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ORIGINAL PAPER

The association of collaterals with myocardial ischemia and viability in chronic total occlusions

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Abstract

Collateral development in chronic total occlusions (CTO) is crucial to perfuse the distal myocardium and its angiographic evaluation is frequently used to assess the need for revascularization. We aimed to analyse the association between the presence of ischemia and hibernating myocardium, evaluated by cardiac [^{13} N]NH3/2-[^{18} F]FDG PET-CT, and the angiographic characterization of the collateral circulation. Prospective study including patients with a CTO who underwent a [^{13} N]NH3 and, when deemed necessary, 2-[^{18} F]FDG PET-CT. Well developed (WD) collaterals were defined as a concomitant angiographic Rentrop grade 3 and Werner collateral connection score 2 or 3, whereas the remaining as poorly developed (PD). 2% thresholds used to identify prognostic benefit of revascularization were applied: ischemia > 10% and hibernating myocardium > 7%. Fifty-nine patients (age 62.9±9.1 years, 58 male) were recruited, WD collaterals were present in 28 (47.5%). No significant differences were found in ischemia (WD 6.4±4.3 vs. PD 7.0±4.1, p = 0.64) and hibernation (WD 1.8±1.9 vs. PD 3.1±3.3, p = 0.18) scores. Most CTO territories demonstrated ischemia, but only 19 (46.3%) were associated with an area > 10% (WD 47.6% vs. PD 45.0%, p = 0.58). Scared non-viable myocardium was limited to 9 (15.3%) patients and was not associated with PD collaterals. Hibernating myocardium was frequent (54.2%), but just 6 (10.2%) CTO patients had an area of > 7% (WD 3.6% vs. PD 16.1%, p = 0.20). Collateral assessment by angiography has a poor association with the ischemic burden and hibernation state of CTO territories. Myocardial viability was present even in most CTO with angiographic PD collaterals.

Keywords Chronic total occlusion · Collateral · PET-CT · Ischemia · Viability

List of abbreviations

CC	Collateral connection
CTO	Chronic total occlusions
CMR	Cardiac magnetic resonance
ICC	Intraclass correlation coefficient
LV	Left ventricular
MIPCI	Myocardial infarction percutaneous coronary intervention
PD	Poorly developed
PET-CT	Positron Emission Tomography-Computed Tomography
SRS	Summed rest score
SSS	Summed stress score
WD	Well developed.

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Introduction

Chronic coronary total occlusions (CTO) are identified in up to one third of patients referred for coronary angiography, although conclusive evidence about its optimal therapeutic approach is still lacking [1–3]. Until recently there was

reluctance in referring CTO patients to percutaneous coronary intervention (PCI) based on lower procedural success, higher complication rates, but also with the assumption that angiographically well-developed (WD) collateral arteries prevented myocardial ischemia. During the past decade, important developments in equipment and techniques have led to the achievement of high rates of procedural success [4]. Randomized clinical trials evaluating the benefit of CTO PCI in addition to medical therapy on patients' symptoms and prognosis have shown conflicting results [5, 6]. In the presence of a CTO, the collateral vessels development can prevent myocardial necrosis and maintain contractile function in the territory distal to the occlusion [7]. A WD collateral system could have the ability to perfuse, normally, the myocardium at rest, but during increased blood flow demand it may be insufficient to avoid ischemia [2]. Coronary angiography is the conventional tool to visualize and evaluate the collateral network flow, and frequently is used as an assumption of the myocardial ischemic burden and viability, leading to the decision of CTO revascularization. There are two main angiographic classification systems to estimate the effect of collaterals in filling the occluded arterial segment: Rentrop and Werner collateral connection [8]. Current guidelines recommend CTO revascularization in the presence of symptoms or large ischemia documentation, with the need to sought objective evidence of viability in cases of regional wall motion abnormalities [1]. Positron Emission Tomography – Computed Tomography (PET-CT) with [^{13} N]NH3/2-[^{18} F]FDG can assess both myocardial ischemia and viability with high accuracy, evaluating both epicardial stenosis and microvascular disease. The aim of this study was to analyse the association between the presence of ischemia and hibernating myocardium, as evaluated by cardiac [^{13} N]NH3/2-[^{18} F]FDG PET-CT, and the angiographic characterization of the collateral circulation.

Materials and methods

Patients presenting with a CTO and evaluated with ^{13}Nitrogen-Ammonia ([^{13} N]NH3) and, when deemed necessary, ^{18} F-Fluorodeoxyglucose (2-[^{18} F]FDG) PET-CT between 2018 and 2020 in a CTO PCI centre were prospectively recruited. Symptomatic as well as asymptomatic patients were included in this database. Exclusion criteria were patients with CTO in an epicardial coronary artery with a reference diameter of < 2.5 mm and with CTO lesions in more than one vessel. Data recorded for each subject included age, past medical history, namely prior myocardial infarction (MI) history and cardiovascular risk factors, and previous medication. This study complied with the ethical guidelines of the 1975 Declaration of Helsinki, all aspects gaining approval of the local ethics committee (CE-022/2018). Each subject granted written informed consent for participation.

A CTO was defined by a complete vessel occlusion with TIMI (Thrombolysis In Myocardial Infarction) 0 flow within the occluded segment and an estimated occlusion duration of at least three months. Collateral circulation was graded as previously described by the Rentrop classification (0 – No contrast filling of collaterals; 1 – Filling of collaterals without filling the epicardial vessel; 2 – Partial epicardial filling of CTO artery; 3 – Complete epicardial filling of the CTO artery) and by Werner classification of collateral connection (CC0 – No continuous connection; CC1 – Thread-like connection; CC2 – Side branch-like connection; CC3 – More than 1 mm diameter of direct connection) [8]. Well developed (WD) collaterals were defined as a concomitant Rentrop grade 3 and Werner collateral connection (CC) score 2 or 3, whereas poorly developed (PD) collaterals were characterized by lower Rentrop or CC scores. Angiographic characteristics were evaluated by two expert observers (LL and EJ), who were blinded to all data. Discrepancies were resolved by a third expert observer (MS).

[^{13} N]NH3 is a cyclotron produced radiotracer with a physical half-life of 9.96 min. The protocol included the acquisition of rest and stress images with the same administered dose of ammonia, 20.2mCi (± 1.9). Stress was performed using a vasodilator - regadenosone (single bolus administration). The two acquisitions were separated by at least one hour interval. A Gemini GXL Philips 16 PET-CT system was used. A low-dose CT scan comprising the heart was performed for attenuation correction (120kv and 10mA). Perfusion images were acquired immediately after the administration of an intravenous bolus of [^{13} N]NH3 for a total duration of 20 min. All the participants underwent the rest perfusion scan. The pharmacological stress perfusion study was executed in 41 (69.5%) patients, regarding the current guidelines' recommendation of CTO revascularization in the presence of large ischemia documentation [1]; the remaining patients had already information about ischemia (previous non-PET exam) and as 13 N-NH3 rest uptake was absent or severely reduced, the viability study was considered to be more clinically relevant than the stress perfusion scan.

2-[^{18} F]FDG is a glucose analogue, and its myocardial uptake reflects the aerobic and anaerobic glycolytic flux. Glucose utilization may be preserved or increased relative to flow in hypoperfused but viable (hibernating) myocardium. PET images using Gemini GXL Philips 16 PET-CT system were obtained after intravenous administration of 15.0 mCi (± 0.9) of 2-[^{18} F]FDG. An appropriate intravenous glucose loading and insulin injection protocol was used to ensure image quality and a low-dose CT scan comprising the heart

was performed for attenuation correction. Viability images were acquired 60 min after the intravenous administration of 2-[^{18} F]FDG and for a total duration of 20 min. The 2-[^{18} F]FDG scan was performed in all patients with perfusion defects on the rest [^{13} N]NH3 PET/CT (45 patients, 76.3%).

Due to the lower sensitivity of the available PET scanner, and to guarantee image quality, both administered activities and acquisition times were on the upper limit of the normal range. As such, average effective dose due to the injection of [13 N]NH3 and 2-[18 F]FDG, when warranted, was 8.7 mSv (± 5.0).

A 17-segment left ventricular (LV) model was used for interpretation of the PET-CT studies, and myocardial uptake was graded in each segment using a visual, semi-quantitative scale (0 = normal, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced, 4 = absent uptake). The Summed Stress Score (SSS) and the Summed Rest Score (SRS) were obtained by adding the individual segment scores from the CTO vascular territory on the stress and rest perfusion studies, respectively; the Ischemia Score (Summed Difference Score - SDS) was calculated as the difference between SSS and SRS. A similar score was calculated for the 2-[^{18} F]FDG PET, and the difference between the SRS and the FDG score was considered as the Hibernation Score. Myocardial [^{13} N]NH3 and 2-[^{18} F]FDG uptakes were separately scored by consensus visual analysis of two observers (MJF and RS) blinded to the rest of the patient data.

The perfusion/metabolism viability PET-CT patterns were assessed by comparison between the rest [^{13} N]NH3 perfusion and 2-[^{18} F]FDG scans: normal resting perfusion (SRS = 0, irrespective of the metabolism), hibernating (mismatch pattern with reduced perfusion but improved/preserved metabolism), and scared non-viable myocardium (matching pattern with reduced perfusion and reduced metabolism). As the aim of performing PET-CT is to identify which patients will have an improvement following revascularization, we divided the population according to the two current thresholds available to identify patients that could benefit more from it: percentage of ischemia > 10% [9] and/or > 7% of hibernating myocardium [10].

Normality of continuous variables was tested by histogram observation and Kolmogorov–Smirnov test. Continuous variables were expressed as mean values ± standard deviations and inter-group differences were compared using Student t-test. Categorical variables were presented as frequency (percentage) and intergroup differences were compared using Chi-square or Fisher's exact test. Intra- and inter-observer variability of Rentrop and Werner classification were assessed in all subjects, including intraclass correlation coefficients. One month later, evaluation was repeated by the same expert observer (LL) to gauge intra-observer reproducibility. Inter-observer reproducibility was addressed by a second expert observer (EJ). A P-value < 0.05 in two-tailed tests was considered statistically significant. Statistical analyses relied on standard software, specifically SPSS v20.0 (SPSS Inc, Chicago, IL, USA) and GraphPad Prism 9.3.1 (GraphPad Software Inc, La Jolla, CA, USA).

Results

A total of 59 patients (mean age 62.9 ± 9.1 years, 58 male) were included. Most patients were submitted to coronary angiography due to chronic coronary syndrome (39.0%), followed by heart failure study (32.2%) and in the setting of acute coronary syndrome / non-culprit vessel (28.8%). Angina symptoms were present in 33 (55.9%) patients. The most frequent CTO arteries were the left anterior descending artery (45.8%), and the right coronary artery (44.1%). Regarding Rentrop classification, 34 (57.6%) patients had "grade 3", 24 (40.7%) "grade 2" and 1 (1.7%) "grade 1". The distribution of the collaterals' Werner classification was 13 (22.0%) CC3, 27 (45.8%) CC2, 16 (27.1%) CC1, and 3 (5.1%) CC0. For the Rentrop classification, the intraclass correlation coefficient (ICC) for intra-observer agreement was 0.91 [95% CI: 0.87, 0.95] and for inter-observer agreement was 0.75 [95% CI: 0.63, 0.84]. The ICC for Werner classification was 0.96 [95% CI: 0.94, 0.98] and 0.82 [95% CI: 0.72, 0.89], for intra-observer and inter-observer agreement, respectively.

WD collaterals were present in 28 (47.5%) patients, PD collaterals in 31 (52.5%). Patient baseline clinical and angiographic characteristics are presented in Tables 1 and 2. An example of a coronary angiography and a [^{13} N]NH3/2-[^{18} F]FDG PET-CT of a CTO patient from our study is given in Fig. 1. There was no significant differences between WD and PD collateral CTO patients regarding age, comorbidities, and clinical presentation. Anticoagulant therapy, mainly due to atrial fibrillation, was more frequent in WD collaterals (25.0% vs. 6.5%, p = 0.04) and antiplatelet therapy in PD collaterals (74.2% vs. 46.4%, p = 0.04) patients. WD collaterals were more prevalent in right coronary artery CTOs (60.7% vs. 32.3%, p < 0.001).

Normal rest perfusion at CTO territory (SRS = 0) was observed in 18 (30.5%) patients, without significant differences regarding collateral angiographic classification (WD 35.7% vs. PD 25.8%, p = 0.41). No significant differences were found in terms of perfusion scores or ischemia concerning the angiographic classification of collaterals (Fig. 2), but PD collaterals CTO had a trend towards a slightly higher ischemia. The perfusion scores were not significantly different regarding presence of angina symptoms (SDS, p = 0.36; SSS, p = 0.68; SRS, p = 0.81). The majority

Table 1 Baseline clinical characteristics

	All patients (n = 59)	WD collaterals (n = 28)	PD collaterals (n = 31)	*p* value
Age	62.9 ± 9.1	61.2 ± 8.8	64.1 ± 9.2	0.23
Past medical history				
Hypertension	46 (78.0%)	21 (75.0%)	25 (80.6%)	0.60
Dyslipidemia	50 (84.7%)	23 (82,1%)	27 (87.1%)	0.72
Diabetes mellitus	28 (47.5%)	13 (46.4%)	15 (48.4%)	0.88
Insulin dependent	13 (22.0%)	4 (14.3%)	9 (29.0%)	0.22
Atrial fibrillation	8 (13.6%)	6 (21.4%)	2 (6.5%)	0.13
Chronic kidney disease	6 (10.2%)	1 (3.6%)	5 (16.1%)	0.20
Smoking history				
Current smoker	20 (33.9%)	12 (42.9%)	8 (25.8%)	0.17
Former smoker (> 1 year)	17 (28.8%)	9 (32.1%)	8 (25.8%)	0.59
Chronic obstructive pulmonary disease	8 (13.6%)	3 (10.7%)	5 (16.1%)	0.71
Clinical presentation				
Clinical setting at diagnosis:				0.23
Chronic coronary syndrome	23 (39.0%)	13 (46.4%)	10 (32.3%)	
Heart failure study	19 (32.2%)	6 (21.4%)	13 (41.9%)	
ACS (non-culpril vessel)	17 (28.8%)	9 (32.1%)	8 (25.8%)	
Angina symptoms	33 (55.9%)	17 (60.7%)	16 (51.6%)	0.48
Previous myocardial infarction	17 (29.3%)	6 (21.4%)	11 (36.7%)	0.20
Q-wave in CTO territory	22 (37.3%)	10 (45.5%)	12 (54.5%)	0.81
Previous CABG	3 (5.1%)	1 (3.6%)	2 (6.5%)	1.00
LVEF (%)	41.9 ± 15.1	43.3 ± 16.3	40.8 ± 14.1	0.55
Medication prior to CTO diagnosis				
Antiplatelets	36 (61.0%)	13 (46.4%)	23 (74.2%)	**0.04**
Anticoagulants	9 (15.3%)	7 (25.0%)	2 (6.5%)	**0.04**
Statins	47 (79.7%)	22 (78.9%)	25 (80.6%)	1.00
RAAS inhibitors	44 (74.6%)	19 (67.9%)	25 (80.6%)	0.37
Beta-blockers	41 (69.5%)	17 (60.7%)	24 (77.4%)	0.16
PET-CT imaging				
Resting [^{13} N]NH3 perfusion PET-CT	59 (100%)	28 (100%)	31 (100%)	-
Stress [^{13} N]NH3 perfusion PET-CT	41 (69.5%)	21 (75.0%)	20 (64.5%)	0.38
2-[^{18} F]FDG viability PET-CT	45 (76.3%)	19 (67.9%)	26 (83.9%)	0.22

ACS - Acute coronary syndrome; CABG - Coronary artery bypass graft; CTO – Chronic total occlusion; LVEF – Left ventricular ejection fraction; PD – Poorly developed; RAAS - Renin-angiotensin-aldosterone system; WD – Well developed

of patients (92.7%) who performed the stress perfusion scan had some degree of myocardial ischemia in the CTO territory. However, only 19 (46.3%) had an area of > 10% ischemia of the total myocardium, without differences between WD and PD collaterals (47.6% vs. 45.0%, p = 0.58).

The combination of rest [^{13} N]NH3 and 2-[^{18} F]FDG PET-CT allowed the categorization into three patterns: normal resting perfusion – 18 (30.5%) patients, hibernating myocardium – 32 (54.2%) patients, and scared non-viable myocardium – 9 (15.3%) patients. Therefore, there were 50 (84.7%) patients with viability in the CTO territory, without differences between WD and PD collaterals (82.1% vs. 87.1%, p = 0.60). No significant difference was found in the hibernation score regarding the angiographic classification of collaterals (Fig. 3), but PD collaterals CTO had a trend for a higher value of hibernating myocardium. The hibernation score was not significantly different if angina symptoms were present (p = 0.25). Regarding quantification of the hibernating myocardium, only six (10.2%) patients had a CTO that involved > 7% hibernating myocardium, without significant differences between WD and PD collaterals (3.6% vs. 16.1%, p = 0.20).

Associating ischemia and viability assessment, a total of 24 (40.7%) patients had > 10% ischemia and/or > 7% hibernating myocardium. No significant differences were shown between WD and PD collaterals in terms of this categorization of revascularization clinical benefit (39.3% vs. 41.9%, p = 0.84).

Table 2 Angiographic characteristics

	All patients (n = 59)	WD collaterals (n = 28)	PD collaterals (n = 31)	*p* value
Multivessel disease	24 (59.3%)	20 (71.4%)	15 (48.4%)	0.11
CTO vessel				
Left anterior descending artery	26 (44.1%)	9 (32.1%)	17 (54.8%)	0.08
Left circunflex artery	6 (10.2%)	2 (7.1%)	4 (12.9%)	0.67
Right coronary artery	27 (45.8%)	17 (60.7%)	10 (32.3%)	**0.03**
CTO characteristics				
J-CTO Score	1.4 ± 1.0	1.1 ± 1.0	1.6 ± 1.0	0.09
Blunt entry shape	25 (42.4%)	8 (28.6%)	17 (54.8%)	0.06
Calcification	25 (42.4%)	11 (39.3%)	14 (45.2%)	0.65
Bending > 45 degrees	3 (5.1%)	2 (7.1%)	1 (3.2%)	0.49
Occlusion length ≥ 20 mm	28 (47.5%)	10 (35.7%)	18 (58.1%)	0.12
Re-try lesion	0 (0%)	0 (0%)	0 (0%)	-
Ostial location	9 (15.3%)	3 (10.7%)	6 (19.4%)	0.36
Intra-stent	12 (20.3%)	3 (10.7%)	9 (29.0%)	0.08

CTO – Chronic total occlusion; PD – Poorly developed; WD – Well developed

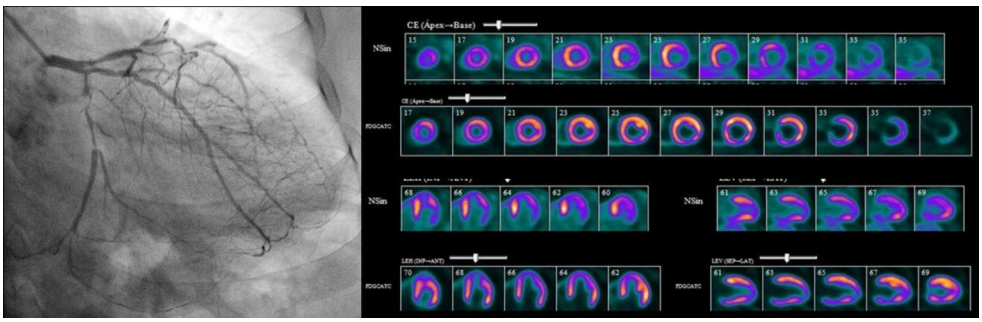

Fig. 1 A 72-year-old male patient with multivessel disease including a left descending artery CTO with WD collaterals, presenting viability at anterolateral walls by [13 N]NH3/2-[18 F]FDG PET-CT assessment CTO – Chronic total occlusion; WD – Well developed; PET-CT - Positron Emission Tomography – Computed Tomography

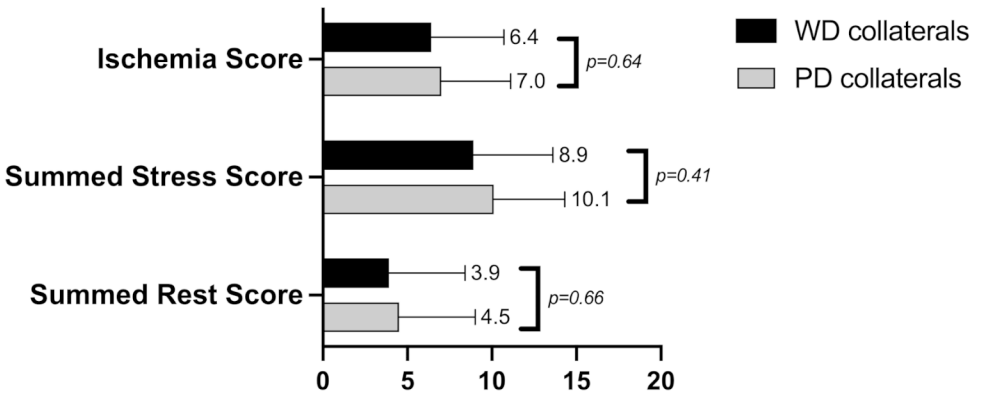

Fig. 2 Comparison of the Ischemia score (SDS), SSS and SRS in the CTO territory, between WD and PD collaterals PD – Poorly developed; SDS - Summed Difference Score; SSS - Summed Stress Score; SRS - Summed Rest Score; WD – Well developed

Discussion

The results of our study confirm that angiographic evaluation of CTO collateral function have a poor association with myocardial perfusion and metabolism, as assessed by [^{13} N]NH3/2-[^{18} F]FDG PET-CT, and should not be used as an assumption of the ischemic burden and myocardial viability. Most CTO territories demonstrated ischemia, but only 46.3% were associated with an area of > 10%. Scared non-viable myocardium associated with a CTO territory was limited to 15.3% of patients. Hibernating myocardium was frequent, but only 10.2% had > 7% hibernating myocardium involved in the CTO area.

In the setting of a complete coronary obstruction, blood supply to the myocardium is solely from collateral vessels. Individual potential to develop well-formed collaterals may avoid a transmural myocardial infarction and preserve ventricular function. The formation and maturation of coronary

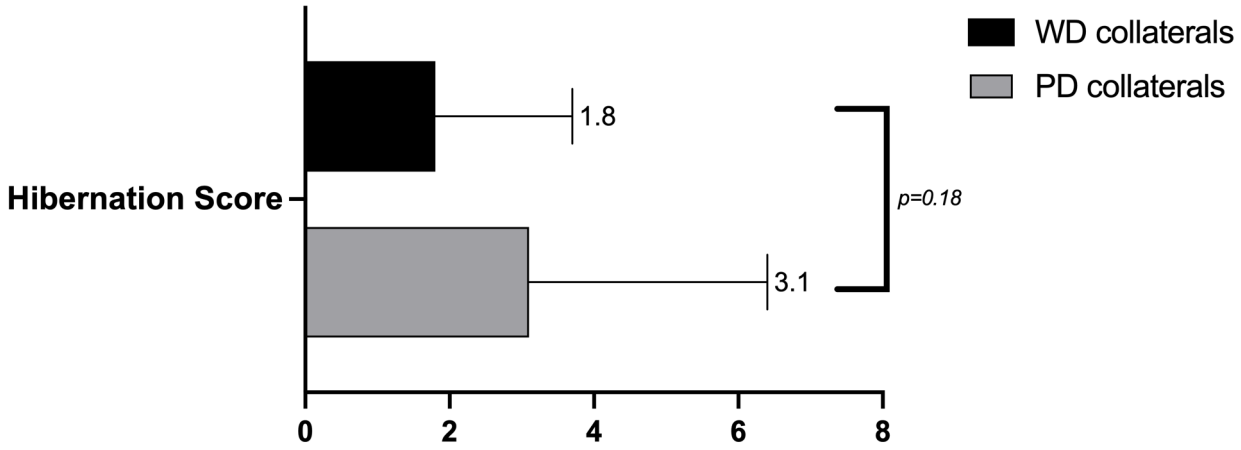

Fig. 3 Comparison of the Hibernating score between WD and PD collaterals PD – Poorly developed; WD – Well developed

collateral circulation is a complex adaptative physiologic response that involves the growth, expansion, and remodelling of pre-existing vessels into a mature, functional vascular network. The process may be induced by angiogenic growth factors and by the pressure gradient created through a hemodynamically relevant stenosis [11].

CTO revascularization procedural volumes have been increasing with the remarkable progress in its technical aspects. However, there are doubts about the clinical benefit of CTO recanalization and no prognostic improvement has been demonstrated in the few available randomized clinical trials [5, 6, 12]. Currently, its main indication is symptom improvement [13]. The relationship between the development of collateral circulation and the therapeutic benefit of the vessel recanalization in unknown. However, the presence of WD collaterals is often described as "benign" and an argument for the lack of benefit to perform PCI. On the other hand, a PD collateral network is sometimes interpreted as a sign of increased likelihood of non-viable myocardium.

In our study, the proportion of WD / PD collaterals was lower than described by other studies [2, 14], which could reflect the nature of our population, which was not restricted just to CTO patients already considered for percutaneous revascularization. The two subgroups of patients were comparable regarding age, clinical presentation, and past medical history. Regarding medication prior to CTO diagnosis, WD collateral patients had a significantly higher proportion of anticoagulant therapy, mainly due to atrial fibrillation, and consequently were less medicated with antiplatelets. The association of anticoagulation therapy with a collateralization enhancement was described in a retrospective study by Zhu et al. [15], which showed that pre-stroke warfarin may improve cerebral collateral grade among acute ischemic stroke patients presenting with a major arterial occlusion. Although there are no data regarding its influence on coronary collateralization, it is an interesting hypothesis-generating finding that could lead to further studies. Concerning the CTO vessel, WD collaterals were significantly more frequent in right coronary CTOs, in comparison with left anterior descending and circumflex arteries CTOs, which was already described in a previous study [16]. This finding is probably associated with the complex process of collateral circulation formation and maturation and suggests that left descending artery has a greater donor potential to create a more extensive collateralization to a right coronary occlusion [17].

The value of the angiographic evaluation in collateral functional capacity assessment is limited. The evaluation of vessels below the spatial resolution of coronary angiography and of endothelial dysfunction distal to the occlusion is not performed with that method but are both crucial for myocardial perfusion [3]. PET-CT is a non-invasive method that can accurately detect and quantify myocardial perfusion, also evaluating microvascular disease [18], which is particularly important in CTO patients as the perfusion is dependent on a collateral circulation network. In our study, no significant differences were found between the PET-CT perfusion scores and the angiographic classification of the collaterals. Considering normal rest perfusion CTO patients, a numerically higher proportion of patients had WD collaterals, but with no significant difference.

Although symptom improvement is the main indication, ischemia in more than 10% of the total myocardium it is still considered a valid indication to perform CTO revascularization [1, 9, 19]. In the ISCHEMIA trial [20] the number of CTO lesions treated in invasive arm of the trial was not revealed and the left ventricular ejection fraction was normal in both groups, so it is not possible to extrapolate its conclusions to a CTO population. A beneficial prognostic effect of revascularization in CTO patients with moderate-to-severe

ischemia was already described [21–23]. The ISCHEMIA-CTO (Revascularization or Optimal Medical Therapy of CTO: NCT03563417) Trial hypothesize that in asymptomatic patients with > 10% of myocardial ischemia, CTO PCI is superior to OMT for reducing major adverse cardiovascular and cerebrovascular events, but the results of this trial are not expected before 2028.

In our study, most patients had some degree of ischemia, which is in line with previous studies that were also performed with PET-CT [2, 23]. However, only 46.3% of CTO had an ischemia score > 10% of total myocardium and the angiographic classification of the collaterals was not able to appropriately identify the patients who had more associated ischemia. Therefore, we consider that an appropriate evaluation of the ischemia burden to determine which patients derive the most benefit is strongly recommended before performing a CTO PCI to outweigh its potential risks.

Historical models presume that extensively infarcted regions are unlikely to benefit from revascularization. A viable myocyte is a cell that is not irreversibly damaged, but in clinical practice the term viability is usually applied to dysfunctional regions with potential to improve its contractile force after revascularization [24]. Myocardial hibernation is a chronic state of matched reduction in coronary blood flow and myocardial contraction. As is this triggered by recurrent episodes inducible ischemia, functional recovery may be most likely to occur in territories with both inducible ischemia and viability [25].

Although there is a lack of evidence to support that viability testing leads to improved survival in patients with ischemic heart disease, as was observed in the sub-study of the Surgical Treatment for Ischemic Heart Failure (STICH) [26], it still plays a role. Functional recovery after revascularization is more likely to be observed in myocardial segments that demonstrate viability, by reducing angina, heart failure symptoms and the burden of rhythm abnormalities [24, 27]. A *post hoc* analysis of PARR-2 randomized controlled trial using 2-[^{18} F]FDG PET-CT in the management of severe LV dysfunction observed that patients who benefit the most with revascularization were those with the most extensive degree of perfusion-metabolism mismatch, using the threshold of > 7% hibernating myocardium [28].

2-[^{18} F]FDG PET-CT is considered the gold-standard for viability assessment, with an excellent sensitivity – superior to dobutamine stress echocardiography and cardiac magnetic resonance (CMR) – but with lower specificity that stress echocardiography [10]. The disadvantages of PET-CT are the limited availability and the radiation exposure.

We found that only 15.3% of patients had a scarred non-viable territory associated with the CTO and the angiographic classification of collaterals was not able to identify this subgroup of patients. Previous studies [29, 30] using 2-[^{18} F]FDG PET-CT also concluded that collateral circulation cannot accurately predict myocardial viability, but studies [14, 31, 32] using late gadolinium enhancement CMR stated that WD collaterals are associated with less myocardial scar. A study by Beitzke D. et al. [33] used hybrid [^{13} N]NH3/2-[^{18} F]FDG PET-MRI to study viability assessment in ischemic heart disease (not only CTO patients); the comparison revealed a good correlation between PET-CT and CMR for the LV scar size, but only a moderate to weak correlation between hibernation and transmural degree of scar. These two parameters represent markers of potential myocardial recovery with revascularization, but hibernation represents a unique functional information that can only be provided with PET-CT. In our study, PD collateral CTOs had a tendency for a numerically higher hibernation index, but without statistical significance. Concerning the prognostic threshold of > 7% hibernating myocardium, only 10.2% of CTO presented it, without significant differences regarding angiographic classification of collaterals. Associating the two prognostic thresholds of ischemia (> 10%) and hibernating myocardium (> 7%), just 40.7% of CTO patients fulfil that. Once again, the classical evaluation of collaterals was not able to identify these patients probably due to the lower spatial resolution of the technique.

This study is limited by its relatively small sample size. Coronary anatomical variability may not totally correspond to the standardized 17-segment model for each territory used. The stress perfusion scans and the viability studies were not performed in all patients; this was a clinical decision based on current recommendations, to avoid unnecessary radiation exposure without clear clinical benefit, but it would have increased the statistical power of some analysis. Finally, the inter-observer agreement of Rentrop and Werner classification was only modest, but that is an inherent limitation of angiography collateral assessment, which is an argument to further study its function previously to the decision to revascularize CTO patients.

To conclude, this study highlight that angiographic evaluation of CTO collateral function has a poor association with myocardial ischemic burden and hibernation state, as assessed by [^{13} N]NH3/2-[^{18} F]FDG PET/CT. Most CTO territories demonstrated ischemia, even with WD collaterals. Scared non-viable myocardium is not frequent and also has no association with the angiographic classification of collaterals. Most patients have not presented the prognostic thresholds of > 10% ischemia or > 7% hibernating myocardium, which reinforces the need to further study CTO patients in the decision-making process that leads to the revascularization.

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Declarations

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