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Meta-analysis

Time-Dependent Changes in the Coronary Circulation Triggered by CTO Revascularization: Insights From Intracoronary Physiology

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ABSTRACT

Background: Physiological changes in the coronary circulation associated with percutaneous coronary intervention (PCI) for chronic total occlusions (CTOs) remain largely unknown. This systematic review and meta-analysis aimed to investigate physiological changes in the CTO and donor vessel before and immediately after PCI, as well as at follow-up.

Methods: A comprehensive search of PubMed/MEDLINE and Embase identified relevant studies. The primary end point was the mean difference (MD) between fractional flow reserve myocardium (FFR_{myo}) of the primary donor vessel before and after CTO revascularization. Secondary outcomes included the difference in FFR_{myo}, FFR collateral (FFR_{coll}), FFR coronary (FFR_{cor}), absolute coronary blood flow, coronary flow velocity reserve, and microvascular resistance before and after CTO revascularization and/or at the follow-up.

Results: A total of 17 studies were included. The myocardial blood flow in the donor vessel increased after CTO revascularization (FFR_{myo}: MD, 0.04; 95% CI, 0.02-0.06; $P < .01$), as well as in the CTO vessel (MD, 0.45; 95% CI, 0.27-0.64; $P < .01$). At follow-up, CTO PCI was associated with a significant shift in collateral (FFR_{coll}: MD, −0.16; 95% CI, −0.18 to −0.15; $P < .01$) and epicardial blood supply (FFR_{cor}: MD, 0.09; 95% CI, −0.01 to 0.20; $P = .06$). Time-dependent changes in the microcirculatory domain of the CTO vessel were observed in terms of improved arteriolar dynamicity and decreased microvascular resistance.

Conclusion: Available evidence suggests that CTO revascularization leads to an immediate and long-term improvement in blood supply to downstream myocardium, mediated in part by a favorable time-dependent shift in epicardial vessel, collateral, and microcirculatory function.

Introduction

Chronic total occlusion (CTO) is defined as a complete obstruction of a native coronary artery that has persisted for ≥3 months.[1] Patients with a CTO often develop collateral circulation, which may provide sufficient blood flow to the affected myocardium and potentially prevent myocardial necrosis.[2] Many CTO patients present with multivessel disease, which may lead to coronary steal, especially during hyperemia, which may be related to anginal relief after CTO percutaneous coronary intervention (PCI).[3,4]

Generally, determining the necessity for coronary revascularization should not rely solely on visual estimation with coronary angiography, but it can be enhanced by intracoronary physiology evaluation.[5] Post-PCI physiology assessment also provides important prognostic value.[6] Given the high risk of CTO PCI, a thorough comprehension of changes in coronary physiology becomes of utmost importance to properly select patients as well as obtain prognostic information.

In contrast to pathophysiological animal models published in the 1930s by Mautz and Gregg[2] and Tennant and Wiggers,[7] recent in vivo studies have generated data aimed at comprehending the coronary physiology of CTO lesions. Some unresolved questions persist in this context, particularly concerning the hemodynamic assessment of intermediate stenoses at the level of the donor artery vessel, which may undergo significant changes after a CTO recanalization. Additionally, the hemodynamic improvement involving both the epicardial and microvascular domains after such procedures prompts inquiries needing

Abbreviations: CFVR, coronary flow velocity reserve; CTO, chronic total occlusion; FFR_{coll}, fractional flow reserve collateral; FFR_{cor}, fractional flow reserve coronary; FFR_{myo}, fractional flow reserve myocardium; MD, mean difference; PCI, percutaneous coronary intervention; SMD, standardized mean difference; μFR, Murray-law based quantitative flow ratio.

Keywords: chronic total occlusion; fractional flow reserve; intracoronary physiology; microcirculation; percutaneous coronary intervention.

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further robust confirmation from available data. Considering these uncertainties and the pressing need for evidence-based guidance, we aimed to perform a systematic review and meta-analysis to investigate the changes in intravascular coronary physiology after CTO PCI, focusing on both immediate changes after recanalization and during follow-up.

Methods

This systematic review and meta-analysis was carried out in accordance with the guidelines from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[8] and was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42023489631).

Eligibility criteria

The PICOS framework[9] was used in developing the literature search strategy: population (P), patients with a CTO; intervention (I), CTO revascularization with PCI and had intracoronary physiology measurements performed; comparator (C), none; outcome (O), differences in the intracoronary physiology indices before and after PCI and/or at the follow-up (>24 hours) in the donor and/or CTO vessel; study type (S), prospective and retrospective cohort or cross-sectional studies and case series. Studies were excluded for the following reasons: (1) written in another language than English, (2) included pediatric patients, (3) did not report data on intracoronary physiology indices, (4) physiology measurements were not repeated (before-after revascularization or after revascularization and at the follow-up), and (5) case reports.

Data sources and searches

A systematic literature search using PubMed/MEDLINE and Embase was made from the inception to May 19, 2024. A combination of terms related to CTO revascularization and intracoronary physiology indices were used. The full search strategy is available in Supplemental Table S1. Study abstracts were screened for established inclusion and exclusion criteria. Studies believed to be relevant to our search were

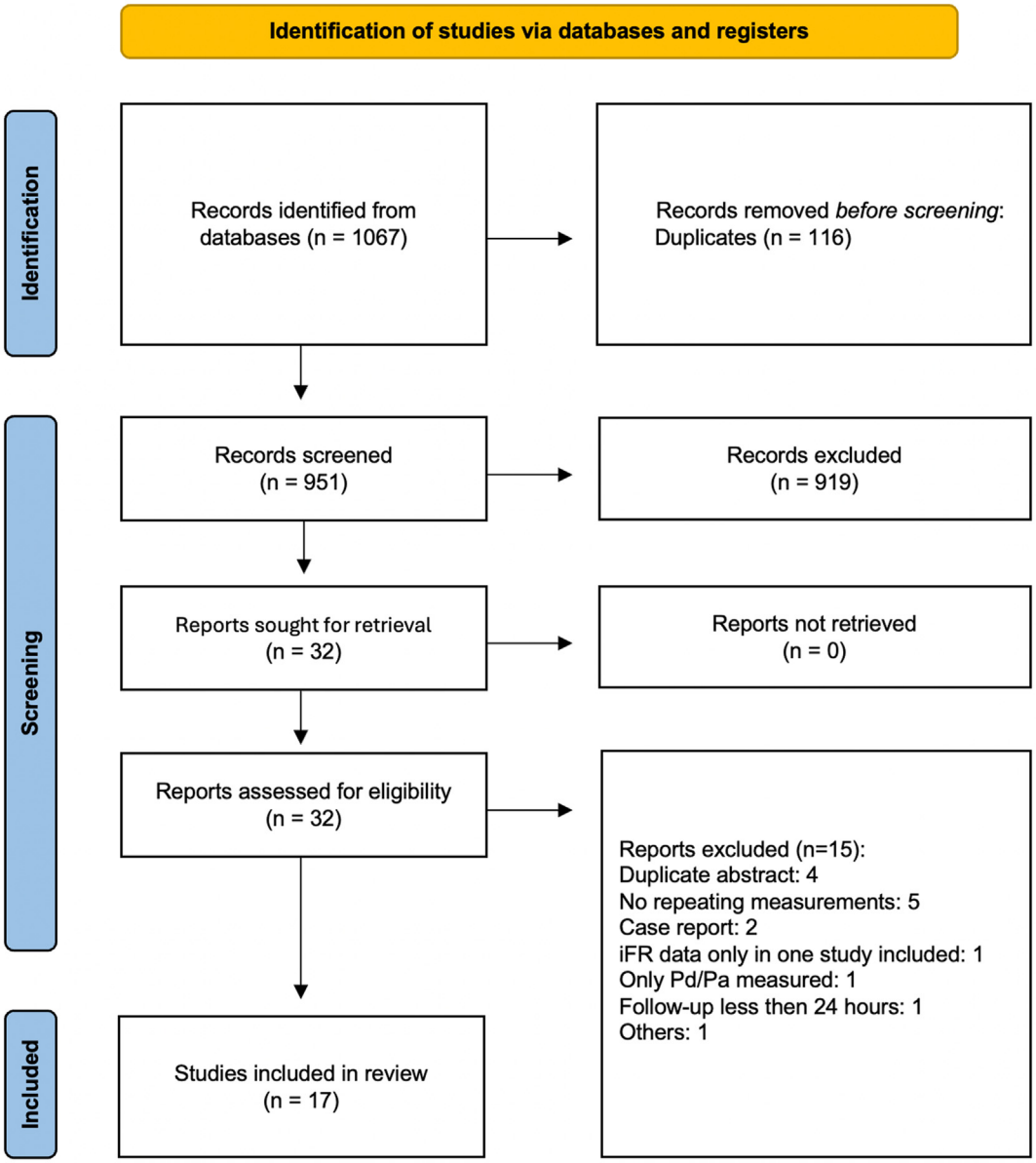


Figure 1.
PRISMA flow diagram.

Table 1. Overview of physiological indices investigated.

Study	Year	N	FFRmyo		FFRcor		FFRcoll		Absolute flow		Collateral flow		Coronary flow reserve		CFRcoll		Resistance	
			BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
Donor vessel																		
Sachdeva et al[26]	2013	50	X															
Ladwiniec et al[24]	2015	34	X						X				X				X	
Sumiyoshi et al[23]	2015	19	X						X									
Mohdnazri et al[20]	2018	28	X	X														
Keulards et al[18]	2020	25							X	X							X	X
Tian et al[19]	2021	45	X															
CTO vessel																		
Werner et al[28]	2001	50					X										X	
Pohl et al[32]	2001	27					X											
Werner et al[29]	2002	49		X										X				
Werner et al[30]	2004	104		X										X				
Zimarino et al[27]	2006	42	X		X		X											
Perera et al[31]	2007	7					X	X										
Sachdeva et al[26]	2013	50	X															
Ladwiniec et al[24]	2015	32														X		
Lee et al[22]	2017	74	X	X	X	X	X	X										
Karamasis et al[21]	2018	25		X		X	X	X										
Mohdnazri et al[20]	2018	28					X	X										
Keulards et al[18]	2020	25								X								X
Keulards et al[17]	2022	81		X		X		X		X		X						
Khan et al[16]	2023	81		X						X								X

BL, baseline; CFRcoll, coronary flow reserve collateral; FFRcoll, fractional flow collateral; FFRcor, fractional flow reserve coronary; FFRmyo, fractional flow reserve myocardium; FU, follow-up.

downloaded and the full manuscripts reviewed. The reference list of each selected article was checked to screen for additionally potentially relevant studies (backward snowballing method).

Data extraction and quality assessment

The reference lists from the 2 databases were merged and the duplicates removed using the reference management software Rayyan.[10] Two investigators (M.L. and E.N.H.) independently reviewed study titles, abstracts, and articles. Those that satisfied the inclusion and exclusion criteria were retrieved for full-text evaluation. When appropriate, full texts of relevant articles underwent subsequent evaluation for eligibility. Discrepancies regarding data incorporation to the database were resolved through consensus among the authors. Titles and abstracts of unresolved papers were screened. Risk of bias and study quality was assessed independently by 2 separate investigators (M.L. and E.N.H.) according to the National Institutes of Health quality assessment tool for before-after (pre-post) studies with no control group.[11]

The primary end point of interest was the difference between fractional flow reserve myocardium (FFR_{myo}) of the primary donor vessel before and after CTO revascularization. Secondary outcomes included FFR_{myo} of the CTO vessel and other intracoronary physiological indices calculated at the level of the major donor vessel and/or the CTO vessel, including FFR collateral (FFR_{coll}), FFR coronary (FFR_{cor}), absolute coronary blood flow, coronary flow velocity reserve (CFVR), and microvascular resistance before and after CTO revascularization and/or at the follow-up, according to the availability of the data.

Data synthesis and analysis

We performed a series of 1-group (pre-post CTO revascularization and post-CTO revascularization and follow-up) meta-analyses using a pre- and post-means model, sample size, and *P* values (paired groups). The mean difference (MD) was calculated as a measure of effect size to compare continuous variables. The standardized mean difference (SMD) was calculated when the included studies assessed the same outcome but measured with different modalities (ie, Doppler velocity vs thermodilution techniques). In contrast to unstandardized MDs, and as pointed out in the Cochrane Handbook, the SMD expresses the difference between 2 groups in SD units and was estimated using Hedges' g, a measure that corrects for bias due to small sample sizes.[12] As extensively reported in the literature, SMD can be treated as equivalent to a *z*-score of a standard normal distribution.[13,14]

Raw effect size data were pooled using the "metacont" function in R software comparing between group MD and/or SMD, as appropriate, and presented as pooled estimates with 95% CIs using forest plots for each outcome of interest. A fixed-effect model was applied in the presence of a low level of heterogeneity ($I^2 < 25\%$), assuming that all studies came from a common population.[12]. A P value $< .05$ was considered statistically significant without adjustment for type I error of multiplicity. The maximum-likelihood estimator was used to estimate the between-study variance (τ^2). For the random effects model, Knapp-Hartung adjustment was used.[15] Sensitivity analyses were conducted comparing random and fixed (or common) effect models along with leave-one-out analysis to detect sources of significant heterogeneity. Meta-regression was performed to explore the relationship between the diameter stenosis and the MD change in FFR_{myo} of the donor vessel after CTO revascularization. Analysis of publication bias was performed by visual inspection of the funnel plot. All analyses were performed with the R statistical software version 4.2.1 (R Project for Statistical Computing) using the R packages "meta" and "metareg."

Results

The PRISMA flowchart is shown in Figure 1 and Supplemental Table S2. In total, 1067 eligible papers were retrieved from the preliminary search of the electronic databases. After automatic removal of duplicates and screening of both titles and abstracts, 32 full-text articles were assessed for eligibility. Eventually, 17 articles were included in the qualitative analysis.[16–32] Table 1[16–24,26–32] presents an overview of the physiology indices explored in the studies included, and Table 2[16–24,26–32] summarizes the key baseline features of the included studies. An overview of calculation methods can be found in Supplemental Table S3. In the data synthesis, 14 prospective and 1

Table 2. Study overview

Author	Year	Type	N	Follow-up	Age	Male	Hypertension	Smoking	Diabetes	Dyslipidemia	Previous MI	Previous PCI	LVEF	CTO RCA	Donor LAD
Werner[28]	2001	P	50	NA	63.1 ± 10.7	90	70	44	28	76	66	NA	57.5 ± 14.3	50	NA
Pohl et al[32]	2001	R	27	NA	62 ± 9	85	33	41	30	44	NA	NA	64 ± 10	19	NA
Werner et al[29]	2002	P	56	5.3 ± 1.5	63.4 ± 10.4	91	71	45	32	77	64	NA	64.1 ± 14.4	NA	NA
Werner et al[30]	2004	P	98	5.0 ± 1.2	63.4 ± 10.1	NA	77.9	NA	29.7	NA	66.4	NA	60 ± 0.19	NA	NA
Zimarino et al[27]	2006	P	42	NA	62 (45-78)	86	52	60	21	55	67	17	51 (31-65)	38.1	NA
Perera et al[31]	2007	P	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sachdeva et al[26]	2013	P	14	NA	62 ± 8.5	100	100	64	36	86	29	50	45 ± 15.7	71.4	93
Sachdeva et al[26]	2013	P	50	NA	63.8 ± 8.9	98	90	48	50	84	38	48	48.5 ± 13.5	36	NA
Ladwiniec et al[24]	2015	P	34	NA	60.8 ± 9.6	79.4	17.6	45	14.7	NA	29.4	26.5	56.2 ± 11	61.7	28.2
Sumiyoshi et al[23]	2015	P	19	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lee et al[22]	2017	P	74	12	59 ± 11	83.8	50	51.4	33.8	36.5	NA	NA	51.6 ± 12.7	35.1	NA
Mohdnazri et al[20]	2018	P	34	4 ± 1.2	61.8 ± 10.5	88	64.7	20.6	26.5	70.6	61.7	41.2	51.3 ± 19.6	100	88
Karamasis et al[21]	2018	P	26	3.6 ± 1.2	61.2 ± 9.7	88.5	61.5	19.2	19.2	73.1	61.5	38.5	49.2 ± 20.9	1	NA
Keulards et al[18]	2020	P	25	2 ± 1.5	66.0 ± 8.7	76	80	16	28	54.3	48	NA	NA	80	17
Tian et al[19]	2021	NA	45	NA	59.4 ± 7.3	82.2	NA	60	42.2	NA	55.6	NA	57 ± 0.08	0	0
Keulards et al[17]	2022	P	81	2.8 ± 1.2	64 ± 9.3	81.5	70.4	14.8	19.8	87.7	50.6	40.7	54 ± 10	65.4	61.7
Khan et al[16]	2023	P	81	2.5 (2.0-3.2)	63.6 ± 8.9	81.5	70.4	14.8	19.8	87.7	50.6	NA	55 ± 11	65	62

Values are mean ± SD, median (IQR), or percentage.
CTO, chronic total occlusion; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; P, prospective; PCI, percutaneous coronary intervention; R, retrospective; RCA, right coronary artery.

retrospective peer-reviewed papers, as well as 1 conference abstract, were included. In 1 paper, it could not be determined if the analysis was retrospective or prospective. The National Institutes of Health risk of bias assessment showed a generally moderate quality of included studies with an overall median score of 8 (IQR, 6.5-8), with one of the included studies having a low quality (Supplemental Table S4).

Donor vessel artery

Overall, 6 studies reported intracoronary physiology performed in the donor artery. All included studies provided repeated measurements of the same physiological indices before and immediately after CTO revascularization. Statistical inconsistency and heterogeneity were not significant among the end points of interest at the level of the donor artery ($I^2 < 25\%$). FFR_{myo} (n = 146) significantly increased after CTO revascularization (MD, 0.04; 95% CI, 0.02-0.06; $P < .01$) (Figure 2A). There was insufficient evidence to conclude a linear association between the pooled MD FFR in the donor vessel and the percentage diameter stenosis at the quantitative coronary angiography by meta-regression ($P = .87$) (Supplemental Figure S1). A decrease in absolute coronary blood flow after CTO revascularization (n = 63) was observed, but this was not statistically significant (SMD, −0.28; 95% CI, −0.64 to 0.07; $P = .11$). An increase in microvascular resistance (n = 44) was observed after CTO revascularization (SMD, 0.44; 95% CI, 0.01-0.86; $P = .04$) (Figure 2B, C). No publication bias affected the analyses (Supplemental Figure S2).

CTO vessel

Overall, 14 studies reported information regarding intracoronary physiology performed in the CTO vessel. Indices and time points can be observed in Table 1.[16–24,26–32] An immediate increase in FFR_{myo} (n = 166) before and after CTO revascularization was found (MD, 0.45; 95% CI, 0.27-0.64; $P < .01$) (Figure 3A1). However, a high degree of heterogeneity was noted ($I^2 = 95\%$; $P < .01$), with visual asymmetry in the funnel plot (Supplemental Figure S3). At follow-up, an increase in FFR_{myo} (n = 262) of MD 0.02 was observed, although it was not statistically significant in the random effects model analysis (Figure 3A2) (MD, 0.02; 95% CI, −0.01 to 0.06; $P = .12$; $I^2 = 35\%$).

FFR_{coll} (n = 256) showed a no statistically significant decrease after CTO revascularization (MD, −0.03; 95% CI, −0.10 to 0.03; $P = .25$; $I^2 = 86\%$) (Figure 3B1). At follow-up, FFR_{coll} (n = 215) significantly decreased with an MD of −0.16 (95% CI, −0.18 to −0.15; $P < .01$, $I^2 = 6\%$) (Figure 3B2).

FFR_{cor} (n = 181) showed an increase at follow-up with an MD of 0.09 (95% CI, −0.01 to 0.20; $P = .06$; $I^2 = 50\%$) (Figure 3C).

Finally, the physiological indices of the coronary microcirculation showed a significant increase in absolute coronary blood flow (n = 187; MD, 53.2 mL/min; 95% CI, 40.3-66.1; $P < .01$; $I^2 = 0\%$) and CFVR (n = 160; MD, 0.46; 95% CI, 0.31-0.61; $P < .01$; $I^2 = 0\%$) between the CTO procedure and follow-up (Figure 4A, B). Conversely, microvascular resistance decreased at the follow-up (n = 106; fixed effects model: MD, −94.3 Wood units; 95% CI, −137.6 to −50.9; $P < .01$; random effects model: MD, −102.6; 95% CI, −521.5 to 316.3; $P = .19$; intermediate heterogeneity, $I^2 = 32\%$) (Figure 4C).

No publication bias affected the analyses, except for visual asymmetry for FFR_{myo} at baseline and FFR_{coll} at baseline and follow-up (Supplemental Figure S2).

Discussion

The intricate changes in coronary circulation resulting from the gradual occlusion of native coronary arteries was meticulously explored in pioneering experimental animal models performed in dogs by Mautz

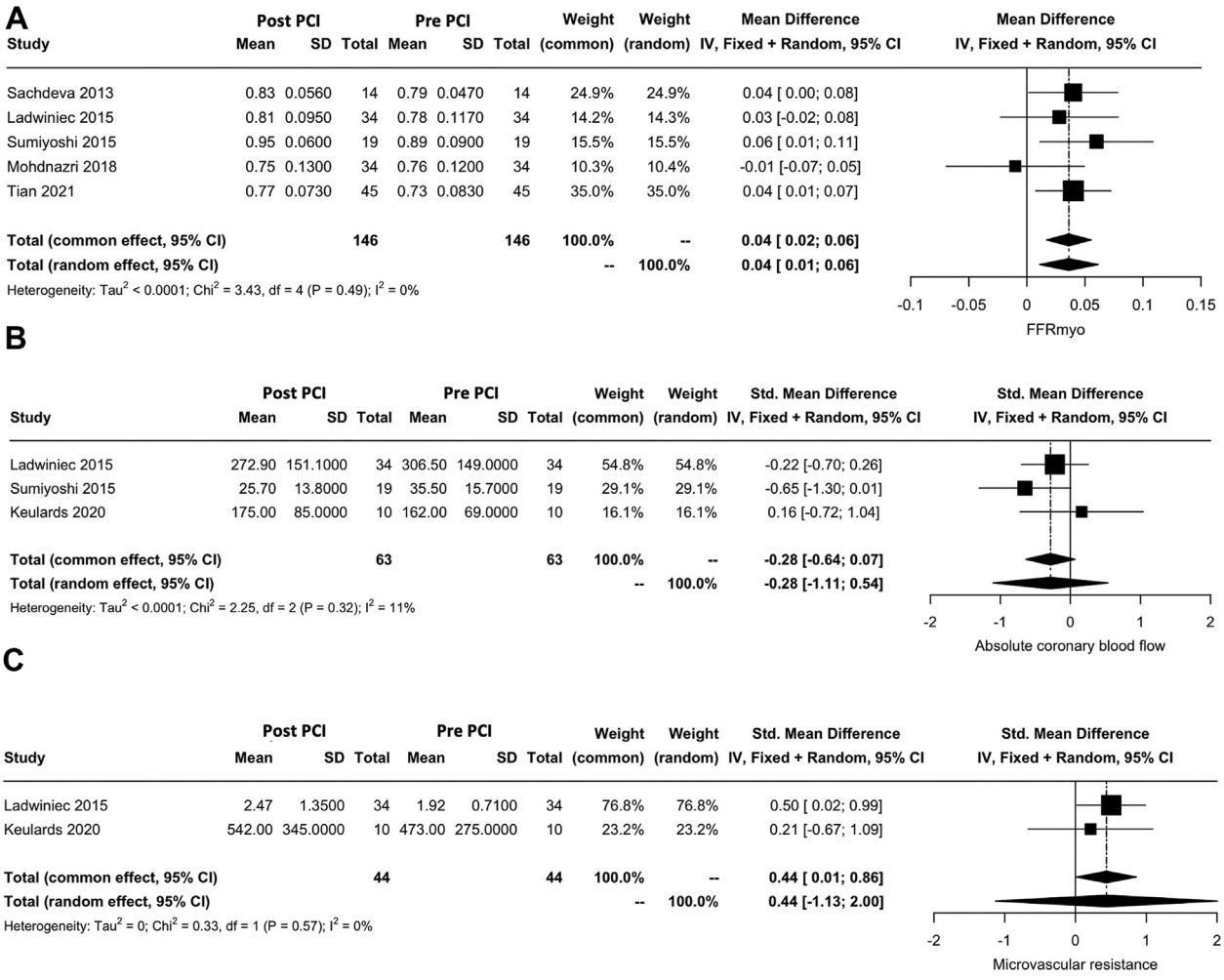


Figure 2.
Physiological changes in the donor vessel. Changes in physiological indices measured before and immediately after PCI of the CTO vessel. (A) FFR_{myo}. (B) Coronary blood flow. (C) Microvascular resistance. CTO, chronic total occlusion; FFR_{myo}, fractional flow reserve myocardium; IV, instrumental variables; PCI, percutaneous coronary intervention.

and Gregg[2] in 1937 and Schaper et al[33] in 1967.[7,34] With the advent of sensor fitted intracoronary guide wires, the journey into the physiology of occluded coronary vessels advanced with in vivo observations into the less-explored realm of CTO recanalization. Surprisingly, despite the wealth of knowledge gained from animal models, physiological changes triggered by restoration of antegrade flow with PCI received minimal attention until the studies performed by Werner et al at the beginning of this century,[29,30,35,36] subsequently complemented by the work of many researchers using increasingly sophisticated means. Based on those studies, and using a meta-analytical approach, we aimed to characterize in vivo the hemodynamic shift in the coronary circulation triggered by CTO recanalization, not only bridging the gap in knowledge from animal models to humans but also obtaining relevant information for the interpretation of currently used intracoronary diagnostic tools.

First, we documented an acute improvement in donor vessel myocardial blood flow (FFR_{myo}) after revascularization in patients with intermediate stenosis that was not dependent on diameter stenosis. Second, an acute improvement in myocardial blood flow (FFR_{myo}) in the CTO vessel was observed. Third, a shift in collateral circulation was documented in the CTO vessel at long-term follow-up due to an improvement in the epicardial flow (FFR_{cor}) and a decrease in the collateral flow (FFR_{coll}). Finally, improvement in the microcirculatory domain was observed with increased arteriolar dynamicity and decreased microvascular resistance. We also found that physiological changes in the coronary circulation caused by CTO lesions may be reversible and are time dependent (Central Illustration). All the described changes in coronary physiology are likely to be the result of processes including arteriogenesis, restoration of vasomotion, and vascular remodeling, which have been demonstrated in animal studies exploring these phenomena.

Effect of CTO revascularization on the collateral donor vessel

The observed acute changes in the donor vessel may be explained by physiological alterations in the CTO vessel and disappearance of the coronary steal phenomena.[34,36] FFR_{myo} in the CTO vessel improved immediately after recanalization due to an increase in the distal pressure. From a practical perspective, this implies that functional assessment of stenoses in the context of multivessel disease must consider the impact of CTO revascularization on the functional relevance of a remote stenosis, provided it is in a vessel providing collateral support. The magnitude of this phenomenon (a mean increase of 0.04 FFR_{myo} units after CTO recanalization) may trigger a change in functional relevance classification of stenoses with FFR values near the 0.80 cutoff value.

We also documented that CTO revascularization was associated with an increased resistance in the donor vessel, although this should

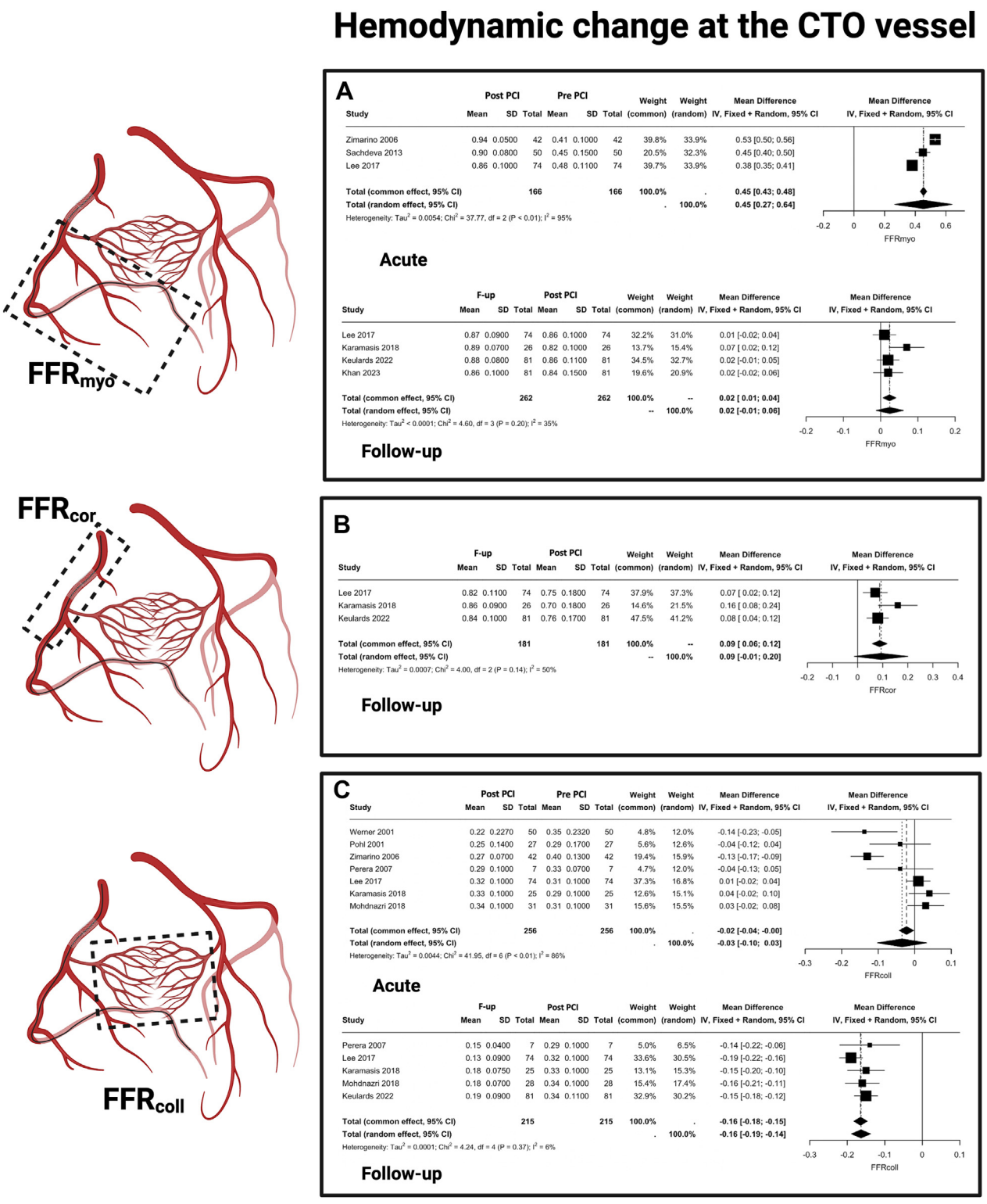


Figure 3.
Changes in fractional flow reserve derived indices in the CTO vessel. Changes from pre- to post-PCI in FFR_{myo} (A1) and FFR_{coll} (C1). Changes from post-PCI to follow-up in FFR_{myo} (A2), FFR_{cor} (B), and FFR_{coll} (C2). CTO, chronic total occlusion; FFR_{coll}, fractional flow reserve collateral; FFR_{myo}, fractional flow reserve myocardium; F-up; follow-up; IV, instrumental variables; PCI, percutaneous coronary intervention.

not be interpreted as an unfavorable consequence of the intervention. It is probably a consequence of a drastic reduction of the myocardial mass dependent on its blood supply, once part of it becomes perfused by the recanalized CTO vessel, and not due to the onset of microcirculatory changes downstream of the collateral donor artery.

CTO vessel and subtended microvascular function

Our meta-analysis reveals a substantial time-dependent reduction in collateral support to the occluded vessel, calculated as FFR_{coll}, once the CTO is recanalized. Most likely this is mainly due to a gradual onset of

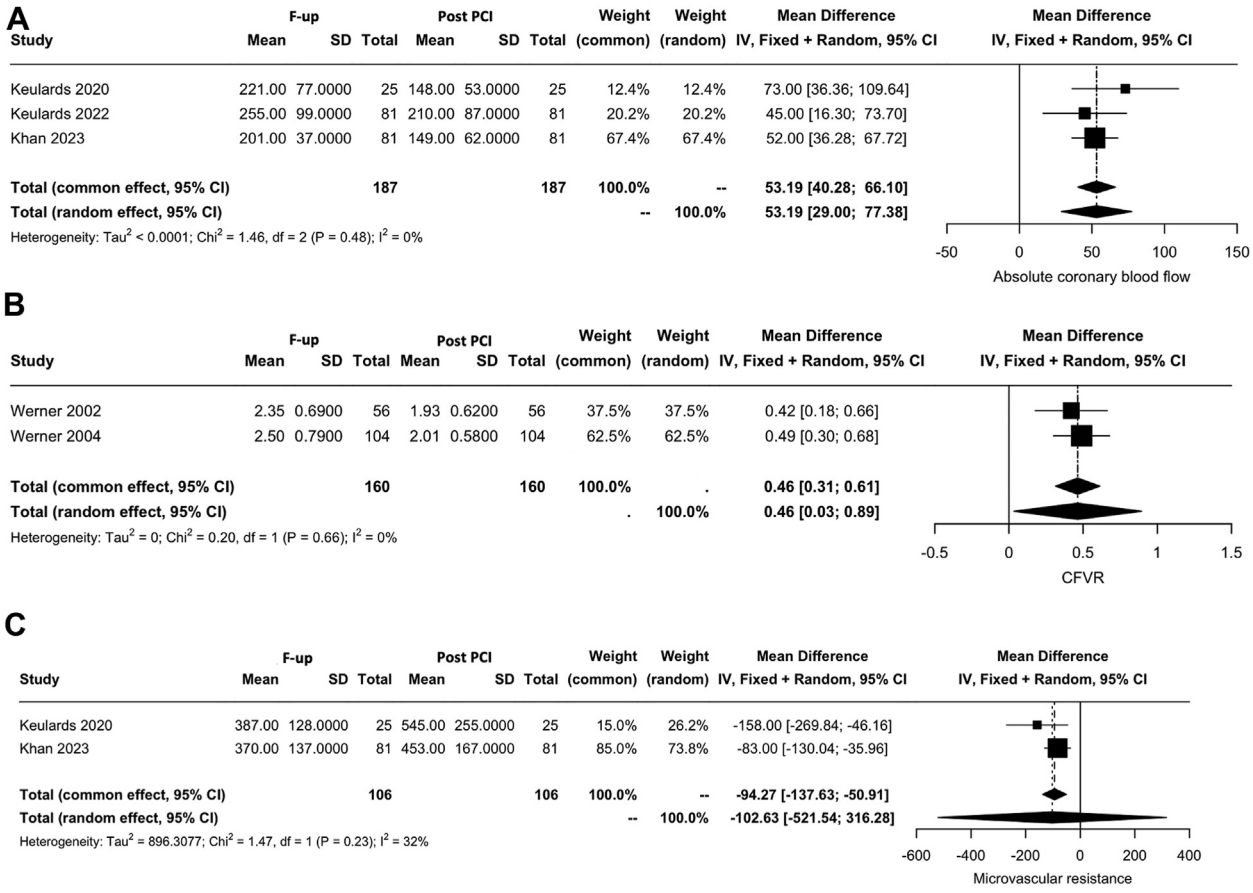


Figure 4.
Changes in microcirculatory domain indices in the CTO vessel. Changes in coronary blood flow (A), CFVR (B), and microvascular resistance (C). CFVR, coronary flow velocity reserve; CTO, chronic total occlusion; F-up, follow-up; IV, instrumental variables.

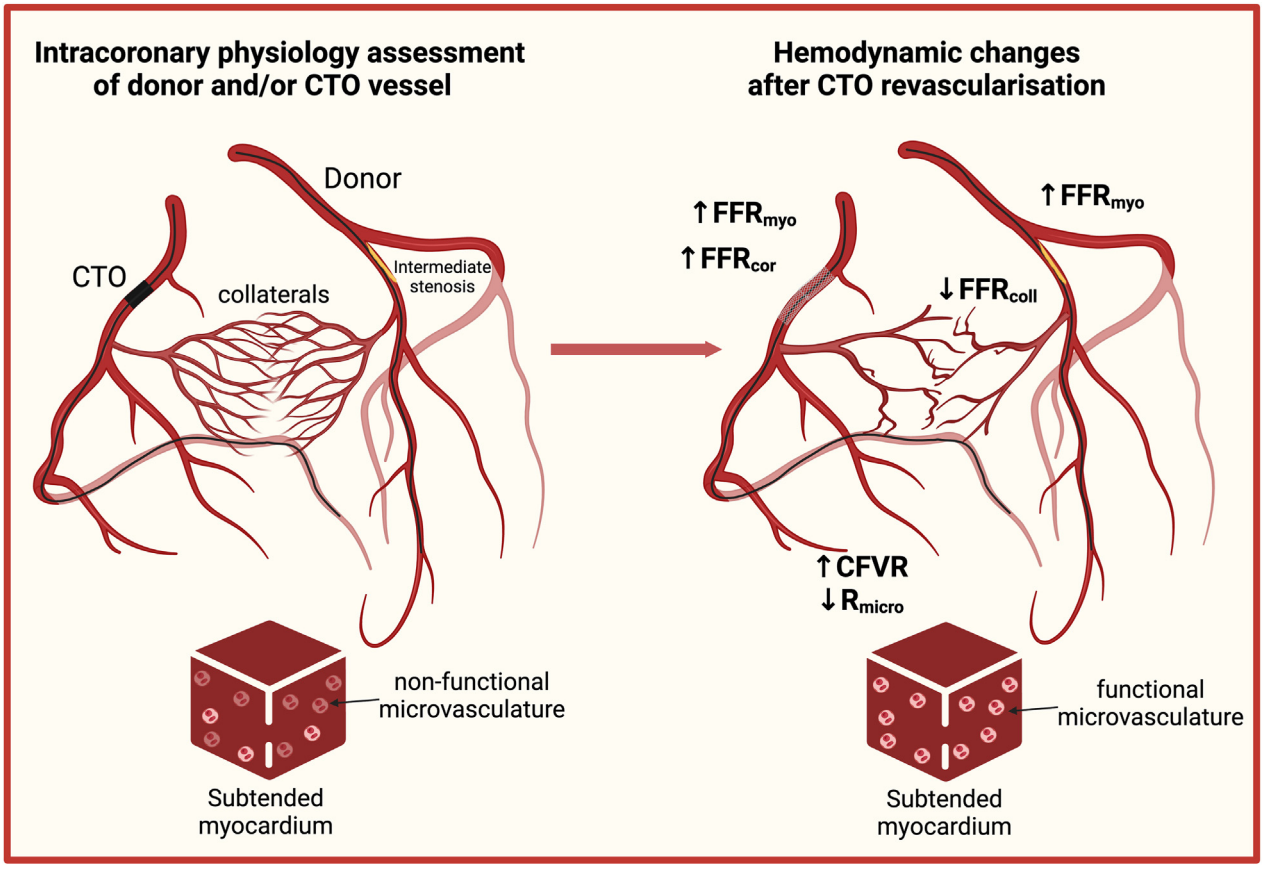
negative remodeling of collateral vessels,[21] although time-dependent improvement in the conductance of the epicardial vessel may also contribute. Overall, our study indicates that positive remodeling of the CTO vessel may be related to an increase in perfusion pressure and shear stress, which has also been confirmed in animal studies.[37,38] On the other hand, negative remodeling of the collateral circulation may be explained by the same mechanism as the acute adaptions, which is a decrease in shear stress due to normalization of the pressure gradient over the collateral vascular bed and thereby less growth factor stimuli.[39–41]

Another contributing factor to the positive remodeling may be a restoration of endothelial function. Brugaletta et al[42] observed in vivo that the coronary segment distal to a successfully recanalized CTO vessel immediately exhibits endothelial and smooth muscle cell dysfunction post-PCI, particularly in patients with suboptimal collateral support as judged from an angiographic standpoint. Putative mechanisms for endothelial dysfunction in this context may include chronic ischemia and absence of laminar flow, both caused by vessel occlusion. Relief of ischemia and restoration of antegrade flow might lead to normalization of endothelial function, which might contribute, through flow-mediated mechanisms, to positive epicardial vessel remodeling with increase in distal vessel diameter in the long term and to normalization of arteriolar function.[43] These assumptions align with the main findings of this meta-analysis, where a substantial improvement in microcirculatory physiological indices, such as an increase in absolute coronary blood flow and CFVR along with a reduction in microcirculatory resistance, were evident after successful CTO recanalization and angiographic follow-up.

The abovementioned changes in microvascular structure and function may provide clues regarding the effects of CTO revascularization on cardiac performance. Many patients with CTO present hibernating myocardium because of combined severe obstructive ischemia and collateral flow.[44] In the context of hibernating myocardium, a time lag between restoration of blood supply with revascularization and recovery of myocardial function has been consistently reported.[45] Our meta-analysis supports the existence of a time-dependent increase in myocardial blood flow after CTO revascularization, which might explain the temporal dissociation between myocardial revascularization and function. While some studies have reported an overall low to modest left ventricular ejection fraction improvement after CTO revascularization,[46–48] others have highlighted that such improvement can be detected in cases with large areas of the myocardium downstream the CTO.[49] The increased myocardial blood flow and reduction in reversible ischemia during stress may also be clinically related to the documented improvement in symptoms after CTO PCI.[50,51]

Based on angiographic evidence only, the results of previous studies cast doubts as to the presence of collateral vessels after CTO revascularization, suggesting that the disappearance of this protective mechanism might jeopardize the subtended myocardium should a new vessel occlusion occur.[52] Our analysis challenges this concern by showing that, after CTO revascularization, collateral circulation remains present in the long term as judged from FFR_{coll} values, which decrease but do not vanish at follow-up.

The observations made in our study extend also to the findings with functional coronary angiography methods to assess functional stenosis relevance,[53] increasingly used due to the advantage of mimicking FFR without the necessity to use pressure guide wires, use of hyperemic



Central Illustration.

Hemodynamic changes of CTO revascularization. CTO, chronic total occlusion. CTO revascularization leads to an immediate and long-term improvement in blood supply to subtended myocardium. This improvement is mediated in part by favorable, time-dependent shift in epicardial vessel, collateral and microvasculature function. The presence of functional and non-functional microvasculature within the subtended myocardium at different timepoints is also represented. CFVR, coronary flow velocity reserve; CTO, chronic total occlusion; FFR_{coll}, fractional flow reserve collateral; FFR_{cor}, fractional flow reserve coronary; FFR_{myo}, fractional flow reserve myocardium; PCI, percutaneous coronary intervention; R_{micro}, microvascular resistance.

agents, and the possibility to perform offline evaluations without exacerbating an already time-consuming procedure.[53,54] In line with the findings from HAWKEYE for non-CTO PCI, it has been observed that post-PCI Murray-law based quantitative flow ratio (μFR) has a prognostic role in patients with CTO. A post-CTO PCI μFR < 0.92 is associated with target lesion failure.[55,56] On the other hand, μFR was observed to overestimate FFR_{myo} immediately after CTO PCI (μFR, 0.93; 95% CI, 0.88-0.96; FFR, 0.83; 95% CI, 0.75-0.89), which could be related to the changes in the microvasculature found in our analysis.[57] Therefore, image-based physiology, both quantitative flow ratio and μFR, should also include image-based assessment of the microcirculation to facilitate the assessment of microcirculatory status,[58] although further larger and prospective studies are currently lacking in the CTO setting.

Other unanswered questions warranting further discussion are still under investigation. First, it is of crucial importance to elucidate the evolution of physiological indices within the donor vessel, evaluating its propensity to remain nonischemic—an inquiry currently being addressed in a substudy of the ISCHEMIA-CTO trial.[59] Second, another open question concerns the association between favorable physiology changes and symptom improvement. The IMPACT-CTO II study aims to investigate the correlation between modifications in physiological indices, increased exercise capacity, and improvement in anginal symptoms (NCT03830853). Finally, there is a pressing need for adequately powered outcome studies to evaluate whether changes in physiological indices may translate into a consequential improvement in prognosis after CTO PCI.

Limitations

The number of studies and observations included in this meta-analysis is relatively small, which may limit the power to detect certain differences, despite our comprehensive approach. Although meta-regression should generally not be considered when there are <10 studies in a meta-analysis, we performed it to assess whether FFR_{myo} of the donor vessel artery might change according to the different diameter stenosis. This result should be considered only as hypothesis-generating and not as hypothesis-testing. Due to the limited number of studies available for each outcome, we did not apply Egger's test to assess publication bias because the small number of studies per outcome would not yield reliable results. We also included studies in which investigators reported data in terms of median and IQR, transforming these data into mean and SD assuming normal distribution. Lee et al[22] did not provide information on the number of patients with CTO for whom physiological measures were repeated. Consequently, we reported the baseline number of patients included, potentially leading to an overestimation of the weight of the results in cases in which the study was incorporated. It cannot be ruled out that there is an overlap in patients in Khan et al[16] in 2023 and Keulards et al[17] in 2022, and in the studies by Werner et al.[16,17,29,30,35]

Conclusion

The available evidence suggests that CTO revascularization leads to a twofold, immediate, and long-term improvement in blood supply to

downstream myocardium, mediated in part by a favorable time-dependent shift in epicardial vessel, collateral, and microcirculatory function. These findings call for further investigations in also assessing the changes of both donor vessel and CTO vessel physiology at follow-up, the potential impact of image-based physiology, and the prognostic value of intracoronary physiological evaluation in CTO patients.

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The central illustration and Figure 3 were created with BioRender platform and templates (license to Marco Lombardi).

Declaration of competing interest

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Ethics statement and patient consent

The authors retrieved and synthesized data from previously published studies; therefore, the study was deemed exempt from institutional review board approval and informed consent.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2024.102452.

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