Imaging in CTO: Should you look before you open?

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It has been almost a decade since the American College of Cardiology recommended percutaneous coronary intervention (PCI) for the treatment of patients with chronic total occlusion (CTO) with appropriate clinical indications and anatomy. Defined as 100% occlusion with TIMI (Thrombolysis in Myocardial Infarction) 0 flow for at least 3 months, CTO is not a rare finding with a prevalence of 16 to 20% in recent registries.^{1,2} However, the decision to revascularize is not trivial and many factors need to be taken into account for the patient's benefit. The use of cardiac imaging plays an important role for both appropriate indication of PCI and procedural planning.

In this section of the journal, Allahwalla et al. have provided a review of the indications and utility of adjunctive non-invasive imaging modalities for CTO, focusing on appropriate patient selection and periprocedural planning. An overview of each modality was given, providing their specific role in the assessment of patients with CTO. Given the scarcity of randomized trials on the subject, most of the studies cited were on viability and ischemic cardiomyopathy. Although they share similar characteristics, patients with CTO present a different pathophysiology with the involvement of, usually, a single-vessel territory with collateral blood supply, making its evaluation even more challenging.

One strength of the review performed is that each modality is considered from the fundamentals of the technique, that enable a clear understanding on how the imaging can assess patients with a CTO of a coronary artery. However, it remains unclear how one imaging modality can relate to another in decision-making and planning. Often, a patient may undergo different imaging modalities, incorporating physiological and anatomical evaluation with an absence of clear recommendations provided in the literature. This may be due in part to the controversial data derived from previous randomized trials that have assessed both symptoms and outcome.

For patients with a CTO, treatment options include standard approaches for stable CAD including lifestyle and risk factor modifications, and medical therapy.³ The primary indication for CTO-PCI is symptom improvement. Both angina and/or heart failure symptoms in a patient with CTO may improve after revascularization. The EUROCTO multicenter trial (A Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) assessed symptoms through the Seattle Angina Questionnaire after randomization of 396 patients to CTO-PCI versus optimal medical therapy (OMT) alone.^{4,5} They had a requirement of a non-invasive imaging study to verify the presence of myocardial viability in the territory of the CTO in case of myocardial dysfunction (reversible ischemia was present in more than 60% of patients and viability in more than 85%). PCI was successful in 86.6% of patients treated. At 12 months, the patients assigned to CTO-PCI had greater improvement in angina frequency (subscale change difference, 5.23; 95% CI 1.75 to 8.71; $P = 0.003$) and quality of life (subscale change difference, 6.62; 95% CI 1.78 to 11.46; $P = 0.007$) than OMT alone. PCI and OMT groups had similar endpoints of death and nonfatal MI (5.0% vs

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3.2%; $P = 0.32$) at 3 years. However, other major cardiovascular adverse events (MACE) such as myocardial infarction, ischemia-driven revascularization, stent thrombosis and cerebrovascular events were lower at 3 years in the PCI arm (10.7% vs 20.1%; $P = 0.019$). This study has shown superiority of PCI over OMT alone in patients with low to intermediate risk but did not include high risk patients. One of the advantages was that all other lesions were treated before randomization, making it a true assessment of the potential benefit of CTO-PCI. Also important from an imaging perspective was that viability +/- ischemia was present in the vast majority of patients. Thus, while the trial did not assess the role of imaging per se, nor did it compare one approach to another, it does suggest that imaging has a role to play in patients with symptoms as most of whom had viability ($> 85\%$) on imaging did derive benefit from CTO-PCI.

On the other hand, the DECISION-CTO trial, which randomized patients to CTO-PCI + OMT ($n = 417$) or OMT ($n = 398$) showed that CTO-PCI + OMT was not superior to OMT alone in reducing cardiovascular outcomes among patients with at least one CTO.⁶ The primary endpoints for CTO-PCI + OMT vs. OMT, at 3 years (all-cause mortality, MI, stroke, repeat revascularization), was 22.3% vs. 22.4%, with a p for noninferiority of 0.014 and for superiority = 0.86. Imaging to demonstrate ischemia or viability was not mandatory as part of the trial design, and only 272 patients underwent myocardial perfusion scan.

The EUROCTO and DECISION-CTO trials have generated some controversy around CTO-PCI. It is important to note that both studies were stopped prematurely due to lack of funds and slow enrolment, severely limiting their power.

The adequate patient selection plays a crucial role for the benefit of the intervention, as well as the expertise of the interventionist. Given the lower procedural success rates when compared to subtotal stenoses (60 to 85% versus 98%), the long procedural times, the difficult visualization of the CTO during invasive angiography and the risk of serious complications, the use of cardiac imaging may help guide the appropriate decision.^{7,8}

Cardiac imaging has the capacity, depending on the modality, to assess different time-points of the ischemic cascade. Driven by symptom, CTO-PCI could potentially benefit from imaging. However, evidence to support use of imaging in CTO is still very limited. The potential applicability of cardiac imaging in coronary CTO is wide, from measurement and assessment of ischemia, viability and left ventricular (LV) function to evaluation of predictors of recovery with revascularization, CTO-PCI planning and procedural assistance.

The use of cardiac imaging for CTO preprocedural planning is based on 3 different types of evaluation: (1) viability (dobutamine stress echocardiography (DSE), single-photon emission computed tomography (SPECT), magnetic resonance with late gadolinium enhancement (MR-LGE) or FDG positron emission tomography (PET)); (2) ischemia, with myocardial perfusion imaging (MPI) or stress MR; and (3) suitable anatomy, with CT angiography (CTA) or MR. Prospect for symptom improvement could be assessed theoretically by imaging modalities assessing physiology (ischemia, viability). On the other hand, procedural planning would benefit from anatomical evaluation, through CT or MRI. Few studies have assessed the usefulness of specific functional imaging prior to intervention. Bucciarelli-Ducci et al., from a center known for both high-volume CMR and intervention, combined the information of myocardial function, perfusion and viability, all present in a CMR study, to potentially predict appropriate candidates for CTO revascularization. They scanned 50 consecutive CTO patients at baseline doing first pass myocardial perfusion reserve quantification and selected for PCI, those with significant perfusion deficit and presence of myocardial viability in the CTO territory.^{9,10} A 3-month follow-up study was performed after successful recanalization. The study showed complete or almost complete resolution of perfusion defects by qualitative assessment associated with an increase in myocardial perfusion reserve after CTO-PCI in patients with baseline evidence of significant myocardial perfusion defect and viability. These patients demonstrated improvement in LV ejection fraction as well as quality of life according to the Seattle Angina Questionnaire. However, 84% of the cohort had no, or limited myocardial infarction (MI) and 70% of the patients had collateral circulation favoring the presence of viable myocardium and likelihood to recover.

Ischemia and viability were also assessed using gated SPECT and DSE in a study by Pavlovic et al. in 30 patients with early MI at baseline and 11 ± 1 months after recanalization.¹¹ The patients were divided into 3 groups according to the success of recanalization (successful, successful with in-stent restenosis and unsuccessful) and the presence of viability was quantified. The study suggested that patients with viable myocardium before PCI had favorable outcome on left ventricular perfusion and function at 1 year after successful recanalization. Despite the small sample size, this study supports the utility of imaging in selecting patients prior to PCI.

In terms of preprocedural planning, CTA and MR are the most utilized techniques. As described by Allahwalla et al., CTA has the capacity to provide additional information to the diagnostic coronary

angiogram, with higher degree of specificity in evaluating the lesion characteristics, in particular the presence of, the location and the degree of calcification as well as coronary tortuosity and vessel size.^{12,13}

Allahwalla et al. described the different non-invasive modalities that can be used in patients being considered for CTO-PCI. They also addressed the potential for improvement (mainly related to the presence of ischemia and/or hibernating myocardium). Additional considerations are worthy of note. It may be that much of the potential benefit of imaging in terms of prognosis is derived if the culprit vessel was the left anterior descending artery. However, CTO-PCI is performed in non-LAD culprit vessels in the majority of cases even in trials, making the expectation of prognostic benefit difficult to demonstrate.^{4,6}

While EXPLORE and EUROCTO have used viability imaging as an enrolment criterion, these studies do not generally evaluate patients with severely impaired LVEF with extensive myocardial involvement of a CTO coronary territory where viability imaging would be most relevant. Both REVASC and EXPLORE trials had mean EF > 40%.^{14,15} While they looked at EF improvement after CTO revascularization, REVASC was not able to demonstrate improvement of global LV function assessed by MR at 6 months, likely because baseline EF was already >43%, so significant improvement may not necessarily be expected. In EXPLORE, CTO-PCI resulted in significant wall thickening recovery compared to no PCI in dysfunctional segments with non-transmural scar (late gadolinium enhancement < 50%).¹⁵

Of note, important trials such as STICH and PARR-2 have had somewhat conflicting findings regarding viability. In STICH viability imaging with SPECT or DSE predicted recovery from revascularization but was not able to show there was a difference with or without CABG on interaction testing and PARR2 which had a trend for outcome benefit with FDG PET guided therapy that did not reach significance but showed outcome benefit when management adhered to imaging recommendations.^{16–18} These trials did not focus on the unique CTO population.

Likewise, the ISCHEMIA trial demonstrated that patients with LVEF >35% and ischemia defined by treadmill testing, SPECT MPI, stress echo or MRI had symptom benefit from a revascularization approach but not outcome benefit compared to OMT alone at 3.2 years follow-up.¹⁹ While it is tempting to extrapolate these trial results to patients with CTO, none of these recent trials focused on patients with CTO and the unique physiology and characteristics of these patients. As highlighted by Allahwalla et al., while imaging likely has a role, it is not clear that imaging is needed in every

patient who is being considered for CTO-PCI or if it should be reserved for patients where decisions are most difficult.¹³ Well-designed trials, and even more importantly, the completion of which to evaluate imaging directed therapy are needed for this special patient population. Two ongoing trials, NOBLE-CTO (The Nordic-Baltic Randomized Registry Study for the Evaluation of PCI in Chronic Total Coronary Occlusion; NCT03392415) and ISCHEMIA-CTO (Revascularization or Optimal Medical Therapy of CTO; NCT03564317), utilizing MRI and nuclear imaging are eagerly awaited. Until then careful consideration should be given to test selection and how it will impact decisions for CTO revascularization.

Disclosures

There is no conflict of interest.

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