or late gadolinium enhancement on cardiac magnetic resonance imaging.

Patients were followed during 1 year after inclusion or until date of death, whichever occurred first. The primary endpoint was defined as the occurrence of a ventricular tachyarrhythmic event (VTE) after hospital discharge. A VTE was defined as appropriate ICD therapy (antitachycardia pacing and/or shock for ventricular tachyarrhythmia), sudden cardiac death (SCD) presumably due to ventricular tachyarrhythmia or documented sustained ventricular tachycardia or ventricular fibrillation during follow-up. Secondary endpoints were all-cause mortality and cardiac mortality.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical variables are presented as frequencies with percentages. Continuous variables were compared between groups using the Student t-test or the Mann-Whitney U test. Categorical variables were compared using the

What’s new?

- Previous implantable cardioverter-defibrillator studies have demonstrated a relationship between the presence of a chronic total coronary occlusion (CTO), especially in an infarct-related artery (IRA), and ventricular tachyarrhythmic events (VTEs).
- An IRA-CTO is a common phenomenon in out-of-hospital cardiac arrest survivors, but was not an independent factor for VTEs in the 1st year after the index event.
- The only independent factor associated with VTEs in the 1st year was the presence of severe left ventricular dysfunction.
A total of 163 patients with coronary artery disease from ten centres were included, who survived the index hospitalisation (Fig. 1). Of the 80 patients (49%) with a CTO in a main vessel, 57 patients had an IRA-CTO based on Q waves on ECG and/or cardiac imaging studies. Of these patients, 14 patients underwent revascularisation of an IRA-CTO, leading to 43 patients (26%) with at least one remaining IRA-CTO (Fig. 1). Baseline patient characteristics are displayed in Tab. 1. Patients in the IRA-CTO group more often had a history of a previous myocardial infarction, more frequently had a left ventricular ejection fraction (LVEF) < 35% and multivessel disease compared to patients without an IRA-CTO. Patients without an IRA-CTO were more likely to undergo a percutaneous coronary intervention (PCI), while patients with an IRA-CTO more often received pharmacological or conservative treatment \( (p < 0.01) \) during the index hospitalisation. Overall, 61% of the study population received an ICD for secondary prevention. Patients with an IRA-CTO were more likely to receive an ICD.

During a follow-up of 1 year, 12 patients (7.4%) experienced at least one VTE. The VTE consisted of appropriate ICD therapy in all cases. The cumulative 1-year event rate was 17.4% versus 5.6% in the IRA-CTO and no IRA-CTO group, respectively \( (p = 0.03) \) (Fig. 2). Multivariable Cox regression analysis demonstrated that only LVEF < 35% was an independent factor associated with a VTE \( (\text{adjusted hazard ratio (HR) 8.7, 95% confidence interval (CI) 2.2–35.4}) \) (Tab. 2). There was no difference in the cycle length of the documented ventricular arrhythmia between patients with and without IRA-CTO \( (212 ± 28 \text{ ms vs } 261 ± 69 \text{ ms, respectively, } p = 0.18) \). Furthermore, when excluding the 14 patients with successful revascularisation from the no IRA-CTO group, the results of the multivariable analysis did not change (data not presented). These 14 patients had no VTE during follow-up.

As a subanalysis we evaluated whether the presence of an unrevascularised CTO \( (n = 54) \), irrespective of a localisation in an IRA, was associated with a VTE. The cumulative 1-year event rate was 16.1% versus 5.1% in the CTO and no CTO group, respectively \( (p = 0.03) \). Multivariable analysis demonstrated that a CTO was also not an independent factor associated with VTEs (Electronic Supplementary Material, Table S1).

During follow-up 3 patients \( (1.8\%) \) died after hospital discharge. One death was classified as a cardiac death and the other 2 deaths were classified as non-cardiac death. No SCD occurred during follow-up.

**Discussion**

In OHCA survivors with coronary artery disease without ST-segment elevation at presentation, the presence of an IRA-CTO was not independently associated with a VTE within the 1st year. Only severe left ventricular (LV) dysfunction was independently associated with a higher risk for VTEs.

**Relationship between IRA-CTO and VTE**

The presence of a CTO is common in patients with coronary artery disease. In the overall COACT population, thus survivors of OHCA without ST-segment elevation, a CTO was present in 36% in patients who underwent CAG \( [13] \). In the present study, including only
patients with coronary artery disease, 49% of patients had a CTO in at least one main vessel. This prevalence is comparable to previously reported prevalence rates of CTO in patients with coronary artery disease [6, 11, 13, 14]. In 71% of patients with a CTO, at least one CTO could be identified as an IRA-CTO based on ECG or cardiac imaging. While there are limited data concerning the prevalence of IRA-CTOs, this percentage is consistent with previous studies in which 56–74% of CTOs were located in an IRA [10, 15]. Several ICD studies have shown that the presence of CTO is an independent predictor for ventricular arrhythmias [6–11]. However, the study by Raja et al. did not demonstrate this relationship [16]. Recent studies showed that this discrepancy may be explained by the presence of a CTO in an IRA or a non-IRA [9, 10, 17]. There are different pathophysiological mechanisms for the increased risk of VTEs in patients with an IRA-CTO, but the most prevailing theory is that the presence of scar with areas of activation delay is a prerequisite for the induction and maintenance of reentry tachycardias [18, 19]. Furthermore, the myocardium supplied by the CTO is a chronically hibernating myocardium which is associated with proarrhythmic properties despite the presence of a well-developed collateral system [20]. The present study demonstrates that patients with an IRA-CTO have an increased risk of a VTE in the 1st year after the index event. This increased VTE risk seems to be related to a higher proportion of patients with severe LV dysfunction in the IRA-CTO group (i.e. collinearity). Severe LV dysfunction was the only independent factor associated with a higher VTE risk. LV dysfunction is a well-known risk factor for recurrent ventricular arrhythmias in survivors of cardiac arrest [6, 11]. The discrepancy in the prognostic role of a CTO between our study and previous studies may be explained by the relative short follow-up period, smaller sample size and lower proportion of ICD carriers in our study population [6, 10, 11]. Despite these limitations of our study, we can conclude that severe LV dysfunction is a stronger predictor of VTE than the presence of an IRA-CTO.

### Table 1  Baseline characteristics

| Characteristic | All patients (n = 163) | No IRA-CTO group (n = 120) | IRA-CTO group (n = 43) | p-value |
|----------------|-----------------------|---------------------------|-----------------------|---------|
| Age, years     | 64 ± 10               | 64 ± 11                   | 66 ± 9                | 0.21    |
| Sex, male      | 148 (91)              | 108 (90)                  | 40 (93)               | 0.76    |
| **Medical history** |                       |                           |                       |         |
| – Diabetes mellitus | 23 (14)               | 20 (17)                   | 3 (7)                 | 0.13    |
| – Hypertension  | 80 (49)               | 60 (50)                   | 20 (48)               | 0.86    |
| – Previous MI   | 50 (31)               | 27 (23)                   | 23 (54)               | <0.01   |
| – Previous PCI  | 33 (20)               | 22 (18)                   | 11 (26)               | 0.38    |
| – Previous CABG | 14 (9)                | 7 (6)                     | 7 (16)                | 0.05    |
| – Hypercholesterolaemia | 53 (33)             | 37 (31)                   | 16 (39)               | 0.34    |
| – Renal dysfunction (MDRD-GFR < 60) | 22 (14)               | 15 (13)                   | 7 (16)                | 0.60    |
| – LVEF ≤35% (n = 159) | 40 (25)               | 22 (19)                   | 18 (43)               | <0.01   |
| – Multivessel disease | 91 (56)              | 59 (49)                   | 33 (74)               | <0.01   |
| **Treatment after CAG** |                   |                           |                       |         |
| – Conservative  | 37 (23)               | 15 (13)                   | 22 (51)               | <0.01   |
| – CABG          | 26 (16)               | 21 (18)                   | 5 (12)                |         |
| – PCI during first CAG | 68 (42)             | 57 (48)                   | 11 (26)               |         |
| – Staged PCI    | 27 (17)               | 22 (19)                   | 5 (12)                |         |
| – PCI during first CAG and staged | 5 (3)          | 5 (4)                     | 0 (0)                 |         |
| **Medication at discharge (n = 160)** |               |                           |                       |         |
| – β-blocker     | 151 (94)              | 110 (94)                  | 41 (95)               | 1.00    |
| – ACE inhibitor | 133 (83)              | 98 (84)                   | 35 (81)               | 0.81    |
| – Statin        | 143 (89)              | 102 (87)                  | 41 (95)               | 0.16    |
| – Diuretics     | 59 (37)               | 40 (34)                   | 19 (44)               | 0.27    |
| – Amiodarone    | 10 (6)                | 7 (6)                     | 3 (7)                 | 0.73    |
| – Digoxin       | 7 (4)                 | 6 (5)                     | 1 (2)                 | 0.68    |
| ICD implantation | 99 (61)              | 62 (52)                   | 37 (86)               | <0.01   |

Results are presented as mean ± SD or count (percentage)

CTB coronary artery bypass graft, CAG coronary angiography, GFR glomerular filtration rate, ICD implantable cardioverter-defibrillator, IRA-CTO infarct-related artery chronic total coronary occlusion, LVEF left ventricular ejection fraction, MDRD Modification of Diet in Renal Disease, MI myocardial infarction, OHCA out-of-hospital cardiac arrest, PCI percutaneous coronary intervention
Observational studies have shown that CTO PCI may be associated with LV reverse remodelling and improvement of various electrocardiographic parameters (e.g. QT dispersion, late potentials) that are associated with ventricular arrhythmias and SCD [4, 21]. Randomised trials, however, only demonstrated improvement in regional LV function and not in global LV function [22, 23]. The number of patients who underwent a CTO PCI in our study population was too small to perform solid statistical analysis. Thus, it is not known whether CTO PCI in the specific subset of OHCA survivors without ST-segment elevation is beneficial.

Prophylactic ICD in CTO patients

Finally, the current guidelines recommend not to implant an ICD in OHCA survivors when there is a reversible factor, such as cardiac ischaemia [24]. The majority of our study population underwent revascularisation and only 61% received an ICD. Small increases in troponin levels may present a challenge for clinicians, as it is difficult to determine whether this elevation is due to ventricular tachyarrhythmia and resuscitation or due to ischaemia causing the ventricular tachyarrhythmia. In the first case, an ICD is warranted; in the second case revascularisation seems to be sufficient. Data from the current study are reassuring; as no patient without an ICD died suddenly in the 1st year.

Study limitations

Several limitations of this study should be considered. First, the small sample size, limited number of events and the short follow-up period hamper the power of our study to detect a potentially clinically significant relationship between IRA-CTOs and the occurrence of VTEs. Second, only 61% of the study population received an ICD, which may lead to underestimation of the true incidence of VTEs. However, patients without an ICD were deemed to be at low risk for a VTE by the treating physician. On the other hand, our study population is unique, as prior studies investigating IRA-CTOs as a potential risk factor for VTEs were limited to an ICD population [6–11].

Conclusions

In OHCA survivors with coronary artery disease without ST-segment elevation, severe LV dysfunction, and not an IRA-CTO, was an independent factor associated with VTEs within the 1st year.

Conflict of interest

M. van der Graaf, L.S.D. Jewbali, J.S. Lemkes, E.M. Spoormans, M. van der Ent, M. Meuwissen, M.J. Blans, P. van der Harst, J.P. Henriques, A. Beishuizen, C. Camaro, G.B. Bleeker, N. van Royen and S.C. Yap declare that they have no competing interests.

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