jaa Just accepted article

EuroIntervention

Title: Relationship between Extent of Ischaemic Burden and Changes in Absolute Myocardial Perfusion after Chronic Total Occlusion Percutaneous Coronary Intervention.

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DOI: 10.4244/EIJ-D-19-00631

Citation: Schumacher SP, Kockx M, Stuijfzand WJ, Driessen RS, van Diemen PA, Bom MJ, Everaars H, Raijmakers PG, Boellaard R, van Rossum AC, Opolski MP, Nap A, Knaapen P. Relationship between Extent of Ischaemic Burden and Changes in Absolute Myocardial Perfusion after Chronic Total Occlusion Percutaneous Coronary Intervention. *EuroIntervention* 2019; Jaa-654 2019, doi: 10.4244/EIJ-D-19-00631

Manuscript submission date: 04 July 2019

Revisions received: 05 September 2019

Accepted date: 19 September 2019

Online publication date: 24 September 2019

Relationship between Extent of Ischaemic Burden and Changes in Absolute Myocardial Perfusion after Chronic Total Occlusion Percutaneous Coronary Intervention

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Short title: Ischaemic burden & ischaemia reduction by CTO PCI

The authors have no conflicts of interest to declare.

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ABSTRACT

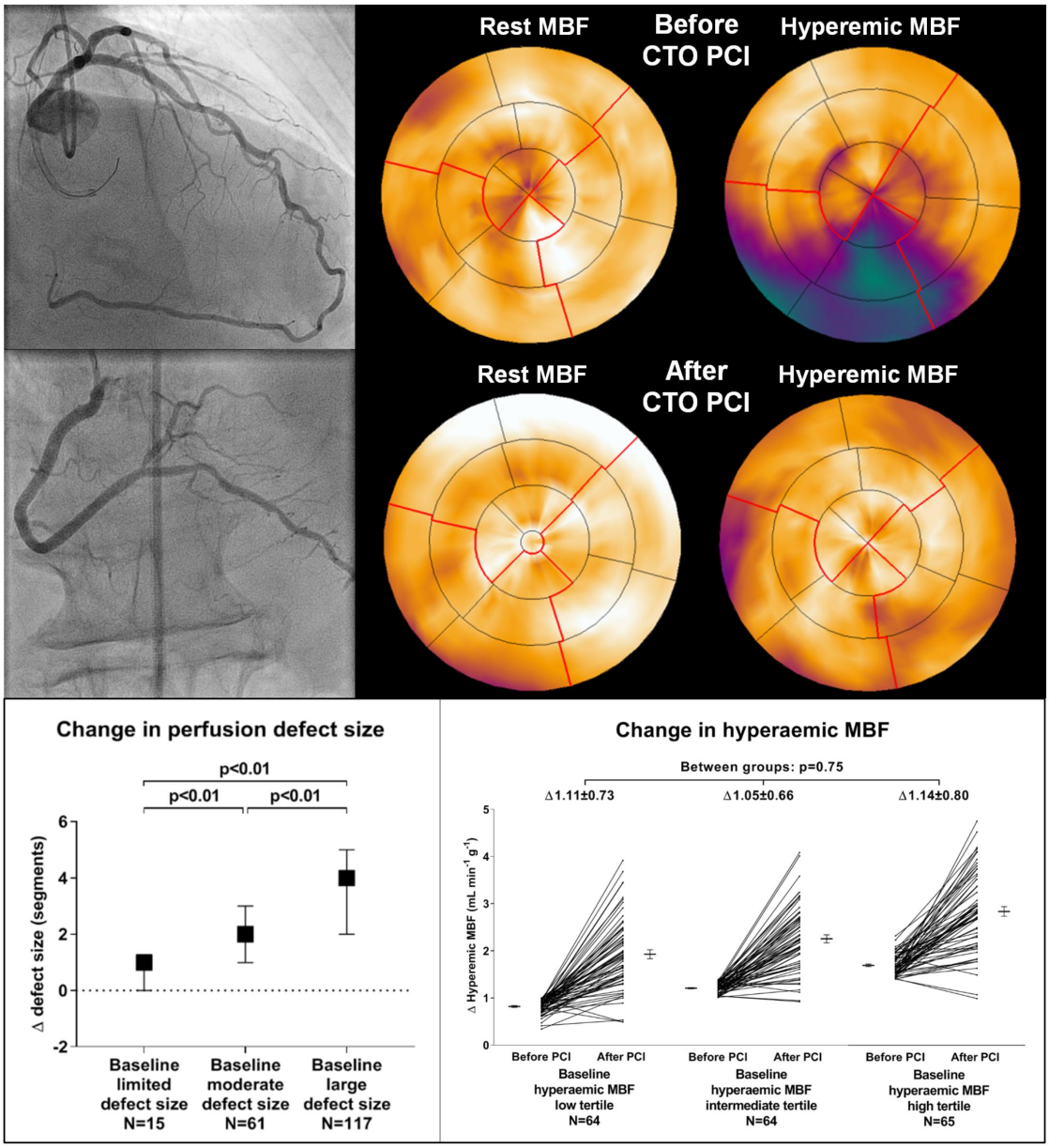
Aims: Exploring relationships between ischaemic burden and changes in absolute myocardial perfusion following chronic coronary total occlusion (CTO) percutaneous coronary intervention (PCI).

Methods and Results: 193 consecutive patients underwent [^{15}O]H_2O positron emission tomography prior and 3 months after successful CTO PCI. Change in perfusion defect size, quantitative hyperaemic myocardial blood flow (MBF) and coronary flow reserve (CFR) within the CTO area were compared between patients with limited (0-1 segment, N=15), moderate (2-3 segments, N=61) and large (≥4 segments, N=117) perfusion defects. Median reductions in defect size were 1 [0-1], 2 [1-3], and 4 [2-5] segments in patients with a limited, moderate and large defect (all comparisons $p<0.01$). Hyperaemic MBF and CFR improved significantly regardless of baseline defect size (overall between groups $p=0.45$ and $p=0.55$). After stratification of patients to a low, intermediate or high tertile according to baseline hyperaemic MBF or CFR levels, changes in hyperaemic MBF and CFR after CTO PCI were comparable between tertiles (overall $p=0.75$ and $p=0.79$).

Conclusions: Major reductions in ischaemic burden can be achieved following CTO PCI, with more defect size reduction in patients with a larger perfusion defect, whereas hyperaemic MBF and CFR improve significantly irrespective of their baseline values or perfusion defect size.

Major reductions in ischaemic burden can be achieved following CTO PCI

- More defect size reduction in patients with a larger baseline perfusion defect
- Significant hyperaemic MBF improvement irrespective of its baseline values



Classifications: Stable angina; Non-invasive imaging; Chronic coronary total occlusion

CONDENSED ABSTRACT

The impact of CTO PCI on relief of different levels of ischaemic burden is unclear. In this study, 193 patients underwent [15O]H2O PET perfusion prior and 3 months after successful CTO PCI. More reduction in perfusion defect size after CTO PCI was observed in patients with a larger defect at baseline. Increases in hyperaemic MBF and CFR were significant but independent of its baseline values or perfusion defect size. These results help understanding the effects of CTO PCI on myocardial perfusion, and show quantitative PET to be an effective tool to select patients with high potential for marked ischaemia reduction.

ABBREVIATIONS

CC	collateral connection
CFR	coronary flow reserve
CTO	chronic coronary total occlusions
LAD	left anterior descending artery
MBF	myocardial blood flow
MI	myocardial infarction
PCI	percutaneous coronary intervention
PET	positron emission tomography
TIMI	Thrombolysis In Myocardial Infarction

INTRODUCTION

Chronic coronary total occlusions (CTO) signify a detrimental impact on long-term prognosis[1,2]. This negative effect has been related to the extent of perfusion defect size associated to the CTO lesion evaluated with myocardial perfusion imaging[3]. Few studies have demonstrated that marked ischaemia is present in the vast majority of patients with a CTO regardless of well-developed collaterals[4,5]. Optimal medical therapy is the first line treatment in patients with a CTO, however, its effect on ischaemic burden is limited and merely aimed at symptom relief[6]. Prior studies showed substantial improvements in myocardial perfusion after CTO percutaneous coronary intervention (PCI) similar to PCI of hemodynamically significant non-occluded lesions[7]. In addition, a beneficial effect of revascularization on long-term prognosis in patients with a CTO and moderate-to-severe ischaemia was previously suggested[8,9]. Current international guidelines therefore recommend CTO revascularization in patients with marked ischemic burden[10]. However, data on the effectiveness of CTO PCI on ischaemia reduction in patients with various degrees of ischaemic burden is lacking. The aim of the present study was to determine the impact of CTO PCI on relief of different extents of ischaemia as quantified with $[^{15}O]H_2O$ positron emission tomography (PET).

METHODS

Study design and participants

Prospectively recruited consecutive patients presenting with a CTO in the Amsterdam UMC location Vrije Universiteit Amsterdam between 2013-2018 were eligible for inclusion if presence of ischaemia was evaluated with $[^{15}O]H_2O$ PET perfusion imaging prior and following successful CTO PCI. Patients were rescheduled for $[^{15}O]H_2O$ PET imaging at least 3 months

after revascularization. Exclusion criteria were pregnancy and contraindications for adenosine administration. A documented history of myocardial infarction (MI) was reported according to patient files or if pathological Q-waves were present on the electrocardiogram[11]. Left ventricular ejection fraction was assessed during clinical work-up by echocardiography or cardiac magnetic resonance imaging. The study was approved by the Amsterdam UMC location Vrije Universiteit Amsterdam Medical Ethics Review Committee, and all patients provided written informed consent.

Angiographic characteristics

Angiographic characteristics were evaluated on a monoplane cardiovascular X-ray system (Allura Xper FD 10/10; Philips Healthcare, Best, The Netherlands). CTOs were defined as a luminal occlusion on invasive coronary angiography for an estimated time of ≥ 3 months with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0-1. Collaterals supplying the vascular territory of the CTO were graded according to the collateral connection (CC) score[12]. CTO PCI was performed according to the hybrid approach and successful revascularization was defined as TIMI flow grade 3 and <30% diameter stenosis[7]. Side branch loss (≥2mm) was scored and cardiac biomarkers were obtained if periprocedural MI was suspected, which was defined according to the Fourth Universal Definition of Myocardial Infarction[11].

Positron emission tomography

Patients underwent a dynamic emission scan at rest and during hyperaemia by administration of intravenous adenosine (140μ□kg^{-1}□min^{-1})[4]. Rest and hyperaemic myocardial blood flow (MBF, in mL□min^{-1}□g^{-1}), and coronary flow reserve (CFR) as the ratio of hyperaemic to rest MBF, were measured in the CTO myocardial area. The standardized 17-segment model of the American Heart Association was used for left ventricular segmentation. The perfusion defect size associated to the CTO was defined by the number of myocardial segments in which hyperaemic MBF was below 2.3 mL·min^{-1}·g^{-1} and <75% compared to hyperaemic MBF in a

normal reference vascular territory[7,13]. The perfusion defect size at baseline was classified per patient as limited (0-1 segments), moderate (2-3 segments) or large (≥4 segments). Furthermore, all patients were stratified in tertiles according to hyperaemic MBF and CFR levels at baseline.

Statistical analyses

Normally distributed data are presented as mean ± standard deviation and analysed with a Paired-Samples-T test, Independent-Samples-T test or one-way ANOVA test. Non-normally continuous data are presented as median [interquartile range] and analysed with a Wilcoxon signed-rank test, Mann-Whitney-U test, or Kruskal-Wallis test. Categorical variables are presented as numbers and percentages and analysed with the Fisher's-Exact test. In case of >2 groups and the overall p value was $p<0.05$, pairwise comparisons were made between groups using a Bonferroni correction to correct for multiple testing. Changes in perfusion indices within the CTO area after PCI were compared between patients with limited, moderate and large perfusion defects at baseline. In addition, change in hyperaemic MBF was compared between patients classified in the lowest (≤1.00 mL·min^{-1}·g^{-1}), intermediate (1.01-1.39 mL·min^{-1}·g^{-1}) and highest (≥1.40 mL·min^{-1}·g^{-1}) tertile of hyperaemic MBF at baseline. Accordingly, change in CFR was compared between patients in the lowest (≤1.30), intermediate (1.31-1.77) and highest (≥1.78) tertile of CFR at baseline. An univariate generalized linear model was used for linear regression analyses to find predictors for change in perfusion defect size after CTO PCI. Variables were entered in the multivariable analysis if $p\leq0.10$ in the univariable analysis. Receiver operating curve analyses were used to identify the optimal baseline perfusion defect size threshold for subsequent ≥1 and ≥2 segments defect size reduction after CTO PCI. A level of $p<0.05$ was considered significant. Statistical analyses were performed using SPSS software (IBM SPSS Statistics 22.0, Chicago, IL) and MedCalc (MedCalc Software 11.6.0.0, Mariakerke, Belgium).

RESULTS

Patient population

Between 2013-2018, 193 patients (84% male, mean age 63±11 years) were successfully treated with CTO PCI and were rescheduled for follow-up PET imaging, whereas 10 patients (out of 203, 5%) could not be successfully treated. Patients with failed CTO PCI did not underwent follow-up PET imaging and were excluded from analysis. Clinical and angiographic characteristics of successfully treated patients are demonstrated in table 1 and Supplemental table 1. A CTO lesion with TIMI flow 0 or 1 was observed in 153 (79%) and 40 (21%) patients, respectively. In patients with a large perfusion defect the CTO was located more often in the left anterior descending artery (LAD) compared to patients with a moderate perfusion defect (p=0.02). Collaterals had a CC score of 2 in 134 (69%) patients, with no differences between groups (overall p=0.59). In 13 (7%) patients, a second procedure was needed to successfully revascularize the CTO. Spontaneous MI or unplanned myocardial revascularization did not occur in any patient between serial PET imaging. After follow-up PET imaging and clinical evaluation, 3 patients were additionally treated with PCI of the CTO artery. In 2 of these 3 patients residual ischemia in the CTO territory was caused by a significant stenosis distal of the former CTO lesion, and in 1 patient residual ischemia was present due to a compromised side branch at the site of the revascularized CTO.

Change in myocardial perfusion after CTO PCI according to baseline defect size

The median number of days between baseline PET and CTO PCI, and between CTO PCI and follow-up PET, was 37 [22-59] and 103 [94-122], respectively. Change of rest MBF and CFR could not be analysed in 3 patients due to one failed rest scan at baseline and 2 failed rest scans at follow-up. Myocardial perfusion findings at baseline and follow-up are shown in table 2. 178 out of 193 patients (92%) had a perfusion defect size of ≥2 segments. Hyperaemic MBF and CFR at baseline were significantly lower in a large perfusion defect compared with a limited

(both p<0.01) or moderate perfusion defect (both p<0.01). In patients with failed CTO PCI, the perfusion defect was larger and both hyperaemic MBF and CFR were lower in comparison with the successfully treated population (Supplemental table 2). In the successfully treated population, myocardium subtended by CTO lesions with TIMI flow grade 0 had lower hyperaemic MBF and CFR values compared to CTO lesions with TIMI flow grade 1 (Supplemental table 3). Overall change in rest MBF, hyperaemic MBF and CFR after PCI were 0.03±0.22 mL·min^{-1}·g^{-1}, 1.10±0.73 mL·min^{-1}·g^{-1} and 1.29±1.03, respectively. These changes were comparable between patients with various defect sizes (figure 1) and after revascularization of a CTO lesion with TIMI flow grade 0 or 1, respectively. An overall median residual perfusion defect of 1 [0-2] segment was found after CTO PCI. The median decrease in defect size after PCI was 3 [1.5-4.5], and was significantly different between patients with a limited, moderate and large perfusion defect at baseline (1 [0-1], 2 [1-3], 4 [2-5], respectively, all comparisons p<0.01, figure 2). Changes of all perfusion indices after CTO PCI were nonsignificantly different between patients with CC score 2 collaterals and patients with CC 0-1 collaterals supplying the myocardium subtended by a CTO (Supplemental table 4). Side branch loss and periprocedural MI did not result in hampered recovery of any perfusion outcome (all p>0.05). Case examples are displayed in figure 3.

Predictors of change in perfusion defect size after CTO PCI

In multivariable analysis, the CTO artery was a significant predictor of defect size reduction after CTO PCI, with relatively more reduction if the CTO was located in the LAD (Supplemental table 5). Receiver operating curve analyses identified a perfusion defect of ≥3 segments as optimal threshold to predict ≥1 segment (83% sensitivity and 50% specificity) and ≥2 segments (92% sensitivity and 56% specificity) defect size reduction.

Change in hyperaemic MBF after CTO PCI according to baseline hyperaemic MBF

Baseline hyperaemic MBF in the CTO area in patients within the low, intermediate and high tertile of hyperaemic MBF was 0.82±0.15, 1.21±0.11 and 1.69±0.22 mL·min^{-1}·g^{-1}, respectively. Baseline characteristics of patients within the 3 tertiles are shown in Supplemental table 6. After PCI, hyperaemic MBF significantly increased (paired data within each tertile p<0.01) towards 1.93±0.75, 2.25±0.69 and 2.84±0.82 mL·min^{-1}·g^{-1} at follow-up (low tertile vs intermediate tertile p=0.048, low tertile vs high tertile p<0.01, intermediate tertile vs high tertile p<0.01). Change in hyperaemic MBF was comparable between the groups (overall p=0.75, shown in figure 4A).

Change in CFR after CTO PCI according to baseline CFR

The CFR in the CTO area at baseline in patients in the low, intermediate and high CFR tertile was 1.04±0.19, 1.52±0.14 and 2.21±0.40, and increased significantly after PCI (paired data within each tertile p<0.01) towards levels of 2.29±0.86, 2.89±1.00 and 3.47±1.24 at follow-up (all comparisons between groups p<0.01). Baseline characteristics of patients within the 3 tertiles are shown in Supplemental table 7. The change in CFR was comparable between the groups (overall p=0.79, figure 4B).

DISCUSSION

The main findings can be summarized as follows: 1) At baseline, 92% of patients had a perfusion defect size of ≥2 segments (>10% of the left ventricle); 2) greater reduction in defect size after CTO PCI was achieved in patients with a larger perfusion defect at baseline; 3) hyperaemic MBF and CFR levels before PCI were more severely impaired in patients with a larger perfusion defect; 4) increases in hyperaemic MBF and CFR were significant and not related to its baseline values or perfusion defect size before PCI.

Extent of the perfusion defect and depth of quantitative MBF in patients with a CTO

Ninety-two percent of patients had a perfusion defect of ≥2 segments (>10% of the left ventricle), which is associated with a negative impact on long-term prognosis and is considered a clinical indication for CTO PCI[3,10]. All patients had hyperaemic MBF and CFR levels well below the cut-off values for ischaemia as defined by [^{15}O]H_2O PET (hyperaemic MBF: 2.3 mL·min^{-1}·g^{-1}, and CFR: 2.5)[13]. These levels of hyperaemic MBF and CFR were impaired irrespective of the visually assessed collateral status in patients. In addition, hyperaemic MBF and CFR levels were more severely hampered in a larger perfusion defect despite the equal distribution of well-developed collaterals across various perfusion defect sizes, questioning the causal relationship between the amount of ischaemia and collateral recruitment. However, the accuracy to quantify the collateral blood supply capacity by visual assessment is limited[12]. From a pathophysiological point of view it could be assumed that collateral blood supply is less pronounced in patients with a larger perfusion defect size and lower MBF. Alternatively, one could argue that arteriogenesis of (un)recognized collaterals is by definition limited. As such, if collateral blood supply has to be distributed over a greater amount of myocardial tissue at risk subtended by a CTO, as is likely in patients with a larger perfusion defect size, this distribution may lead to lower (hyperaemic) MBF and CFR levels.

Perfusion defect size reduction after CTO PCI

Recently the 12-month outcomes of the randomized EuroCTO trial were revealed[14]. The aim of this trial was to compare the change in health status and prognostic outcomes between patients with a CTO randomized to CTO PCI or optimal medical therapy. All non-occlusive lesions in patients with multivessel disease were treated before randomization to establish a genuine comparison. Greater improvements in the Seattle angina questionnaire subscales quality of life and angina frequency were observed after CTO PCI, whereas major adverse cardiac events were comparable between the two groups. The prognostic outcomes at 3-year follow-up in the EuroCTO trial are eagerly awaited. In the present study, CTO PCI resulted in

a median defect size reduction of 3 segments which equals 17.5% of the left ventricle myocardium and may be classified as prognostically relevant according to prior literature[8,9]. A CTO located in the LAD was a significant predictor for more defect size reduction. This finding is consistent with prior literature demonstrating that the LAD in general subtends a larger myocardial area than the other epicardial vessels[15]. In 2011, Safley et al. reported that ischaemia detection could enhance the recognition of patients with a high potential for major ischaemic burden reduction after CTO PCI, which in turn might contribute to improved long-term survival[8]. Importantly, the additional value of the current study to the work of Safley et al. is that: 1) CTO PCI was performed according to the current standards of the hybrid approach; 2) absolute myocardial perfusion was measured by [^{15}O]H_2O PET being the gold standard for non-invasive myocardial perfusion imaging, and 3) patients were prospectively approached for follow-up PET after a fixed period of time. At follow-up, a median defect size of 1 [0-2] segment was observed. Recovery of myocardial perfusion in patients with a residual perfusion defect could have been hampered due to the presence of microvascular dysfunction and lower baseline hyperaemic MBF which predispose a patient to end up with lower follow-up hyperaemic MBF levels[16,17]. Secondly, restenosis in the CTO artery could have stayed unrecognized in some patients due to a lack of re-invasive coronary angiography at time of follow-up PET. It should be noted, however, that a median residual defect size of 0-1 segment (<10% of the left ventricle) among all patient subgroups suggests that CTO PCI generally results in no or limited residual ischaemia.

Improvements in hyperaemic MBF and CFR after CTO PCI

Patients with lower baseline hyperaemic MBF had suffered more frequently from prior MI in the CTO territory and had less often a preserved left ventricular ejection fraction, which are both risk factors for microvascular dysfunction[16,17]. However, hyperaemic MBF and CFR improved significantly after CTO PCI irrespective of their baseline values and perfusion defect

size before revascularization. Collaterals with lower CC scores supplying the CTO artery have been related to more pronounced endothelial and smooth muscle dysfunction in myocardium subtended by a CTO, and could potentially limit recovery of absolute myocardial perfusion after CTO PCI[18]. In the present study, however, hyperaemic MBF and CFR significantly improved regardless of visually assessed collateral status. While prior studies have suggested that perfusion defect size reduction might be prognostically relevant, the prognostic validation of change in hyperaemic MBF and CFR after revascularization is lacking [8,9]. Theoretically, CTO PCI might be prognostically beneficial even in patients with a limited perfusion defect size due to the significant improvements in hyperaemic MBF and CFR[19].

Limitations

Although marked ischaemia is found in the vast majority of patients with a CTO, asymptomatic patients with a limited perfusion defect have not been included in the current analysis due to the lack of a clinical indication for CTO PCI[4,5]. Change in myocardial perfusion in patients with failed CTO PCI could not be evaluated as follow-up PET imaging was not performed to limit radiation exposure. As cardiac biomarkers were not systematically obtained before and after CTO PCI, incidence of periprocedural myocardial injury might have been underestimated. In addition, the potential relationship between change in myocardial perfusion and change in cardiac enzymes after CTO PCI could not be adequately explored, and the influence of periprocedural MI on recovery of myocardial perfusion stays unclear. A gradual increase of myocardial perfusion up to 3 months after coronary revascularization has been reported previously[20]. In the present study, myocardial perfusion findings after CTO PCI (e.g. residual defect sizes) might would have further improved if the follow-up duration of 3 months was prolonged.

CONCLUSIONS

Significant reduction in ischaemia can be achieved with CTO PCI across all levels of ischaemic burden as expressed by perfusion defect size, with greater defect size reduction in patients with a larger perfusion defect at baseline. Patients with a CTO and a larger perfusion defect have more severely impaired hyperaemic MBF and CFR levels. Notwithstanding, hyperaemic MBF and CFR improve significantly after recanalization of CTO irrespective of their baseline values or perfusion defect size before PCI. Ischaemia detection by quantitative PET could be used as an effective tool to recognize patients with a high potential for marked ischaemia reduction after CTO PCI.

IMPACT ON DAILY PRACTICE

There is a lack of evidence regarding the effects of CTO PCI on relief of different levels of ischaemic burden. The present study showed that significant reduction in ischaemia can be achieved with CTO PCI across all levels of ischaemic burden. More defect size reduction was observed in patients with a larger perfusion defect at baseline, whereas increases in hyperaemic MBF and CFR were significant but independent of its baseline values or perfusion defect size. These results demonstrate that quantitative PET can be an effective tool to select patients with high potential for marked ischaemia reduction.

ACKNOWLEDGMENTS

None

FUNDING

None

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

Figure 1. Per patient paired measurements (lines) of rest MBF (A), hyperaemic MBF (B) and CFR (C) in patients with a limited, moderate and large perfusion defect at baseline. Horizontal lines and error bars are mean and standard error of the mean. Δ, change; CFR, coronary flow reserve; CTO, chronic coronary total occlusion; MBF, myocardial blood flow; PCI, percutaneous coronary intervention.

Figure 2. Change in defect size after CTO PCI in patients with a limited, moderate and large perfusion defect. Boxes and error bars are median [interquartile range]. Abbreviations as in figure 1.

Figure 3. CTO PCI in a patient with a limited and a large perfusion defect size. 1A) The vascular territory (arrow) subtended by a CTO in the right coronary artery and [^{15}O]H_2O PET perfusion showing a limited associated perfusion defect. After successful CTO PCI, antegrade blood flow restored (arrow, 1B) with restoration of PET perfusion after 3 months. 2A) The vascular territory (arrow) distal of a CTO in the right coronary artery and [^{15}O]H_2O PET perfusion displays a large associated perfusion defect. Successful CTO PCI (arrow, 2B) led to a major reduction in defect size. PET, positron emission tomography; other abbreviations as in figure 1.

Figure 4. A) Per patient paired measurements (lines) of hyperaemic MBF in the CTO area in patients stratified to the low, intermediate and high tertile according to hyperaemic MBF values at baseline. B) Per patient paired measurements (lines) of CFR in the CTO area in patients stratified to the low, intermediate and high tertile based on CFR values at baseline. Horizontal lines and error bars are mean and standard error of the mean. Abbreviations as in figure 1.

Table 1. Baseline clinical characteristics

	All patients N=193
Age (years)	63±11
Male	163 (84)
Body Mass Index (kg□m^{-2})	28±4
Prior MI	96 (50)
In CTO territory	55 (28)
Prior PCI	135 (70)
In CTO territory	34 (18)
Prior CABG	19 (10)
Graft on CTO vessel	14 (7)
LVEF (%)	
>55	78 (40)
45-55	62 (32)
<45	53 (27)
Cardiac risk factors	
Hypertension	103 (53)
Hypercholesterolemia	87 (45)
Current smoking	59 (31)
History of smoking	78 (40)
Family history CAD	88 (46)
Diabetes	49 (25)
Number of CAD risk factors	2 [1-3]
Medication	

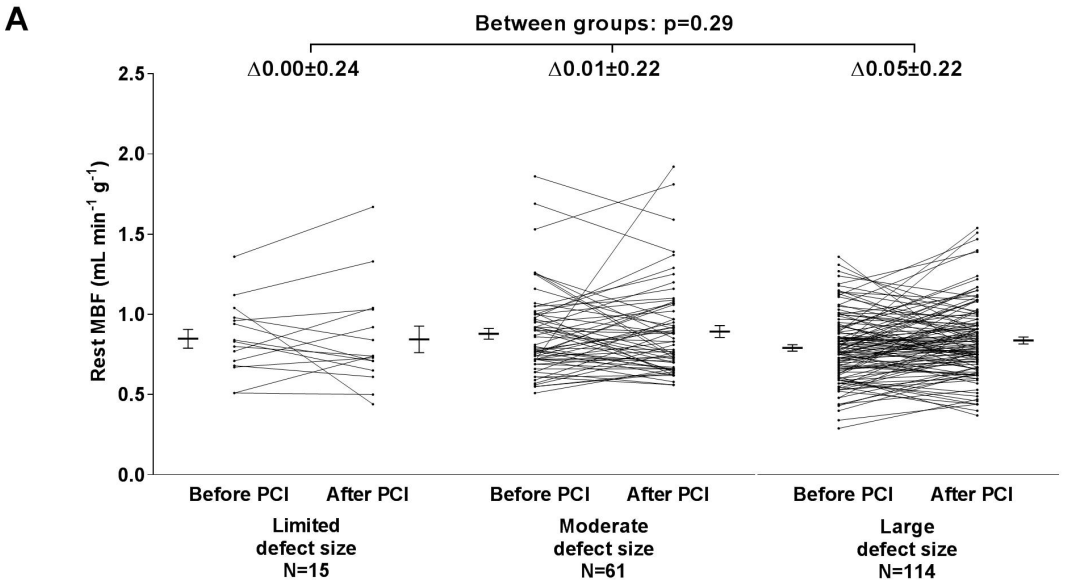
Aspirin	176 (91)
Dual anti-platelets	122 (63)
Anticoagulant	22 (11)
Statins	163 (85)
Beta-blockers	153 (79)
Calcium channel blockers	46 (24)
Long-acting nitrates	36 (19)
Clinical presentation	
Free of symptoms	36 (19)
Stable angina	143 (74)
Acute coronary syndrome	2 (1)
Other	12 (6)

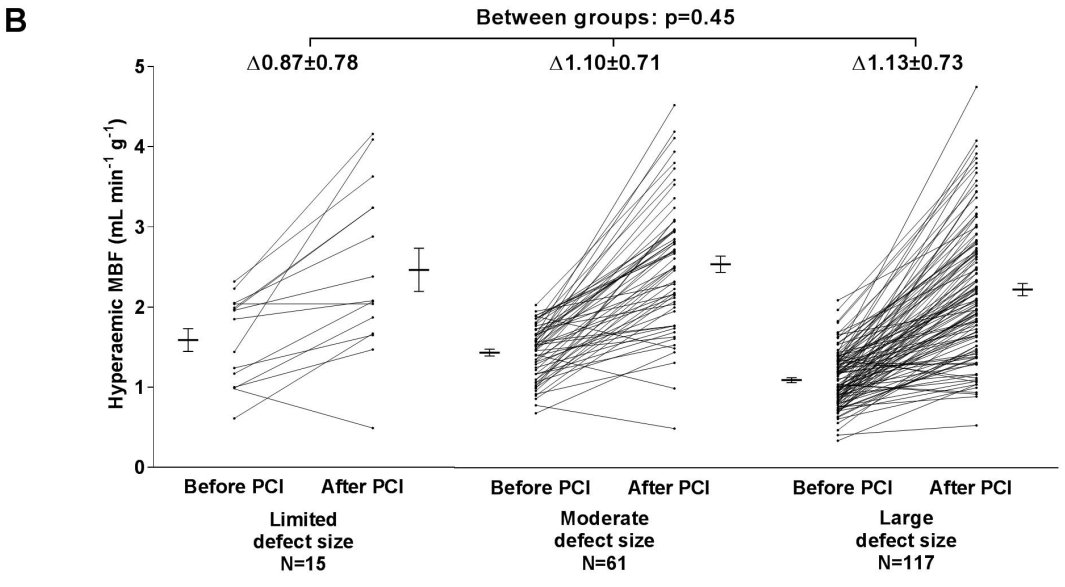
Values are mean ± SD, median [interquartile range] or N (%). CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CTO, chronic coronary total occlusion, LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

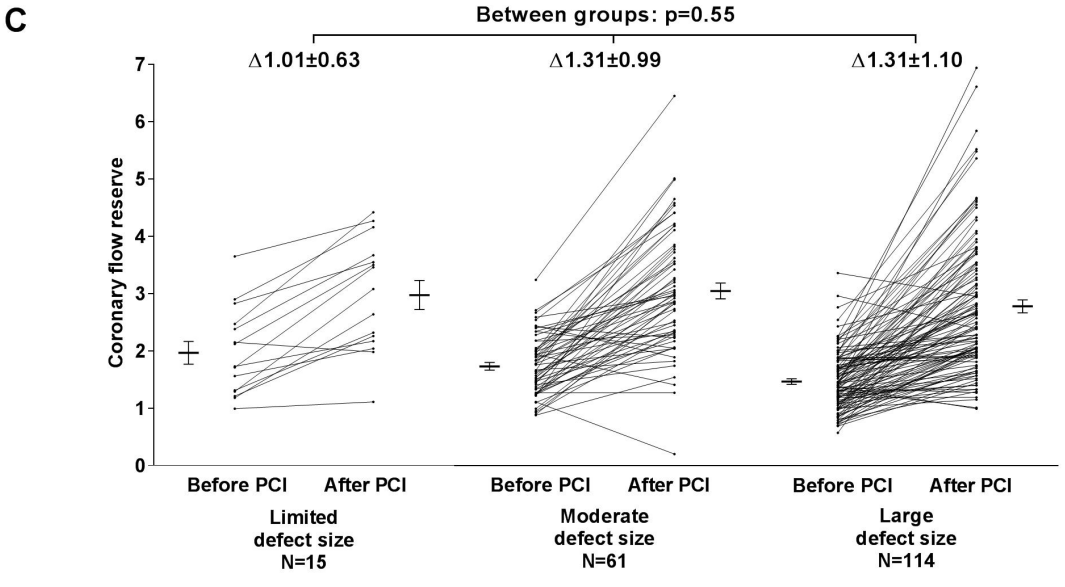
Table 2. Myocardial perfusion in the CTO area in patients with various perfusion defect sizes.

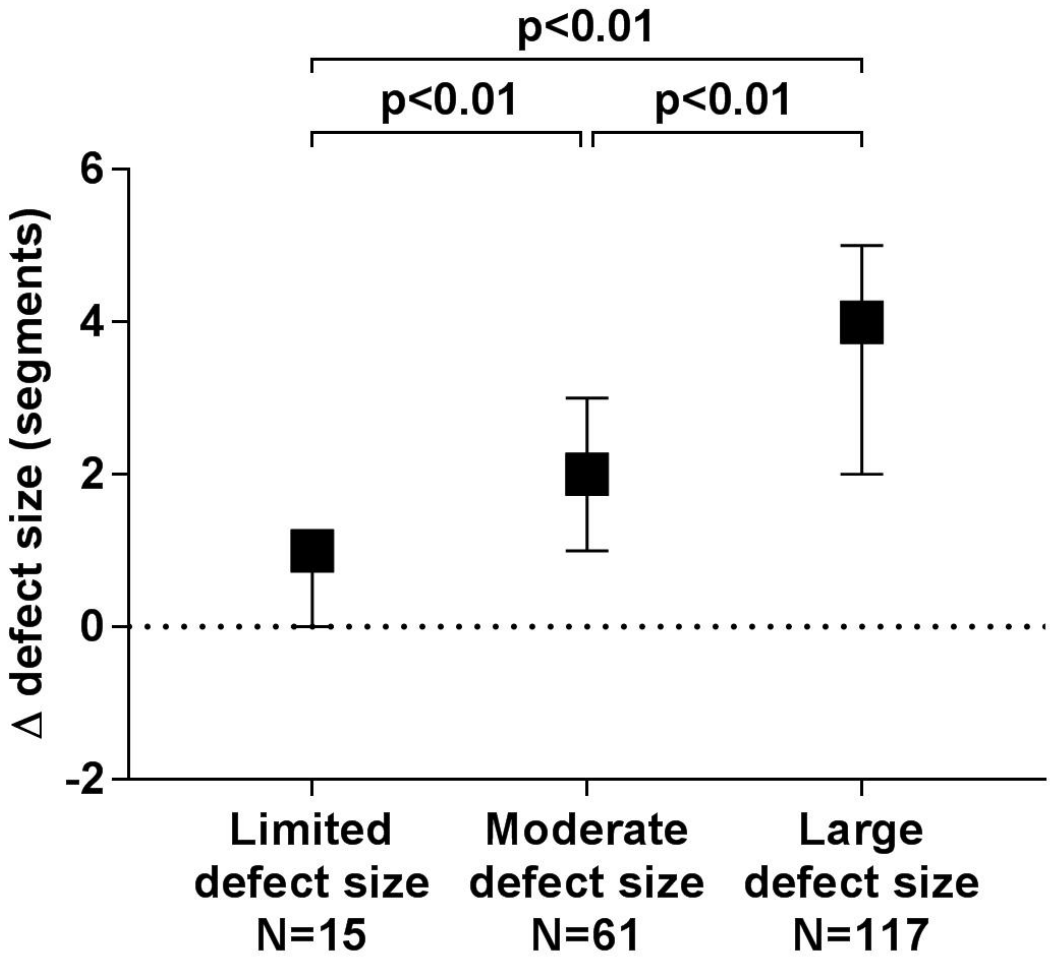
		Perfusion defect size at baseline			
	All patients	**Limited**	**Moderate**	**Large**	
	N=193	**N=15**	**N=61**	**N=117**	**p Value**
Rest MBF					
Before PCI	0.82±0.23	0.85±0.23	0.88±0.27	0.79±0.21	0.06
After PCI	0.86±0.26	0.84±0.32	0.89±0.29	0.84±0.23	0.39
p Value	0.06	0.95	0.68	0.02	
Hyperaemic MBF					
Before PCI	1.24±0.40	1.59±0.55	1.44±0.33	1.10±0.33*	<0.01
After PCI	2.34±0.84	2.46±1.04	2.54±0.80	2.22±0.82	0.05
p Value	<0.01	<0.01	<0.01	<0.01	
Coronary flow reserve					
Before PCI	1.59±0.55	1.97±0.77	1.73±0.52	1.47±0.51*	<0.01
After PCI	2.88±1.14	2.98±0.98	3.05±1.08	2.78±1.20	0.32
p Value	<0.01	<0.01	<0.01	<0.01	
Perfusion defect size					
Before PCI	4 [3-5]	1 [1-1]	3 [2-3] †	5 [4-6]*	<0.01
After PCI	1 [0-2]	0 [0-0]	0 [0-1]	1 [0-3]‡	<0.01
p Value	<0.01	0.06	<0.01	<0.01	

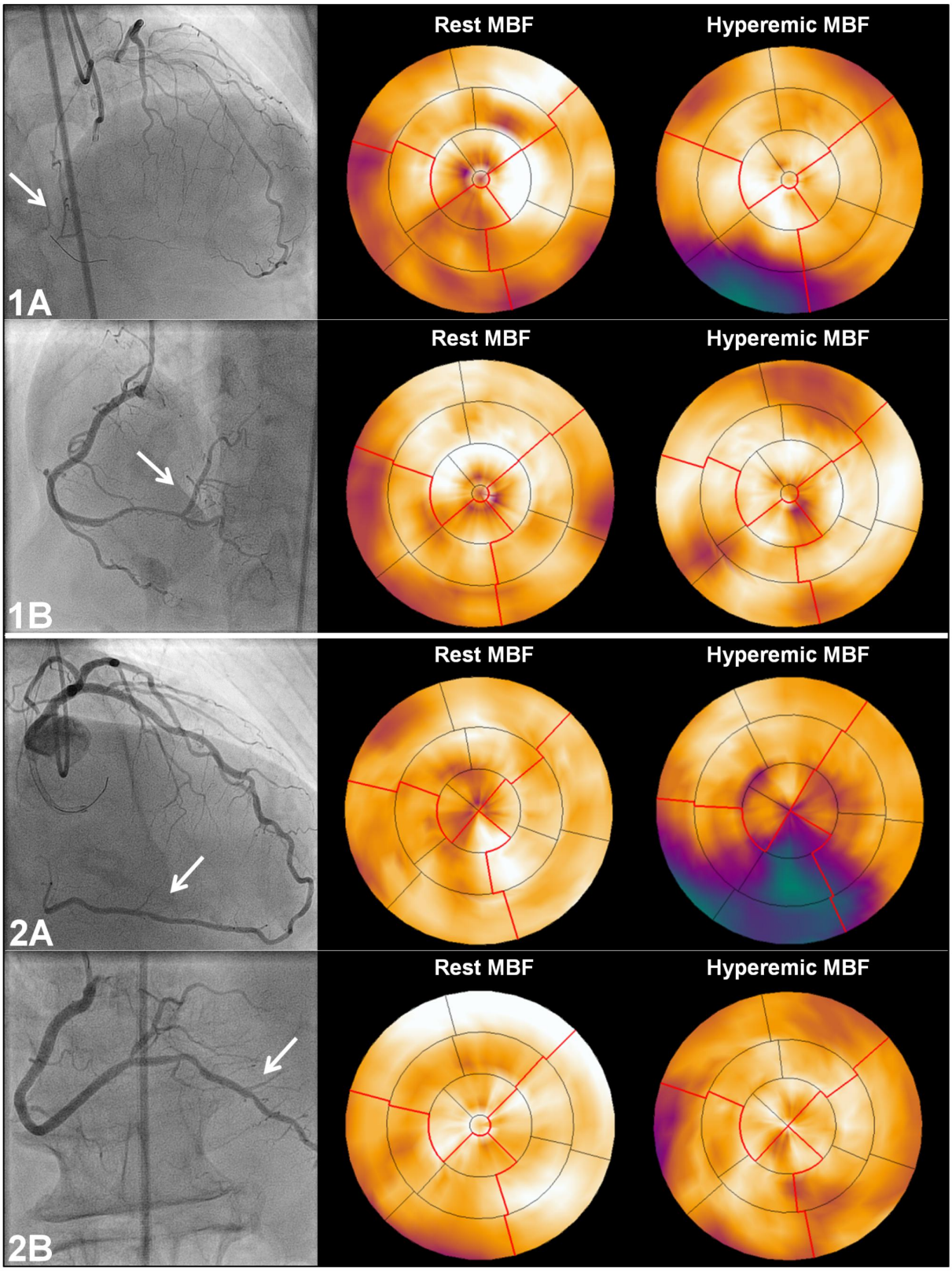
Values are mean ± SD or median [interquartile range]. *p<0.01 vs limited and vs moderate. †p<0.01 vs limited. ‡p<0.05 vs limited and p<0.01 vs moderate. MBF, myocardial blood flow; other abbreviations as in table 1.

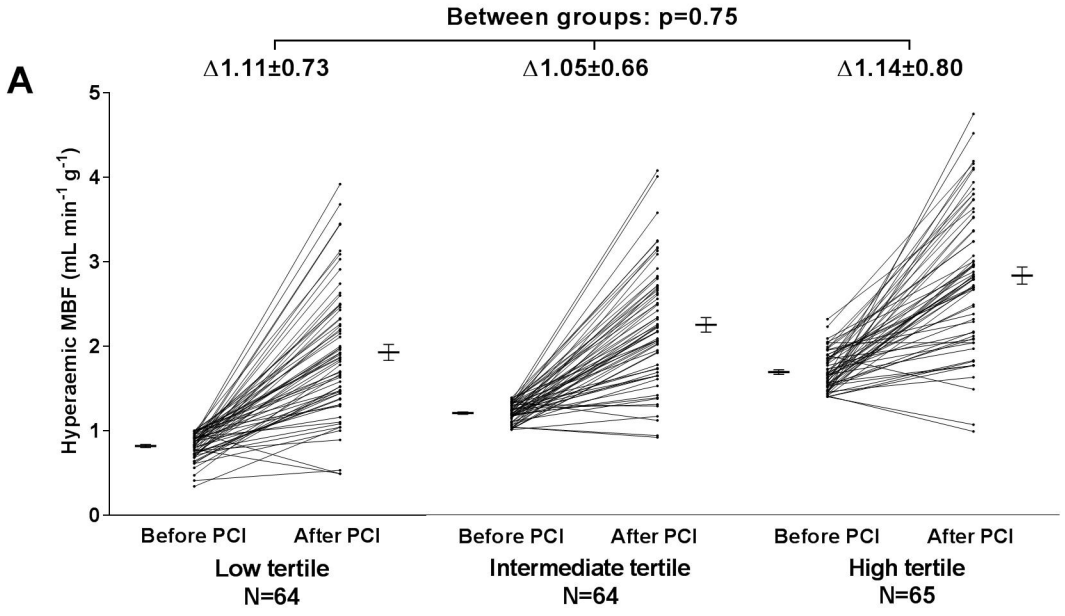


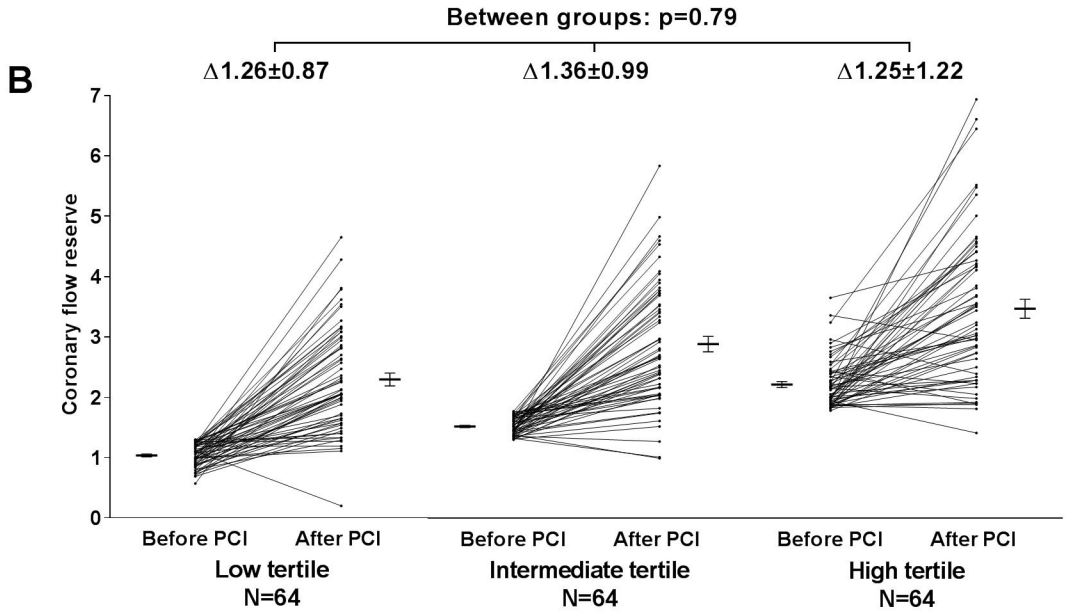












Supplementary table 1. Angiographic characteristics in patients with various perfusion defect sizes.

		Perfusion defect size at baseline			
	Total N=193	Limited N=15	Moderate N=61	Large N=117	p Value
CTO artery					0.02*
RCA	130 (67)	10 (67)	45 (74)	75 (64)	
LAD	40 (21)	4 (27)	5 (8)	31 (26)	
LCX	23 (12)	1 (7)	11 (18)	11 (9)	
CTO characteristics					
Previous attempt	28 (15)	3 (20)	6 (10)	19 (16)	0.42
Blunt cap	72 (38)	9 (60)	23 (38)	40 (34)	0.17
Calcification	109 (56)	10 (67)	31 (51)	68 (58)	0.49
Lesion length ≥20 mm	83 (43)	6 (40)	23 (38)	54 (47)	0.52
Tortuosity >45°	68 (35)	2 (13)	23 (38)	43 (37)	0.19
J-CTO score	2 [1-3]	2 [1-3]	2 [1-2]	2 [1-3]	0.42
Number of vessel disease					0.31
Single vessel	134 (69)	13 (87)	43 (70)	78 (67)	
Multivessel	59 (31)	2 (13)	18 (30)	39 (33)	
Werner CC score					0.59
CC 0-1	59 (31)	4 (27)	16 (26)	39 (33)	
CC 2	134 (69)	11 (73)	45 (74)	78 (67)	
Number vessel PCI					0.71
Single vessel	150 (78)	13 (87)	46 (75)	91 (78)	

Multivessel	43 (22)	2 (13)	15 (25)	26 (22)	
Stent length (mm)	82±39	79±37	79±44	84±36	0.68
Successful approach					0.54
AWE	90 (47)	6 (40)	31 (51)	53 (45)	
RWE	24 (12)	4 (27)	5 (8)	15 (13)	
ADR	35 (18)	3 (20)	9 (15)	23 (20)	
RDR	44 (23)	2 (13)	16 (26)	26 (22)	
Side branch loss	12 (6)	0 (0)	2 (3)	10 (9)	0.30
Periprocedural MI	14 (7)	0 (0)	5 (8)	9 (8)	0.82

Values are mean ± SD, median [interquartile range] or N (%). *moderate vs large $p<0.05$, other comparisons $p>0.05$. ADR, antegrade dissection and reentry; AWE, antegrade wire escalation; CC, collateral connection; CTO, chronic coronary total occlusion; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; RDR, retrograde dissection and reentry; RWE, retrograde wire escalation.

Supplementary table 2. Baseline myocardial perfusion in the CTO area in patients with successful vs. non-successful CTO PCI.

	Successful CTO PCI N=193	Failed CTO PCI N=10	p Value
Rest MBF	0.82±0.23	0.92±0.22	0.20
Hyperaemic MBF	1.24±0.40	1.05±0.22	0.03
Coronary flow reserve	1.59±0.55	1.19±0.40	0.03
Perfusion defect size	4 [3-5]	6 [4.5-6.5]	0.02

Values are mean ± SD or median [interquartile range]. MBF, myocardial blood flow; other abbreviations as in supplemental table 1.

Supplementary table 3. Myocardial perfusion in the CTO area in patients stratified according to CTO lesion TIMI flow grade.

	TIMI flow grade 0 N=153	TIMI flow grade 1 N=40	p Value
Rest MBF			
Before PCI	0.84±0.24	0.78±0.23	0.18
After PCI	0.85±0.24	0.88±0.32	0.44
p Value	0.48	0.01	
Δ	0.01±0.23	0.07±0.17	0.12
Hyperaemic MBF			
Before PCI	1.21±0.38	1.35±0.44	0.04
After PCI	2.30±0.81	2.49±0.95	0.20
p Value	<0.01	<0.01	
Δ	1.09±0.72	1.14±0.77	0.70
Coronary flow reserve			
Before PCI	1.53±0.53	1.81±0.59	<0.01
After PCI	2.83±1.11	3.07±1.27	0.24
p Value	<0.01	<0.01	
Δ	1.30±1.02	1.26±1.11	0.83
Perfusion defect size			
Before PCI	4 [3-6]	4 [3-5]	0.76
After PCI	0 [0-2]	0 [0-1.75]	0.07
p Value	<0.01	<0.01	

Δ	3 [2-4]	3 [1-5]	0.66

Values are mean ± SD or median [interquartile range]. Δ, change between before and after PCI; TIMI, Thrombolysis in myocardial infarction; other abbreviations as in supplemental table 1 and 2.

Supplementary table 4. Myocardial perfusion in the CTO area in patients stratified according to collateral status.

	CC score 0-1 N=59	CC score 2 N=134	p Value
Rest MBF			
Before PCI	0.85±0.23	0.82±0.24	0.38
After PCI	0.91±0.28	0.83±0.25	0.07
p Value	0.10	0.30	
Δ	0.04±0.23	0.02±0.21	0.55
Hyperaemic MBF			
Before PCI	1.21±0.38	1.26±0.40	0.46
After PCI	2.38±0.78	2.33±0.87	0.69
p Value	<0.01	<0.01	
Δ	1.17±0.70	1.07±0.74	0.39
Coronary flow reserve			
Before PCI	1.49±0.49	1.63±0.57	0.12
After PCI	2.82±1.07	2.91±1.18	0.62
p Value	<0.01	<0.01	
Δ	1.32±1.03	1.28±1.04	0.77
Perfusion defect size			
Before PCI	4 [3-6]	4 [3-5]	0.60
After PCI	1 [0-2]	0 [0-2]	0.44
p Value	<0.01	<0.01	

Δ	3 [2-5]	3 [1-4.25]	0.72

Values are mean ± SD or median [interquartile range]. Abbreviations as in supplemental table 1 and 2.

Supplementary table 5. Predictors of change in perfusion defect size after CTO PCI.

		Univariable		Multivariable	
		β	p Value	β	p Value
Age (years)		<-0.001	0.98		
Gender female		0.22	0.60		
Body mass index (kg□m^{-2})		0.05	0.17		
≥2 cardiac risk factors		-0.14	0.68		
≥2 antianginals		0.55	0.10	0.55	0.09
Prior MI in CTO territory		-0.33	0.33		
Prior revascularization in CTO territory		0.12	0.73		
LVEF <50%		-0.22	0.47		
CTO artery			<0.01		<0.01
	RCA*	0		0	
	LAD	1.19	<0.01	1.21	<0.01
	LCX	-0.58	0.62	-0.51	0.80
J-CTO score ≥2		-0.10	0.74		
Werner CC score <2		0.03	0.93		
Multivessel disease		-0.29	0.37		
Multivessel PCI		-0.38	0.29		
Stent length (mm)		-0.003	0.46		
Successful PCI approach			0.77		
	AWE*	0			
	RWE	-0.17			
	ADR	-0.42			
	RDR	-0.23			

An univariate generalized linear model was used with a Bonferroni correction for post hoc analysis when appropriate. The variable entered the multivariable analysis if p value was ≤0.10 in univariable analysis. *Variable was used as reference in case of >2 groups. LVEF, left ventricular ejection fraction; other abbreviations as in supplemental table 1.

Supplementary table 6. Baseline characteristics according to baseline hyperaemic MBF tertiles.

	Total cohort N = 193	Low N = 64	Intermediate N = 64	High N = 65	p Value
Age (years)	63±11	64±10	63±12	61±9	0.24
Male	163 (84)	53 (83)	57 (89)	53 (82)	0.51
Body Mass Index (kg□m^{-2})	28±4	27±5	28±4	28±5	0.70
Prior MI	96 (50)	36 (56)	28 (44)	32 (49)	0.38
In CTO territory	55 (28)	28 (44)*	15 (23)	12 (18)	<0.01
Prior PCI	135 (70)	46 (72)	47 (73)	42 (65)	0.54
In CTO territory	34 (18)	15 (23)	10 (16)	9 (14)	0.31
Prior CABG	19 (10)	7 (11)	9 (14)	3 (5)	0.15
Graft on CTO vessel	14 (7)	6 (9)	7 (11)	1 (2)	0.08
LVEF (%)					<0.01†
>55	78 (40)	13 (20)	32 (50)	33 (51)	
45-55	62 (32)	24 (38)	15 (23)	23 (35)	
<45	53 (27)	27 (42)	17 (27)	9 (14)	
CAD risk factors					
Hypertension	103 (53)	32 (50)	36 (56)	35 (54)	0.77
Hypercholesterolemia	87 (45)	25 (39)	30 (47)	32 (49)	0.49
Current smoking	59 (31)	25 (39)	15 (23)	19 (29)	0.16
History of smoking	78 (40)	24 (38)	26 (41)	28 (43)	0.84
Family history CAD	88 (46)	25 (39)	34 (53)	29 (45)	0.29
Diabetes	49 (25)	22 (34)	12 (19)	15 (23)	0.11
Number of CAD risk factors	2 [1-3]	2 [1-3]	2 [1-3]	3 [1-3]	0.93

Values are mean ± SD, median [Q1-Q3] or n (%). *p<0.01 vs high tertile. †low vs intermediate and vs high both p<0.01, intermediate vs high p=0.40. CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; other abbreviations as in Supplemental table 1, 2 and 5.

Supplementary table 7. Baseline characteristics according to baseline CFR tertiles.

	Total cohort N = 192	Low N = 64	Intermediate N = 64	High N = 64	p Value
Age (years)	62±11	64±11	62±11	61±10	0.28
Male	162 (84)	48 (75)	57 (89)	57 (89)	0.06
Body Mass Index (kg□m^{-2})	28±4	28±4	27±4	28±5	0.53
Prior MI	96 (50)	31 (48)	30 (47)	35 (55)	0.72
In CTO territory	55 (29)	22 (34)	19 (30)	14 (22)	0.31
Prior PCI	134 (70)	44 (69)	48 (75)	42 (66)	0.55
In CTO territory	33 (17)	16 (25)	9 (14)	8 (13)	0.16
Prior CABG	19 (10)	8 (13)	7 (11)	4 (6)	0.56
Graft on CTO vessel	14 (7)	6 (9)	6 (9)	2 (3)	0.32
LVEF (%)					0.60
>55	78 (40)	22 (34)	25 (39)	30 (47)	
45-55	62 (32)	21 (33)	23 (36)	18 (28)	
<45	53 (27)	21 (33)	16 (25)	16 (25)	
CAD risk factors					
Hypertension	103 (54)	34 (53)	36 (56)	33 (52)	0.90
Hypercholesterolemia	86 (45)	24 (38)	33 (52)	29 (45)	0.30
Current smoking	59 (31)	21 (33)	21 (33)	17 (27)	0.70
History of smoking	78 (41)	27 (42)	25 (39)	26 (41)	0.98
Family history CAD	88 (46)	26 (41)	30 (47)	32 (50)	0.60
Diabetes	49 (26)	12 (19)	24 (38)	13 (20)	0.04
Number of CAD risk factors	2 [1-3]	2 [1-3]	3 [1-4]	2 [1-3]	0.23

Values are mean ± SD, median [interquartile range] or n (%). CFR, coronary flow reserve; other abbreviations as in supplemental table 1, 2 and 6.