EuroIntervention 2020;16:e462-e471 published online September 2019 ■ published online e-edition August 2020

DOI: 10.4244/EIJ-D-19-00631

Special feature: Chronic total occlusion

Ischaemic burden and changes in absolute myocardial perfusion after chronic total occlusion percutaneous coronary intervention

Stefan P. Schumacher[1], MD; Marly Kockx[1], BSc; Wijnand J. Stuijfzand[1], MD; Roel S. Driessen[1], MD; Pepijn A. van Diemen[1], MD; Michiel J. Bom[1], MD; Henk Everaars[1], MD; Pieter G. Raijmakers[2], MD, PhD; Ronald Boellaard[2], PhD; Albert C. van Rossum[1], MD, PhD; Maksymilian P. Opolski[3], MD, PhD; Alexander Nap[1], MD, PhD; Paul Knaapen[1]*, MD, PhD

1. Department of Cardiology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; 2. Radiology, Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; 3. Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00631

KEYWORDS

- chronic coronary total occlusion
- non-invasive imaging
- stable angina

Abstract

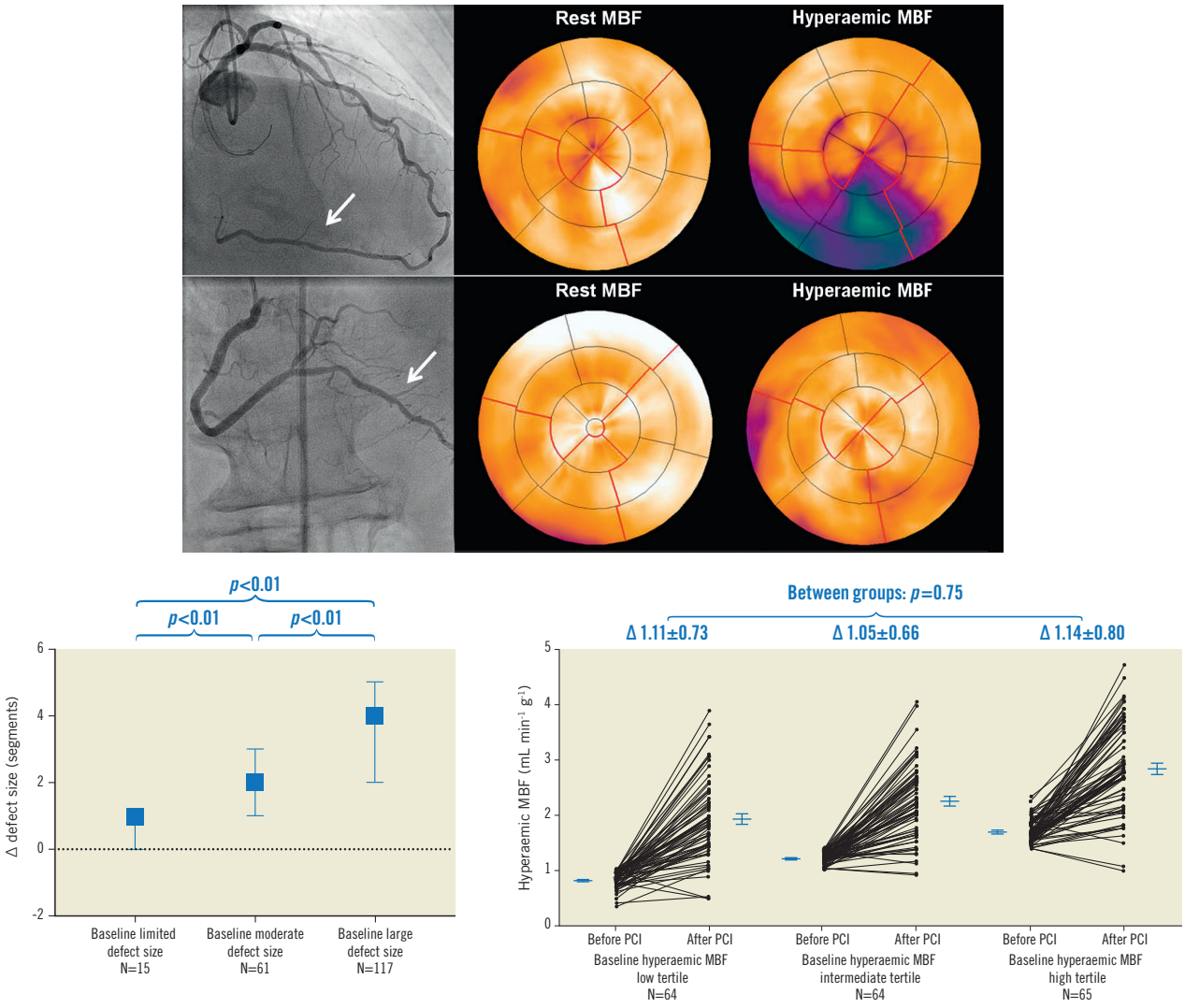
Aims: The aim of this study was to explore the relationships between ischaemic burden and changes in absolute myocardial perfusion following chronic coronary total occlusion (CTO) percutaneous coronary intervention (PCI).

Methods and results: A total of 193 consecutive patients underwent [^{15}O]H_2O positron emission tomography prior to and three 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 among 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.

**Corresponding author: Department of Cardiology, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. E-mail: p.knaapen@vumc.nl*

SUBMITTED ON 04/07/2019 - REVISION RECEIVED ON 05/09/2019 - ACCEPTED ON 19/09/2019



Visual summary. *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.*

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 with the CTO lesion evaluated with myocardial perfusion imaging[3]. A 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 haemodynamically significant non-occluded lesions[7]. In addition, a beneficial effect of revascularisation 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 revascularisation in patients with a marked ischaemic burden[10]. However, data on the effectiveness of CTO PCI on ischaemia reduction in patients with various degrees of ischaemic burden are lacking. The aim of the present study was to determine the impact of CTO PCI on the relief of different extents of ischaemia as quantified with [^{15}O]H_2O positron emission tomography (PET).

Editorial, see page 441

Methods

STUDY DESIGN AND PARTICIPANTS

Prospectively recruited consecutive patients presenting with a CTO in the Amsterdam UMC location Vrije Universiteit Amsterdam between 2013 and 2018 were eligible for inclusion if the presence of ischaemia was evaluated with [^{15}O]H_2O PET perfusion imaging prior to and following successful CTO PCI. Patients were rescheduled for [^{15}O]H_2O PET imaging at least three months after revascularisation. 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 revascularisation was defined as TIMI flow grade 3 and <30% diameter stenosis[7]. Side branch loss (≥2 mm) 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 (140 $\mu \cdot kg^{-1} \cdot min^{-1}$)[4]. Rest and hyperaemic myocardial blood flow (MBF, in $mL \cdot min^{-1} \cdot g^{-1}$) and coronary flow reserve (CFR) as the ratio of hyperaemic to rest MBF were measured in the CTO myocardial area. The standardised 17-segment model of the American Heart Association was used for left ventricular segmentation. The perfusion defect size associated with the CTO was defined by the number of myocardial segments in which hyperaemic MBF was below 2.3 $mL \cdot min^{-1} \cdot g^{-1}$ 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 ANALYSIS

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 being $p<0.05$, 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 $mL \cdot min^{-1} \cdot g^{-1}$), intermediate (1.01-1.39 $mL \cdot min^{-1} \cdot g^{-1}$) and highest (≥1.40 $mL \cdot min^{-1} \cdot g^{-1}$) tertiles 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) tertiles of CFR at baseline. A univariate generalised linear model was used for linear regression analyses to find predictors for change in perfusion defect size after CTO PCI. Variables were entered into the multivariable analysis if the p-value was ≤0.10 in the univariable analysis. Receiver operating curve analyses were used to identify the optimal baseline perfusion defect size threshold for subsequent ≥1 and ≥2 segment defect size reduction after CTO PCI. A level of $p<0.05$ was considered significant. Statistical analyses were performed using SPSS software, Version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc software 11.6.0.0 (MedCalc, Mariakerke, Belgium).

Results

PATIENT POPULATION

Between 2013 and 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 undergo follow-up PET imaging and were excluded from analysis. Clinical and angiographic characteristics of the successfully treated patients are shown in **Table 1** and **Supplementary 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 revascularise the CTO successfully. Spontaneous MI or unplanned myocardial revascularisation did not occur in any patient between serial PET imaging. After follow-up PET imaging and clinical evaluation, three patients were additionally treated with PCI of the CTO artery. In two of these three patients, residual ischaemia in the CTO territory was caused by a significant stenosis distal of the former CTO lesion, and in one patient residual ischaemia was present due to a compromised side branch at the site of the revascularised CTO.

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)
Hypercholesterolaemia		87 (45)
Current smoking		59 (31)
History of smoking		78 (40)
Family history of CAD		88 (46)
Diabetes		49 (25)
Number of CAD risk factors		2 [1-3]
Medication		
Aspirin		176 (91)
Dual antiplatelets		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

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 three patients due to one failed rest scan at baseline and two failed rest scans at follow-up. Myocardial perfusion findings at baseline and follow-up are shown in **Table 2**. A total of 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 **(Supplementary 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 **(Supplementary Table 3)**. Overall changes 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 revascularisation 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 among patients with a limited, moderate or 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 non-significantly different between patients with CC score 2 collaterals and patients with CC 0-1 collaterals supplying the myocardium subtended by a CTO **(Supplementary 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 **(Supplementary Table 5)**. Receiver operating curve analyses identified a perfusion defect of ≥3 segments as the optimal threshold to predict ≥1 segment (83% sensitivity and 50% specificity) and ≥2 segment (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 tertiles 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 three tertiles are shown in **Supplementary Table 6**. After PCI, hyperaemic MBF increased significantly (paired data within each tertile p<0.01) to 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 among the groups (overall p=0.75) **(Figure 4A)**.

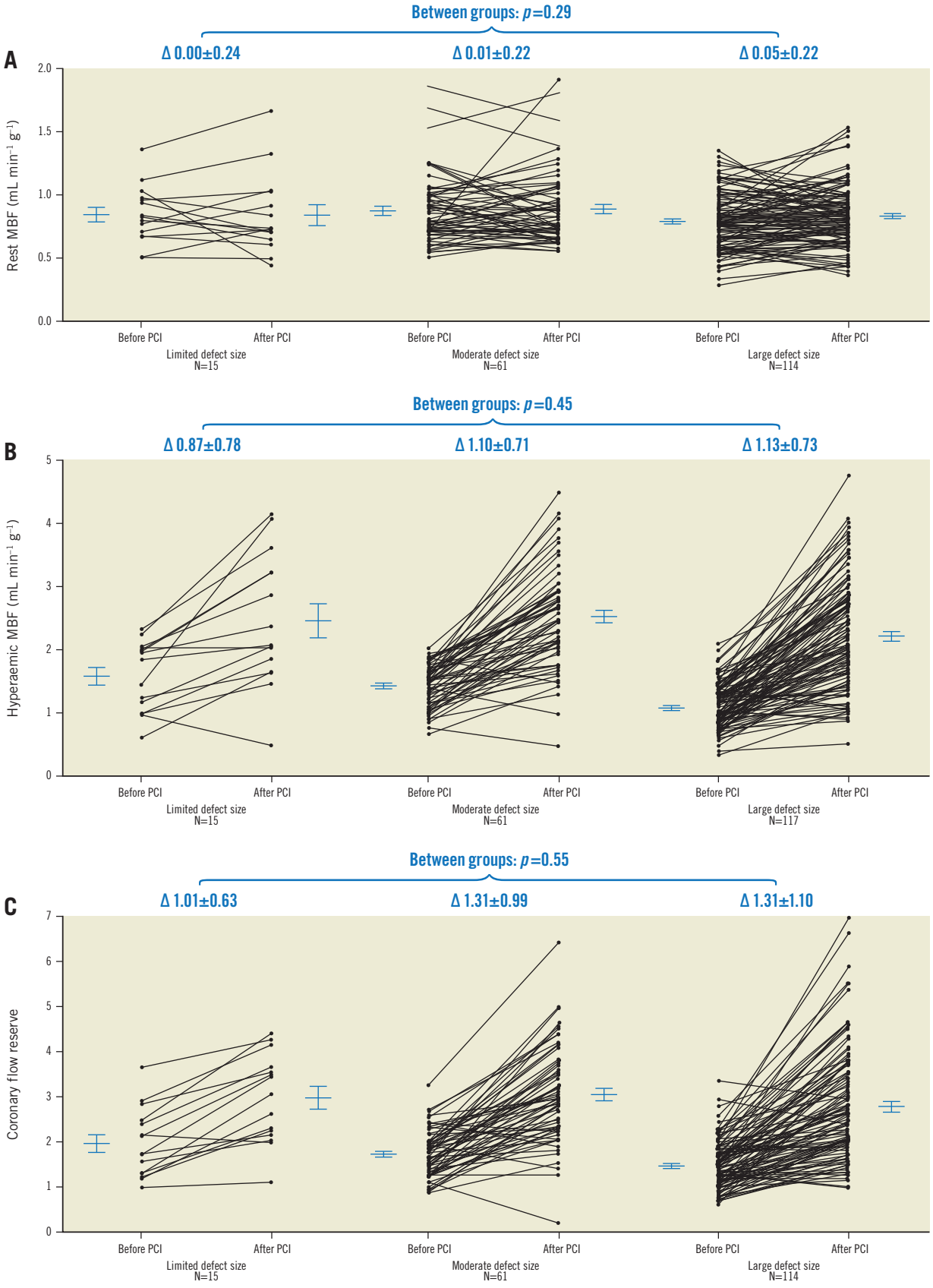


Figure 1. *Per patient paired measurements. Per patient paired measurements (lines) of rest MBF (A), hyperaemic MBF (B) and CFR (C) in patients with a limited, moderate and large perfusion defect at baseline. Horizontal lines and error bars are mean and standard error of the mean. Δ: change; CFR: coronary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

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

	All patients N=193	Perfusion defect size at baseline			*p*-value
		Limited N=15	Moderate N=61	Large N=117	
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 versus limited and versus moderate. †p<0.01 versus limited. ‡p<0.05 versus limited and p<0.01 versus moderate. CTO: chronic coronary total occlusion; MBF: myocardial blood flow; PCI: percutaneous coronary intervention

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 tertiles was 1.04±0.19, 1.52±0.14 and 2.21±0.40, respectively, and increased significantly after PCI (paired data within each tertile p<0.01) to levels of 2.29±0.86, 2.89±1.00 and 3.47±1.24, respectively, at follow-up (all comparisons between groups p<0.01). Baseline characteristics of patients within the three tertiles are shown in **Supplementary Table 7**. The change in CFR was comparable between the groups (overall p=0.79) **(Figure 4B)**.

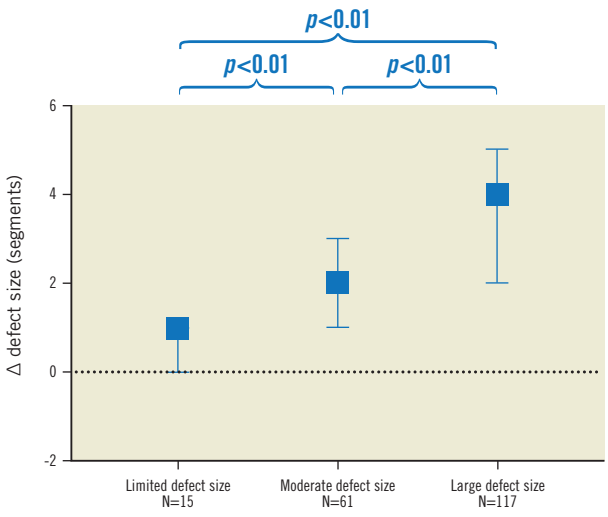


Figure 2. *Change in defect size after CTO PCI in patients with a limited, moderate and large perfusion defect. Boxes and error bars are median (interquartile range). Δ: change; CTO: chronic coronary total occlusion; PCI: percutaneous coronary intervention*

Discussion

The main findings can be summarised 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; and 4) increases in hyperaemic MBF and CFR were significant and not related to 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

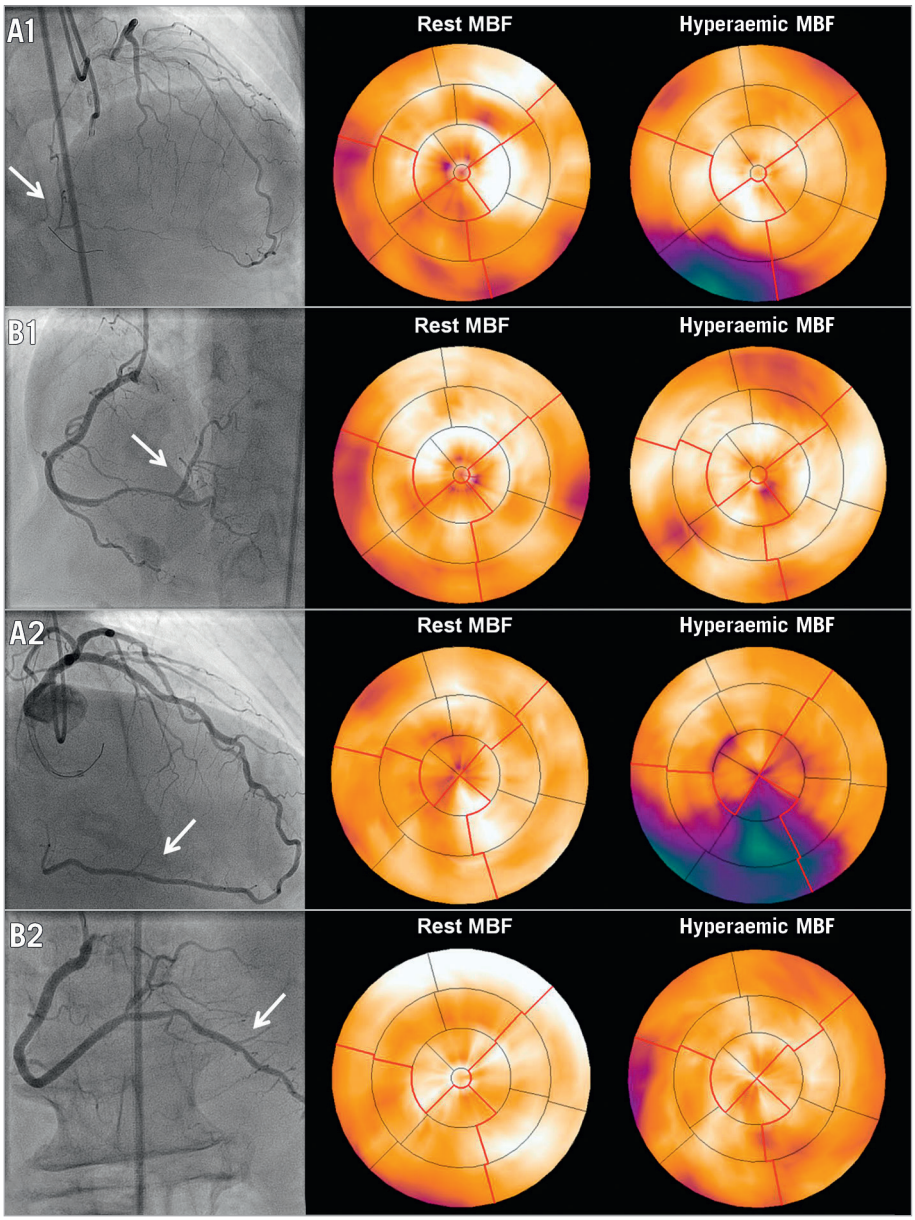


Figure 3. *CTO PCI in a patient with a limited and a large perfusion defect size. A1) The vascular territory (arrow) subtended by a CTO in the right coronary artery and [^{15}O]H_2O PET perfusion showing a limited associated perfusion defect. After successful CTO PCI, antegrade blood flow was restored (arrow, B1) with restoration of PET perfusion after three months. A2) The vascular territory (arrow) distal of a CTO in the right coronary artery and [^{15}O]H_2O PET perfusion displaying a large associated perfusion defect. Successful CTO PCI (arrow, B2) led to a major reduction in defect size. CTO: chronic coronary total occlusion; MBF: myocardial blood flow; PCI: percutaneous coronary intervention; PET: positron emission tomography*

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)recognised 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 randomised 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 randomised to CTO PCI and those randomised to optimal medical therapy. All non-occlusive lesions in patients with multivessel disease were treated before randomisation to establish

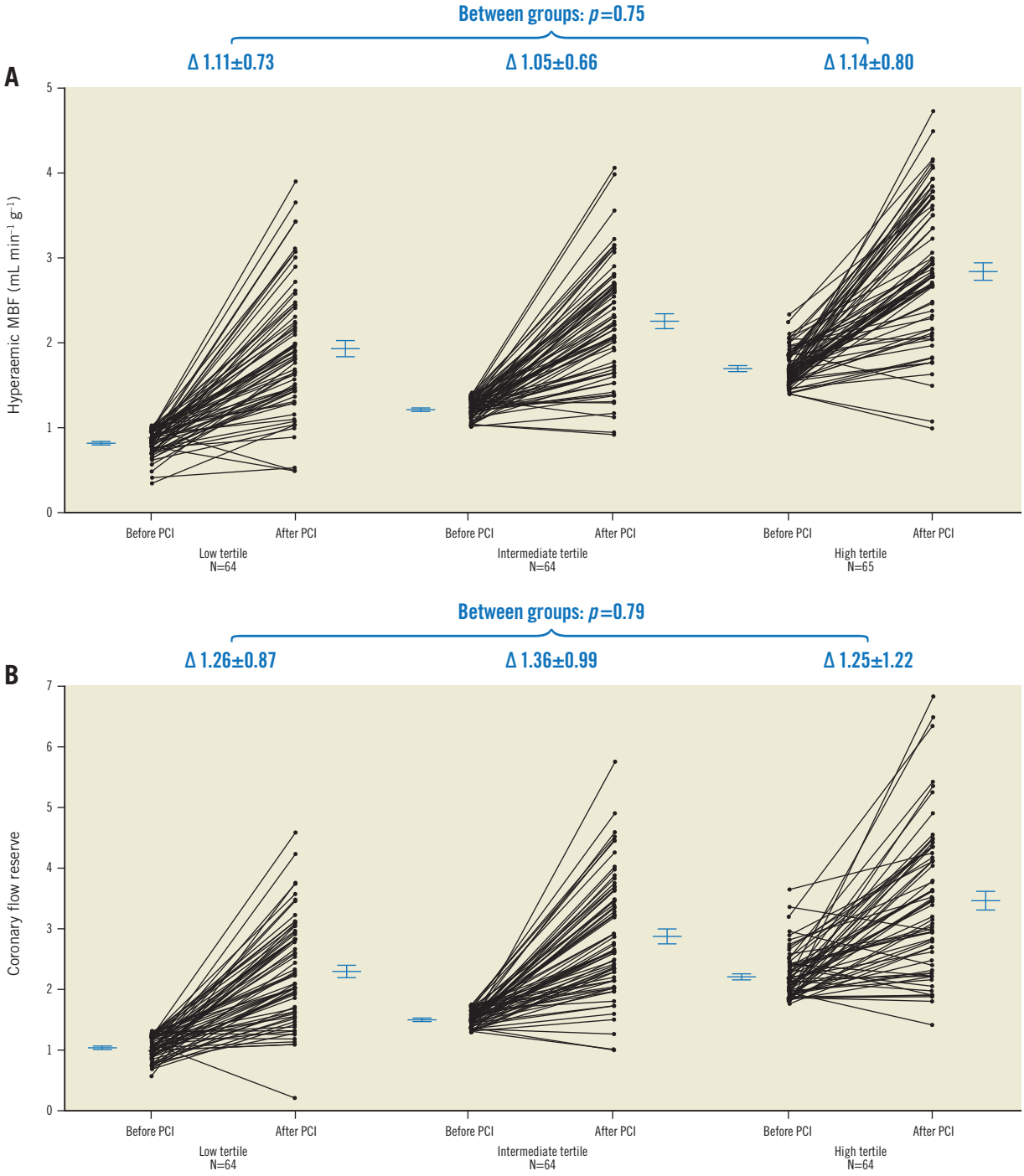


Figure 4. *Per patient paired measurements. A) Per patient paired measurements (lines) of hyperaemic MBF in the CTO area in patients stratified to the low, intermediate and high tertiles according to hyperaemic MBF values at baseline. B) Per patient paired measurements (lines) of CFR in the CTO area in patients stratified to the low, intermediate and high tertiles based on CFR values 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*

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 three-year follow-up in the EuroCTO trial are eagerly awaited. In the present study, CTO PCI resulted in a median defect size reduction of three 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 greater 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 unrecognised in some patients due to a lack of re-invasive coronary angiography at the time of follow-up PET. It should be noted, however, that a median residual defect size of 0 to 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 less often had 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 revascularisation. 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 improved significantly 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 revascularisation 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, the 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 remains unclear. A gradual increase of myocardial perfusion up to three months after coronary revascularisation has been reported previously[20]. In the present study, myocardial perfusion findings after CTO PCI (e.g., residual defect sizes) might have improved further if the follow-up duration of three months had been 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 recanalisation 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 recognise 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. Greater 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 their 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.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol.* 2013;61:282-94.

2. Azzalini L, Candilio L, Ojeda S, Dens J, La Manna A, Benincasa S, Bellini B, Hidalgo F, Chavarria J, Maeremans J, Gravina G, Miccichè E, D'Agosta G, Venuti G, Tamburino C, Pan M, Carlino M, Colombo A. Impact of Incomplete

Revascularization on Long-Term Outcomes Following Chronic Total Occlusion Percutaneous Coronary Intervention. *Am J Cardiol.* 2018;121:1138-48.

3. Galassi AR, Werner GS, Tomasello SD, Azzarelli S, Capodanno D, Barrano G, Marza F, Costanzo L, Campisano M, Tamburino C. Prognostic value of exercise myocardial scintigraphy in patients with coronary chronic total occlusions. *J Interv Cardiol.* 2010;23:139-48.

4. Stuijfzand WJ, Driessen RS, Raijmakers PG, Rijnierse MT, Maeremans J, Hollander MR, Lammertsma AA, van Rossum AC, Dens J, Nap A, van Royen N, Knaapen P. Prevalence of ischaemia in patients with a chronic total occlusion and preserved left ventricular ejection fraction. *Eur Heart J Cardiovasc Imaging.* 2017;18:1025-33.

5. Sachdeva R, Agrawal M, Flynn SE, Werner GS, Uretsky BF. The myocardium supplied by a chronic total occlusion is a persistently ischemic zone. *Catheter Cardiovasc Interv.* 2014;83:9-16.

6. Obedinskiy AA, Kretov EI, Boukhris M, Kurbatov VP, Osiev AG, Ibn Elhadj Z, Obedinskaya NR, Kasbaoui S, Grazhdankin IO, Prokhorikhin AA, Zubarev DD, Biryukov A, Pokushalov E, Galassi AR, Baystrukov VI. The IMPACTOR-CTO Trial. *JACC Cardiovasc Interv.* 2018;11:1309-11.

7. Schumacher SP, Driessen RS, Stuijfzand WJ, Raijmakers PG, Danad I, Dens J, Spratt JC, Hanratty CG, Walsh SJ, Boellaard R, van Rossum AC, Opolski MP, Nap A, Knaapen P. Recovery of myocardial perfusion after percutaneous coronary intervention of chronic total occlusions is comparable to hemodynamically significant non-occlusive lesions. *Catheter Cardiovasc Interv.* 2019;93:1059-66.

8. Safley DM, Koshy S, Grantham JA, Bybee KA, House JA, Kennedy KF, Rutherford BD. Changes in myocardial ischemic burden following percutaneous coronary intervention of chronic total occlusions. *Catheter Cardiovasc Interv.* 2011;78:337-43.

9. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation.* 2003;107:2900-7.

10. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

11. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol.* 2018;72:2231-64.

12. Werner GS, Surber R, Ferrari M, Fritzenwanger M, Figulla HR. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. *Eur Heart J.* 2006;27:2406-12.

13. Danad I, Uusitalo V, Kero T, Saraste A, Raijmakers PG, Lammertsma AA, Heymans MW, Kajander SA, Pietila M, James S, Sorensen J, Knaapen P, Knuuti J. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H_2O PET imaging. *J Am Coll Cardiol.* 2014;64:1464-75.

14. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, Rumoroso JR, Erglis A, Christiansen EH, Escaned J, di Mario C, Hovasse T, Teruel L, Bufe A, Lauer B, Bogaerts K, Goicolea J, Spratt JC, Gershlick AH, Galassi AR, Louvard Y; EUROCTO trial investigators. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J.* 2018;39:2484-93.

15. Bom MJ, Schumacher SP, Driessen RS, Raijmakers PG, Everaars H, van Diemen PA, Lammertsma AA, van de Ven PM, van Rossum AC, Knuuti J, Maki M, Danad I, Knaapen P. Impact of individualized segmentation on diagnostic performance of quantitative positron emission tomography for haemodynamically significant coronary artery disease. *Eur Heart J Cardiovasc Imaging.* 2019;20:525-32.

16. Stuijfzand WJ, Biesbroek PS, Raijmakers PG, Driessen RS, Schumacher SP, van Diemen P, van den Berg J, Nijveldt R, Lammertsma AA, Walsh SJ, Hanratty CG, Spratt JC, van Rossum AC, Nap A, van Royen N, Knaapen P. Effects of successful percutaneous coronary intervention of chronic total occlusions on myocardial perfusion and left ventricular function. *EuroIntervention.* 2017;13:345-54.

17. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. *Nat Rev Cardiol.* 2015;12:48-62.

18. Brugaletta S, Martin-Yuste V, Padro T, Alvarez-Contreras L, Gomez-Lara J, Garcia-Garcia HM, Cola C, Liuzzo G, Masotti M, Crea F, Badimon L, Serruys PW, Sabaté M. Endothelial and smooth muscle cells dysfunction distal to recanalized chronic total coronary occlusions and the relationship with the collateral connection grade. *JACC Cardiovasc Interv.* 2012;5:170-8.

19. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ, Di Carli MF. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation.* 2011;124:2215-24.

20. Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Delayed recovery of coronary resistive vessel function after coronary angioplasty. *J Am Coll Cardiol.* 1993;21:612-21.

Supplementary data

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

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

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

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

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

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

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

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00631

Supplementary data

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 vessels diseased					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 of PCI vessels					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 re-entry; 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 re-entry; RWE: retrograde wire escalation

Supplementary Table 2. Baseline myocardial perfusion in the CTO area in patients with successful versus 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).

CTO: chronic coronary total occlusion; MBF: myocardial blood flow; PCI: percutaneous coronary intervention

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; CTO: chronic coronary total occlusion; MBF: myocardial blood flow; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

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). Δ: change between before and after PCI; CC: collateral connection; CTO: chronic coronary total occlusion; MBF: myocardial blood flow; PCI: percutaneous coronary intervention

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 ($kg \cdot m^{-2}$)		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 revascularisation 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 generalised linear model was used with a Bonferroni correction for *post hoc* analysis when appropriate. The variable entered the multivariable analysis if the p-value was ≤0.10 in univariable analysis. *Variable was used as reference in case of >2 groups.

ADR: antegrade dissection and re-entry; AWE: antegrade wire escalation; CC: collateral connection; CTO: chronic coronary total occlusion; LAD: left anterior descending artery; LCX: left circumflex artery; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; RDR: retrograde dissection and re-entry; RWE: retrograde wire escalation

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, $kg \cdot m^{-2}$	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
Hypercholesterolaemia	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 of 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; CTO: chronic coronary total occlusion; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

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, $kg \cdot m^{-2}$	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
Hypercholesterolaemia	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 of 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 (%).

CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CFR: coronary flow reserve; CTO: chronic coronary total occlusion; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention