Viability and functional recovery after chronic total occlusion percutaneous coronary intervention

Stefan P. Schumacher MD | Henk Everaars MD | Wijnand J. Stuijfzand MD | Pepijn A. van Diemen MD | Roel S. Driessen MD | Michiel J. Bom MD | Ruben W. de Winter MD | Yvemarie B. O. Somsen MD | Jennifer W. Huynh BSc | Ramon B. van Loon MD, PhD | Peter M. van de Ven PhD | Albert C. van Rossum MD, PhD | Maksymilian P. Opolski MD, PhD | Alexander Nap MD, PhD | Paul Knaapen MD, PhD

1Department of Cardiology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
2Department of Epidemiology and Biostatistics, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
3Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland

Abstract

Objectives: This study evaluated myocardial viability as well as global and regional functional recovery after successful chronic coronary total occlusion (CTO) percutaneous coronary intervention (PCI) using sequential quantitative cardiac magnetic resonance (CMR) imaging.

Background: The patient benefits of CTO PCI are being questioned.

Methods: In a single high-volume CTO PCI center patients were prospectively scheduled for CMR at baseline and 3 months after successful CTO PCI between 2013 and 2018. Segmental wall thickening (SWT) and percentage late gadolinium enhancement (LGE) were quantitatively measured per segment. Viability was defined as dysfunctional myocardium (<2.84 mm SWT) with no or limited scar (≤50% LGE).

Results: A total of 132 patients were included. Improvement of left ventricular ejection fraction was modest after CTO PCI (from 48.1 ± 11.8 to 49.5 ± 12.1%, p < 0.01). CTO segments with viability (N = 216, [31%]) demonstrated a significantly higher increase in SWT (0.80 ± 1.39 mm) compared to CTO segments with pre-procedural preserved function (N = 456 [65%], 0.07 ± 1.43 mm, p < 0.01) or extensive scar (LGE >50%, N = 26 [4%], −0.08 ± 1.09 mm, p < 0.01). Patients with ≥2 CTO segments viability showed more SWT increase in the CTO territory compared to patients with 0–1 segment viability (0.49 ± 0.93 vs. 0.12 ± 0.98 mm, p = 0.03).

Conclusions: Detection of dysfunctional myocardial segments without extensive scar (≤50% LGE) as a marker for viability on CMR aids in identifying patients with significant regional functional recovery after CTO PCI.

Keywords: chronic total occlusion, left ventricular ejection fraction, myocardial viability, percutaneous coronary intervention
1 | INTRODUCTION

Chronic coronary total occlusions (CTO) are diagnosed in approximately 20% of patients with coronary artery disease.1 Technical developments and increase in success rates in CTO percutaneous coronary intervention (PCI) have brought attention to CTO revascularization as a potentially valuable treatment option.2 International guidelines recommend viability assessment next to evaluation of symptoms and ischemia detection to establish judicious patient selection for CTO PCI.3 Nevertheless, contradictory findings have been previously reported regarding the association of myocardial viability testing and functional and prognostic improvements after revascularization.4–7 Increase in left ventricular ejection fraction (LVEF) after CTO revascularization is often found to be modest (<5%), whereas a few studies demonstrated higher increases in LVEF after viability assessment.8–11 Downsides of these studies are their small sample size, suboptimal non-invasive imaging modalities, a lack of functional reassessment after a fixed duration of time after revascularization, or an imprecise definition of myocardial viability. Cardiac magnetic resonance (CMR) imaging is a non-invasive imaging technique that is considered the reference standard for evaluation of myocardial function and infarction.12 The aim of the present study was to evaluate the extent of viability before and functional recovery 3 months after successful PCI in a large CTO population using sequential quantitative CMR imaging.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Prospectively recruited patients with a CTO evaluated for viability with CMR imaging in a single high-volume CTO PCI center (Amsterdam UMC, Vrije Universiteit Amsterdam) between 2013 and 2018 were eligible for inclusion. Patients were rescheduled for CMR approximately 3 months after successful percutaneous revascularization to evaluate the impact of CTO PCI on LVEF. Exclusion criteria were a non-occluded bypass graft with an anastomosis on the CTO artery, signs of microvascular obstruction or non-ischemic cardiomyopathy on CMR, or insufficient CMR images for analysis. A documented history of myocardial infarction (MI) was scored as Q-wave MI or non-Q-wave MI depending on the presence of pathological Q-waves on the electrocardiogram.13 The study was approved by the Medical Ethics Review Committee of the Amsterdam UMC, Vrije Universiteit Amsterdam, and all patients provided written informed consent.

2.2 | Angiographic characteristics

An experienced observer (S.P.S.) scored the angiographic characteristics. Invasive coronary angiography was performed using a monoplane cardiovascular X-ray system (Allura Xper FD 10/10; Philips Healthcare, Best, the Netherlands). Definition of a CTO was a luminal occlusion in a native coronary artery for an estimated or documented time of ≥3 months with no or minimal contrast penetration through the CTO body (Thrombolysis in Myocardial Infarction flow grade 0 or 1). A concomitant collateral connection score of 2 and Rentrop contrast flow grade of 3 defined well-developed collaterals.14 CTO PCI was performed according to the hybrid approach and CTO crossing strategies were left at the discretion of the operator.2 Successful revascularization of a CTO was defined as Thrombolysis in Myocardial Infarction flow grade 3 and residual stenosis <30%. Side branch loss (≥2 mm diameter) was noted and cardiac biomarkers were obtained if peri-procedural MI was suspected. Periprocedural MI was scored according to the Fourth Universal Definition of Myocardial Infarction.13

2.3 | CMR imaging acquisition

All images were obtained on a 1.5-T scanner (Magnetom Avanto, Siemens Healthineers, Erlangen, Germany). Cine imaging was performed using a steady-state-free precession sequence in three long-axis and multiple contiguous short-axis views encompassing the entire left ventricle (LV) from base to apex. Typical parameters were: spatial...
resolution $1.6 \times 1.6 \text{ mm}^2$; slice thickness/gap 5/5 mm; repetition/echo time 3.2/1.5 ms; temporal resolution 30–50 ms. Late gadolinium enhancement (LGE) was performed 10–15 minutes after administration of 0.2 mmol/kg of a gadolinium-based contrast agent (DOTAREM®, Guerbet, Villepinte, France), using a segmented inversion recovery gradient-echo pulse sequence. Slice positions were identical to the cine images. Typical parameters were: spatial resolution $1.6 \times 1.6 \text{ mm}^2$, slice thickness 5 mm, repetition/echo time 9.6/4.4 ms; $\alpha$ 25°; inversion time 250–300 ms nulled to normal myocardium.

### 2.4 | CMR analysis

Image analysis was performed by an experienced observer (HE) blinded to clinical and angiographic data, using commercially available software (QMass v7.6, Medis medical imaging systems, Leiden, the Netherlands). LV volumes and LVEF were calculated from the cine images and were indexed to body surface area. In addition, the LV was divided into 16 segments (true apex not included) according to the AHA segmentation model. Segments were assigned to vascular territories, accounting for coronary dominance. Segmental wall thickening (SWT), defined as absolute difference between end-diastolic and end-systolic wall thickness, was calculated from the short-axis cine images for each segment and as a mean for the CTO territory. Dysfunctional myocardium was defined as SWT < 2.84 mm, based on the mean SWT of 5.07 ± 1.43 mm (5th percentile = 2.84 mm) in a group of 35 healthy volunteers (age 36 ± 16 years) who underwent the same CMR acquisition. Infarct size was calculated from LGE images and expressed as percentage of the LV. Additionally, percentage scar was calculated for each segment and as a mean for the CTO territory, with 0, ≤ 50 and > 50% defining no, limited and extensive scar, respectively. Viability was defined as dysfunctional myocardium in the presence of no or limited scar.

### 2.5 | Statistical analyses

Normally distributed data are presented as mean ± standard deviation and analyzed with an Independent-Samples T-Test, Paired-Samples T-Test, and Wilcoxon signed-rank test. Baseline characteristics were compared with a Chi-square test and Fisher’s exact test. All tests were two-tailed and a p-value of < 0.05 was considered statistically significant. All analyses were performed using SPSS 24 (IBM, Armonk, NY).
T Test or one-way ANOVA test. Non-normally distributed data are presented as median [interquartile range] and tested using a Mann–Whitney U test, Wilcoxon signed-rank test or Kruskal–Wallis test. Categorical data are presented as numbers (percentages). Pearson’s correlation and Spearman’s correlation were used to quantify association between normally and non-normally distributed continuous variables. Change in SWT after CTO PCI in CTO segments was compared between groups using Generalized Estimating Equations for normally distributed data. The identity link was used together with an unstructured working correlation matrix to account for the correlation within the segments.

**FIGURE 2** Case example. (1A) The distal vascular territory (arrows) of a CTO in the right coronary artery receives collateral blood supply from the left coronary artery. Two-chamber (1B) and short-axis (1C) views in baseline CMR show (from top to bottom) the end-diastolic and end-systolic phase during cine imaging and LGE. Two segments in the inferior wall consisted of dysfunctional myocardium (SWT < 2.84 mm, arrows) in the presence of a limited amount of scar (≤50% LGE, arrows), defining viability. (2A) After successful CTO PCI and restoration of antegrade blood flow (arrows), regional function in these two segments normalized (arrows) as displayed in 2-chamber (2B) and short-axis (2C) views. LGE, late gadolinium enhancement; SAX, short-axis; SWT, segmental wall thickening; LV, left ventricular; EDV, end-diastolic volume; CMR, cardiac magnetic resonance; CTO, chronic coronary total occlusion; ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention

| TABLE 3 CMR imaging results (N = 132) |
|--------------------------------------|
|                                        | Baseline          | Follow-up         | \( p \) Value |
| Left ventricle                        |                   |                   |               |
| Ejection fraction (%)                 | 48.1 ± 11.8       | 49.5 ± 12.1       | <0.01         |
| End-diastolic volume (ml)             | 99.1 ± 31.8       | 95.7 ± 30.2       | <0.01         |
| End-systolic volume (ml)              | 54.4 ± 30.5       | 51.2 ± 29.3       | <0.01         |
| Scar tissue (%)                       | 4.4 (1.0–9.9)     | 4.8 (2.1–14.0)    | <0.01         |
| CTO territory                         |                   |                   |               |
| Segmental wall thickening (mm)        | 3.51 ± 1.41       | 3.79 ± 1.59       | <0.01         |
| End-diastolic wall thickness (mm)     | 6.68 ± 1.41       | 6.85 ± 1.60       | 0.03          |
| End-systolic wall thickness (mm)      | 10.20 ± 2.18      | 10.65 ± 2.39      | <0.01         |
| Scar tissue (%)                       | 6.4 (4.0–16.7)    | 8.1 (1.6–16.1)    | 0.06          |

Abbreviations: CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CTO, chronic coronary total occlusion; MI, myocardial infarction; PCI, percutaneous coronary intervention; LGE, late gadolinium enhancement.

Note: Values are mean ± SD or median (Q1–Q3). At follow-up, LGE was not performed or images were of insufficient quality for analysis in three and six patients, respectively.
for possible dependency between outcome measured in CTO segments in the same individual. When the overall effect for comparing ≥ 2 groups was significant, Bonferroni correction was applied for posthoc pairwise comparisons between groups. An univariable linear regression analysis was performed to find patient characteristics associated to SWT improvement in the CTO area after PCI. A level of \( p < 0.05 \) was considered significant. Statistical analyses were performed using SPSS software (IBM SPSS Statistics 24.0, Chicago, IL).

### RESULTS

#### 3.1 Patient population

Of 228 consecutive patients with a CTO who underwent viability assessment by CMR prior to revascularization, 132 patients (62 ± 11 years, 81% male) met the study inclusion criteria (Figure 1). Patient clinical and angiographic characteristics are listed in Tables 1 and 2. Duration between baseline CMR and CTO PCI and between CTO PCI and

![Figure 3](image_url)  
**Figure 3** Per-patient improvement in LVEDV, LVESV, LVEF and SWT in the CTO territory after CTO PCI. LV volumes are indexed to body surface area. Numbers on top represent the mean ± SD. Red lines indicate the mean. LV, left ventricular; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; CMR, cardiac magnetic resonance; SWT, segmental wall thickening; CTO, chronic coronary total occlusion; PCI, percutaneous coronary intervention

![Figure 4](image_url)  
**Figure 4** Baseline CMR parameters and change in regional SWT. The correlation between baseline degrees of scar and SWT in the CTO territory (A), and plots displaying the lack of correlation between change in regional SWT after CTO PCI and baseline degree of scar (B), SWT (C) and EDWT (D), respectively. EDWT, end-diastolic wall thickness; CMR, cardiac magnetic resonance; SWT, segmental wall thickening; CTO, chronic coronary total occlusion; PCI, percutaneous coronary intervention
follow-up CMR was 38 (IQR 22–59) days and 102 (IQR 94–118) days, respectively. A case example is displayed in Figure 2.

3.2 | Change in global LV function and volumes

At baseline, scar tissue was demonstrated in the LV and specifically in the CTO territory in 117 (89%) and 108 (82%) patients, respectively. Baseline mean LVEF was 48.1 ± 11.8%, with an LVEF of >50%, 35–50% or < 35% observed in 71 (54%), 38 (29%) and 23 (17%) patients, respectively. Overall, a small increase (p < .01) in mean LVEF of 1.4 ± 4.7% was observed following CTO PCI (displayed in Table 3 and Figure 3). In addition, LV end-diastolic and end-systolic volumes decreased with 3.5 ± 12.1 and 3.3 ± 9.5 ml, respectively (both p < .01). Increase in LVEF in patients with baseline LVEF 35%–50% (Δ3.1 ± 4.5%) was significantly higher compared to patients with LVEF >50% (Δ0.7 ± 4.7%, p = 0.03) but not different than that in patients with LVEF <35% (Δ0.9 ± 4.5%, p = 0.20, Supporting Information, Figure S1A). Two of 23 (9%) patients with baseline LVEF <35% had an LVEF of 35%–50% at follow-up. Change in LVEF did not differ between patients with or without periprocedural MI (p = 0.34).

3.3 | Change in regional function

At baseline, median percentage scar in the CTO territory was 6.4 (0.0–16.7). A total of 698 segments in CTO territories were analyzed, of which only 26 (4%) segments demonstrated extensive scar (>50% LGE). In 241 (35%) segments SWT was considered dysfunctional (<2.84 mm). As shown in Figure 4(A), a moderate negative correlation was observed between baseline percentage scar and SWT in the CTO territory. Increase in SWT was significant (p < 0.01) after CTO PCI with a mean of 0.28 ± 0.97 mm (Figure 3). In an univariable linear regression analysis no patient characteristics were found to be associated with SWT improvement in the CTO area after PCI (Table S1). Dysfunctional segments at baseline showed a higher increase in SWT compared to segments with already preserved function at baseline (0.72 ± 1.38 vs. 0.06 ± 1.43 mm, p < 0.01). Change in SWT was not influenced by the incidence of prior Q-wave MI in the CTO territory, degree of collateral development, or the successful crossing technique used in CTO PCI (Figure S1B–D). In addition, change in SWT after revascularization was not correlated with baseline percentage scar, SWT, or end-diastolic wall thickness, respectively (Figure 4B–D).

3.4 | Change in regional function in relation to baseline viability

Viability, defined as SWT < 2.84 mm and LGE ≤50%, was present at baseline in 216 (31%) CTO segments. Of the remaining CTO segments, 456 (65%) had a preserved function and ≤50% LGE, 25 (4%) segments had dysfunctional myocardium and > 50% LGE, and 1 (0%) segment had a preserved function and > 50% LGE. After CTO PCI, SWT increased to normal (≥2.84 mm) in 83 of 216 (38%) segments with viability. Segments with viability showed more improvement in SWT compared to segments with preserved function and ≤50% LGE and segments with >50% LGE (Figure 5A). Further stratification of segments with viability according to the degree of LGE (0, >0–25 and > 25–50%) did not show different absolute increases in SWT (Figure 5B). Fifty-eight of 132 (44%) patients had ≥2 segments (>10% of the LV) with viability in the

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**Figure 5** Viability and regional functional recovery in the CTO territory. (A) Change in SWT after CTO PCI in CTO segments with or without viability. (B) Change in SWT after CTO PCI in subgroup analysis of segments with viability stratified according to the degree of scar formation. (C) Change in regional SWT in the CTO territory after PCI compared between patients with 0–1 and ≥ 2 segments with viability at baseline. CMR, cardiac magnetic resonance; CTO, chronic coronary total occlusion; SWT, segmental wall thickening; PCI, percutaneous coronary intervention.
CTO territory at baseline, and increase of regional SWT after CTO PCI was higher in these subjects compared to patients with no or only 1 segment viability (Figure 5(C)).

4 | DISCUSSION

This prospectively conducted study is the largest to date evaluating global and regional functional recovery after successful CTO PCI using CMR, the gold standard for evaluation of myocardial function. The main results indicate that the overall improvements in LVEF and LV volumes are modest following CTO PCI. By selecting dysfunctional segments without extensive scar as a marker for viability on baseline CMR, CTO segments and patients with enhanced regional functional recovery after CTO revascularization could be identified.

4.1 | Viability detection as part of clinical decision making in a CTO population

In the current study subjects were prospectively enrolled from an all-comer CTO program in a dedicated CTO PCI center (~175 procedures per year). Cine imaging and LGE in CMR were used to: (1) confirm the presence of substantial non-scarred myocardial tissue subtended by the CTO lesion and (2) detect viability with potential for functional recovery. Viability, defined as dysfunctional but viable myocardium due to chronic hypoperfusion (hibernating myocardium), is a prerequisite for functional recovery after revascularization. In contrast, extensive myocardial fibrosis can identify segments with limited or absent functional improvement. In this study, referral of patients to CTO PCI did not solely depend on viability, but as well on symptom severity and presence of ischemia. As such, patients over the entire LVEF spectrum were evaluated including patients with preserved LV function in whom no large functional improvement can be expected. Still, the results in this study do reflect the functional recovery that can be anticipated after contemporary CTO PCI in a population carefully selected according to clinical guidelines.

4.2 | Change in global LV function and volumes after CTO PCI

Recently, a meta-analysis including 34 observational studies reported a mean LVEF improvement of 3.8% after successful CTO PCI. The randomized EXPLORE-trial demonstrated that CTO PCI of a non-infarct-related artery within 7 days in patients presenting with ST-elevation MI did not result in an enhanced CMR-derived LVEF at 4 months follow-up as compared to optimal medical therapy (OMT). The REVASC-trial randomized 200 stable patients with a CTO in a 1:1 fashion to CTO PCI or OMT, and measured LV function at baseline and 6-month follow-up. Median increase in LVEF [0.9% (−1.3−4.1)] and decreases in LV end-diastolic and end-systolic volumes [−3 (−13−6) and −2 (−8−4) ml/m², respectively] after CTO PCI in the REVASC-trial were limited and consistent with findings in this population. These overall small extents of LV functional improvement after PCI probably do not reflect clinical significance in the general CTO population, nor cannot be excluded that such limited differences observed between baseline and follow-up are the result of a methodological error despite the CMR analyses were performed blinded to clinical and angiographic data. Noteworthy, in this study subjects with a baseline LVEF ranging from 35% to 50% seemed to benefit more from CTO PCI. It could be hypothesized that these individuals had an advantageous combination of dysfunctional myocardium without excess of myocardial fibrosis. To date no randomized trial used marked viability as an inclusion criterion before randomization to evaluate the impact of myocardial revascularization on LV functional recovery. The ongoing REVIVED-BCIS2 trial (NCT01920048) will address this issue in patients with chronic coronary syndrome and LVEF ≤35%. At last, although LVEF improvement was only modest in the present study, it may be postulated that successful CTO PCI can halt the process of further adverse LV remodeling as was previously shown to continue over time after failed CTO PCI.

4.3 | Change in regional myocardial function after CTO PCI

In the REVASC trial, change of SWT in the CTO territory did not differ between patients treated with CTO PCI or OMT. In this study, mean SWT improvement (8% of mean baseline SWT) was comparable with the observed SWT improvement after CTO PCI in the REVASC trial [4.1% (IQR -14.6,19.3)]. The presence of pathological Q-waves on the electrocardiogram and collateral status are two regularly used characteristics to appraise viability in a myocardial region in clinical practice. Regional contractile improvement was numerically but non-significantly higher in patients with poorly developed collaterals and in the absence of a CTO vessel-related prior Q-wave MI. Statistical power may have been insufficient in this study to achieve a significance due to the sample size of the study. The combined assessment of both SWT and LGE enabled detection of myocardial segments with viability that showed subsequent functional improvement after CTO PCI. The results therefore support that patients with a CTO and extensively impaired myocardium accompanied by limited myocardial fibrosis (<50% LGE) in the CTO territory probably have the highest chance to benefit from CTO PCI. It should be recognized, however, that the degree of change in SWT highly varied between segments with viability as well as segments without viability. Viability was observed in only one-third of segments in the CTO territory, which equals 1.5–2 segments in a standardized vascular territory according to the 17-segment model. This relatively low extent of viability substantiates the limited LV functional recovery that can be anticipated after revascularization in a general CTO population selected according to clinical guidelines.
4.4 | Extent of viability and long-term prognosis

Previous studies using multiple imaging modalities have shown conflicting results regarding the concept of viability and improved survival after revascularization.4–7 In addition, (randomized) studies comparing different imaging modalities in defining viability and its predictive value on functional improvement and long-term prognosis, are lacking.

In this study, enhanced regional functional recovery was observed in patients with ≥2 CTO segments with viability (>10% of the LV). These findings lend support to the notion that in case of large areas of viability in the CTO territory, revascularization may lead to improved (regional) myocardial function and thereby potentially prognostic outcomes. However, the potential clinical benefit of CTO PCI upon OMT is an ongoing debate since adverse events are more likely to occur during and after complex PCI.19 The results of the randomized EuroCTO trial (NCT01760083), which compared the 3-year clinical outcomes between CTO PCI and OMT, were recently presented and demonstrated similar prognostic outcomes between both treatment arms. However, the pertinent publication is awaited. The impact of revascularization on prognostic outcomes in patients with documented viability is addressed in the randomized REVIVED-BCIS2 trial (NCT01920048).

4.5 | Limitations

Subtle discords between standardized myocardial segmentation in CMR imaging and variable coronary anatomy in patients cannot be excluded.20 Follow-up CMR imaging was not performed after failed CTO PCI and the effect of such a procedure on myocardial function remains unclear. The reported findings were achieved after a short follow-up period whilst ongoing improvements in global and regional myocardial function up to 3 years after CTO PCI have been previously reported.21 Translating the results to other imaging modalities, for example nuclear perfusion and metabolism imaging and low-dose dobutamine stress echocardiography, should be done with caution due to different physiologic properties of the modalities.

5 | CONCLUSION

Detection of dysfunctional segments without extensive scar as a marker for viability on CMR aids in identifying candidates for regional functional recovery after CTO PCI.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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