EuroIntervention 2023;19:e123-e133 published online ahead of print February 2023 ■ published online e-edition June 2023

Changes in absolute flow, myocardial resistance and FFR after chronic total occlusion percutaneous coronary intervention

Sarosh A. Khan[1,2], MBBS; Osama Alsanjari[1,2], MBBS; Daniëlle C.J. Keulards[3], MD; Pieter-Jan Vlaar[3], MD, PhD; Jufen Zhang[2], PhD; Klio Konstantinou[1,2], MBBS; Samer Fawaz[1,2], MBBS; Rupert Simpson[1,2], MBBS; Gerald Clesham[1,2], MA, PhD; Paul A. Kelly[2], MD; Kare H. Tang[2], MBBS; Christopher M. Cook[1,2], MBBS, MD; James Cockburn[4], MBBS, PhD; Nico H.J. Pijls[3], MD, PhD; David Hildick-Smith[4], MD; Koen Teeuwen[3], MD; Thomas R. Keeble[1,2], MBBS, MD; Grigoris V. Karamasis[1,2,5], MD; John R. Davies[1,2]*, MBBS, PhD

1. Essex Cardiothoracic Centre, Basildon University Hospital, Basildon, UK; 2. Anglia Ruskin University, Chelmsford, UK; 3. Catharina Hospital, Eindhoven, the Netherlands; 4. Royal Sussex County Hospital, Brighton, UK; 5. Attikon University Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00694

KEYWORDS

- chronic coronary total occlusion
- clinical research
- other technique
- stable angina

Abstract

Background: Randomised studies of percutaneous coronary intervention (PCI) in patients with chronic total occlusion (CTO) have shown inconsistent outcomes, suggesting incomplete understanding of this cohort and their coronary physiology. To address this shortcoming, we designed a prospective observational study to measure the recovery of absolute coronary blood flow following successful CTO PCI

Aims: We sought to identify patient and procedural characteristics associated with a favourable physiological outcome after CTO PCI.

Methods: Consecutive patients with a CTO subtending viable myocardium underwent PCI utilising contemporary techniques and the hybrid algorithm. Immediately after PCI, and at 3-month follow-up, physiological measurements were performed utilising continuous thermodilution.

Results: A total of 81 patients were included with a mean age of 63.6±8.9 years, and 66 (81.5%) were male. Physiological measurements of absolute coronary blood flow in the CTO vessel increased by 30% ($p<0.001$) and microvascular resistance reduced by 16% ($p<0.001$) from immediately post-CTO PCI to follow-up assessment. Fractional flow reserve increased by 0.02 ($p=0.015$) in the same period. Prior coronary artery bypass graft (CABG) and a higher estimated glomerular filtration rate (eGFR) were associated with a larger change in absolute flow. An extraplaque strategy was associated with a smaller change in absolute flow.

Conclusions: Post-CTO PCI, there is a continued augmentation in absolute coronary blood flow and reduction in microvascular resistance from baseline to follow-up at 3 months. Prior CABG and a higher baseline eGFR were predictors of a larger change in absolute coronary flow, whilst an extraplaque final wire path strategy predicted a smaller change. Lastly, the patient characteristics and comorbidities had a larger influence than procedural factors on the observed change in absolute flow.

**Corresponding author: Essex Cardiothoracic Centre, Mid and South Essex NHS Foundation Trust, Basildon University Hospital, Nethermayne, Basildon SS16 5NL, UK. E-mail: john.davies32@nhs.net*

SUBMITTED ON 11/08/2022 - REVISION RECEIVED ON 1st 07/11/2022 / 2nd 30/11/2022 - ACCEPTED ON 07/12/2022

DOI: 10.4244/EIJ-D-22-00694

Abbreviations

CFR	coronary flow reserve
CTO	chronic total occlusion
FFR	fractional flow reserve
IVUS	intravascular ultrasound
J-CTO	Japanese chronic total occlusion score
LAD	left anterior descending artery
LCx	left circumflex artery
PCI	percutaneous coronary intervention
Q	absolute coronary blood flow
RCA	right coronary artery

Introduction

Percutaneous coronary intervention (PCI) in chronic coronary syndromes (CCS) is considered to improve symptoms by increasing coronary blood flow following the return of vessel patency[1]. Chronic total occlusions (CTO) can be considered a special subset of coronary lesions within the spectrum of CCS. Firstly, CTO vessels have a higher atherosclerotic burden of disease and a higher incidence of severe calcification[2]. Secondly, CTO PCI carries a higher risk of complication, including periprocedural infarction and major branch occlusion[3]. Finally, vessels that contain a CTO have a considerably greater collateral supply compared with vessels affected by subocclusive disease[4]. Therefore, CTO PCI represents a complex intervention that could possibly have different outcomes to PCI for subocclusive disease and, thus, requires exclusive scientific studies to assess its efficacy. Randomised studies looking at outcomes following PCI have revealed inconsistent results[5-8], suggesting that a more in-depth understanding of CTO PCI patients and their coronary physiology is required. There is a need for a robust, objective method for determining procedural success beyond angiography, and coronary physiology allows us to document a quantitative change following CTO PCI. In the absence of direct measurements of flow, this has been demonstrated by different invasive physiological measurements considered surrogates of flow, such as Doppler-derived coronary flow reserve (CFR)[9], fractional flow reserve (FFR)[10] and non-invasive methods like myocardial positron emission tomography (PET)[11]. All these modalities have drawbacks, including indirect estimation of flow (e.g., FFR), a lack of operator independence for invasive measurements and the absence of vessel-specific assessment for non-invasive methods.

Therefore, there remains an opportunity to utilise more novel techniques, specifically continuous thermodilution, which has the benefit of being both operator-independent and vessel-specific[12].

The aim of this study was to use continuous thermodilution to document the change in coronary flow following successful CTO PCI. Furthermore, we sought to identify both patient- and procedural-related predictors of the change in flow.

Methods

STUDY DESIGN & POPULATION

This was a prospective, multicentre, observational study of culprit vessel physiology following successful CTO PCI (ClinicalTrials.gov: NCT03830853). Patients scheduled for elective, clinically indicated CTO PCI with demonstrable viability of myocardium in the CTO-subtended territory were recruited (inclusion and exclusion criteria are detailed in **Supplementary Appendix 1**). The participating centres were the Essex Cardiothoracic Centre (Basildon, UK), Royal Sussex County Hospital (Brighton, UK) and Catharina Hospital (Eindhoven, the Netherlands). Invasive physiological measurements were performed immediately following successful CTO PCI (index) and repeated at 3 months after the index procedure (90-day follow-up).

CTO-subtended myocardium was considered viable if there was normal left ventricular function, as assessed by either transthoracic echocardiography, left ventricular angiography or cardiac magnetic resonance imaging (cMRI). When assessed by cMRI, late gadolinium enhancement of less than 50% of myocardial wall thickness was defined as being viable.

All patients provided written informed consent, and the study had local regional ethical committee approval. The study adhered to the principles of the Declaration of Helsinki.

CHRONIC TOTAL OCCLUSION PERCUTANEOUS CORONARY INTERVENTION

CTO PCI was performed according to contemporary techniques utilising the hybrid algorithm. Prior to the procedure, patients were commenced on dual antiplatelet therapy. Recanalisation strategy was at the operator's discretion. The use of intravascular ultrasound (IVUS) was strongly encouraged. A procedure was considered technically successful when achieving Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or greater with <30% angiographic residual stenosis in the CTO vessel by visual assessment[13]. All patients received drug-eluting stents. Patients were discharged on dual antiplatelet therapy for a minimum of 6 months.

PHYSIOLOGICAL MEASUREMENTS

After successful CTO PCI, coronary physiology measurements were performed using the continuous thermodilution method. For this purpose, a pressure/thermistor guidewire (Pressure Wire X; Abbott Vascular), a monorail infusion catheter (RayFlow; Hexacath) and a dedicated software system (CoroFlow v3.01; Coroventis) were used. Absolute coronary blood flow was measured using the previously published methodology[14]. In brief, the dedicated infusion catheter was positioned in the proximal vessel and the pressure wire, after equalisation of pressure and temperature, was placed in the distal vessel at least 60 mm from the tip of the infusion catheter. This pressure wire position was documented at the index procedure with an angiographic acquisition; this image was reviewed at follow-up to ensure that the pressure wire was placed at the same location. Room temperature saline was infused (20-25 ml/min for the left anterior descending artery [LAD] and left circumflex artery [LCx]; 15-20 ml/min for the right coronary artery [RCA]) and the reduction in mixed blood temperature (T) was measured. The saline infusion itself creates a hyperaemic state, and additional adenosine is not necessary[15,16].

A steady state was reached within 10-15 seconds and the pressure wire was pulled back into the infusion catheter to determine the infusion temperature (Ti). Absolute flow (Q, ml/min) was calculated utilising the Coroventis software (CoroFlow v3.01) alongside microvascular resistance (Rmicro, Wood units [WU]) and continuous thermodilution-derived fractional flow reserve (FFR).

FOLLOW-UP

Patients with a completed physiological assessment at the time of the CTO PCI procedure were scheduled for follow-up at 3 months. Patients underwent repeated physiological assessments as per the index procedure. Any optimisation of CTO PCI or further treatment was undertaken only after completion of research measurements.

STATISTICAL ANALYSIS

Continuous data are expressed as mean (standard deviation) or median (25^{th} and 75^{th} percentile) depending on the distribution of data, and categorical data are expressed as percentages. Normality of data distribution was assessed by the Shapiro-Wilk test. Comparisons of index and follow-up procedure data were performed with a paired t-test or the Wilcoxon signed-rank test. Two independent samples were compared with an independent t-test or the Mann-Whitney U test, as appropriate. Simple linear regression models were used to evaluate the associations between each preselected clinically significant parameter and change in absolute coronary flow from index to follow-up. Within a hierarchical multivariate model, specific patient characteristics associated with coronary artery disease (age, diabetes, hypertension, and hypercholesterolaemia) or increased complexity of procedure (prior coronary artery bypass graft [CABG]) were included within the base model and potentially modifiable procedural factors (extraplaque final wire path, length of stent and maximal balloon diameter) were added into the multiple regression analysis including variables with a p-value <0.10 on univariate analysis. Procedural variables that demonstrated collinearity were not included together. Model assumptions were checked, such as multicollinearity. A two-tailed p-value of <0.05 was considered significant. The statistical analyses were performed using SPSS 26 (IBM).

Results

STUDY POPULATION

The study flowchart is included in **Supplementary Figure 1**. An initial 119 patients underwent a CTO PCI procedure, of which 106 (89%) had a successful procedure. In total, 81 patients completed physiological assessments utilising continuous thermodilution of the CTO vessel immediately after PCI and at follow-up. The median interval between the index procedure and follow-up was 77 (interquartile range [IQR] 61-97) days. The timing of some follow-up physiological measurements were expedited due to the impact of the COVID-19 pandemic.

PATIENT CHARACTERISTICS

Full patient characteristics are displayed in **Table 1**. The mean age was 64±9 years, and 66 (81.5%) were male. Sixty-three percent of patients had CCS angina class II or higher. Details of medical therapy are displayed in **Supplementary Table 1**. Of the 44 (54%) patients who underwent ischaemia testing, 41 (93%) had an ischaemic burden ≥10%, and the overall mean ischaemic burden of the CTO territory was 19.0±8.4%. The median left ventricular ejection fraction was 55% (IQR 48-60%).

Table 1. Baseline characteristics.

			Mean±SD/N (%)
Demographics	Age		63.6±8.9
	Male		66 (81.5)
	BMI, kg/m^2		29.2±4.4
	eGFR, ml/min		88.6±25.0
Cardiovascular risk factors	Hypertension		57 (70.4)
	Current smoker		12 (14.8)
	Diabetes mellitus		16 (19.8)
	Dyslipidaemia		71 (87.7)
	Previous myocardial infarction		41 (50.6)
	Prior CABG		12 (14.8)
Symptoms	CCS angina class	CCS I	18 (22.2)
		CCS II	37 (45.7)
		CCS III	23 (28.4)
		CCS IV	3 (3.7)
	NYHA Class (I/II/III/IV)	NYHA I	35 (43.2)
		NYHA II	27 (33.3)
		NYHA III	19 (23.5)
		NYHA IV	0 (0)
Medication	No. of antianginal agents		2 (IQR 1-3)
Viability assessment	LVEF, %		55±11
Viability if LVEF <50% (n=23)	MIBI		3 (13.0)
	MRI		17 (73.9)
	Stress echo		3 (13.0)
Ischaemia assessment (n=44)	Ischaemic burden, %		19±8.4
	Ischaemia ≥10%		41 (93.2)

BMI: body mass index; CABG: coronary artery bypass graft; CCS: coronary calcium score; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; MIBI: myocardial perfusion imaging; MRI: magnetic resonance imaging; NYHA: New York Heart Association; SD: standard deviation

ANATOMICAL CHARACTERISTICS

The anatomical characteristics are described in **Table 2**. The CTO vessel frequency was as follows: RCA: 65%; LAD: 25%; and LCx: 10%. The proportion of patients with a Japanese CTO (J-CTO) score ≥2 was 63%.

PROCEDURAL CHARACTERISTICS

The procedural characteristics are reported in **Table 3**, with detailed procedural observations in **Supplementary Table 2**. The

Table 2. Anatomical characteristics.

			Mean±SD/median (IQR)/N (%)
CTO vessel	Right coronary artery		53 (65)
	Left anterior descending artery		20 (25)
	Circumflex artery		8 (10)
Major donor vessel	Right coronary artery		20 (25)
	Left anterior descending artery		50 (62)
	Circumflex artery		8 (10)
	SVG		2 (3)
	LMS		1 (1)
Lesion characteristics	Tapered/blunt		35 (43)
	Calcification present		46 (57)
	Bending >45 degrees		28 (35)
	Length >20 mm		44 (54)
	Previous attempt		13 (16)
	Total J-CTO score	J-CTO 0	12 (15)
		J-CTO 1	18 (22)
		J-CTO 2	20 (25)
		J-CTO 3	21 (26)
		J-CTO 4	8 (10)
		J-CTO 5	2 (2)
Collateral filling	None		1 (1)
	Bridge collaterals		6 (8)
	Retrograde filling		40 (50)
	Both		33 (41)
	Collateral size	CC0	4 (5)
		CC1	43 (54)
		CC2	20 (25)
		CC3	13 (16)
	Rentrop grade	0	0 (0)
		1	3 (4)
		2	25 (31)
		3	52 (65)

CTO: chronic total occlusion; J-CTO: Japanese CTO score; IQR: interquartile range; LMS: left main stem; SD: standard deviation; SVG: saphenous vein graft

Table 3. Procedural characteristics.

		Mean±SD/median (IQR)/N (%)
Successful crossing strategy	AW	52 (64)
	RW	2 (3)
	ADR	7 (9)
	RDR	20 (25)
Lumen re-entry technique if dissection	CART	0 (0.0)
	Reverse CART	17 (21.0)
	Stingray	3 (3.7)
	LAST	6 (7.4)
	STAR	1 (1.2)
PCI detail	Length of stented segment	68.4±30.3
	Number of stents	2±1
	I	24 (29.6)
	II	33 (40.7)
	II	19 (23.5)
	IV	5 (6.2)
	Max stent diameter	3.5±0.5
	Max balloon diameter	3.5±1.0
	Predicted subintimal length (n=26)	22.65±12.20
Duration and radiation	Procedure time (min)	171±56.5
	Wire time (min)	38±59
	Contrast volume (ml)	282±89
	DAP (cGycm^2)	20,013±12,580
	Skin dose (mGy)	2,804±1,353

ADR: antegrade dissection re-entry; AW: antegrade wire escalation; CART: controlled antegrade and retrograde tracking and dissection; DAP: dose area product; IQR: interquartile range; LAST: limited antegrade subintimal tracking; PCI: percutaneous coronary intervention; RDR: retrograde dissection re-entry; RW: retrograde wire escalation; SD: standard deviation

successful crossing strategies are summarised as follows: anterior wire escalation (AW): 64.2%; retrograde wire escalation (RW): 2.5%; antegrade dissection re-entry (ADR): 8.6%; and retrograde dissection re-entry (RDR): 24.7%. The mean number of stents was 2±2 stents, and the mean length of stented segments was 68.4±30.3 mm. The maximum stent and balloon diameters were 3.5 (IQR 3.0-3.5) mm and 3.5 (IQR 3.0-4.0) mm, respectively. Post-procedural TIMI 3 flow was achieved in 79 (98%) patients, and the remaining 2/81 (2%) had TIMI 2 flow.

CHANGES IN ABSOLUTE FLOW (Q)

The median absolute coronary blood flow in the CTO vessel at index and follow-up were 149 (IQR 121-205) ml/min and 201 (IQR 155-205) ml/min, respectively, delta +30% (IQR 6-51); p<0.001 **(Central illustration)**. On a per vessel analysis, the median change in absolute flow was as follows: RCA 47.0 (IQR 12.0-90.0) ml/min; p<0.001; LAD 45.5 (IQR 11.0-58.5) ml/min; p<0.001; and LCx 39.5 (3.8-92.5) ml/min; p=0.152 **(Figure 1)**.

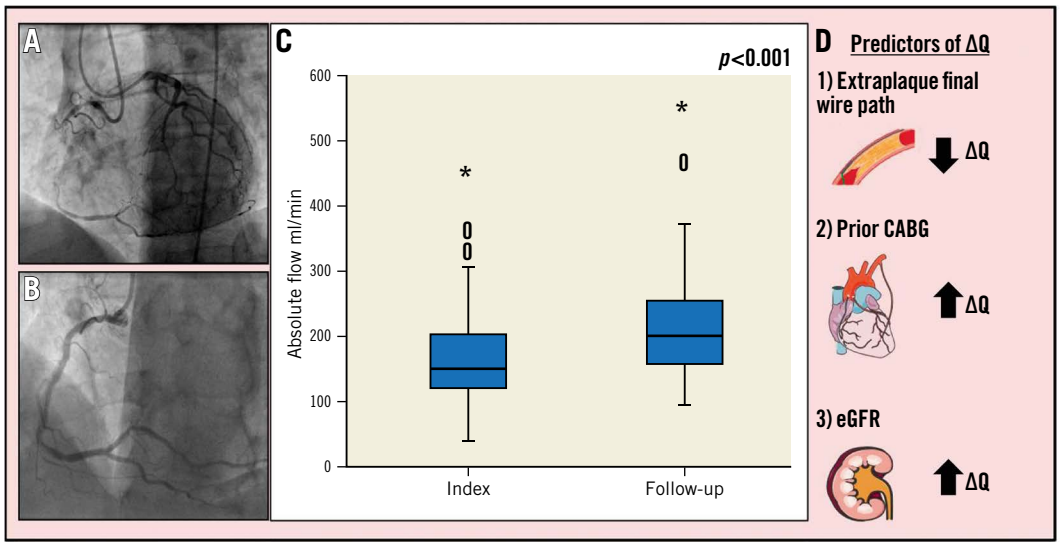
CHANGES IN RESISTANCE

The median microvascular resistance (Rmicro) at index and follow-up were 453 (IQR 353-579) WU and 370 (IQR 286-471) WU, respectively, delta −70 (IQR −168 to −2) WU; p<0.001. The change in epicardial (Repi) and total vessel resistance (Rtot) was −30 (IQR −83 to 5) WU and −115 (IQR −254 to −35) WU, respectively; p<0.001 for both **(Table 4)**. The Spearman's rank correlation (rho) for the correlation of change in Rmicro and change in Repi to change in absolute coronary flow were 0.522 (p<0.001) and 0.322 (p=0.322), respectively **(Supplementary Table 3)**. Detailed

EuroIntervention 2023;19:e123-e133

EuroIntervention

CENTRAL ILLUSTRATION Absolute coronary flow after successful CTO PCI and clinical predictors of change in flow.



Patients underwent CTO-vessel PCI (A) followed by immediate measurements of absolute flow in the culprit vessel. These measurements were repeated at follow-up (B). Absolute coronary flow increased from index to follow-up by 30% (C). Predictors of change in absolute flow (ΔQ) (D); an extraplaque final wire path predicted a smaller change in absolute flow, whereas prior CABG and a higher eGFR predicted a larger change in absolute flow. CABG: coronary artery bypass graft; CTO: chronic total occlusion; eGFR: estimated glomerular filtration rate; PCI: percutaneous coronary intervention

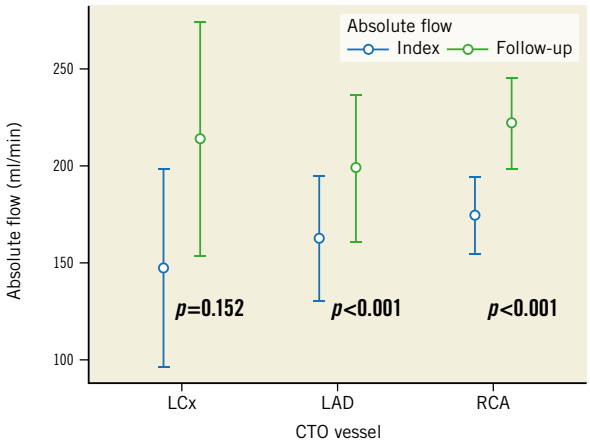


Figure 1. *Absolute coronary blood flow at index and follow-up per vessel. Absolute coronary blood flow at index and follow-up by CTO vessel. Bars: interquartile range (IQR). Dots: median value. CTO: chronic total occlusion; LAD: left anterior descending artery (n=20); LCx: left circumflex artery (n=8); RCA: right coronary artery (n=53)*

histograms of absolute flow and resistance variables are presented in **Supplementary Figure 2** and **Supplementary Figure 3**.

CHANGES IN FRACTIONAL FLOW RESERVE (FFR)

The median FFR at index and follow-up were 0.84 (IQR 0.73-0.93) and 0.86 (IQR 0.79-0.91), respectively, delta +0.02 (IQR −0.04 to 0.10); p=0.015. On a per vessel analysis, the median change in FFR was as follows: RCA 0.02 (IQR −0.05 to 0.07); p=0.138; LAD 0.04 (IQR −0.003 to 0.11); p=0.017; LCx −0.005 (IQR −0.10 to 0.17); p=0.554 **(Table 5)**.

PATIENT CHARACTERISTICS AS PREDICTORS OF CHANGE IN ABSOLUTE CORONARY FLOW

Univariate linear regression analysis of patient characteristics identified age (unstandardised correlation coefficient B= −1.93, 95% confidence interval [CI]: −3.38 to −0.48; p=0.01), diabetes (B= −43.53, 95% CI: −75.72 to −11.34; p=0.009) and estimated glomerular filtration rate (eGFR; B=0.61, 95% CI: 0.09 to 1.13; p=0.021) as predictors of change in absolute coronary flow **(Table 6)**. Increased age and diabetes were associated with a smaller change in absolute flow, whereas a higher eGFR was associated with a larger change.

ANATOMICAL CHARACTERISTICS AS PREDICTORS OF CHANGE IN ABSOLUTE CORONARY FLOW

There were no clinically significant anatomical factors that were associated with change in absolute coronary flow. Specifically, neither the complexity of the lesion (J-CTO score >2), nor an in-stent occlusion location, nor the type or grade of collateral flow correlated with change in absolute flow. TIMI 3 flow in the CTO vessel post-CTO PCI was associated with a lower change in absolute flow than TIMI 2 (p-value 0.016). Further univariate analysis of the J-CTO score elements is provided in **Supplementary Table 4**.

Table 4. Resistance measurements at index immediately after CTO PCI and at 3-month follow-up by vessel.

	Index (median [IQR]) WU	Follow-up (median [IQR]) WU	Delta (median [IQR]) WU [% (IQR)]	*p*-value
Total resistance (Rtot)	569 (450-703)	433 (333-550)	–254 (–115 to –35) [–24% (–37 to –6)]	<0.001
RCA	559 (449-674)	432 (333-515)	–113 (–253 to –35)	<0.001
LAD	617 (465-823)	462 (367-606)	–120 (–243 to –42)	<0.001
LCx	674 (451-905)	421 (335-602)	–212 (–358 to –54)	0.078
Microvascular resistance (Rmicro)	453 (353-579)	370 (286-471)	–70 (–168 to –2) [–16% (–33 to –0.4)]	<0.001
RCA	468 (356-555)	367 (288-452)	–72 (–168 to –2)	<0.001
LAD	424 (332-581)	373 (272-482)	–52 (–149 to –9)	0.004
LCx	540 (360-671)	388 (282-532)	–66 (–174 to –11)	0.250
Epicardial resistance (Repi)	101 (37-162)	60 (33-94)	–30 (–83 to 5) [–36% (–64 to –6)]	<0.001
RCA	51 (31-145)	47 (31-82)	–19 (–64 to 13)	0.003
LAD	137 (114-204)	95 (64-123)	–52 (–83 to –32)	<0.001
LCx	79 (18-157)	54 (40-72)	–10 (–132 to 38)	0.547

Rtot = Pa/Q; Rmicro =Pd/Q; Repi= (Pa-Pd)/Q. CTO: chronic total occlusion; IQR: interquartile range; LCx: circumflex artery; LAD: left anterior descending artery; Pa: aortic pressure; PCI: percutaneous coronary intervention; Pd: distal coronary pressure; Q: absolute coronary flow; RCA: right coronary artery; WU: Wood units

Table 5. FFR at index and follow-up.

	Index (median [IQR])	Follow-up (median [IQR])	Delta (median [IQR])	*p*-value
FFR	0.84 (0.73-0.93)	0.86 (0.79-0.91)	0.02 (–0.04 to 0.10)	0.015
RCA	0.87 (0.75-0.95)	0.89 (0.81-0.93)	0.02 (–0.05 to 0.07)	0.138
LAD	0.76 (0.68-0.82)	0.80 (0.74-0.85)	0.04 (–0.003 to 0.11)	0.017
LCx	0.86 (0.68-0.98)	0.88 (0.84-0.89)	–0.005 (–0.10 to 0.17)	0.554

IQR: interquartile range; FFR: fractional flow reserve; LCx: circumflex artery; LAD: left anterior descending artery; RCA: right coronary artery

PROCEDURAL CHARACTERISTICS AS PREDICTORS OF CHANGE IN ABSOLUTE CORONARY FLOW (ΔQ)

Univariate regression analysis for procedural factors demonstrated that only an extraplaque final wire path was a significant predictor of change in absolute flow **(Table 6)**. When analysed by crossing strategy, compared with RDR, AW (B=30.30, 95% CI: −0.81 to 61.42; p=0.056) showed a trend towards a greater change in absolute flow than RW (B=50.65, 95% CI: −37.94 to 138.34; p=0.254) and ADR (B=0.01, 95% CI: −51.92 to 51.94; p=1.00); however, this trend did not cross the threshold for significance. The maximum diameter of the balloon or stent used, as well as the length of the stented segment, were not significantly associated with change in absolute flow (p=0.559, 0.805 and 0.809, respectively).

COMBINED PATIENT AND PROCEDURAL CHARACTERISTICS AS PREDICTORS OF CHANGE IN ABSOLUTE FLOW

The results generated from the hierarchical multiple regression analysis of selected procedural characteristics on a baseline model of clinically important patient characteristics indicated that prior CABG (B=41.71, 95% CI: 6.37-77.04; p=0.021), eGFR (B=0.62, 95% CI: 0.09-1.16; p=0.023) and an extraplaque final wire path (B= −39.61, 95% CI: −72.98 to −6.24; p=0.021) were predictors of change in absolute flow **(Table 6)**. Patient characteristics of age and diabetes, identified on univariate analysis, were no longer significant using this model. TIMI flow at the end of the procedure was not included in the multivariate analysis, as only 2 patients had TIMI grade 2 flow and the rest had grade 3. This combined model of patient and procedural characteristics explained 28.6% (R2 0.286) of variation in change in absolute flow, where the selected patient characteristics independently explained 28% and procedural factors 0.6%. An alternative multivariate model using significant univariate variables only is shown in **Supplementary Table 5**.

Discussion

This study provides the largest contemporary cohort of CTO patients undergoing serial invasive physiological measurements of absolute coronary flow immediately post-CTO PCI and at short-term follow-up. The three key findings were as follows: firstly, absolute coronary blood flow continued to augment by ~30% from immediately post-CTO PCI to follow-up at 3 months. Secondly, prior CABG and a higher eGFR were predictors of a larger change in absolute coronary flow. Conversely, an extraplaque final wire path strategy predicted a smaller change in absolute flow. Lastly, patient characteristics and comorbidities had a larger influence than procedural factors on the change in absolute flow.

THE AUGMENTATION OF CORONARY BLOOD FLOW IN THE TARGET VESSEL FOLLOWING SUCCESSFUL CTO PCI

The understanding of post-CTO physiology has significantly improved over the previous two decades. This study demonstrates

Table 6. Univariate and multiple linear regression on change in absolute flow immediately post CTO PCI and follow-up.

		Simple linear regression model				Multiple regression model			
		B (95% CI)	t value	*p*-value	Beta	B (95% CI)	t value	*p*-value	Beta
Patient characteristics	Age	–1.93 (–3.38 to –0.48)	–2.655	0.01	–0.286	–1.41 (–2.83 to 0.01)	–1.974	0.052	–0.208
	Male gender	17.29 (–16.97 to 51.55)	1.005	0.317	0.112				
	BMI	0.62 (–2.43 to 3.68)	0.406	0.686	0.046				
	Diabetes	–43.53 (–75.72 to –11.34)	–2.691	0.009	–0.290	–20.09 (–54.02 to 13.84)	–1.181	0.242	–0.134
	HTN	0.32 (-29.01,– 29.65)	0.021	0.983	0.002	1.10 (–25.43 to 27.63)	0.083	0.934	0.008
	Hyper-cholesterolaemia	–1.65 (–42.36 to 39.06)	–0.081	0.936	–0.009	–7.16 (–45.42 to 31.11)	–0.373	0.710	–0.039
	Smoker	1.5 (–36.20 to 39.20)	0.079	0.937	0.009				
	Prior MI	–13.13 (–39.75 to 13.50)	–0.981	0.329	–0.110				
	Previous PCI	12.77 (–14.34 to 39.87)	0.938	0.351	0.105				
	Prior CABG	30.261 (–6.82 to 67.35)	1.624	0.108	0.180	41.71 (6.37 to 77.04)	2.354	0.021	0.248
	eGFR	0.61 (0.09 to 1.13)	2.352	0.021	0.256	0.62 (0.09 to 1.16)	2.322	0.023	0.262
	LVEF	0.08 (–1.28 to 1.43)	0.112	0.911	0.013				
	Ischaemic burden	0.08 (–2.29 to 2.46)	0.072	0.943	0.012				
Anatomical characteristics	J-CTO score >2 (ref: J-CTO ≤2)	–8.32 (–35.81 to 19.17)	–0.602	0.549	–0.068				
	In-stent CTO	5.52 (–45.602 to 56.642)	0.215	0.83	0.024				
Collateral flow	Ipsilateral	–98.208 (–228.226 to 31.809)	–1.504	0.137	–0.433				
	Contralateral	–89.010 (–210.878 to 32.858)	–1.455	0.15	–0.744				
	Both	–86.747 (–208.93 to 35.436)	–1.414	0.161	–0.714				
	CC grade ≥2- ref Grade <2	16.81 (–10.34 to 43.96)	1.233	0.221	0.138				
	Rentrop grade ≥2 - ref grade <2	–22.12 (–87.74 to 43.50)	–0.671	0.504	–0.076				
	End-TIMI grade III (ref: TIMI 2)	–102.475 (–185.668 to –19.281)	–2.452	0.016	–0.266				
Post-PCI Rentrop grade- ref 0	Grade 1	4.923 (–27.291 to 37.136)	0.306	0.761	0.043				
	Grade 2	4.381 (–39.993 to 48.750)	0.198	0.844	0.028				
Procedural characteristics	Extraplaque* final wire path	–31.056 (–58.600 to –3.510)	–2.244	0.028	–0.245	–39.61 (–72.98 to –6.24)	–2.367	0.021	–0.312
Crossing strategy (ref RDR) *	AW	30.304 (–0.809 to 61.416)	1.939	0.056	0.243				
	RW	50.650 (–37.043 to 138.343)	1.150	0.254	0.131				
	ADR	0.007 (–51.921 to 51.935)	0.000	1.00	0.000				
	Pred extraplaque length*	–0.56 (–1.69 to –0.57)	–0.992	0.324	–0.113				

Table 6. Univariate and multiple linear regression on change in absolute flow immediately post CTO PCI and follow-up. (cont'd)

		Simple linear regression model				Multiple regression model			
		B (95% CI)	t value	*p*-value	Beta	B (95% CI)	t value	*p*-value	Beta
Method of lumen entry (ref: none)*	Reverse CART	–35.672 (–68.749 to –2.595)	–2.148	0.035	–0.243				
	Stingray	–18.574 (–89.125 to 51.977)	–0.524	0.602	–0.059				
	LAST	–22.907 (–74.090 to 28.275)	–0.891	0.376	–0.100				
	STAR	–38.907 (–158.942 to 81.127)	–0.646	0.521	–0.072				
	Max balloon diameter	8.316 (–19.890 to 36.521)	0.587	0.559	0.066	2.83 (–23.28 to 28.93)	0.216	0.830	0.022
	Max stent diameter	–3.596 (–32.420 to 25.228)	–0.248	0.805	–0.028				
	Total length of stents	–0.054 (–0.499 to 0.39)	–0.242	0.809	–0.027	0.16 (–0.31 to 0.62)	0.677	0.501	0.080
	Number of stents	–3.091 (–18.298 to 12.116)	–0.405	0.687	–0.045				

*significant collinearity therefore not included in multiple regression together. B: unstandardised regression coefficient; Beta: standardised regression coefficient. ADR: antegrade dissection re-entry; AW: antegrade wire escalation; BMI: body mass index; CABG: coronary artery bypass graft; CART: controlled antegrade and retrograde tracking and dissection; CC: Calgary Collateral score; CI: confidence interval; CTO: chronic total occlusion; eGFR: estimated glomerular filtration rate; HTN: hypertension; J-CTO; Japanese CTO score; LAST: limited antegrade subintimal tracking; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coroanry intervention; RDR: retrograde dissection re-entry RW: retrograde wire escalation; STAR: subintimal tracking and re-entry; TIMI: Thrombolysis in Myocardial Infarction

that absolute coronary flow continues to improve after CTO PCI. Similar changes of flow in the CTO vessel post-PCI have been demonstrated in CFR by Doppler[9], FFR[10] and PET[11].

Karamasis et al[10] demonstrated FFR in right coronary arteries improved immediately post-CTO PCI to follow-up (delta +0.07±0.08; p<0.001)). Similarly, within this cohort, FFR improved from index to follow-up (delta +0.02 [IQR −0.04 to 0.10]; p=0.015). This increment was demonstrated in all three epicardial vessels, although it was only statistically significant in the LAD (p=0.017). The different technique in this study, continuous thermodilution of saline-derived hyperaemia compared to adenosine, to measure FFR may reflect the difference in magnitude observed.

Myocardial blood flow measured using [^{15}O]H_2O PET perfusion imaging is considered by some as the gold standard measure of coronary blood flow, as it takes into account myocardial mass. However, absolute coronary flow using continuous thermodilution provides a highly robust and reproducible measure that is vessel specific[15]. This is possible as the saline infusion creates localised hyperaemia in the myocardial bed of that vessel without inducing hyperaemia in others, which occurs with systemic adenosine.

The 30% increase in absolute flow was associated with a 24% reduction in Rtot, a 16% reduction in Rmicro and a 36% reduction in Repi (all p<0.001). The large reduction in epicardial resistance is likely due to vascular remodelling of the epicardial vessel after recanalisation[17,18]. The proportionally smaller reduction in Rmicro is likely due to initial maximal microvascular vasodilatation within the CTO-subtended myocardium[19] providing minimal resistance. The subsequent reduction in microvascular resistance at follow-up has also been shown by Werner et al[9] to be a transient microvascular dysfunction that improves.

FACTORS INFLUENCING THE AUGMENTATION OF CORONARY BLOOD FLOW

The change in absolute flow over time is thought to occur due to a reduction of myocardial resistance within the subtended territory and distal vessel remodelling[18]. Furthermore, the observed changes in absolute flow could also be as a result of changes in the endothelial function of the previously occluded vessel[20,21]. Our study has highlighted that there is a significant difference in the change in flow achieved between an intraplaque and extraplaque wire path. Extraplaque wiring predicted a smaller change in absolute flow. When analysed by each crossing strategy there was no significant difference; however, an AW strategy compared to RDR was associated with a larger change in absolute flow (p=0.056). A larger sample may have had sufficient power to demonstrate the difference between extra- and intraplaque strategies.

Our findings are contrary to previous literature, where no difference was identified between intraplaque or extraplaque strategies. Recovery of hyperaemic (adenosine-derived) myocardial blood flow (MBF) measured using PET was similar regardless of the crossing strategy utilised, and the crossing strategy was not predictive of hyperaemic MBF (p=0.40) on univariate analysis in 193 patients undergoing CTO PCI[22]. However, the authors did note significantly lower improvements in flow depending on the type of wiring utilised within the extraplaque strategy, and specifically within ADR, a subintimal tracking and re-entry (STAR) technique resulted in less favourable recovery of hyperaemic blood flow. This suggests that outcomes of extraplaque wiring are

heterogenous. Extraplaque wiring causes dissections which can lead to intimal haematoma formation, endothelial dysfunction, periprocedural complications and occlusion of side branches[23]. Side branch loss may explain why, in our study, extraplaque wiring was associated with a lower change in absolute coronary flow, as this would lead to a lower absolute coronary flow. However, prior studies have shown no significant difference in vascular healing between crossing strategies at 12 months, although there was a non-significant increase in CTO vessel revascularisation after an extraplaque strategy[24]. Continuous intracoronary thermodilution provides vessel-specific data, whereas PET imaging specifically measures segmental and global myocardial blood flow, therefore, loss of side branch may influence absolute coronary blood flow measurements more than PET. Our data highlight that the procedural strategy used may impact the change in absolute flow gained, it must be remembered that an extraplaque strategy is dictated by the anatomy and complexity of the lesion, as opposed to operator choice alone, and can be associated with a higher rate of stent implantation.

The change in absolute flow is influenced by patient characteristics of eGFR, prior CABG and an extraplaque final pathway. A lower baseline eGFR may represent an increased complexity due to higher calcification of the CTO vessel[2]. Furthermore, patients with lower eGFR have lower coronary flow reserve compared to those with higher renal function[25,26]. Possible coronary microvascular dysfunction (CMD), as part of a systemic process[27], may be the mechanism for the lower rate of change in absolute flow; however, this requires a dedicated CMD assessment that was not performed in this study.

Of the 12 participants who had prior CABG, nine had a bypass of the target CTO vessel, and only two had an occluded graft **(Supplementary Table 6)**. The mechanism of why prior CABG predicts a larger change in flow may be related to the continuous thermodilution technique employed to measure absolute flow. There may be a dilutional effect of the bypass graft blood interacting with the saline infusion within the recanalised CTO, providing a higher mixed blood temperature (T) and, thus, providing a lower absolute coronary flow value at index. At follow-up, the remodelled native vessel with brisker flow has a comparatively higher flow with less competitive flow from the graft and a lower mixed blood temperature and higher absolute flow. The physiological impact of bypass grafts requires further investigation as, historically, CTO PCI in this cohort is associated with a higher rate of procedural failure, likely as a consequence of multimorbidity[28], and, as such, a positive signal in the change in flow has to be interpreted cautiously.

Prior literature demonstrates that the improvement of FFR, therefore a surrogate of coronary flow, leads to improved outcomes for standard (non-CTO) PCI[29]. Within this cohort, we are firstly demonstrating there is an improvement of absolute coronary flow with a novel method of continuous thermodilution that is operator-independent and avoids the need for adenosine-induced hyperaemia. Subsequently, future avenues of research will establish any correlation of this method to both symptomatic and prognostic outcomes in this complex cohort of chronic coronary syndrome patients.

Limitations

There are several limitations with our observational study. Our sample size is modest and, therefore, may not provide sufficient power to identify predictors with smaller but significant effect sizes. Every attempt was made to ensure the positioning of the pressure wire at follow-up was the same as at the index procedure, as described, but small deviations of the wire position cannot be excluded. However, this is the largest set of paired data utilising an operator-independent method of measuring absolute coronary blood flow which can mitigate somewhat for the limitations of size.

Determination of the extraplaque final wire path was by successful crossing strategy, therefore, dissection re-entry (ADR, RDR). There may have been instances of extraplaque wiring within wire escalation strategies (AW, RW) that were not identified at the time of the procedure. Similarly, the subintimal length was determined angiographically by the operator. The former can occur during contemporary practice of CTO PCI, whereas the latter may be mitigated with intravascular imaging. This lack of intravascular imaging data meant we could not provide detailed measurements of lesion length, minimum stent size, minimum balloon size, and minimum stent diameter or area. Finally, we could not determine the impact of vasodilatory medications at follow-up on the change in absolute flow as this was not collected and, although these agents had no significant predictive value at index **(Supplementary Table 7)**, the impact of medications on coronary collateral flow after CTO PCI may be important.

Conclusions

This study demonstrates that absolute coronary blood flow values continue to improve over time after CTO PCI. An extraplaque crossing strategy was associated with a lower change in absolute flow and was an independent procedural predictor. However, patient characteristics contributed to a larger proportion of change in absolute flow than procedural aspects, and prior CABG and eGFR, specifically, were associated with a higher change in absolute coronary flow.

Impact on daily practice

Success of CTO PCI is judged angiographically and is performed for symptomatic benefit. We demonstrate that coronary blood flow augmentation post-CTO PCI can be objectively recorded utilising continuous thermodilution. Patient factors play a larger role than CTO recanalisation strategy on the final flow observed at 3 months. This highlights both the importance of patient selection and the strategy adopted for successful CTO PCI physiological outcomes. Future studies to correlate the change in absolute coronary flow to improvement in symptoms will be required.

Conflict of interest statement

C. Cook is a consultant for Philips, Boston Scientific, and Viz.ai; has received an institutional grant from Edwards Lifesciences; and has equity in Cerebria. N. Pijls has received institutional grants from Abbott and Hexacath; is a consultant for Abbott and GE Healthcare; and has minor equities in Philips, ASML, and HeartFlow. T. Keeble has received research grants from Boston Scientific, Volcano, Terumo, and Abbott Vascular. G. Karamasis has received honoraria from Abbott Vascular; and has received a research grant from Abbott Vascular. J. Davies has received a research grant from Medtronic. The other authors have no conflicts of interest to declare.

References

1. Nijjer SS, Petraco R, van de Hoef TP, Sen S, van Lavieren MA, Foale RA, Meuwissen M, Broyd C, Echavarria-Pinto M, Al-Lamee R, Foin N, Sethi A, Malik IS, Mikhail GW, Hughes AD, Mayet J, Francis DP, Di Mario C, Escaned J, Piek JJ, Davies JE. Change in coronary blood flow after percutaneous coronary intervention in relation to baseline lesion physiology: results of the JUSTIFY-PCI study. *Circ Cardiovasc Interv.* 2015;8:e001715.

2. Cosgrove C, Mahadevan K, Spratt JC, McEntegart M. The Impact of Calcium on Chronic Total Occlusion Management. *Interv Cardiol.* 2021;16:e30.

3. Guo Y, Peng H, Zhao Y, Liu J. Predictors and complications of side branch occlusion after recanalization of chronic total occlusions complicated with bifurcation lesions. *Sci Rep*. 2021;11:4460.

4. Werner GS. The role of coronary collaterals in chronic total occlusions. *Curr Cardiol Rev.* 2014;10:57-64.

5. 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.

6. Lee SW, Lee PH, Ahn JM, Park DW, Yun SC, Han S, Kang H, Kang SJ, Kim YH, Lee CW, Park SW, Hur SH, Rha SW, Her SH, Choi SW, Lee BK, Lee NH, Lee JY, Cheong SS, Kim MH, Ahn YK, Lim SW, Lee SG, Hiremath S, Santoso T, Udayachalerm W, Cheng JJ, Cohen DJ, Muramatsu T, Tsuchikane E, Asakura Y, Park SJ. Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. *Circulation.* 2019;139:1674-83.

7. Henriques JP, Hoebers LP, Råmunddal T, Laanmets P, Eriksen E, Bax M, Ioanes D, Suttorp MJ, Strauss BH, Barbato E, Nijveldt R, van Rossum AC, Marques KM, Elias J, van Dongen IM, Claessen BEPM, Tijssen JG, van der Schaaf RJ; EXPLORE Trial Investigators. Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI: The EXPLORE Trial. *J Am Coll Cardiol.* 2016;68:1622-32.

8. Mashayekhi K, Nührenberg TG, Toma A, Gick M, Ferenc M, Hochholzer W, Comberg T, Rothe J, Valina CM, Löffelhardt N, Ayoub M, Zhao M, Bremicker J, Jander N, Minners J, Ruile P, Behnes M, Akin I, Schäufele T, Neumann FJ, Büttner HJ. A Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion: The REVASC Trial. *JACC Cardiovasc Interv.* 2018;11:1982-91.

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.

10. Karamasis GV, Kalogeropoulos AS, Mohdnazri 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.

11. de Winter RW, Schumacher SP, van Diemen PA, Jukema RA, Somsen YBO, Stuijfzand WJ, Driessen RS, Bom MJ, Everaars H, van Rossum AC, van de Ven PM, Opolski MP, Verouden NJ, Danad I, Raijmakers PG, Nap A, Knaapen P. Impact of percutaneous coronary intervention of chronic total occlusions on absolute perfusion in remote myocardium. *EuroIntervention.* 2022;18(e314):23.

12. Xaplanteris P, Fournier S, Keulards DCJ, Adjedj J, Ciccarelli G, Milkas A, Pellicano M, Van't Veer M, Barbato E, Pijls NHJ, De Bruyne B. Catheter-Based Measurements of Absolute Coronary Blood Flow and Microvascular Resistance Feasibility, Safety, and Reproducibility in Humans. *Circ Cardiovasc Interv.* 2018;11:e006194.

13. Ybarra LF, Rinfret S, Brilakis ES, Karmpaliotis D, Azzalini L, Grantham JA, Kandzari DE, Mashayekhi K, Spratt JC, Wijeysundera HC, Ali ZA, Buller CE, Carlino M, Cohen DJ, Cutlip DE, De Martini T, Di Mario C, Farb A, Finn AV, Galassi AR, Gibson CM, Hanratty C, Hill JM, Jaffer FA, Krucoff MW, Lombardi WL, Maehara A, Magee PFA, Mehran R, Moses JW, Nicholson WJ, Onuma Y, Sianos G, Sumitsuji S, Tsuchikane E, Virmani R, Walsh SJ, Werner GS, Yamane M, Stone GW; Chronic Total Occlusion Academic Research Consortium. Definitions and Clinical Trial Design Principles for Coronary Artery Chronic Total Occlusion Therapies CTO-ARC Consensus Recommendations. *Circulation.* 2021;143:479-500.

14. van't Veer M, Adjedj J, Wijnbergen I, Tóth GG, Rutten MCM, Barbato E, van Nunen LX, Pijls NH, De Bruyne B. Novel monorail infusion catheter for volumetric coronary blood flow measurement in humans: in vitro validation. *EuroIntervention.* 2016;12:701-7.

15. De Bruyne B, Adjedj J, Xaplanteris P, Ferrara A, Mo Y, Penicka M, Floré V, Pellicano M, Toth G, Barbato E, Duncker DJ, Pijls NH. Saline-Induced Coronary Hyperemia: Mechanisms and Effects on Left Ventricular Function. *Circ Cardiovasc Interv.* 2017;10:e004719..

16. Gallinoro E, Candreva A, Fernandez-Peregrina E, Bailleul E, Meeus P, Sonck J, Bermpeis K, Bertolone DT, Esposito G, Paolisso P, Heggermont W, Adjedj J, Barbato E, Collet C, De Bruyne B. Saline-induced coronary hyperemia with continuous intracoronary thermodilution is mediated by intravascular hemolysis. *Atherosclerosis.* 2022;352:46-52.

17. Allahwala UK, Ward MR, Bhindi R. Change in the distal vessel luminal diameter following chronic total occlusion revascularization. *Cardiovasc Interv Ther.* 2018;33:345-9.

18. 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.

19. Werner GS, Figulla HR. Direct assessment of coronary steal and associated changes of collateral hemodynamics in chronic total coronary occlusions. *Circulation.* 2002;106:435-40.

20. Galassi AR, Tomasello SD, Crea F, Costanzo L, Campisano MB, Marz F, Tamburino C. Transient impairment of vasomotion function after successful chronic total occlusion recanalization. *J Am Coll Cardiol.* 2012;59:711-8.

21. Brugaletta S, Martin-Yuste V, Padr 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.

22. Schumacher SP, Stuijfzand WJ, Driessen RS, van Diemen PA, Bom MJ, Everaars H, Kockx M, Raijmakers PG, Boellaard R, van de Ven PM, van Rossum AC, Opolski MP, Nap A, Knaapen P. Impact of Specific Crossing Techniques in Chronic Total Occlusion Percutaneous Coronary Intervention on Recovery of Absolute Myocardial Perfusion. *Circ Cardiovasc Interv.* 2019;12:e008064.

23. Michael TT, Papayannis AC, Banerjee S, Brilakis ES. Subintimal dissection/reentry strategies in coronary chronic total occlusion interventions. *Circ Cardiovasc Interv.* 2012;5:729-38.

24. Walsh SJ, Hanratty CG, McEntegart M, Strange JW, Rigger J, Henriksen PA, Smith EJ, Wilson SJ, Hill JM, Mehmedbegovic Z, Chevalier B, Morice MC, Spratt JC. Intravascular Healing Is Not Affected by Approaches in Contemporary CTO PCI: The CONSISTENT CTO Study. *JACC Cardiovasc Interv.* 2020;13:1448-57.

25. Chade AR, Brosh D, Higano ST, Lennon RJ, Lerman LO, Lerman A. Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. *Kidney Int.* 2006;69:266-71.

26. Charytan DM, Skali H, Shah NR, Veeranna V, Cheezum MK, Taqueti VR, Kato T, Bibbo CR, Hainer J, Dorbala S, Blankstein R, Di Carli MF. Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage. *Kidney Int.* 2018;93:501-9.

27. Nowroozpoor A, Gutterman D, Safdar B. Is microvascular dysfunction a systemic disorder with common biomarkers found in the heart, brain, and kidneys?-A scoping review. *Microvasc Res*. 2021;134:104123.

28. Guo L, Lv H, Yin X. Chronic Total Occlusion Percutaneous Coronary Intervention in Patients With Prior Coronary Artery Bypass Graft: Current Evidence and Future Perspectives. *Front Cardiovasc Med.* 2022;9:753250.

29. Fournier S, Ciccarelli G, Toth GG, Milkas A, Xaplanteris P, Tonino PAL, Fearon WF, Pijls NHJ, Barbato E, De Bruyne B. Association of Improvement in Fractional Flow Reserve With Outcomes, Including Symptomatic Relief, After Percutaneous Coronary Intervention. *JAMA Cardiol.* 2019;4:370-4.

Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Table 1. Medical management at time of index procedure.

Supplementary Table 2. Procedural observations.

Supplementary Table 3. Correlation of changes in microvascular and epicardial resistance and change in absolute flow.

Supplementary Table 4. Univariate regression of J-CTO score elements on change in absolute flow.

Supplementary Table 5. Alternative multiple regression of only variables that were statistically significant on univariate analysis.

Supplementary Table 6. Coronary artery bypass graft patient details.

Supplementary Table 7. Univariate analysis of medical therapy at index procedure and change in absolute coronary flow.

Supplementary Figure 1. Study flow chart.

Supplementary Figure 2. Histograms of variables of absolute coronary blood flow at index, follow-up and difference.

Supplementary Figure 3. Histograms of variables of microvascular resistance at index, follow-up and difference.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00694

Supplementary data

Supplementary Appendix 1. Methods.

Inclusion Criteria

• > 18 years of age

• Presence of a coronary CTO scheduled for elective PCI

• Evidence of viability in the CTO territory

Exclusion Criteria

• Unable to give informed consent

• Known severe chronic kidney disease (creatinine clearance ≤30 mL/min), unless the patient is on dialysis

• Unable to receive antiplatelets or anticoagulation (i.e. coagulation disorders, bleeding etc.)

• Contraindications to adenosine

• Any study lesion characteristic resulting in the expected inability to deliver FD-OCT catheter at the distal vessel post CTO PCI (e.g. moderate or severe vessel calcification or tortuosity)

• Pregnancy, planning to get pregnant during the research period, or breastfeeding

Supplementary Table 1. Medical management at time of index procedure.

Medication (n=70)	**% of patients**
Anti-platelet	
Aspirin	100%
Clopidogrel	77%
Ticagrelor	22%
Prasugrel	1%
Secondary prevention	
ACE/ARB	69 %
Statin	94%
Anti-anginal	
Beta-blocker	86%
Calcium channel blocker (DHP)	36%
Calcium channel blocker (nDHP)	4%
Nitrate	46%
Ranolazine	13%
Nicorandil	4%
Ivabradine	1%

Supplementary Table 2. Procedural observations.

Index Procedure	Mean ± SD
Resting heart rate (bpm)	65 ± 11
Resting systolic BP (mmHg)	130 ± 22
Resting diastolic BP (mmHg)	69 ± 10
Follow-up Procedure	
Resting heart rate (bpm)	62 ± 12
Resting systolic BP (mmHg)	123 ± 20
Resting diastolic BP (mmHg)	64 ± 14

Supplementary Table 3. Correlation of changes in microvascular and epicardial resistance and change in absolute flow.

	Change in Absolute flow (Q)	
	Spearmans Rho	p-value
Change in Microvascular resistance (Rmicro)	-0.522	<0.001
Change in Epicardial Resistance (Repi)	0.322	0.322

Supplementary Table 4. Univariate regression of J-CTO score elements on change in absolute flow.

Univariate regression model				
	B (95%CI)	**t value**	**p value**	**Beta**
Entry shape	**0.934 (-26.10, 27.97)**	**0.069**	**0.945**	**0.008**
Length >20mm	**3.71 (-23.16, 30.58)**	**0.275**	**0.784**	**0.031**
Calcium	**-6.27 (-33.27, 20.73)**	**-0.462**	**0.645**	**-0.052**
Bending	**-11.86 (-39.91, 16.16)**	**-0.843**	**0.402**	**-0.094**
Previous failed attempt	**-29.07 (-64.97, 6.83)**	**-1.612**	**0.111**	**-0.178**

Supplementary Table 5. Alternative multiple regression of only variables that were statistically significant on univariate analysis.

Multiple regression model				
	B (95%CI)	**t value**	**p value**	**Beta**
Age	-0.001 (-0.003, 0.000)	-1.876	0.065	-0.194
Diabetes	-0.021 (-0.054, 0.011)	-1.307	0.195	-0.142
eGFR	0.001 (0.000, 0.001)	2.156	0.034	0.236
End TIMI-grade	-0.079 (-0.156,-0.001)	-2.028	0.046	-0.205
Extra-plaque final wire-path	-0.025 (-0.054, 0.004)	-1.726	0.088	-0.198

*B: unstandardised regression coefficient; Beta: standardised regression coefficient; * significant collinearity therefore not included in multiple regression together.*

eGFR: estimated glomerular filtration rate; end TIMI-grade: TIMI grade at end of CTO PCI procedure

Supplementary Table 6. Coronary artery bypass graft patient details.

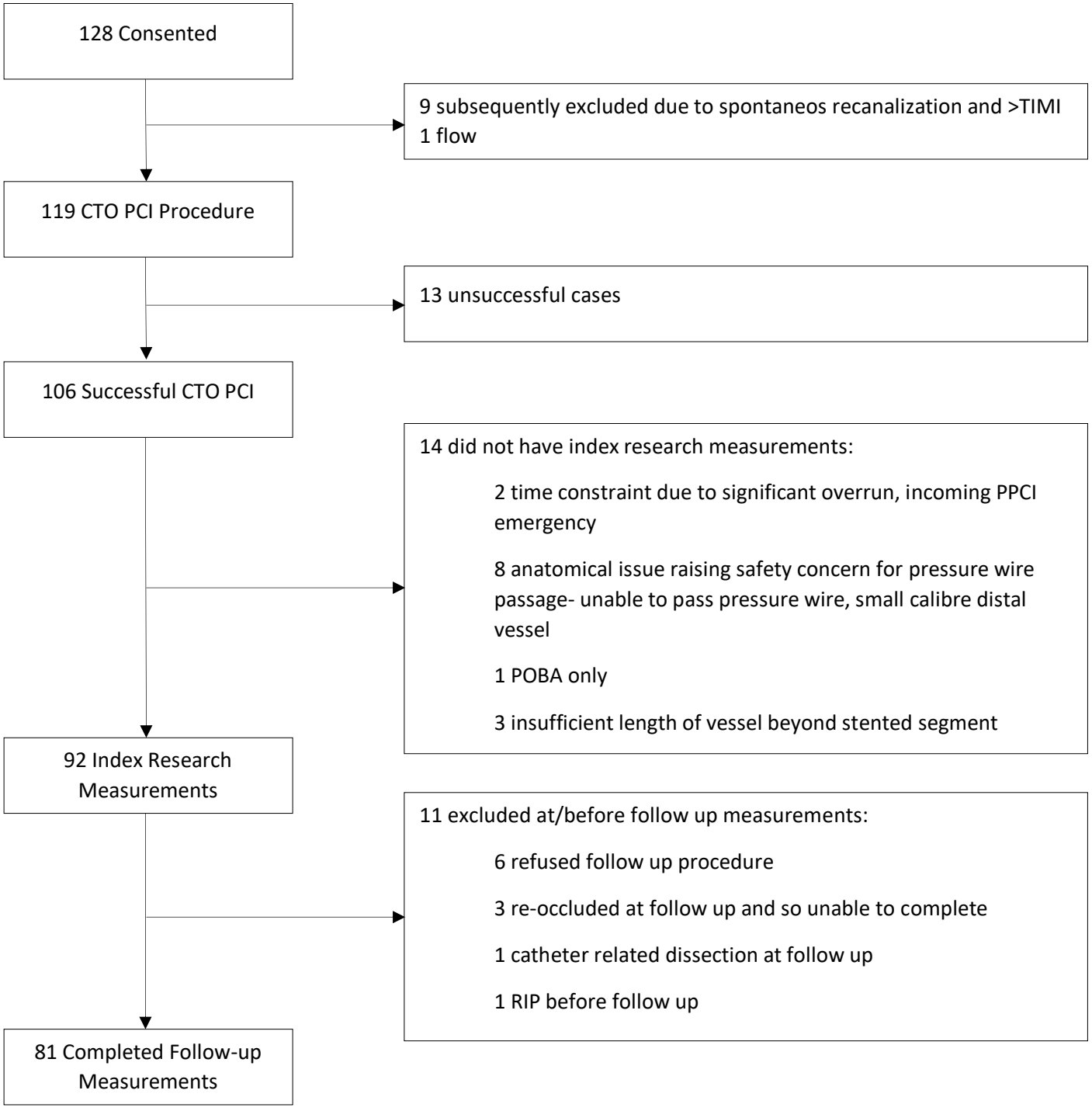
CABG	CTO Vessel	CTO Vessel Bypassed	Bypass occluded	Donor vessel of collaterals	Donor diseased (>50%)	No. of grafted vessels
1	RCA	Yes	Yes	Cx	No	3
2	Cx	No	-	RCA	No	2
3	RCA	Yes	No	SVG	No	2
4	RCA	Yes	Yes	RCA	No	2
5	RCA	No	-	LAD	No	2
6	Cx	Yes	No	SVG	No	2
7	RCA	Yes	Yes	LAD	No	3
8	RCA	Yes	Yes	LAD	No	2
9	RCA	Yes	Yes	Cx	No	3
10	RCA	No	-	LAD	No	3
11	RCA	Yes	Yes	Cx	No	2
12	RCA	Yes	Yes	LAD	No	3

Supplementary Table 7. Univariate analysis of medical therapy at index procedure and change in absolute coronary flow.

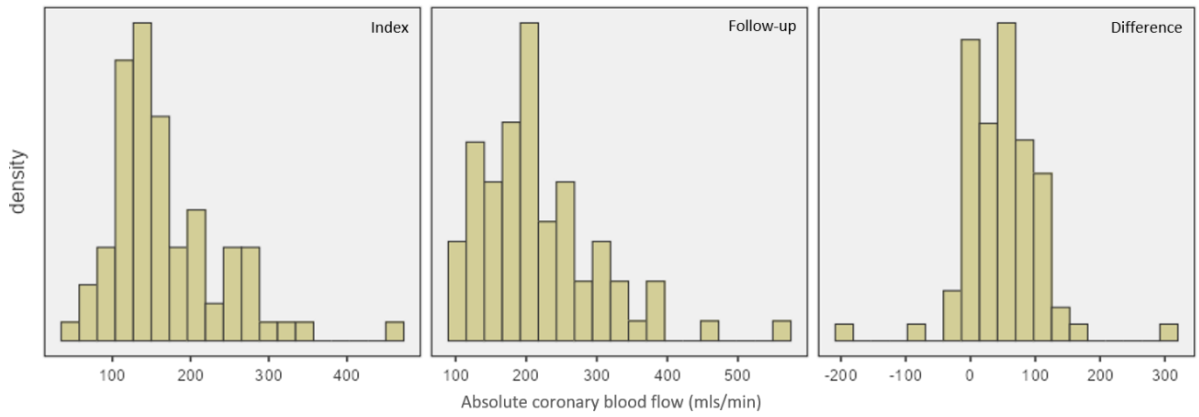
Univariate regression model				
Index	**B (95%CI)**	**t value**	**p value**	**Beta**
Beta-blocker	**-3.76 (-46.94, 39.42)**	**-0.174**	**0.862**	**-0.021**
DHP calcium channel blocker	**-5.27 (-35.41, 24.88)**	**-0.349**	**0.729**	**-0.042**
Non-DHP calcium channel blocker	**46.70 (31.93, 61.48)**	**-0.096**	**0.924**	**-0.012**
Nitrate	**-18.82 (-47.56, 9.93)**	**-1.306**	**0.196**	**-0.156**
Ranolazine	**4.379 (-38.80, 47.56)**	**0.202**	**0.840**	**0.025**
Nicorandil	**24.89 (-46.24, 96.01)**	**0.698**	**0.487**	**0.084**
Vasodilatory anti-anginals	**-9.31 (-39.40, 20.78)**	**-0.617**	**0.539**	**-0.075**

*B: unstandardised regression coefficient; Beta: standardised regression coefficient; * significant collinearity therefore not included in multiple regression together.*

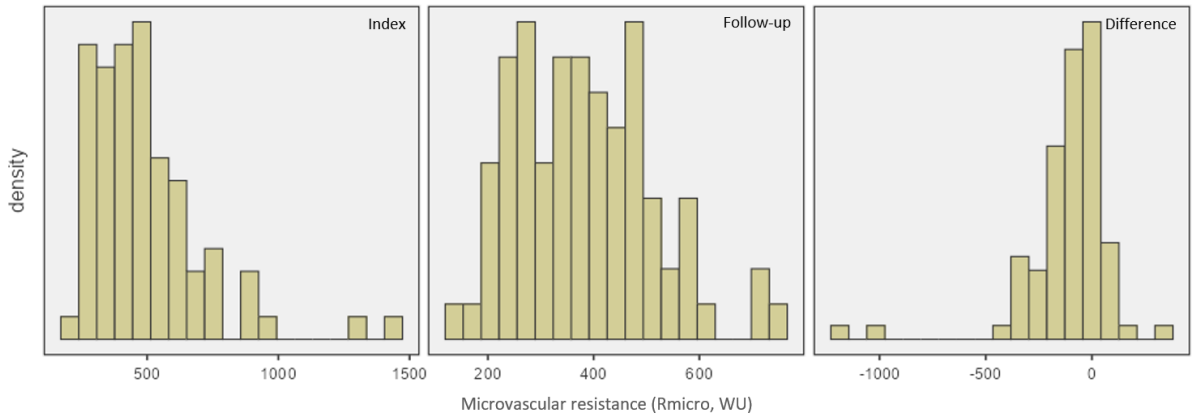
DHP: dihydropyridine; vasodilatory anti-anginals: DHP calcium channel blocker, nitrate, ranolazine and nicorandil.



Supplementary Figure 1. Study flow chart.



Supplementary Figure 2. Histograms of variables of absolute coronary blood flow at index, follow-up and difference.



Supplementary Figure 3. Histograms of variables of microvascular resistance at index, follow-up and difference.