

Chronic total improvement in ventricular function and survival

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Abstract: Coronary chronic total occlusions (CTOs) represent a frequent lesions' subset observed in everyday catheterization laboratory practice. Previously considered to be an indication for surgical myocardial revascularization, the interest of interventional community in CTOs has exponentially grown during the last decade, particularly thanks to an important development in dedicated equipment and techniques, and has led to the achievement of high rates of success and low rates of complications by expert operators. In absence of available data from randomized trials, several observational studies have shown the benefits of CTO percutaneous coronary intervention (PCI) in insuring better cardiovascular outcome, particularly by improving ventricular function and reducing cardiac mortality.

Keywords: Chronic total occlusion (CTO); percutaneous coronary intervention (PCI); left ventricular function; clinical outcome

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Introduction

Coronary chronic total occlusions (CTOs) are defined as an occluded coronary segment with thrombolysis in myocardial infarction (TIMI) flow 0 for ≥ 3 months duration (1). According to EuroCTO club consensus, the occlusion duration could be divided into 3 levels of certainty: (I) "certain" (angiographically confirmed), in cases where a previous angiogram performed greater than 3 months ago, confirmed the presence of TIMI 0 flow; (II) "likely" (clinically confirmed), objective evidence of an acute myocardial infarction in the territory of the occluded artery without other possible culprit arteries of more than 3 months before the current angiogram; (III) "undetermined", TIMI 0 flow and angiographic anatomy suggestive of long-standing occlusion with stable anginal symptoms unchanged in the last 3 months or evidence of silent ischemia (1). Coronary CTOs represent a frequent lesions' subset observed in ~15 % of patients undergoing coronary angiography, with a higher prevalence in those with previous coronary artery bypass grafting (CABG) (2,3). Previously considered to be an indication for surgical

myocardial revascularization, the interest of interventional community in CTOs has exponentially grown during the last decade, particularly thanks to an important development in dedicated equipment and techniques (4), and has led to the achievement of high rates of success and low rates of complications by expert operators.

In absence of available data from randomized trials, several observational studies (5-10) have shown the benefits of CTO percutaneous coronary intervention (PCI) in insuring better cardiovascular outcome, particularly by improving ventricular function and reducing cardiac mortality.

Impact of successful CTO PCI on left ventricular function

Although ipsi- and contralateral collaterals are generally well developed in presence of a CTO, coronary flow reserve is significantly reduced in 95% of the cases, thus not preventing ischemia, but ensuring myocardial viability which allows further recovery after revascularization (11).

Indeed, when coronary flow is restored, the hibernating or stunned but viable myocardium at least partially restores the contractile function, resulting in regional and global left ventricular function improvement (5).

Several methods have been used to assess left ventricular function before and after CTO PCI such as: left ventricular angiography, echocardiography, nuclear imaging, and magnetic resonance imaging (MRI). Chung *et al.* (6) showed, 6 months after successful CTO recanalization, a significant improvement in left ventricular ejection fraction (LVEF) in patients without previous myocardial infarction (from $59.5\% \pm 13.7\%$ to $67.3\% \pm 14.6\%$, $P < 0.001$), while in patients with prior myocardial infarction the LVEF increased, albeit not significantly. Erdogan *et al.* (7) reported a significant increase in global longitudinal strain after successful CTO PCI; furthermore, this increase in the global longitudinal strain was correlated with an increase in LVEF. Although LVEF did not change significantly, Baks and colleagues (8) observed a favorable effect on ventricular remodeling with a significant decrease in both mean end-systolic and end-diastolic volume indexes as assessed by MRI.

Recently, Hoebers and coworkers (12) performed a weighted meta-analysis of 34 studies (including 2,243 patients) addressing the change of LVEF after successful CTO PCI. After a follow-up period ranging from 1 to 36 months, LVEF increased significantly with a pooled estimate of 4.44% [95% confidence interval (CI): 3.52-5.35, $P < 0.01$]. Although it is common to consider a difference of at least 5% in LVEF as clinically significant, the impact of CTO revascularization on LVEF was relatively underestimated in the latter meta-analysis because of the heterogeneity ($I^2 = 44\%$) between studies due to the difference in cohort sizes, CTO definition, CTO location, success definition, imaging modality and follow-up duration. Conversely, in patients with failed CTO procedures, a non-significant increase in LVEF was observed [2.21% (95% CI, 3.52-5.35; $P = 0.24$)]. Whereas, in case of re-occlusion of the CTO-target vessel, LVEF was similar and even relatively worse than that at baseline [-0.15% (95% CI, -3.14 to 2.83 ; $P = 0.92$)]. This latter fact might be explained by the loss of the protective effect of collaterals after initial restoration of antegrade flow.

In addition to LVEF, Hoebers *et al.* (12) analysed the impact of CTO PCI on ventricular remodeling. At follow up, the left ventricular end-diastolic volume, assessed in 8 studies (including 412 patients) was reduced by 6.14 mL/m^2 (95% CI, -9.31 to -2.97 , $P < 0.01$) as compared to baseline,

reflecting less adverse remodeling after successful CTO PCI.

It is well established that the improvement of LVEF and cardiac remodeling contributes to better cardiovascular outcome. Moreover, successful CTO PCI was reported to be associated with enhanced myocardial flow (5) and decreased arrhythmic vulnerability (9). For these reasons, CTO revascularization plays an important role in reducing mortality in patients with coronary artery disease.

Impact of successful CTO PCI on cardiac mortality

In a single centre experience, Jones *et al.* (10) reported the long-term survival of patients with stable angina who underwent CTO PCI attempts, showing a reduction of mortality in patients with successful CTO revascularization, in comparison with patients with PCI failure (4.5% *vs.* 17.2%, respectively; $P < 0.0001$). Similarly, in a prospective multicenter registry, Mehran *et al.* (13), showed that successful PCI was an independent predictor of lower cardiac mortality and reduced need for CABG at long-term follow up. In a recent analysis of UK Central Cardiac Audit Database, George *et al.* (14) reported that successful PCI of at least one CTO was associated with improved survival [hazard ratio (HR): 0.72; 95% CI, 0.62-0.83; $P < 0.001$]. Likewise, a reduction of cardiac mortality was also observed with successful retrograde and antegrade dissection/re-entry techniques (15,16).

A meta-analysis of 13 observational studies by Joyal *et al.* (17), addressed the outcomes of patients who underwent successful versus unsuccessful CTO interventions. The investigators demonstrated a survival benefit for those who underwent CTO recanalization [14.3% *vs.* 17.5%; odds ratio (OR): 0.56] as well as reductions in the need for subsequent CABG and in residual or recurrent angina. A more recent meta-analyzing of 27 studies (15,432 CTO patients) confirmed that successful CTO PCI was associated with reduced mortality in comparison to failed CTO PCI (OR: 0.52; 95% CI, 0.43-0.62; $P < 0.01$) (9).

On the other hand, comparing the different management strategies of patients affected by CTOs, outcome data reported in the Italian Registry of Chronic Total Occlusion (IRCTO) were in favor of PCI. Indeed, at 1 year follow-up, patients undergoing PCI showed lower rate of cardiac death (1.4% *vs.* 4.7% and *vs.* 6.3%; $P < 0.001$ and $P < 0.001$) in comparison with those treated with only medical therapy and CABG, respectively (18). Interestingly, this benefit remains after propensity score matching analysis.

However, despite the high achievable success rates and the

development of equipment and techniques, a wise patients' selection remains the key issue able to insure the best clinical outcome of CTO PCI and to avoid complications. In fact, the decision-making process of whom to undergo CTO PCI, should pass through a rational analysis, taking into account patient's symptoms, ischemia burden, and viability demonstration (19). In addition, operator's experience was reported to be closely correlated to the success of CTO PCI (15). Thus, current guidelines state that CTO PCI is reasonable in "patients with appropriate clinical indications and suitable anatomy when performed by operators with appropriate expertise" (Class IIA) (20).

Ongoing randomized trials

At least three major randomized trials are under way. The EXPLORE trial is a randomized clinical trial aiming to investigate the impact of recanalizing a CTO in a non-infarct related artery after primary PCI for STEMI. Three hundred patients were randomized to either elective PCI of the CTO within seven days or standard medical treatment. The primary endpoints are LVEF and left ventricular dimensions, as assessed by MRI; the results are expected during 2015. A Korean group is currently randomizing patients with CTOs and stable angina to PCI *vs.* medical therapy [DECISION-CTO (NCT01078051)] to evaluate the impact of the intervention on cardiac mortality and myocardial infarction during a 5-year follow-up period. Finally, the EURO-CTO trial (NCT01760083), is focusing on the impact of PCI on the quality of life parameters as compared to optimal medical therapy alone within 12 months of treatment. Moreover, the safety of PCI is being assessed by comparing clinical endpoints at 3 years. The results of this latter trial are not expected before 2016.

Conclusions

In conclusion, in experienced hands PCI represents an efficient and safe alternative in treating patients affected by CTOs able to restore at least in part left ventricular function and to reduce cardiac mortality. The expected results of the ongoing randomized trials might confirm those of observational studies and hence increase the appropriateness of CTO PCI in future guidelines.

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Footnote

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