

Impact of percutaneous coronary intervention of chronic total occlusions on absolute perfusion in remote myocardium

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KEYWORDS

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

Abstract

Background: Revascularisation of a chronic total coronary occlusion (CTO) impacts on the coronary physiology of the remote myocardial territory.

Aims: This study aimed to evaluate the intrinsic effect of CTO percutaneous coronary intervention (PCI) on changes in absolute perfusion in remote myocardium.

Methods: A total of 164 patients who underwent serial [¹⁵O]H₂O positron emission tomography (PET) perfusion imaging at baseline and three months after successful single-vessel CTO PCI were included to evaluate changes in hyperaemic myocardial blood flow (hMBF) and coronary flow reserve (CFR) in the remote myocardium supplied by both non-target coronary arteries.

Results: Perfusion indices in CTO and remote myocardium showed a positive correlation before (resting MBF: $r=0.84$, hMBF: $r=0.75$, and CFR: $r=0.77$, $p<0.01$ for all) and after (resting MBF: $r=0.87$, hMBF: $r=0.87$, and CFR: $r=0.81$, $p<0.01$ for all) CTO PCI. Absolute increases in hMBF and CFR were observed in remote myocardium following CTO revascularisation (from 2.29 ± 0.67 to 2.48 ± 0.75 mL·min⁻¹·g⁻¹ and from 2.48 ± 0.76 to 2.74 ± 0.85 , respectively, $p<0.01$ for both). Improvements in remote myocardial perfusion were largest in patients with a higher increase in hMBF (β 0.58, 95% CI: 0.48-0.67, $p<0.01$) and CFR (β 0.54, 95% CI: 0.44-0.64, $p<0.01$) in the CTO territory, independent of clinical, angiographic and procedural characteristics.

Conclusions: CTO revascularisation resulted in an increase in remote myocardial perfusion. Furthermore, the quantitative improvement in hMBF and CFR in the CTO territory was independently associated with the absolute perfusion increase in remote myocardial regions. As such, CTO PCI may have a favourable physiologic impact beyond the intended treated myocardium.

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Abbreviations

AHA	American Heart Association
CAD	coronary artery disease
CC	collateral connection
CFR	coronary flow reserve
CTO	chronic total coronary occlusion
FFR	fractional flow reserve
MBF	myocardial blood flow
MI	myocardial infarction
PCI	percutaneous coronary intervention
PET	positron emission tomography

Introduction

Chronic total coronary occlusions (CTOs) have been reported in approximately 20% of patients with significant coronary artery disease (CAD) referred for invasive coronary angiography¹. Myocardial ischaemia in the CTO territory is observed in the vast majority of patients, despite the presence of well-developed collaterals². A growing body of evidence shows that successful CTO percutaneous coronary intervention (PCI) results in a reduction of ischaemic burden and is associated with improved quality of life^{3,4}. Physiological evaluation is increasingly used in the selection of revascularisation strategies for obstructive lesions in coronary donor arteries supplying collaterals to the myocardium subtended by a CTO⁵. Distal flow characteristics of the CTO vessel are affected by microvascular function, the development and integrity of the collateral circulation, the effect of collateral steal, and obstructive disease in the collateral donor arteries⁶⁻⁸. Vice versa, the presence of a concomitant CTO results in alterations in coronary haemodynamics in remote myocardium subtended by the collateral donor coronary arteries⁵. Prior studies showed improvement in absolute myocardial perfusion in the myocardium subtended by a CTO and an increase in fractional flow reserve (FFR) in the CTO vessel after successful CTO PCI, whereas a concomitant immediate and subsequent further gradual decrease in collateral function was observed⁹⁻¹². In addition, physiologic changes in collateral donor vessel flow velocity and pressure-derived estimations of coronary flow have been described following CTO PCI, largely attributable to collateral regression^{13,14}. To date, comprehensive studies evaluating coronary physiology in remote myocardium after CTO PCI have lacked quantitative perfusion assessment. The present study aimed to explore the intrinsic effect of CTO PCI on changes in absolute perfusion in remote myocardium as assessed by serial [¹⁵O]H₂O positron emission tomography (PET) perfusion imaging.

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Methods

STUDY DESIGN AND PARTICIPANTS

This study comprised prospectively recruited patients who underwent functional assessment with [¹⁵O]H₂O PET perfusion imaging at baseline and approximately three months after successful single-vessel CTO PCI in the Amsterdam University Medical Center, Vrije Universiteit, between December 2013 and March 2019. The clinical

indication for revascularisation was based on cardiac symptom burden, the extent of myocardial ischaemia, viability testing when indicated, and invasive coronary angiography. The decision to perform CTO revascularisation was left to the discretion of the Heart Team. Patients who underwent ischaemia detection using quantitative [¹⁵O]H₂O PET perfusion imaging prior to referral for CTO PCI were screened for potential inclusion in the study. Patients in whom successful CTO revascularisation was performed were rescheduled for [¹⁵O]H₂O PET imaging three months after the index procedure. Exclusion criteria comprised pregnancy and contraindications for the administration of adenosine. The flow chart of the study population has been described previously¹⁵. Patients included in the study cohort described by Schumacher et al¹⁵ were eligible for inclusion in the present study if they were successfully treated by single-vessel CTO PCI and additional revascularisation was not performed nor scheduled. The study complied with the Declaration of Helsinki and was approved by the institutional Medical Ethics Committee. All participants provided written informed consent.

ANGIOGRAPHIC AND PROCEDURAL CHARACTERISTICS

Angiographic and procedural characteristics were evaluated using a monoplane cardiovascular X-ray system (Allura Xper FD 10/10; Philips Healthcare). A CTO was defined as a luminal occlusion of a coronary artery with a documented or estimated duration of ≥ 3 months and no or minimal contrast penetration through the lesion on invasive coronary angiography (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0-1)¹⁶. The extent of collateral development was assessed angiographically using the collateral connection (CC) score and Rentrop flow grade. Patients with a concomitant CC score 2 (branch-like connection) and Rentrop grade 3 (complete epicardial filling of the recipient CTO artery via collateral channels) were considered to have well-developed collaterals¹⁷. The angiography-derived Japanese (J)-CTO score was calculated for all CTO lesions and the operators applied the hybrid approach to achieve recanalisation of the CTO¹⁸. The CTO vessel was considered successfully revascularised if TIMI grade 3 flow was achieved and the residual diameter stenosis was $< 30\%$. Periprocedural myocardial infarction (MI) was scored following the Fourth Universal Definition of Myocardial Infarction¹⁹.

[¹⁵O]H₂O PET ACQUISITION

[¹⁵O]H₂O PET perfusion images were acquired on a hybrid PET/computed tomography (CT) scanner (Ingenuity TF 128; Philips Healthcare), as described previously²⁰. Briefly, a dynamic emission scan was performed using 370 MBq of [¹⁵O]H₂O during resting conditions and adenosine (140 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)-induced maximal vasodilator stress. Both resting and stress sequences were followed by a low-dose CT scan for scatter and attenuation correction. Parametric perfusion images were used for quantitative analysis to obtain the absolute myocardial blood flow (MBF) in $\text{mL}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$ of perfusable tissue, using in-house developed software (Cardiac VUer)²¹. Resting MBF, hyperaemic MBF (hMBF) and coronary flow reserve (CFR), defined as the ratio between hMBF and resting MBF, were calculated

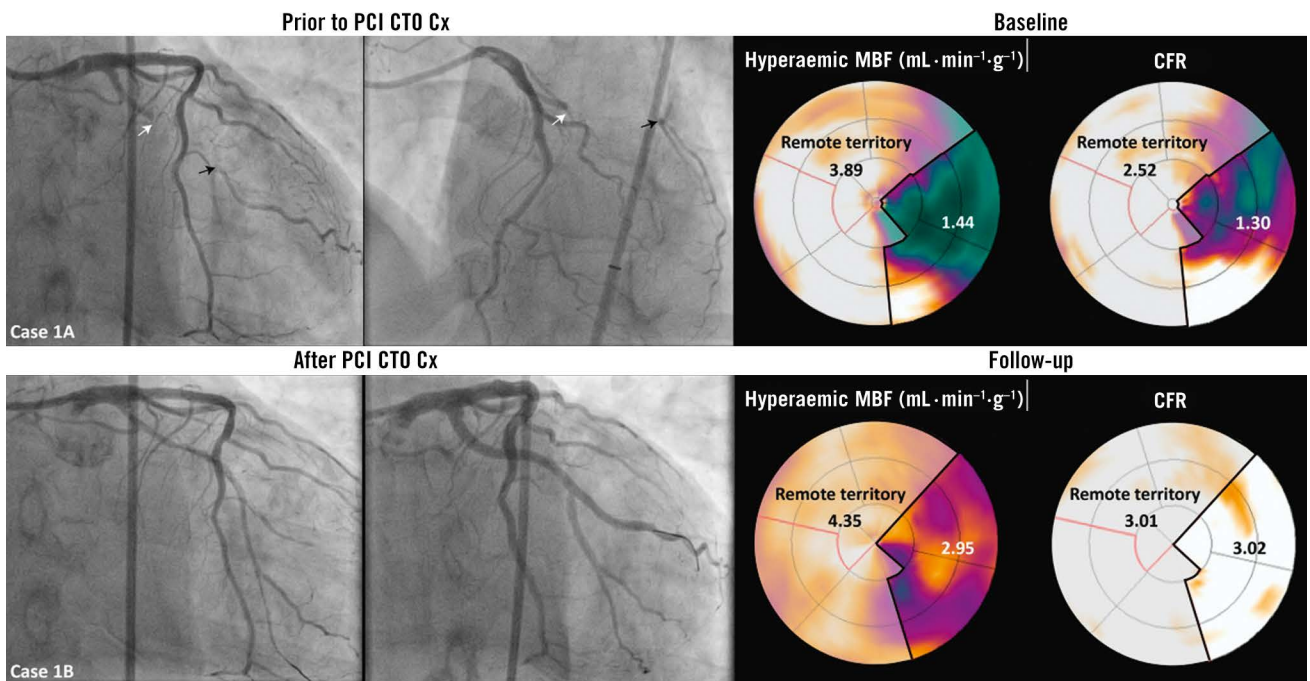
for the myocardium subtended by the CTO lesion and the remote myocardial territory allocated according to the standardised vascular territories (right coronary artery, left anterior descending coronary artery and left circumflex coronary artery) of the 17-segment model of the American Heart Association (AHA)²². The myocardium supplied by the two non-target coronary arteries was defined as remote myocardium. The perfusion defect size in the CTO territory was calculated by adding up the segments within the CTO region in which hMBF was $\leq 2.3 \text{ mL} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ and $< 75\%$ of the hMBF in a normal reference vascular territory^{4,20}. A baseline perfusion defect size of ≥ 4 segments was classified as large⁴. A case example showing coronary angiograms and [¹⁵O]H₂O PET perfusion images at baseline and after CTO PCI is presented in the **Central illustration**. To correct for the potential impact of overlapping adjacent vascular regions, analyses were repeated with remote myocardium excluding myocardial segments adjacent to the CTO region (**Supplementary Figure 1**). For all figures illustrating remote myocardial perfusion, a concomitant supplementary figure was included showing myocardial perfusion in the remote myocardial territory non-adjacent to the CTO region.

STATISTICAL ANALYSIS

Categorical variables are presented as frequencies with percentages, whereas continuous variables are displayed as mean \pm standard deviation (SD) or median (interquartile range). Differences between normally distributed data were tested using the paired samples t-test for paired data, and the independent samples t-test for comparing two independent groups. Differences between continuous variables that were not normally distributed were analysed using the Wilcoxon signed-rank test for paired data or the Mann-Whitney U test for independent groups. Linear regression was used to assess the associations between absolute perfusion in the CTO and remote myocardium at baseline and after CTO revascularisation. Furthermore, a general linear model was fitted to evaluate the relationship between the absolute change in myocardial perfusion in the CTO territory and the remote myocardial territory after CTO revascularisation, adjusting for clinical, angiographic and procedural characteristics (age, gender, body mass index [BMI], hypertension, hypercholesterolaemia, diabetes mellitus, a positive family history of

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CENTRAL ILLUSTRATION Coronary angiograms and [¹⁵O]H₂O PET perfusion images illustrating the change in absolute remote myocardial perfusion following CTO PCI.



A case example illustrating angiograms before and directly after successful recanalisation of a CTO in the circumflex coronary artery. [¹⁵O]H₂O PET perfusion images of vasodilator stress flow and coronary flow reserve show absolute myocardial perfusion in the CTO and remote myocardial territory at baseline and follow-up PET imaging. Case 1A. Dual injection angiography images show a CTO of the Cx (white arrow). The black arrows indicate the well-developed collaterals (CC score 2 and Rentrop grade 3). hMBF and CFR in the CTO territory are lower compared to the remote myocardial territory. Case 1B. Angiography shows the circumflex coronary artery of the same patient during and directly after CTO revascularisation. Follow-up PET perfusion imaging shows improvements in hMBF and CFR in the CTO and remote myocardial territory. CC: collateral connection; CFR: coronary flow reserve; CTO: chronic total occlusion; Cx: left circumflex coronary artery; hMBF: hyperaemic myocardial blood flow; PCI: percutaneous coronary intervention; PET: positron emission tomography

CAD, smoking status, prior cardiac history, CTO vascular territory, J-CTO score, CTO crossing technique, collateral development, the dominant collateral pathway and CTO vessel stent length) as potential confounders. Additionally, a general linear model was used to find predictors of change in perfusion indices in the remote myocardial territory following CTO PCI. All statistical analyses were performed using the SPSS software package, Version 26.0 (IBM).

Results

STUDY POPULATION

A total of 164 patients (mean age 62 ± 11 years, 84% male) were included in the study (Table 1). The median interval between baseline PET imaging and CTO revascularisation was 40 (23-59)

Table 1. Baseline characteristics.

		n=164
Demographics		
Age, years		62±11
Male gender		137 (84)
BMI, kg/m ²		28±4
Cardiovascular risk factors		
Hypertension		169 (54)
Hypercholesterolaemia		83 (51)
Diabetes mellitus		41 (25)
Smoking		53 (32)
Family history of CAD		77 (47)
Cardiac history		
No prior cardiac history		29 (18)
Prior MI		78 (48)
Prior PCI		122 (74)
Prior CABG		13 (8)
LVEF (%)	>55	63 (38)
	45-55	56 (34)
	30-45	37 (23)
	<30	8 (5)
Medication		
Aspirin		152 (92)
β-blocker		129 (79)
ACE inhibitor/ARB		92 (56)
Statin		139 (85)
Calcium channel blockers		39 (24)
Clinical presentation		
Typical angina		65 (40)
Atypical angina		25 (15)
Non-anginal chest pain		39 (24)
Dyspnoea on exertion		35 (21)
Mean±standard deviation/n (%). ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention.		

days, followed by a median interval of 101 (92-119) days until the follow-up PET perfusion scan was performed. Between CTO PCI and follow-up PET imaging, no cardiac events occurred and additional revascularisation was not performed. Angiographic and procedural characteristics are listed in Table 2. In 17 (10%) patients, a residual significant coronary stenosis remained after single-vessel CTO PCI. These lesions were triaged by the Heart Team and/or two experienced CTO operators (P. Knaapen/A. Nap). Additional revascularisation was not performed nor scheduled due to technical unfeasibility or an absent clinical indication for further revascularisation therapy, e.g., a limited myocardial territory subtended by the lesion. **Supplementary Table 1** shows the residual coronary lesion location, the degree of coronary stenosis and its potential impact on coronary flow through the collateral circulation to the CTO territory in these patients. In five patients, a residual coronary lesion limited flow from the coronary collateral donor

Table 2. Angiographic and procedural characteristics.

		n=164
CTO vessel		
Right coronary artery		115 (70)
Left anterior descending coronary artery		32 (20)
Left circumflex coronary artery		17 (10)
J-CTO score		
0-1		68 (41)
2		55 (34)
≥3		41 (25)
Collaterals		
Well-developed collaterals		111 (68)
Collateral connection score 2		118 (72)
Rentrop score 3		134 (82)
Dominant collateral pathway		
Epicardial		74 (45)
Bridging		44 (27)
Septal		41 (25)
Graft		5 (3)
Revascularisation		
Successful CTO crossing strategy	Antegrade wire escalation	78 (48)
	Antegrade dissection and re-entry	27 (16)
	Retrograde wire escalation	22 (13)
	Retrograde dissection and re-entry	37 (23)
CTO vessel stent length (mm)		81±39
Periprocedural complications	Side branch loss (>2 mm)	8 (5)
	Right ventricular branch	5 (3)
	Myocardial infarction	10 (6)
	Stroke or TIA	1 (1)
	Perforation	9 (5)
	Tamponade	4 (2)
Emergency revascularisation		0 (0)
Mean±standard deviation/n (%). CTO: chronic coronary total occlusion; TIA: transient ischaemic attack		

arteries to the myocardium subtended by the CTO prior to successful CTO revascularisation.

CORRELATION BETWEEN CTO AND REMOTE MYOCARDIAL TERRITORY

PET perfusion measurements before and after CTO PCI are shown in **Table 3**. Strong positive correlations were observed between resting MBF, hMBF and CFR in the CTO and remote myocardium, both before and after CTO PCI (**Figure 1**). Lower baseline resting MBF, hMBF and CFR values in the CTO myocardium were concurrent

with lower perfusion measurements in the remote myocardial territory (resting MBF: $r=0.84$, $p<0.01$; hMBF: $r=0.75$, $p<0.01$ and CFR: $r=0.77$, $p<0.01$). Similar correlations were observed at follow-up PET imaging ($r=0.87$, $p<0.01$; $r=0.87$, $p<0.01$ and $r=0.81$, $p<0.01$ for resting MBF, hMBF and CFR, respectively).

INCREASE IN MYOCARDIAL PERFUSION AFTER CTO PCI

Resting MBF did not significantly change following CTO PCI (**Table 3**). In remote myocardium, hMBF ($\Delta 0.19 \pm 0.54 \text{ mL} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$, $p<0.01$) and CFR ($\Delta 0.25 \pm 0.68$, $p<0.01$) increased following CTO

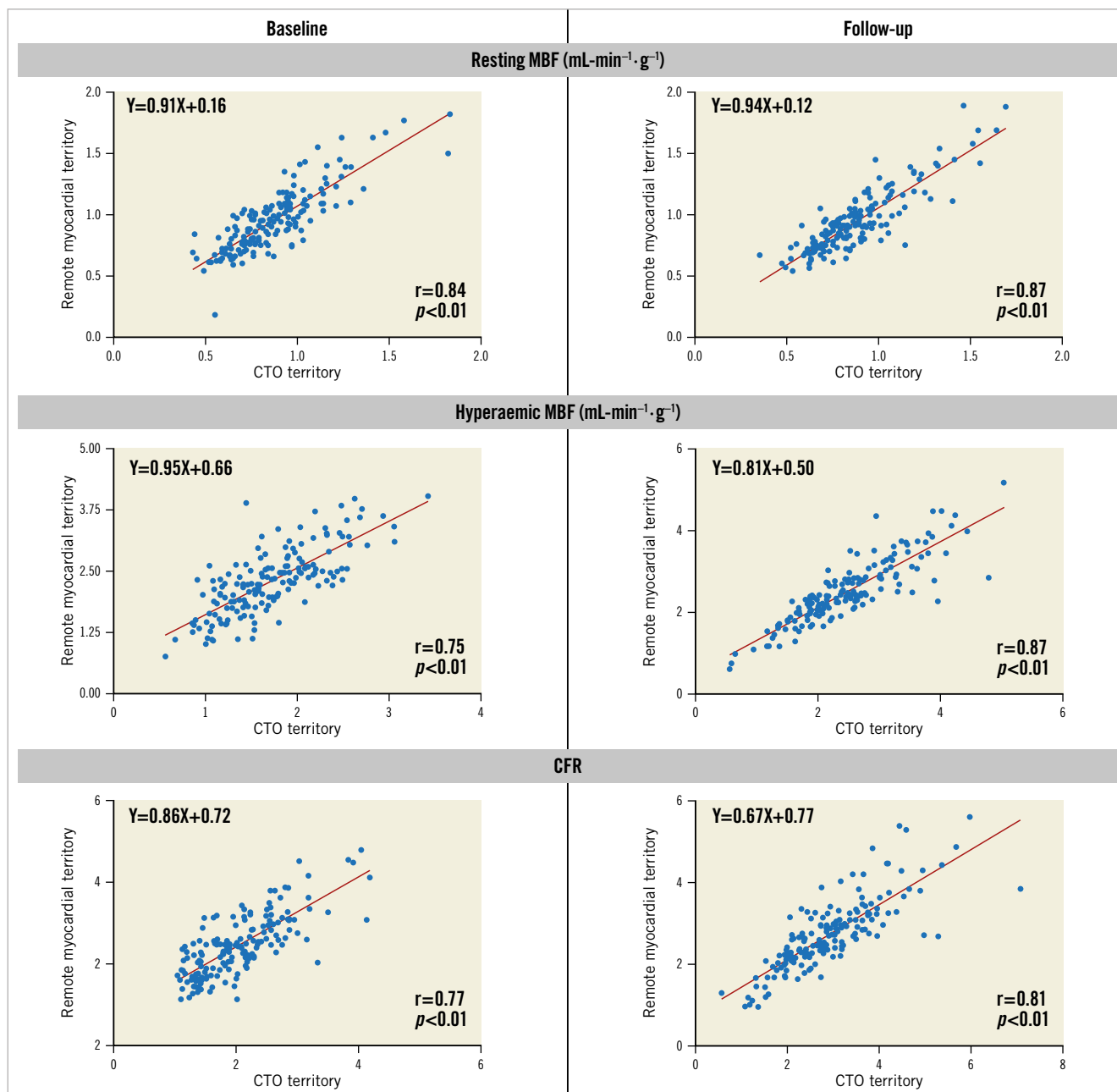


Figure 1. Association between perfusion indices in the CTO territory versus remote myocardial territory. A positive correlation was found between resting MBF, hMBF and CFR in the CTO and remote myocardial territory, both before and after CTO revascularisation. CFR: coronary flow reserve; CTO: chronic total occlusion; hMBF: hyperaemic myocardial blood flow; MBF: myocardial blood flow; PCI: percutaneous coronary intervention; PET: positron emission tomography

Table 3. Changes in [¹⁵O]H₂O PET perfusion in CTO and remote myocardium.

	Time point		Δ perfusion	p-value
	Baseline	Follow-up		
Resting MBF (mL·min⁻¹·g⁻¹)				
CTO myocardium	0.87±0.24	0.87±0.24	0.004±0.19	0.81
Remote myocardium	0.95±0.26	0.94±0.25	-0.01±0.17	0.42
p-value	<0.01	<0.01	0.07	
Hyperaemic MBF (mL·min⁻¹·g⁻¹)				
CTO myocardium	1.71±0.53	2.46±0.81	0.75±0.70	<0.01
Remote myocardium	2.29±0.67	2.48±0.75	0.19±0.54	<0.01
p-value	<0.01	0.46	<0.01	
CFR				
CTO myocardium	2.05±0.68	2.91±1.02	0.8 ±0.93	<0.01
Remote myocardium	2.48±0.76	2.74±0.85	0.25±0.68	<0.01
p-value	<0.01	<0.01	<0.01	

Values are mean±SD. CFR: coronary flow reserve; CTO: chronic coronary total occlusion; Δ: delta; MBF: myocardial blood flow; PET: positron emission tomography

revascularisation. In the myocardium subtended by the CTO, perfusion increase between baseline and follow-up PET perfusion imaging was $\Delta 0.75 \pm 0.70$ mL·min⁻¹·g⁻¹ and $\Delta 0.87 \pm 0.93$ for hMBF and CFR, respectively ($p < 0.01$ for both). Perfusion increase in the CTO myocardium was positively correlated with increase in remote myocardial perfusion ($r = 0.71$, $p < 0.01$ for hMBF and $r = 0.68$, $p < 0.01$ for CFR) (Figure 2). In a model adjusted for clinical, angiographic and procedural characteristics, the increase in perfusion indices in the CTO territory remained independently associated with the increase in remote myocardial perfusion (Table 4). We performed additional analyses to compare absolute myocardial perfusion indices between patients with and without a history of previous MI and found that the change in remote myocardial perfusion was similar in patients with a history of MI versus no MI for resting MBF (-0.02 ± 0.18 mL·min⁻¹·g⁻¹ vs -0.01 ± 0.16 mL·min⁻¹·g⁻¹, $p = 0.84$), hMBF (0.16 ± 0.49 mL·min⁻¹·g⁻¹ vs 0.22 ± 0.58 mL·min⁻¹·g⁻¹, $p = 0.51$) and CFR (0.23 ± 0.65 vs 0.28 ± 0.71 , $p = 0.64$) (Supplementary Table 2). Similarly, the change in myocardial perfusion indices in the remote myocardial regions did not differ in patients with a prior MI in the CTO territory compared to patients without a prior MI (resting MBF: -0.03 ± 0.20 mL·min⁻¹·g⁻¹ vs -0.01 ± 0.16 mL·min⁻¹·g⁻¹, $p = 0.62$; hMBF: 0.19 ± 0.56 mL·min⁻¹·g⁻¹ vs 0.22 ± 0.58 mL·min⁻¹·g⁻¹, $p = 0.81$ and CFR: 0.32 ± 0.75 vs 0.28 ± 0.71 , $p = 0.75$).

VARIABLES ASSOCIATED WITH CHANGE IN REMOTE MYOCARDIAL PERFUSION

There was a negative correlation between baseline remote myocardial perfusion and the change in perfusion in remote myocardium after CTO PCI (hMBF: $r = -0.23$, $p < 0.01$, CFR: $r = -0.31$, $p < 0.01$). Furthermore, a negative correlation was observed between baseline perfusion in the myocardium subtended by the CTO and the change in remote myocardial perfusion (hMBF: $r = -0.23$, $p < 0.01$, CFR: $r = -0.26$, $p < 0.01$) (Supplementary Figure 2). The change

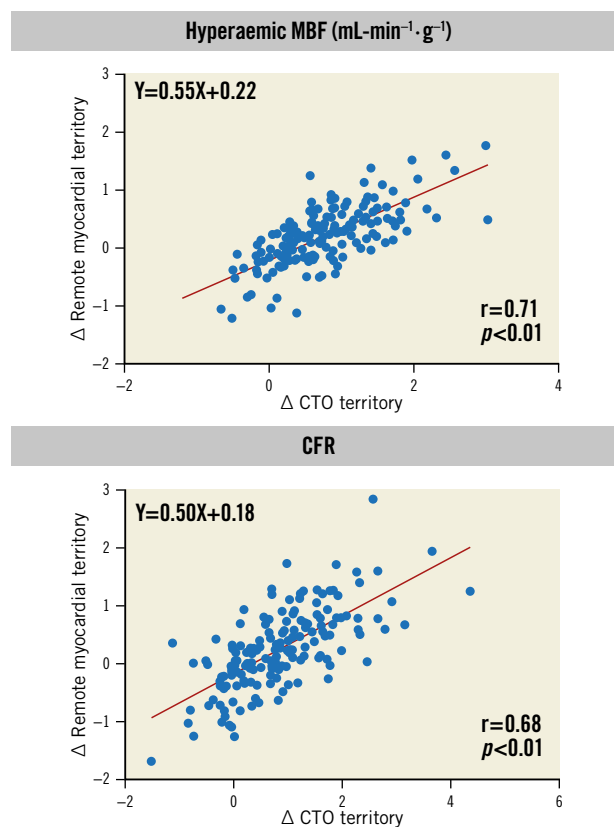


Figure 2. Association between Δ PET perfusion CTO territory versus Δ remote myocardial territory. Scatterplots demonstrating the correlation between the change in absolute myocardial perfusion in the CTO and the remote myocardial territory following CTO PCI. In patients with a larger increase in hMBF and CFR in CTO myocardium following CTO PCI, a larger increase in quantitative perfusion indices was observed in remote myocardium. CFR: coronary flow reserve; CTO: chronic total occlusion; hMBF: hyperaemic myocardial blood flow; MBF: myocardial blood flow; PCI: percutaneous coronary intervention; PET: positron emission tomography

Table 4. General linear model illustrating predictors of Δ remote myocardial perfusion (multivariable analyses).

		Beta (95% CI)	p-value
Δ hyperaemic MBF remote myocardium			
Perfusion variables	Δ hyperaemic MBF CTO territory	0.58 (0.48, 0.67)	<0.01
Demographics	Age (in years)	0.003 (-0.01, 0.01)	0.50
	Male gender	0.05 (-0.15, 0.25)	0.60
	BMI	-0.01 (-0.02, 0.01)	0.28
Cardiovascular risk factors	Hypertension	0.09 (-0.05, 0.22)	0.21
	Hypercholesterolaemia	-0.01 (-0.15, 0.14)	0.93
	Diabetes mellitus	0.05 (-0.10, 0.21)	0.52
	Family history of CAD	-0.06 (-0.19, 0.07)	0.35
	Smoking	0.12 (-0.03, 0.26)	0.11
Cardiac history	History of MI	0.04 (-0.11, 0.20)	0.58
	History of PCI	0.04 (-0.12, 0.19)	0.67
	History of CABG	-0.05 (-0.35, 0.25)	0.75
	LVEF		0.46
Angiography and revascularisation	CTO vessel (RCA vs LAD)	-0.11 (-0.36, 0.13)	0.81
	CTO vessel (RCA vs Cx)	0.28 (-0.02, 0.57)	0.07
	CTO vessel (LAD vs Cx)	0.39 (0.07, 0.71)	0.01
	J-CTO score		0.84
	Successful CTO crossing technique (intimal vs subintimal)	0.06 (-0.08, 0.20)	0.42
	Well-developed collaterals	-0.01 (-0.16, 0.14)	0.89
	Dominant collateral pathway (septal vs epicardial)	-0.23 (-0.46, 0.004)	0.06
	Stent length (mm)	0.001 (-0.002, 0.002)	0.91
Δ CFR remote myocardium			
Perfusion variables	Δ CFR CTO territory	0.54 (0.44, 0.64)	<0.01
Demographics	Age (in years)	0.002 (-0.01, 0.01)	0.65
	Male gender	0.01 (-0.26, 0.28)	0.95
	BMI	-0.004 (-0.02, 0.02)	0.73
Cardiovascular risk factors	Hypertension	0.08 (-0.11, 0.27)	0.42
	Hypercholesterolaemia	0.06 (-0.14, 0.26)	0.56
	Diabetes mellitus	-0.02 (-0.23, 0.20)	0.89
	Family history of CAD	-0.05 (-0.23, 0.14)	0.60
	Smoking	0.08 (-0.12, 0.27)	0.46
Cardiac history	History of MI	0.10 (-0.11, 0.31)	0.34
	History of PCI	0.01 (-0.21, 0.23)	0.94
	History of CABG	0.07 (-0.35, 0.49)	0.74
	LVEF		0.87
Angiography and revascularisation	CTO vessel (RCA vs LAD)	-0.25 (-0.60, 0.09)	0.24
	CTO vessel (RCA vs Cx)	0.22 (-0.19, 0.63)	0.56
	CTO vessel (LAD vs Cx)	0.48 (0.02, 0.93)	0.04
	J-CTO score		0.94
	Successful CTO crossing technique (intimal vs subintimal)	0.02 (-0.18, 0.22)	0.85
	Well-developed collaterals	-0.07 (-0.27, 0.14)	0.53
	Dominant collateral pathway (septal vs epicardial)	-0.17 (-0.49, 0.16)	1.00
	Stent length (mm)	-0.001 (-0.003, 0.003)	0.97

General linear model analyses showing that the increase in hMBF and CFR in myocardium subtended by the CTO was independently associated with the increase in remote myocardial perfusion following CTO PCI. In addition, we found that the CTO vessel territory (LAD vs Cx) was a statistically significant predictor of absolute change in remote myocardial perfusion for both hMBF and CFR. This finding may be explained by interaction with the other variables included in the model. Furthermore, the significant difference may be related to the relatively small number of LAD (N=32) and Cx (N=17) CTO vessels included in our study cohort. Of note, the relationship may be partly explained by the lower baseline hyperaemic myocardial perfusion (CTO LAD: 2.16 ± 0.52 mL·min⁻¹·g⁻¹ vs CTO Cx: 2.59 ± 0.75 mL·min⁻¹·g⁻¹, $p=0.04$) and CFR (CTO LAD: 2.57 ± 0.72 vs CTO Cx: 2.85 ± 0.01 , $p=0.31$) in the remote myocardial territory, as we found that a lower baseline perfusion in remote myocardium was associated with a higher increase in perfusion indices in the remote myocardial territory after successful CTO PCI (**Supplementary Figure 2**). BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CFR: coronary flow reserve; CTO: chronic coronary total occlusion; Cx: left circumflex coronary artery; Δ : delta; LAD: left anterior descending coronary artery; MBF: myocardial blood flow; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery

in hMBF in remote myocardium was higher in patients with a large baseline perfusion defect (≥ 4 segments) in the CTO territory ($p=0.02$). Clinical (except female gender, $p=0.02$ for hMBF), angiographic and procedural characteristics were not predictive of absolute changes in remote myocardial perfusion (**Supplementary Table 3**). The analyses limited to remote myocardium non-adjacent to the CTO territory yielded similar results (**Supplementary Figure 3-Supplementary Figure 5**).

Discussion

The present study evaluated the impact of successful single-vessel CTO PCI on the change in absolute myocardial perfusion in the remote myocardial territory supplied by non-target coronary arteries with the following major findings. First, absolute perfusion indices in remote and CTO myocardium showed a positive linear correlation, before and after CTO revascularisation. Second, an overall increase in absolute hMBF and CFR in remote myocardium was observed following CTO PCI. Third, the quantitative improvement in hMBF and CFR in the CTO territory was independently associated with the absolute increase in remote myocardial perfusion after CTO PCI. Finally, lower baseline perfusion indices in remote and CTO myocardium were associated with the increase in absolute remote myocardial perfusion.

PHYSIOLOGICAL CONNECTION BETWEEN CTO AND REMOTE MYOCARDIAL TERRITORY

Coronary haemodynamics in patients with CTOs are complex since absolute perfusion in CTO myocardium largely depends on the function of the collateral circulation⁵. Myocardium subtended by the CTO and remote myocardium supplied by collateral donor arteries are connected by collateral channels and, as such, compose one large myocardial territory. In the present study, we found a positive association between absolute perfusion values in CTO and remote myocardium, both before and after CTO revascularisation. Several studies have demonstrated that, even despite well-developed collaterals, collateral supply is not sufficient during conditions of increased demand, leading to myocardial ischaemia in the CTO territory in over 90% of patients^{2,7}. One could argue that a supply-demand mismatch is present in ischaemic myocardium subtended by the CTO, with maximally recruited collateral supply being insufficient to prevent diminished perfusion in the CTO territory, yet simultaneously resulting in reduced perfusion in remote myocardium⁴. In addition, the correlation between perfusion indices in remote and CTO myocardium might be largely attributable to the extent of microvascular disease. Van de Hoef et al described a paired relationship between microvascular dysfunction in significantly obstructed coronary arteries and remote non-obstructed reference vessels in the same patient, which may be part of a global cardiac phenomenon of microvascular and endothelial disease²³. Furthermore, Ladwiniec et al observed abnormal CFR in 71% of patients after CTO PCI, with concomitant abnormal CFR in $>50\%$ of patients in non-obstructed remote coronary arteries²⁴. These findings substantiate the proposed interplay between

the coronary haemodynamics in the CTO and remote myocardium before and after CTO revascularisation.

INCREASE IN REMOTE MYOCARDIAL PERFUSION AFTER CTO PCI

Prior studies have shown coronary flow and absolute myocardial perfusion improvement in the CTO territory following CTO PCI^{4,6,12}. In addition, several reports demonstrated an instantaneous and subsequent further regression in the function of the collateral circulation after CTO revascularisation^{9,11,12}. Before antegrade flow in the CTO artery is restored, collateral flow to the CTO territory enlarges the myocardial mass supplied by the remote collateral donor arteries¹³. Leone et al investigated the influence of the amount of perfused myocardial tissue on FFR values and in this context reported a significant association between the presence of a collateralised CTO and lower FFR measurements in collateral donor arteries²⁵. Germane to this, several small studies showed an increase in FFR and a decrease in average peak flow velocity in the collateral donor arteries after CTO PCI. This was related to a concomitant reduction in collateral flow to the CTO myocardium, even in the absence of obstructive CAD in the collateral donor arteries^{8,13}. In line with these findings, the increase of FFR in collateral donor arteries after CTO PCI may result in reclassification of vessels from below to above the ischaemic thresholds¹⁴. Based on these observations, a change in absolute remote myocardial perfusion induced by collateral regression after CTO PCI might be hypothesised. Indeed, the present study demonstrates a significant increase in hMBF and CFR in remote myocardium after single-vessel CTO PCI. In contrast, Keulards et al performed thermodilution measurements in the collateral donor artery after CTO PCI ($N=10$) and did not find differences in stress flow²⁶. In addition, two studies evaluated remote myocardial perfusion values after CTO PCI with cardiovascular magnetic resonance imaging using quantitative ($N=17$) and qualitative ($N=26$) perfusion assessment, and could not demonstrate perfusion increases^{27,28}. The discordant results of these small-sized reports compared to our study may be related to differences in sample size and applied perfusion imaging methods. The significant increase in remote myocardial perfusion following CTO revascularisation may have several explanations. First, the capacity of the collateral donor arteries before CTO PCI is adapted to supply both CTO and remote myocardium. After the restoration of antegrade flow in the CTO vessel and subsequent collateral regression over time, flow velocity decreases and coronary perfusion pressure may significantly increase in the vascular territory of the collateral donor arteries, leading to enhanced perfusion in remote myocardium. Second, CTO PCI is associated with an increase in left ventricular performance which may improve overall hyperaemic perfusion conditions, including those in remote myocardium^{10,29}. Third, in patients with stable obstructive lesions causing myocardial ischaemia, Uren et al demonstrated reduced coronary vasodilator reserve in remote myocardium subtended by non-obstructed coronary arteries, which may be attributed to increased work load and the contractile response of the remote

regions to compensate for temporary dysfunction in the ischaemic myocardium³⁰. In concordance, we found a positive correlation between the absolute myocardial perfusion increase in the CTO territory and improvement in remote myocardial perfusion following CTO PCI. Successful CTO revascularisation with potential adaptation of global microvascular autoregulation results in col-linear improvement in both CTO and remote myocardial perfusion.

Limitations

First, this is a single-centre experience. Second, according to contemporary CTO expert consensus, a CTO is defined as a luminal occlusion of a coronary artery with a documented or estimated duration of ≥ 3 months without antegrade flow through the lesion (TIMI 0)¹⁸. However, the present study recruited patients with TIMI flow grade 0-1 in the CTO vessel as the study enrolment period largely preceded the establishment of the current CTO definition which mandates a TIMI 0 lesion.

Although the criteria to define a CTO lesion as applied in our study deviate from the contemporary CTO definition, the large proportion of well-developed collaterals observed in the included patient population suggest that our cohort is suitable to explore the impact of PCI CTO on changes in absolute perfusion in remote myocardium. Third, invasive pressure measurements, flow velocity assessment and collateral function evaluation have not been performed in the CTO and collateral donor arteries; hence physiological alterations in pressure and flow could not be related to changes in absolute myocardial perfusion following CTO PCI. Fourth, although patients were prospectively recruited, only subjects with serial [¹⁵O] H₂O PET perfusion imaging available were included.

Conclusions

CTO revascularisation resulted in a significant increase in absolute remote myocardial perfusion. Furthermore, the quantitative improvement in stress flow and coronary flow reserve in the CTO territory was independently associated with the absolute perfusion increase in remote myocardial regions. As such, CTO PCI may have a favourable physiologic impact beyond the intended treated myocardium.

Impact on daily practice

The presence of a concomitant CTO results in alterations in coronary haemodynamics in remote myocardium subtended by the collateral donor coronary arteries. In the present study, we found that CTO PCI resulted in a significant increase in quantitative myocardial perfusion in remote myocardium, which was independently associated with the perfusion increase in the CTO territory. The beneficial effect of successful CTO PCI on absolute myocardial perfusion may extend beyond the revascularised CTO territory.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

- Fefer P, Knudson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, Sparkes JD, Wright GA, Strauss BH. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol*. 2012;59:991-7.
- Werner GS. The role of coronary collaterals in chronic total occlusions. *Curr Cardiol Rev*. 2014;10:57-64.
- 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.
- Schumacher SP, Kockx M, Stuijzand WJ, Driessen RS, van Diemen PA, Bom MJ, Everaars H, Raijmakers PG, Boellaard R, van Rossum AC, Opolski MP, Nap A, Knaapen P. Ischaemic burden and changes in absolute myocardial perfusion after chronic total occlusion percutaneous coronary intervention. *EuroIntervention*. 2020;16:e462-71.
- Keulards DCJ, Vlaar PJ, Wijnbergen I, Pijs NHJ, Teeuwen K. Coronary physiology before and after chronic total occlusion treatment: what does it tell us? *Neth Heart J*. 2021;29:22-9.
- Werner GS, Emig U, Bahrmann P, Ferrari M, Figulla HR. Recovery of impaired microvascular function in collateral dependent myocardium after recanalisation of a chronic total coronary occlusion. *Heart*. 2004;90:1303-9.
- 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.
- Werner GS, Fritzenwanger M, Prochnau D, Schwarz G, Ferrari M, Aarnoudse W, Pijs NH, Figulla HR. Determinants of coronary steal in chronic total coronary occlusions donor artery, collateral, and microvascular resistance. *J Am Coll Cardiol*. 2006;48:51-8.
- Werner GS, Emig U, Mutschke O, Schwarz G, Bahrmann P, Figulla HR. Regression of collateral function after recanalization of chronic total coronary occlusions: a serial assessment by intracoronary pressure and Doppler recordings. *Circulation*. 2003;108:2877-82.
- Stuijzand 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.
- Lee JH, Kim CY, Kim N, Jang SY, Bae MH, Yang DH, Cho Y, Chae SC, Park HS. Coronary Collaterals Function and Clinical Outcome Between Patients With Acute and Chronic Total Occlusion. *JACC Cardiovasc Interv*. 2017;10:585-93.
- Karamasis GV, Kalogeropoulos AS, Mohdazri SR, Al-Janabi F, Jones R, Jagathesan R, Aggarwal RK, Clesham GJ, Tang KH, Kelly PA, Davies JR, Werner GS, Keeble TR. Serial Fractional Flow Reserve Measurements Post Coronary Chronic Total Occlusion Percutaneous Coronary Intervention. *Circ Cardiovasc Interv*. 2018;11:e006941.
- Ladwiniec A, Cunnington MS, Rossington J, Mather AN, Alahmar A, Oliver RM, Nijjer SS, Davies JE, Thackray S, Alamgir F, Hoyer A. Collateral donor artery physiology and the influence of a chronic total occlusion on fractional flow reserve. *Circ Cardiovasc Interv*. 2015;8:e002219.
- Mohdazri SR, Karamasis GV, Al-Janabi F, Cook CM, Hampton-Till J, Zhang J, Al-Lamee R, Dzung JN, Gedela S, Tang KH, Kelly PA, Davies JE, Davies JR, Keeble TR. The impact of coronary chronic total occlusion percutaneous coronary intervention upon donor vessel fractional flow reserve and instantaneous wave-free ratio: Implications for physiology-guided PCI in patients with CTO. *Catheter Cardiovasc Interv*. 2018;92:E139-48.
- Schumacher SP, Stuijzand WJ, de Winter RW, van Diemen PA, Bom MJ, Everaars H, Driessen RS, Kamperman L, Kockx M, Hagen BSH, Raijmakers PG, van de Ven PM, van Rossum AC, Opolski MP, Nap A, Knaapen P. Ischemic Burden Reduction and Long-Term Clinical Outcomes After Chronic Total Occlusion Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. 2021;14:1407-18.
- Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, Moussa I, Teirstein PS, Dargas G, Baim DS, Selmon M, Strauss BH, Tamai H, Suzuki T, Mitsudo K, Katoh O, Cox DA, Hoyer A, Mintz GS, Grube E, Cannon LA, Reifart NJ, Reisman M, Abizaid A, Moses JW, Leon MB, Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation*. 2005;112:2364-72.
- Schumacher SP, Everaars H, Stuijzand WJ, Huynh JW, van Diemen PA, Bom MJ, de Winter RW, van Loon RB, van de Ven PM, van Rossum AC, Opolski MP, Nap A, Knaapen P. Coronary collaterals and myocardial viability in patients with chronic total occlusions. *EuroIntervention*. 2020;16:e453-61.

18. Brilakis ES, Mashayekhi K, Tsuchikane E, Rafef N, Alaswad K, Araya M, Avran A, Azzalini L, Babunashvili AM, Bayani B, Bhindi R, Boudou N, Boukhris M, Božinović NŽ, Bryniarski L, Bufe A, Buller CE, Burke MN, Büttner HJ, Cardoso P, Carlino M, Christiansen EH, Colombo A, Croce K, Damas de Los Santos F, De Martini T, Dens J, Di Mario C, Dou K, Eged M, ElGuindy AM, Escaned J, Furkalo S, Gagnor A, Galassi AR, Garbo R, Ge J, Goel PK, Goktekin O, Grancini L, Grantham JA, Hanratty C, Harb S, Harding SA, Henriques JPS, Hill JM, Jaffer FA, Jang Y, Jussila R, Kalnins A, Kalyanasundaram A, Kandzari DE, Kao HL, Karpaliotis D, Kassem HH, Knaapen P, Kornowski R, Krestyaninov O, Kumar AVG, Laamets P, Lamelas P, Lee SW, Lefevre T, Li Y, Lim ST, Lo S, Lombardi W, McEntegart M, Munawar M, Navarro Lecaro JA, Ngo HM, Nicholson W, Olivecrona GK, Padilla L, Postu M, Quadros A, Quesada FH, Prakasa Rao VS, Reifart N, Saghatelian M, Santiago R, Sianos G, Smith E, C Spratt J, Stone GW, Strange JW, Tammam K, Ungi I, Vo M, Vu VH, Walsh S, Werner GS, Wollmuth JR, Wu EB, Wyman RM, Xu B, Yamane M, Ybarra LF, Yeh RW, Zhang Q, Rinfret S. Guiding Principles for Chronic Total Occlusion Percutaneous Coronary Intervention. *Circulation*. 2019;140:420-33.
19. 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.
20. Danad I, Uusitalo V, Kero T, Saraste A, Rajmakers 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 [¹⁵O]H₂O PET imaging. *J Am Coll Cardiol*. 2014;64:1464-75.
21. Harms HJ, Knaapen P, de Haan S, Halbmeijer R, Lammertsma AA, Lubberink M. Automatic generation of absolute myocardial blood flow images using [¹⁵O]H₂O and a clinical PET/CT scanner. *Eur J Nucl Med Mol Imaging*. 2011;38:930-9.
22. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539-42.
23. van de Hoef TP, Nolte F, Echavarría-Pinto M, van Lavieren MA, Damman P, Chamuleau SA, Voskuil M, Verberne HJ, Henriques JP, van Eck-Smit BL, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Meuwissen M, Piek JJ. Impact of hyperaemic microvascular resistance on fractional flow reserve measurements in patients with stable coronary artery disease: insights from combined stenosis and microvascular resistance assessment. *Heart*. 2014;100:951-9.
24. Ladwiniec A, Cunnington MS, Rossington J, Thackray S, Alamgir F, Hoye A. Microvascular dysfunction in the immediate aftermath of chronic total coronary occlusion recanalization. *Catheter Cardiovasc Interv*. 2016;87:1071-9.
25. Leone AM, De Caterina AR, Basile E, Gardi A, Laezza D, Mazzari MA, Mongiardo R, Kharbada R, Cuculi F, Porto I, Niccoli G, Burzotta F, Trani C, Banning AP, Rebuzzi AG, Crea F. Influence of the amount of myocardium subtended by a stenosis on fractional flow reserve. *Circ Cardiovasc Interv*. 2013;6:29-36.
26. Keulards DCJ, Karamasis GV, Alsanjari O, Demandt JPA, Van't Veer M, Zelis JM, Dello SA, El Farissi M, Konstantinou K, Tang KH, Kelly PA, Keeble TR, Pijls NHJ, Davies JR, Teeuwen K. Recovery of Absolute Coronary Blood Flow and Microvascular Resistance After Chronic Total Occlusion Percutaneous Coronary Intervention: An Exploratory Study. *J Am Heart Assoc*. 2020;9:e015669.
27. Jones RE, Karamasis GV, Dungu JN, MohdNazri SR, Al-Janabi F, Hammersley DJ, Prasad SK, Tang KH, Kelly PA, Gedela S, Davies JR, Keeble TR. Stress perfusion cardiovascular magnetic resonance and serial fractional flow reserve assessment of the left anterior descending artery in patients undergoing right coronary artery chronic total occlusion revascularization. *Cardiol J*. 2022;29:80-87.
28. Cheng AS, Selvanayagam JB, Jerosch-Herold M, van Gaal WJ, Karamitsos TD, Neubauer S, Banning AP. Percutaneous treatment of chronic total coronary occlusions improves regional hyperemic myocardial blood flow and contractility: insights from quantitative cardiovascular magnetic resonance imaging. *JACC Cardiovasc Interv*. 2008;1:44-53.
29. Megaly M, Saad M, Tajti P, Burke MN, Chavez I, Gössl M, Lips D, Mooney M, Poulouse A, Sorajja P, Traverse J, Wang Y, Kohl LP, Bradley SM, Brilakis ES. Meta-analysis of the impact of successful chronic total occlusion percutaneous coronary intervention on left ventricular systolic function and reverse remodeling. *J Interv Cardiol*. 2018;31:562-71.
30. Uren NG, Marraccini P, Gistri R, de Silva R, Camici PG. Altered coronary vasodilator reserve and metabolism in myocardium subtended by normal arteries in patients with coronary artery disease. *J Am Coll Cardiol*. 1993;22:650-8.

Supplementary data

Supplementary Table 1. Residual obstructive CAD following CTO revascularisation.

Supplementary Table 2. Changes in [¹⁵O]H₂O PET perfusion indices in patients with versus without prior MI.

Supplementary Table 3. Variables associated with change in remote myocardial perfusion (univariable analyses).

Supplementary Figure 1. Case example demonstrating the change in absolute myocardial perfusion in the remote myocardial territory non-adjacent to the CTO region.

Supplementary Figure 2. Association between baseline PET perfusion versus Δ perfusion remote myocardial territory.

Supplementary Figure 3. Association between perfusion indices in the CTO territory versus non-adjacent remote myocardial territory.

Supplementary Figure 4. Association between Δ PET perfusion CTO territory versus Δ non-adjacent remote myocardial territory.

Supplementary Figure 5. Association between baseline PET perfusion CTO territory versus Δ non-adjacent remote myocardial territory.

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Supplementary data

Supplementary Table 1. Residual obstructive CAD following CTO revascularisation.

	Residual lesion segment	Degree of stenosis (%)	Obstructing collateral flow to CTO territory
Revascularised CTO vessel			
RCA	12 (OM1)	100 %	No
RCA	10 (D2)	90 %	No
RCA	16 (RPL)	100 %	No
RCA	9 (D1), 10 (D2)	90 %, 90 %	No
RCA	9 (D1)	100%	No
RCA	11 (proximal Cx)	70%	No
RCA	12 (intermediate)	70 %	Yes
RCA	12 (OM1)	100 %	No
RCA	9 (D1), 12 (intermediate)	100 %, 99%	No
RCA	12 (OM1)	90%	No
RCA	6 (proximal LAD)	80%	Yes
RCA	6 (proximal LAD)	80 %	Yes
LAD	13 (mid Cx)	70 %	No
LAD	4 (RPDA)	100 %	Yes
LAD	9 (D1)	90%	No
Cx	1 (proximal RCA)	100%	Yes
Cx	9 (D1)	99%	No

In 17 (10%) patients a residual significant coronary stenosis remained after single-vessel CTO PCI.

This Table shows the residual coronary lesion location, the degree of coronary stenosis and its potential impact on coronary flow through the collateral circulation to the CTO territory in these patients. In 5 patients, a residual coronary lesion limited flow from the coronary collateral donor arteries to the myocardium subtended by the CTO prior to successful CTO revascularisation.

CTO: chronic coronary total occlusion; Cx: left circumflex coronary artery; D: diagonal branch; LAD: left anterior descending coronary artery; OM: obtuse marginal branch; RCA: right coronary artery; RPDA: right posterior descending artery; RPL: right posterolateral artery

Supplementary Table 2. Changes in [¹⁵O]H₂O PET perfusion indices in patients with versus without prior MI.

	Prior MI (N=78)	No prior MI (N=86)	p-value
Resting MBF (mL·min⁻¹·g⁻¹)			
CTO myocardium (baseline)	0.85±0.20	0.89±0.26	0.26
Remote myocardium (baseline)	0.93±0.23	0.97±0.28	0.35
CTO myocardium (follow-up)	0.85±0.24	0.89±0.23	0.39
Remote myocardium (follow-up)	0.91±0.25	0.96±0.25	0.22
Δ CTO myocardium	0.01±0.18	-0.001±0.19	0.71
Δ Remote myocardium	-0.02±0.18	-0.01±0.16	0.84
Hyperaemic MBF (mL·min⁻¹·g⁻¹)			
CTO myocardium (baseline)	1.71±0.54	1.71±0.52	0.96
Remote myocardium (baseline)	2.18±0.60	2.39±0.71	0.04
CTO myocardium (follow-up)	2.30±0.82	2.60±0.78	0.02
Remote myocardium (follow-up)	2.34±0.77	2.61±0.72	0.02
Δ CTO myocardium	0.60±0.65	0.89±0.72	<0.01
Δ Remote myocardium	0.16±0.49	0.22±0.58	0.51
CFR			
CTO myocardium (baseline)	2.06±0.60	2.05±0.75	0.91
Remote myocardium (baseline)	2.42±0.75	2.54±0.78	0.31
CTO myocardium (follow-up)	2.79±1.13	3.02±0.90	0.15
Remote myocardium (follow-up)	2.65±0.93	2.82±0.77	0.20
Δ CTO myocardium	0.72±0.91	1.00±0.92	0.05
Δ Remote myocardium	0.23±0.65	0.28±0.71	0.64
	Prior MI (CTO territory) (N=42)	No prior MI (N=86)	p-value
Resting MBF (mL·min⁻¹·g⁻¹)			
CTO myocardium (baseline)	0.82±0.18	0.89±0.26	0.08
Remote myocardium (baseline)	0.94±0.20	0.97±0.28	0.49
CTO myocardium (follow-up)	0.82±0.24	0.89±0.23	0.15
Remote myocardium (follow-up)	0.91±0.25	0.96±0.25	0.25
Δ CTO myocardium	0.01±0.19	-0.001±0.19	0.82
Δ Remote myocardium	-0.03±0.20	-0.01±0.16	0.62
Hyperaemic MBF (mL·min⁻¹·g⁻¹)			

CTO myocardium (baseline)	1.52±0.46	1.71±0.52	0.05
Remote myocardium (baseline)	2.04±0.58	2.39±0.71	<0.01
CTO myocardium (follow-up)	2.10±0.78	2.60±0.78	<0.01
Remote myocardium (follow-up)	2.23±0.73	2.61±0.72	<0.01
Δ CTO myocardium	0.59±0.72	0.89±0.72	0.03
Δ Remote myocardium	0.19±0.56	0.22±0.58	0.81

CFR

CTO myocardium (baseline)	1.90±0.54	2.05±0.75	0.20
Remote myocardium (baseline)	2.20±0.59	2.54±0.78	0.02
CTO myocardium (follow-up)	2.66±1.15	3.02±0.90	0.05
Remote myocardium (follow-up)	2.53±0.93	2.82±0.77	0.06
Δ CTO myocardium	0.75±1.03	1.00±0.92	0.16
Δ Remote myocardium	0.32±0.75	0.28±0.71	0.75

Values are mean±SD.

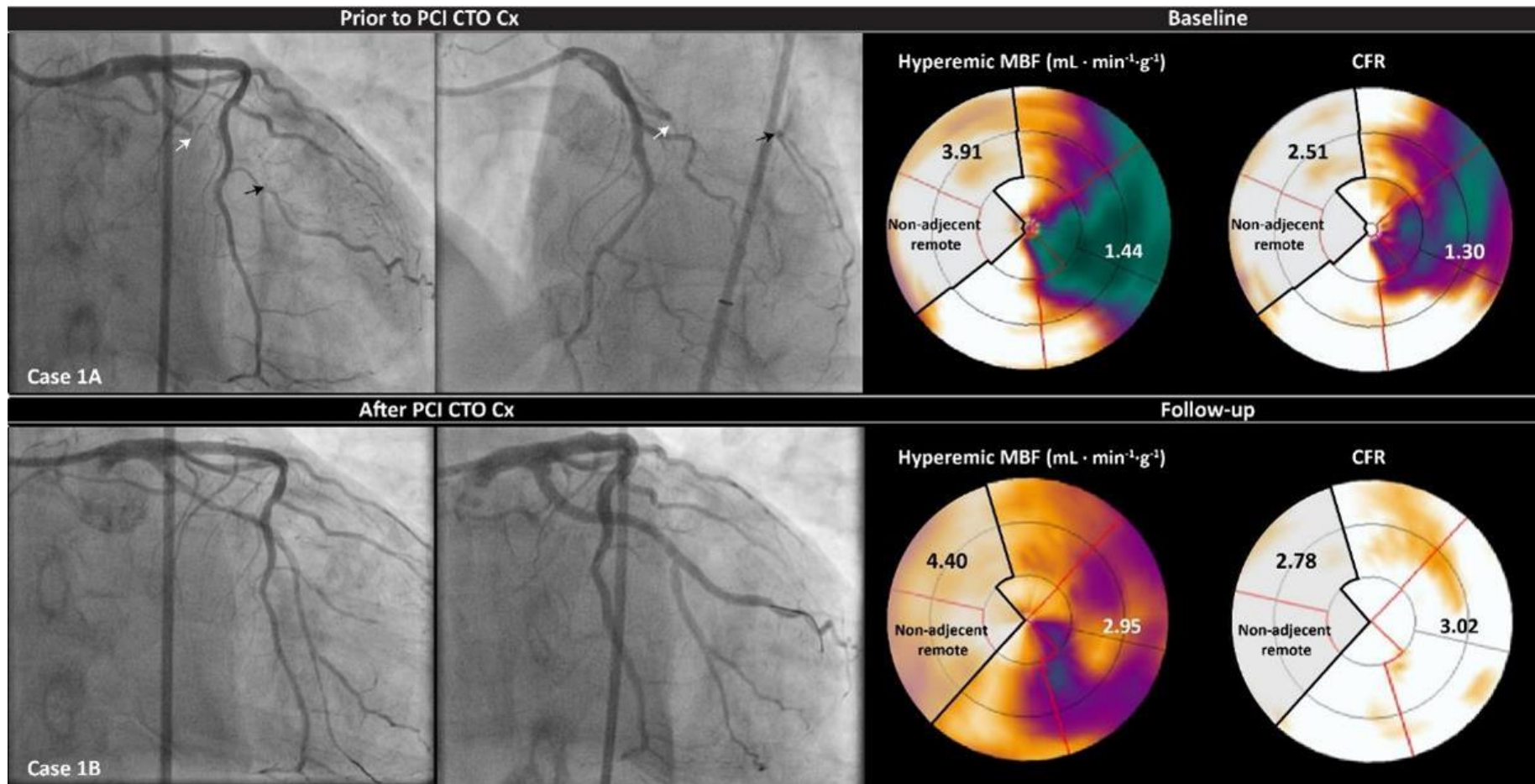
CFR: coronary flow reserve; CTO: chronic coronary total occlusion; Δ: delta; MBF: myocardial blood flow; MI: myocardial infarction; PET: positron emission tomography

Supplementary Table 3. Variables associated with change in remote myocardial perfusion (univariable analyses).

	Beta (95% CI)	p-value
Δ hyperaemic MBF remote myocardium		
Perfusion variables		
Baseline hyperaemic MBF CTO myocardium	-0.24 (-0.39, -0.08)	< 0.01
Baseline hyperaemic MBF remote myocardium	-0.18 (-0.31, -0.06)	< 0.01
Δ hyperaemic MBF CTO territory	0.55 (0.46, 0.63)	< 0.01
Large baseline perfusion defect in CTO territory	0.21 (0.04, 0.37)	0.02
Demographics		
Age, years	0.01 (-0.002, 0.01)	0.14
Male gender	-0.27 (-0.48, -0.05)	0.02
BMI, kg/m ²	-0.01 (-0.03, 0.01)	0.26
Cardiovascular risk factors		
Hypertension	0.11 (-0.05, 0.28)	0.18
Hypercholesterolaemia	-0.004 (-0.17, 0.16)	0.96
Diabetes mellitus	0.09 (-0.11, 0.28)	0.37
Family history of CAD	-0.02 (-0.19, 0.15)	0.83
Smoking	0.03 (-0.15, 0.20)	0.78
Cardiac history		
History of MI	-0.06 (-0.22, 0.11)	0.51
History of PCI	0.13 (-0.06, 0.32)	0.18
History of CABG	0.15 (-0.16, 0.46)	0.33
LVEF		0.57
Angiography and revascularisation		
CTO vessel (RCA vs LAD)	-0.001 (-0.26, 0.26)	1.00
CTO vessel (RCA vs Cx)	0.25 (-0.08, 0.59)	0.21
CTO vessel (LAD vs Cx)	0.25 (-0.13, 0.64)	0.35
J-CTO score		1.00
Successful CTO crossing technique (intimal vs	-0.07 (-0.24, 0.10)	0.42
Well-developed collaterals	0.06 (-0.12, 0.25)	0.49
Dominant collateral pathway (septal vs epicardial)	0.06 (-0.25, 0.13)	0.51
Stent length (mm)	0.001 (-0.001, 0.003)	0.42
Δ CFR remote myocardium		
Perfusion variables		
Baseline CFR CTO myocardium	-0.26 (-0.41, -0.11)	< 0.01
Baseline CFR remote myocardium	-0.28 (-0.41, -0.15)	< 0.01
Δ CFR CTO territory	0.50 (0.42, 0.59)	< 0.01
Demographics		

Age (in years)	0.01 (-0.004, 0.02)	0.24
Gender (male vs. female)	-0.27 (-0.55, 0.01)	0.06
BMI	0.001 (-0.02, 0.03)	0.92
Cardiovascular risk factors		
Hypertension	0.13 (-0.08, 0.34)	0.24
Hypercholesterolaemia	0.14 (-0.07, 0.35)	0.18
Diabetes mellitus	0.10 (-0.14, 0.34)	0.42
Family history of CAD	-0.02 (-0.23, 0.19)	0.86
Smoking	-0.002 (-0.23, 0.22)	0.99
Cardiac history		
History of MI	-0.05 (-0.26, 0.16)	0.64
History of PCI	0.13 (-0.11, 0.37)	0.29
History of CABG	0.11 (-0.28, 0.50)	0.58
LVEF		0.57
Angiography and revascularisation		
CTO vessel (RCA vs LAD)	-0.12 (-0.45, 0.21)	1.00
CTO vessel (RCA vs Cx)	0.16 (-0.27, 0.59)	1.00
CTO vessel (LAD vs Cx)	0.28 (-0.22, 0.77)	0.53
J-CTO score		0.97
Successful CTO crossing technique (intimal vs	-0.08 (-0.30, 0.14)	0.46
Well-developed collaterals	-0.04 (-0.27, 0.20)	0.77
Dominant collateral pathway (septal vs epicardial)	-0.03 (-0.27, 0.22)	0.85
Stent length, mm	0.001 (-0.002, 0.004)	0.44

BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CFR: coronary flow reserve; CTO: chronic coronary total occlusion; Cx: left circumflex coronary artery; Δ : delta; LAD: left anterior descending coronary artery; MBF: myocardial blood flow, MI: myocardial infarction; RCA: right coronary artery



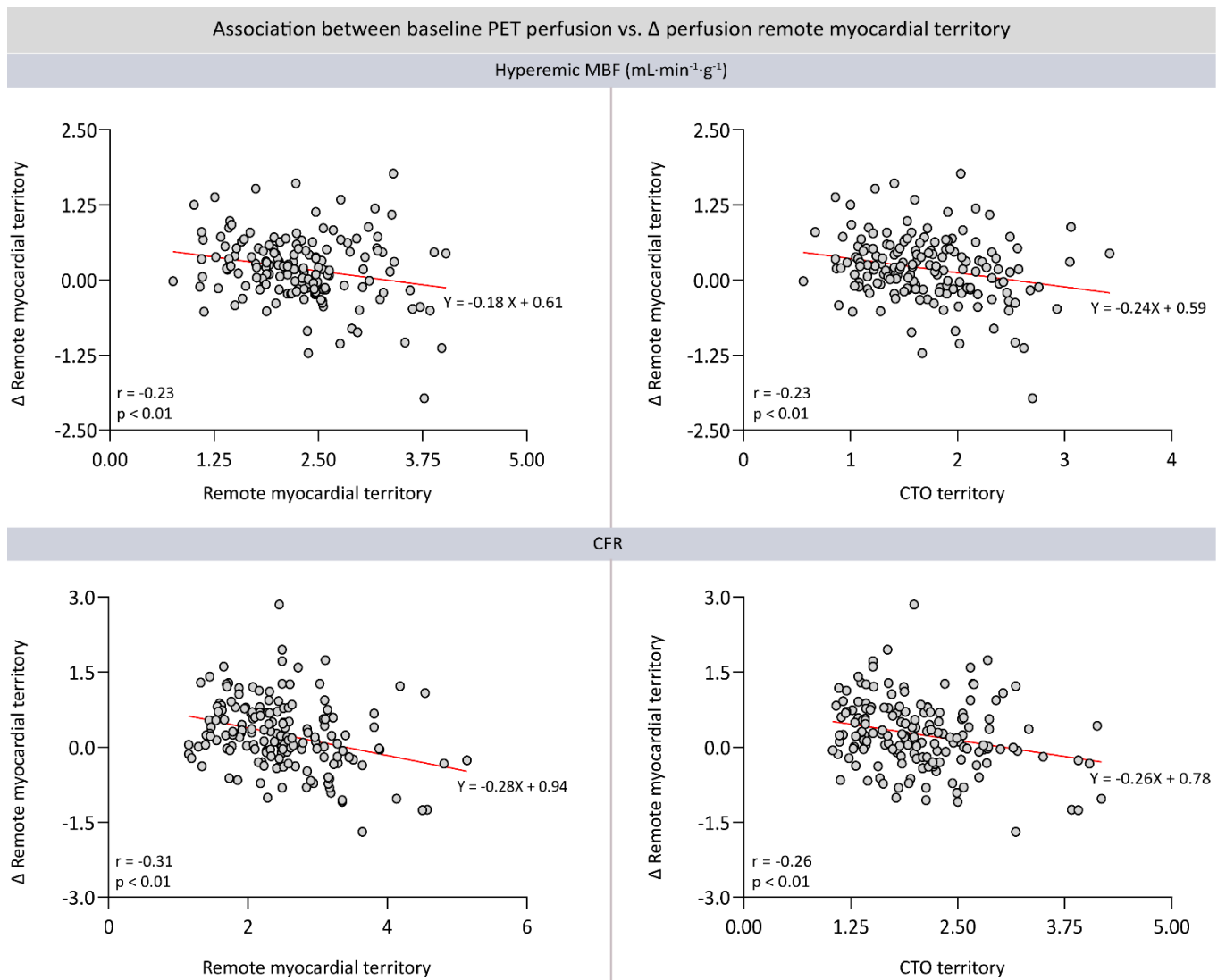
Supplementary Figure 1. Case example demonstrating the change in absolute myocardial perfusion in the remote myocardial territory non adjacent to the CTO region.

A case example illustrating angiograms before and directly after successful recanalisation of a CTO in the circumflex coronary artery. [^{15}O]H $_2\text{O}$ PET perfusion images of vasodilator stress flow and coronary flow reserve show the absolute myocardial perfusion in the CTO and remote myocardial territory at baseline and follow-up PET imaging.

Case 1A. Dual injection angiography images show a CTO of the Cx (white arrow). The black arrows indicate the well-developed collaterals (CC score 2 and Rentrop grade 3). Quantitative hMBF and CFR in the CTO territory are lower compared to the remote myocardial territory to the CTO region.

Case 1B. Angiography shows the Cx of the same patient during and directly after CTO revascularisation. Follow-up PET perfusion imaging shows improvements in hMBF and CFR in the CTO and non-adjacent remote myocardial territory.

CC: collateral connection; CFR: coronary flow reserve; CTO: chronic total occlusion; Cx: circumflex coronary artery; hMBF: hyperaemic myocardial blood flow; PCI: percutaneous coronary intervention; PET: positron emission tomography

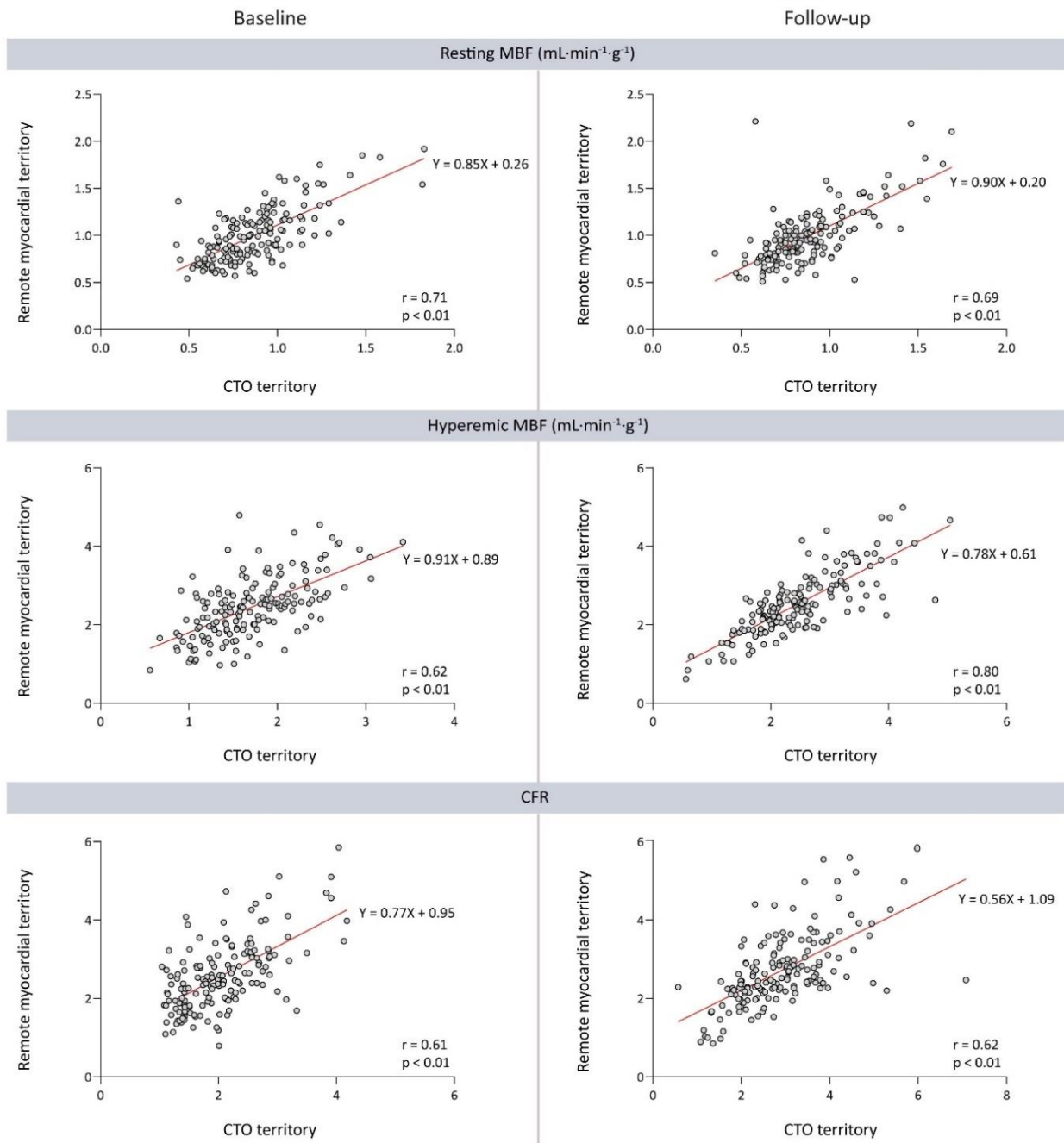


Supplementary Figure 2. Association between baseline PET perfusion versus Δ perfusion remote myocardial territory.

Patients with lower baseline perfusion values in myocardium subtended by the CTO and myocardium supplied by the non-target collateral donor arteries showed larger increases in quantitative perfusion indices in the remote myocardial territory following CTO PCI.

CFR: coronary flow reserve; CTO: chronic total occlusion; Δ : delta; hMBF: hyperaemic myocardial blood flow; PCI: percutaneous coronary intervention; PET: positron emission tomography

Association between PET perfusion CTO territory vs. remote myocardial territory before and after PCI CTO



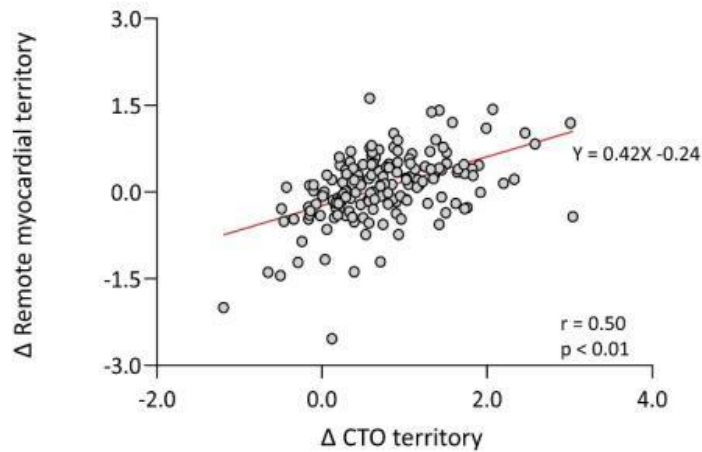
Supplementary Figure 3. Association between perfusion indices in the CTO territory versus non-adjacent remote myocardial territory.

Scatterplots demonstrating the correlation between resting MBF, hMBF and CFR in the CTO and remote myocardial territory non-adjacent to the CTO region, both before and after CTO revascularisation.

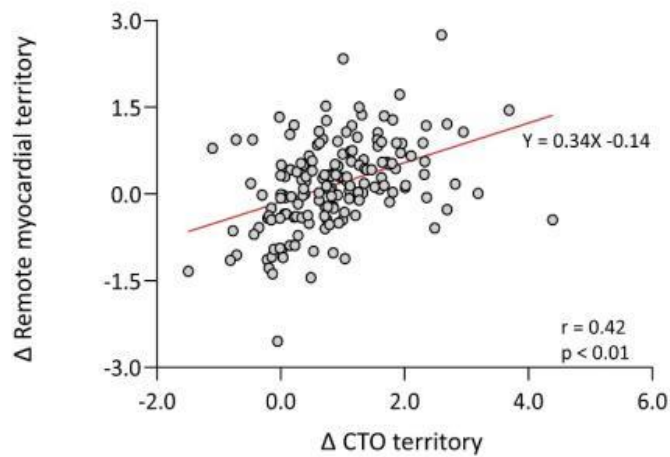
CFR: coronary flow reserve; CTO: chronic total occlusion; hMBF: hyperaemic myocardial blood flow; PCI: percutaneous coronary intervention; PET: positron emission tomography

Association between Δ PET perfusion CTO territory vs. Δ remote myocardial territory following CTO PCI

Hyperemic MBF ($\text{mL}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$)



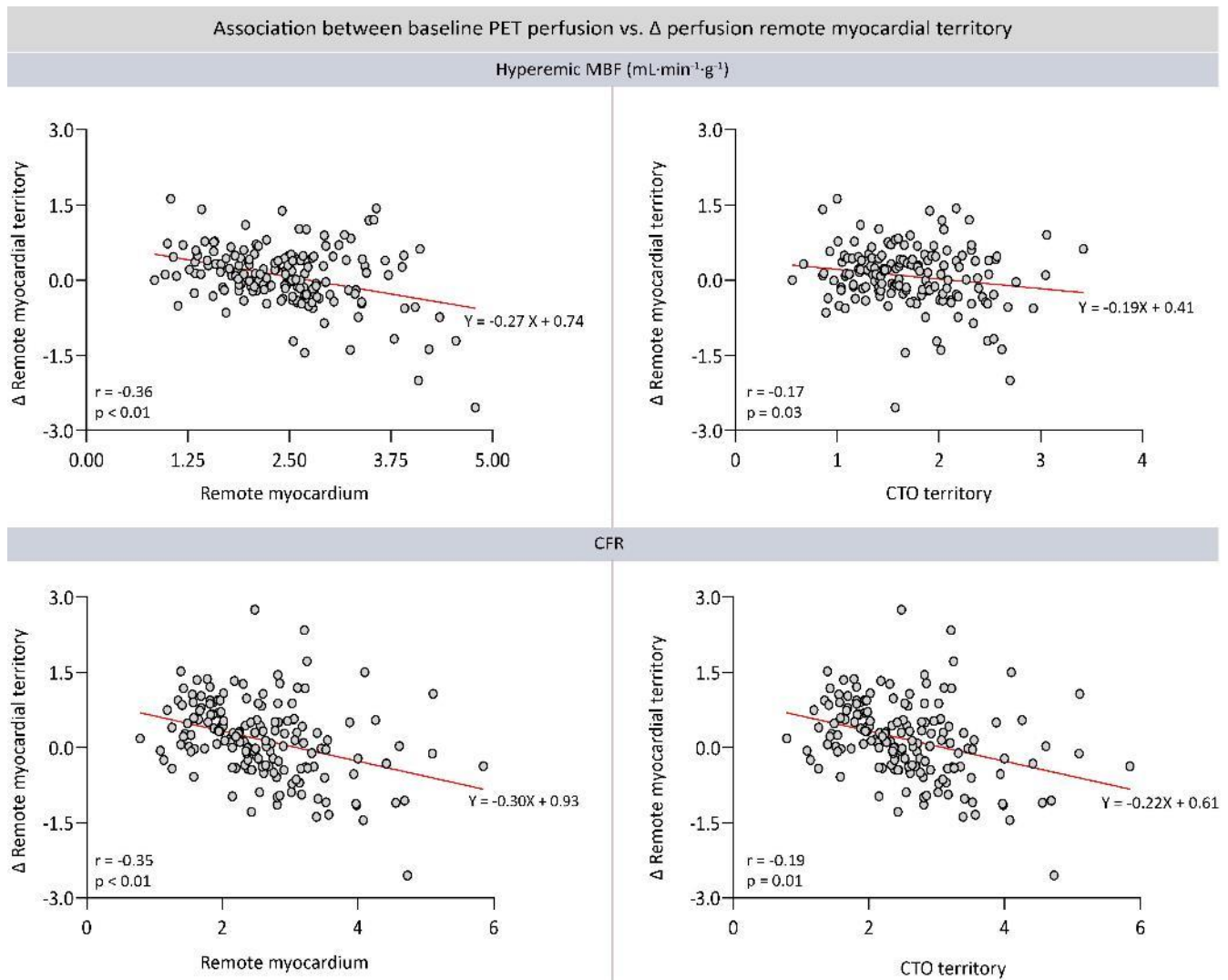
CFR



Supplementary Figure 4. Association between Δ PET perfusion CTO territory versus Δ non-adjacent remote myocardial territory.

Scatterplots demonstrating the correlation between the change in absolute myocardial perfusion in the CTO and remote myocardial territory non-adjacent to the CTO region.

CFR: coronary flow reserve; CTO: chronic total occlusion; Δ : delta; hMBF: hyperaemic myocardial blood flow; PCI: percutaneous coronary intervention; PET: positron emission tomography



Supplementary Figure 5. Association between baseline PET perfusion CTO territory vs Δ non-adjacent remote myocardial territory.

In patients with lower perfusion values at baseline, a larger increase in quantitative perfusion indices was observed in the remote myocardial territory non-adjacent to the CTO region.

CFR: coronary flow reserve; CTO: chronic total occlusion; Δ : delta; hMBF: hyperaemic myocardial blood flow; PET: positron emission tomography