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# Prevalence of Ischemia in Patients with a Chronic Total Occlusion and Preserved Left Ventricular Ejection Fraction

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Short title: Prevalence of Ischemia in CTO patients

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#### 1 ABSTRACT

Aims: Previous studies on invasive assessment of collateral function in CTO patients have displayed only a limited increase in collateral flow and high occurrence of coronary steal during pharmacological stress. This could question the necessity for ischemia testing prior to revascularization of CTOs in the presence of myocardial viability. The purpose of the present study was to determine the prevalence of perfusion impairments in patients with a CTO as assessed by [<sup>15</sup>O]H<sub>2</sub>O positron emission tomography (PET).

8 Methods and Results: Seventy-six consecutive patients (60 men, 62±10 years) with a documented 9 CTO and preserved left ventricular ejection fraction (LVEF) were included. All patients underwent PET 10 to assess (hyperemic) myocardial blood flow (MBF) and coronary flow reserve (CFR). Collateral 11 connection score was zero in 7 (9%), 1 in 13 (17%), and 2 in 56 (74%) of the cases, with 12 predominantly a high Rentrop grade (96% $\geq$ 2). MBF of the target area during hyperemia was 13 significantly lower as compared to the remote area (1.37 $\pm$ 0.37 vs. 2.63 $\pm$ 0.71 mL·min<sup>-1</sup>·g<sup>-1</sup>, p<0.001). 14 Target to remote ratio during hyperemia was on average 0.54±0.13, and 73 (96%) patients 15 demonstrated a significantly impaired target to remote ratio ( $\leq 0.75$ ). Only 7 (9%) patients displayed a 16 preserved CFR of  $\geq$  2.50, whereas coronary steal (CFR<1.0) was observed in 10 (13%) patients.

17 Conclusions: Even in the presence of angiographically well-developed collateral arteries, the vast 18 majority of CTO patients with a preserved LVEF showed significantly impaired perfusion. These 19 results suggest that collateral function during increased blood flow demand in viable myocardium is 20 predominantly insufficient.

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### 1 ABBREVIATIONS LIST

- 2 CTO, chronic coronary total occlusions
- 3 CAD, coronary artery disease
- 4 PET, positron emission tomography
- 5 LVEF, left ventricular ejection fraction
- 6 MBF, myocardial blood flow
- 7 ICA, invasive coronary angiograms
- 8 CC, collateral connection score
- 9 RFR, relative flow reserve
- 10 CFR, coronary flow reserve
- 11 J-CTO, Japanese CTO score
- 12 SPECT, single photon emission computed tomography

#### 1 INTRODUCTION

2 Chronic coronary total occlusions (CTO) are encountered in up to one third of patients with known or 3 suspected coronary artery disease (CAD).(1-3) A CTO is defined as a native coronary artery with 4 complete discontinuity of contrast opacification and TIMI flow grade zero or 1 for  $\geq$  3 months.(4-6) 5 Successful percutaneous coronary intervention (PCI) of a CTO is associated with symptom relief, 6 recovery of left ventricular function, and improved survival as opposed to patients in whom the 7 procedure was unsuccessful(3;5;7;8). Still, patients with a CTO are less likely to be treated with 8 percutaneous revascularization.(1) The reluctance of physicians to refer patients for PCI of a CTO is 9 based on lower procedural success, traditionally higher complication rates, contrast and radiation 10 burden, and potentially the assumption that angiographically well-developed collateral arteries 11 (Rentrop grade 2-3) prevent myocardial ischemia.(5;9) Consequently, non-invasive evaluation of 12 myocardial ischemia and viability has been proposed to justify percutaneous revascularization of a 13 documented CTO.(10;11) An ischemic burden of  $\geq$  10% has been considered of prognostic value and 14 has been incorporated in those decision schemes.(12) However, these decision schemes are mainly 15 based on the uncertainty of the hemodynamic significance of non-occlusive CAD, whereas CTOs are 16 purely dependent on collateral flow.(13;14) Previous invasive flow investigations have demonstrated 17 the inability of collateral arteries to comply with the demand during exercise.(15;16) This could 18 question the necessity for ischemia testing prior to revascularization of CTOs in the presence of 19 myocardial viability. The present study was designed to evaluate the prevalence and extent of 20 absolute myocardial perfusion impairment using cardiac positron emision tomography (PET) in 21 patients with a documented CTO and a preserved left ventricular ejection fraction (LVEF).

#### 1 METHODS

#### 2 Study design and participants

3 All CTO-patients considered for percutaneous revascularization at the VU University Medical Center 4 are analyzed in a dedicated program with two experienced CTO operators. Invasive coronary 5 angiograms, myocardial viability, ischemia, and cardiac symptoms of all patients were analyzed to 6 determine indication for revascularization and a prospective database of all patients is maintained. 7 Symptomatic as well as asymptomatic patients are included in this database. Patients with a 8 documented CTO referred for [<sup>15</sup>O]H<sub>2</sub>O PET to assess myocardial blood flow (MBF) were included in 9 the present study. Inclusion criteria were a documented CTO of a native coronary artery and a 10 preserved LVEF ( $\geq$  50%) on echocardiography or magnetic resonance imaging to guarantee viable 11 myocardium of the downstream myocardial territory of the CTO. Exclusion criteria were symptomatic 12 asthma, pregnancy, high degree AV-block, and three-vessel disease. The study was approved by the 13 institutional ethics committee.

#### 14 Angiographic CTO characteristics

Pre-interventional invasive coronary angiograms (ICA) were evaluated by two experienced CTO operators (PK & AN) during a consensus meeting to determine angiographic CTO characteristics. A CTO was defined as an occlusion on ICA with no or minimal antegrade filling of the distal vessel (TIMI 0-I).(5) Collateral connection score was graded as no visible connection (CCO), thread-like connection (CC1), or small branch like connection (CC2).(15) Collateral flow was scored based on contra-lateral filling of the occluded artery consistent with the Rentrop and Cohen classification.(17) Angiographic CTO morphology was assessed according to the J-CTO score.(18)

#### 22 Positron emission tomography

1 PET studies using [<sup>15</sup>O]H<sub>2</sub>O were performed as described previously.(19) Briefly, patients were 2 scanned on an Ingenuity TF 128 PET/CT scanner (Philips Healthcare, Best, The Netherlands). All 3 patients were asked to refrain from any caffeine or xanthine containing products for 24 hours prior 4 to scanning. After a scout-CT for patient positioning, a dynamic emission scan was performed at rest 5 followed by an identical scan during intravenous adenosine (140  $\mu$ ·kg<sup>-1</sup>·min<sup>-1</sup>) induced hyperemia. 6 Parametric MBF images were generated and analyzed quantitatively by an experienced analyst using 7 Cardiac VUer.(20) MBF during baseline and hyperemia was calculated according to standard 8 segmentation procedures for each of the following three vascular territories, left anterior descending 9 (LAD), circumflex (Cx), and right coronary artery (RCA).(21) CFR was calculated as the ratio of 10 hyperemic MBF to baseline MBF and relative flow reserve (RFR) was calculated as the ratio of 11 hyperemic MBF of the downstream myocardial area of a CTO (target) to hyperemic MBF of a normal 12 reference vascular territory (remote). Remote area was defined as four adjacent segments supplied 13 by a non-obstructive vessel with the highest hyperemic perfusion values. Parametric hyperemic MBF 14 polar maps were visually assessed to delineate defect areas. Quantitative MBF values of CTO vessels 15 were obtained for the perfusion defect only as opposed to entire vascular territories.

#### 16 Statistical analyses

Continuous variables are presented as mean values ± standard deviation (SD), whereas categorical variables are expressed as actual numbers. Continuous variables of paired data were compared with the paired sample t-test. Intergroup differences were determined with ANOVA and a posthoc Bonferroni for localizing the source of the difference. Differences in MBF and CFR predicted by given variables were estimated by linear regression analysis. Each variable was first modeled separately. All variables that were significant with univariate analyses were entered simultaneously in a multivariate

- 1 regression analyses model using backward elimination. A level of p < 0.05 was considered significant.
- 2 Statistical analyses were performed using SPSS software (IBM SPSS Statistics 20.0, Chicago, IL).

#### 1 **RESULTS**

#### 2 Clinical characteristics

3 Seventy-six consecutive patients with a documented CTO and preserved LVEF who underwent 4 [<sup>15</sup>O]H<sub>2</sub>O cardiac PET to determine indication for revascularization were included. Baseline patient 5 characteristics are shown in table 1. Seventeen patients (22%) were asymptomatic at time of cardiac 6 PET, whilst the majority of patients were analyzed for stable angina (n=43, 57%), dyspnea (n=13, 7 17%), or unstable angina (n=3, 4%). Asymptomatic patients were analyzed to determine indication 8 for PCI CTO after PCI for (Non-)ST-elevated myocardial infarction (n=12), staged PCI for stable angina 9 (n=3), cardiovascular screening (n=1), or an episode of ventricular arrhythmia (n=1). CTOs were 10 predominantly located in the RCA (n=52, 68%) and less frequently in the LAD (n=15, 20%), or Cx (n=9, 11 12%). The majority of the included patients had single vessel disease (CTO), whilst seventeen patients 12 (22%) had an additional obstructive lesion in a non-CTO vessel. Medical history exposed 34 (45%) 13 patients with prior myocardial infarction, 53 (70%) patients with previous PCI, and in 5 (7%) patients 14 coronary artery bypass grafting was performed previously. In 6 (8%) patients, with prior myocardial 15 infarction, pathologic Q-waves of the downstream CTO-territory were observed on 16 electrocardiogram. In all these six patients myocardial viability of the CTO territory was confirmed 17 with late gadolinium enhanced magnetic resonance imaging (<50% transmurality). CTO 18 characteristics are listed in table 2.

#### 19 Hemodynamic conditions during PET

The hemodynamic conditions during baseline and hyperemia PET are summarized in table 3. Heart rate and rate pressure product increased from baseline to hyperemia (both p < 0.001). Systolic blood pressure and mean arterial pressure were significantly lower during hyperemia as compared to baseline PET (p < 0.01 and p = 0.04, respectively).

#### 1 Baseline myocardial blood flow

Global MBF was 0.95  $\pm$  0.22 mL·min<sup>-1</sup>·g<sup>-1</sup>, whereas MBF of the target area during baseline was significantly lower as compared to the remote area (0.89  $\pm$  0.25 vs. 0.98  $\pm$  0.23 mL·min<sup>-1</sup>·g<sup>-1</sup>, p < 0.001). A high J-CTO score ( $\geq$  3) resulted in a more reduced baseline perfusion (p < 0.01), whilst baseline perfusion was comparable for different CC scores and Rentrop grades (table 4). An example of severely impaired baseline perfusion in the presence of angiographically well-developed collateral arteries is illustrated in figure 1.

#### 8 Hyperemic myocardial blood flow

9 During hyperemia, mean MBF was significantly lower for target than remote myocardial area (1.37 ± 10 0.37 vs. 2.63  $\pm$  0.71 mL·min<sup>-1</sup>·g<sup>-1</sup>, p < 0.001, respectively). Relative flow reserve during hyperemia was 11 on average 0.54  $\pm$  0.13, and 73 (96%) patients demonstrated a significantly impaired RFR ( $\leq$  0.75). 12 Four (5%) patients did not show any or only limited ischemic burden (0-1 myocardial segments), 13 whilst 72 (95%) patients displayed moderate (2-4 myocardial segments, n=38 (50%) to severe (> 4 14 myocardial segments, n=34 (45%)) ischemic burden. Patients with only 0-1 segments of perfusion 15 defect were all in the J-CTO group 0-1, showed a CC score ranging from 0-2 and a Rentrop grade 2 or 16 3. A J-CTO score of 0-1 resulted in a less pronounced target perfusion impairment as compared to J-17  $CTO \ge 2$  (figure 2). Hyperemic perfusion was not related to higher CC score and Rentrop grade (Table 18 4). Figure 3 illustrates the lack of association between collateral arteries and myocardial perfusion of 19 the downstream CTO area. Hyperemic perfusion of the target area of asymptomatic patients did not differ from symptomatic patients (1.36  $\pm$  0.37 vs. 1.37  $\pm$  0.37 mL·min<sup>-1</sup>·g<sup>-1</sup>, p = 0.96, respectively). 20 21 Univariate analysis showed that age, J-CTO score, CTO calcification, and the presence of a 22 microchannel had a significant impact on hyperemic MBF of the downstream CTO territory, whilst

- 1 multivariate analysis specified that only CTO calcification and the presence of a microchannel were
- 2 independently related to hyperemic MBF of the CTO territory (table 5).

### 3 Coronary flow reserve

- 4 Mean CFR of target area was significantly lower compared to the mean CFR of remote area (1.67 ±
- 5 0.80 vs. 2.79  $\pm$  0.84, p <0.001). Only 7 (9%) patients displayed a preserved CFR of  $\geq$  2.50 in the target
- 6 area. Coronary steal (CFR < 1.0) of the target area was observed in 10 (13%) patients. Univariate
- 7 analysis did not identify any predictors for differences in CFR of the CTO territory (table 5).

#### 1 **DISCUSSION**

The present study was conducted to evaluate the extent of PET perfusion deficits in presence of a
documented CTO. Results indicate that the vast majority of patients demonstrate severe perfusion
impairment on cardiac PET independent of CC score and Rentrop grade in the co-existence of viable
myocardium.

#### 6 **CTO characteristics**

7 Well-developed collateral arteries preserve left ventricular function in the manifestation of a 8 coronary occlusion.(22) In the present cohort of CTO patients with a preserved LVEF, predominantly 9 well-developed collateral arteries were observed. Almost all patients displayed a CC score  $\geq 1$  and 10 Rentrop grade  $\geq 2$ , which is in line with previous studies in patients without prior Q-wave myocardial 11 infarction.(15;16) However, intracoronary flow and pressure measurements allow for a more 12 accurate estimation of the functional capacity of the collateral circulation than coronary 13 angiography.(23) These invasive measurements have demonstrated the inability of the collateral 14 arteries to comply with increased oxygen demand, which is confirmed by the present data.(16;24) 15 Also, van der Hoeven et al. showed that when using invasive pressure measurements, the mean 16 collateral flow index (CFI) in CTO patients is only 0.39, pointing at limited functional collateral 17 capacity in the majority of patients, albeit with a large heterogeneity.(25) Interestingly, baseline and 18 hyperemic perfusion were significantly lower in patients with unfavorable occlusion characteristics as 19 expressed by higher J-CTO. It could be hypothesized that a high J-CTO represents more pronounced 20 CAD, which is correlated with increased myocardial perfusion impairment. In addition, collateral 21 supply to the CTO territory could be hampered by obstructive or diffuse disease of the donor vessels. 22 Two-vessel disease was observed in seventeen patients (22%) in the present study, possibly altering 23 the hyperemic perfusion of the downstream CTO territory. However, there was no significant

difference in hyperemic perfusion of the downstream CTO as well as remote area between patients
 with single-vessel CTO and two-vessel disease (data not shown, p=0.42 and p=0.20, respectively).

#### 3 Baseline perfusion

Baseline PET of the present study showed that myocardial perfusion was reduced in the downstream CTO area during resting conditions. This finding was not completely unexpected since multiple studies have observed, with invasive pressure interrogation, that invasive CFI was < 0.8 in the majority of CTO patients.(24;25) Given the wide variation of perfusion demand during resting conditions, these results do not imply that those patients are in a continuous ischemic state. However, it may emphasize the limited functional reserve of the microvasculature in collateraldepending myocardium or represent downregulation of flow as an early sign of hibernation.(26)

#### 11 Hyperemic myocardial perfusion

12 Multiple studies have shown that hyperemic invasive fractional flow reserve of CTOs is severely 13 reduced, and that hyperemic Doppler flow distal to the CTO is impaired in a significant proportion of 14 patients (> 90%).(15;16;24) Also, studies using SPECT showed extensive relative stress perfusion 15 deficits.(27;28) However, actual quantitative myocardial flow data of CTO-patients is lacking. The present study demonstrated a severely compromised hyperemic myocardial perfusion of the 16 17 downstream CTO area, and a reduction of almost 50% as compared to remote perfusion. (29;30) 18 Furthermore, 96% of the patients displayed a perfusion target to remote perfusion difference  $\geq 25\%$ 19 (RFR  $\leq$  0.75). This would be comparable with a fractional flow reserve  $\leq$  0.75 in the co-existence of 20 completely normal remote perfusion(31), although, the presence of a CTO is associated with a lower 21 FFR of the contralateral vessel due to donor collateral supply.(16;32) This suggest that remote 22 perfusion in CTO patients is an unsuitable reference standard for RFR calculation as it would 23 underestimate the relative perfusion impairment.

1 In addition to the prevalence and severity of perfusion impairment, CTO patients with large ischemic 2 burden have a worse cardiovascular outcome compared to those with small ischemic burden.(33) 3 Oxygen labeled water ( $[^{15}O]H_2O$ ), used as cardiac PET tracer in the current study, is freely diffusible in 4 perfusable tissue only and thereby excludes areas of scar. The defect size on  $([^{15}O]H_2O$  PET should 5 therefore solely represent the ischemic burden, which is predictive for myocardial infarction(12). 6 Furthermore, Safley et al. identified an ischemic extent of 12.5% at nuclear imaging as an optimal 7 cut-off to select patients who will be likely to have significant ischemia reduction after PCI of a 8 CTO.(28) According to the standardized 17-segment model of the American Heart Association, two 9 myocardial segments equals 12% of the myocardium.(21) In the present study seventy-two (95%) 10 patients revealed  $\geq$  2 ischemic myocardial segments, and could be considered for revascularization. 11 However, Simonsen J.A. et al. showed that the benefit of revascularization is more marked in 12 patients with a LVEF <50%, suggesting that LVEF should also be included in the decision making 13 process(34).

#### 14 Coronary flow reserve

15 Werner et al. reported coronary steal during hyperemic Doppler flow measurements in one-third of 16 patients with a CTO.(16) In the present study, myocardial steal (i.e. CFR < 1.0) was only observed in a 17 small subset (13%) of patients.(35) In case of antegrade blood flow, flow of the epicardial vessel will 18 be distributed to the myocardium distal to the location of the Doppler flow wire. Under these 19 circumstances, the Doppler flow wire will detect representative flow velocity to the downstream 20 myocardial territory. However, if flow originates from the distal end of the vessel, as with collateral 21 flow, a significant proportion of the blood flow could be disseminated to the myocardium before 22 arriving at the Doppler flow wire. This phenomenon could hamper the accuracy of Doppler flow 23 measurements distal of a CTO, especially during hyperemia as microvascular resistance is minimized.

#### 1 Limitations

2 Results should not be generalized to completely different patients groups (i. e. heart failure), 3 particularly since some degree of patient selection bias is present when using clinical populations. 4 Furthermore, patients with small vessel CTOs may not even be considered for PCI CTO and are 5 missing from this analysis. Also, capacity of the collateral circulation was only graded by angiographic 6 scoring rather than using invasively measured CFI. Last, the present study did not analyze response to 7 revascularization, therefore, it remains debatable if  $\geq$  2 ischemic myocardial segments are sufficient 8 to justify the accompanied risks of PCI CTO.

#### 9 Conclusions

10 The vast majority of CTO patients with a preserved LVEF showed significant perfusion impairment, 11 even in the presence of angiographically well-developed collateral arteries. These results suggest 12 that collateral function during increased blood flow demand in viable myocardium is predominantly 13 insufficient and that revascularization should be considered. Given the large perfusion deficits in this 14 patient population, PET might prove as valuable surrogate endpoint in future clinical trials to 15 determine the effects of mechanical or pharmacological (re)vascularization.

#### 16 **Funding and Conflict of interest statement**

17 None

#### 18 Impact on daily practice

The results suggests that additional ischemia testing prior to revascularization of a CTO should be questioned, since the proportion of patients with PET-defined stress perfusion deficits is exceptionally high in CTO patients with a preserved left ventricular ejection fraction.

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1	(35)	Heijne M, Raijmakers PG, Harms HJ, Lubberink M, Halbmeijer R, Appelman YE, et al.
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3		Cardiol 2010 Dec;17(6):1118-21.
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### **1** Table 1. Baseline patient characteristics (n = 76)

Characteristic	N (%) or mean ± SD
Age (years)	62 ± 10
Male	60 (79%)
Body Mass Index (kg · m <sup>-2</sup> )	28.4 ± 3.9
CAD risk factors	
Hypertension	33 (43%)
Hypercholesterolemia	28 (37%)
Current smoking	21 (28%)
History of smoking	23 (30%)
Family history CAD	36 (47%)
Diabetes	16 (21%)
Medication	
Aspirin	75 (99%)
Calcium channel blockers	22 (29%)
Beta-blockers	62 (82%)
Statins	67 (88%)
Dual anti-platelets	34 (45%)
Long-acting nitrates	17 (22%)
Cardiac symptoms	
Stable angina	43 (57%)
Free of symptoms	17 (22%)
Dyspnea	13 (17%)
Unstable angina	3 (4%)
Culprit arteries	
RCA	52 (68%)
LAD	15 (20%)
СХ	9 (12%)

2 SD, standard deviation; CAD, coronary artery disease; RCA, right coronary artery; LAD, left anterior

descending; Cx, circumflex; MI, myocardial infarction; PCI, percutaneous coronary intervention;

4 CABG, coronary artery bypass graft surgery

#### 1 Table 2. CTO and collateral characteristics

Characteristic	N (%)
Stump cap morphology	21 (28%)
Proximal cap bifurcation	32 (42%)
Microchannel	15 (20%)
≥ 20mm length	35 (46%)
Calcification	41 (54%)
Bending (> 45°)	12 (16%)
Previous PCI attempt	10 (13%)
J-CTO score	
0-1	36 (47%)
2	25 (33%)
≥ 3	15 (20%)
CC score	
0	7 (9%)
1	13 (17%)
2	56 (74%)
Rentrop grade	
0-1	3 (4%)
2	19 (25%)
3	54 (71%)

CTO, chronic total occlusion; mm, millimeters; PCI, percutaneous coronary intervention

Parameter	Baseline	Hyperemia	p- value	
Heart rate (bpm)	63 ± 8	81 ± 10	p < 0.001	
Systolic blood pressure (mmHg)	123 ± 23	117 ± 20	p < 0.01	
Diastolic blood pressure (mmHg)	64 ± 9	63 ± 11	p = 0.31	
Mean arterial pressure (mmHg)	84 ± 12	81 ± 13	p = 0.04	
Rate-pressure product	7861 ± 2027	9505 ± 2167	p < 0.001	

## 1 Table 3. Hemodynamic conditions during PET at baseline and hyperemia

2 PET, positron emission tomography; bpm, beats per minute

3

#### 1 Table 4. Perfusion in relation to CTO characteristics

Characteristic	Baseline MBF	Hyperemic MBF	CFR	RFR
CTO arteries				
RCA (n=52)	0.91 ± 0.25	1.37 ± 0.38	1.62 ± 0.59	0.55 ± 0.12
LAD (n=15) CX (n=9)	0.85 ± 0.25 0.88 ± 0.23	1.21 ± 0.33 1.57 ± 0.31	1.75 ± 1.39 1.89 ± 0.55	0.47 ± 0.15 0.56 ± 0.13
p-value	p = 0.70	p = 0.07	p = 0.59	p = 0.10
J-CTO score				
0-1 (n=36) 2 (n=25)	$0.97 \pm 0.24^{\mu}$	$1.50 \pm 0.39^{+5}$ 1 28 ± 0 28	1.63 ± 0.60	0.55 ± 0.14
≥ 3( n=15)	0.75 ± 0.20	$1.20 \pm 0.20$ $1.20 \pm 0.35$	$1.91 \pm 1.39$	$0.47 \pm 0.11$
p-value	p < 0.01	p < 0.01	p = 0.45	p = 0.10
CC score				
0 (n=7)	0.87 ± 0.23	1.40 ± 0.36	1.67 ± 0.43	0.57 ± 0.13
1 (n=13) 2 (n=56)	$0.94 \pm 0.20$ 0.88 ± 0.26	$1.37 \pm 0.44$ 1.36 ± 0.36	$1.53 \pm 0.65$ $1.70 \pm 0.87$	$0.50 \pm 0.15$ $0.54 \pm 0.13$
p-value	p = 0.73	p = 0.97	p = 0.79	p = 0.44
Rentrop grade				
0-1( n=3) 2 (n=19) 3 (n=54)	$0.87 \pm 0.31$ $0.94 \pm 0.21$ $0.87 \pm 0.26$	1.38 ± 0.45 1.38 ± 0.39 1.37 ± 0.37	1.75 ± 0.80 1.51 ± 0.47 1.67 ± 0.80	$0.46 \pm 0.09$ $0.56 \pm 0.14$ $0.54 \pm 0.13$
p-value	p = 0.56	p = 0.98	p = 0.61	p = 0.38

 $^{\mu}p < 0.01 \text{ vs. J-CTO} \ge 3$ ;  $^{\dagger}p < 0.05 \text{ vs. J-CTO } 2$ ;  $^{\$}p = 0.02 \text{ vs. J-CTO} \ge 3$ 

CTO, chronic total occlusion; standard deviation; MBF, myocardial blood flow; CFR, coronary flow
 reserve; RFR, relative flow reserve; RCA, right coronary artery; LAD, left anterior descending artery;
 CX, circumflex artery; J-CTO, Japanese chronic total occlusion; CC, collateral connection; Intergroup
 significance was determined with ANOVA and a posthoc Bonferroni for localizing the source of the
 difference.

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Variable	Hyperemic MBF				CFR			
	Univa ana	ariate Iysis	Multi <sup>.</sup> ana	variate Iysis	Univ ana	ariate alysis	Mult an	ivariate alysis
	β	p-value	β	p-value	β	p-value	β	p-value
Age (years)	-0.01	0.07	-	-	-0.01	0.49	_	_
Gender (male)	-0.16	0.12	-	-	0.37	0.10	-	-
Body Mass Index	-0.01	0.32	-	-	-0.02	0.33	-	-
Hypertension	0.07	0.41	-	-	-0.02	0.90	-	-
Hypercholesterolemia	0.01	0.68	-	-	0.00	0.97	-	-
Smoking	-0.07	0.39	-	-	-0.13	0.49	-	_
Family history CAD	-0.04	0.67	-	-	-0.22	0.24	-	_
Diabetes	-0.03	0.75	-	-	-0.35	0.12	-	-
J-CTO score	-0.09	0.02	-	-	0.08	0.35	-	-
Calcification	-0.25	< 0.01	-0.25	< 0.01	-0.11	0.55	-	-
Microchannel	0.18	0.09	0.18	0.08	0.05	0.85	-	-
CTO length (>20mm)	-0.02	0.78	-	-	0.03	0.86	-	-
CC core	-0.02	0.80	-	-	0.06	0.68	-	_
Rentrop grade	-0.02	0.83	_	_	0.11	0.51	-	-

#### 1 Table 5. Results of univariate and multivariate linear regression analysis of hyperemic MBF and CFR

2 MBF, myocardial blood flow; CFR, coronary flow reserve; CAD, coronary artery disease; J-CTO,

3 Japanese chronic total occlusion; CTO, chronic total occlusion; CC, collateral connection

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#### 1 LEGEND TO THE FIGURES

Figure 1. Illustration of a patient with severe reduced perfusion of the anterior wall during baseline
PET in the territory of a CTO LAD. Even the presence of excellent epicardial collaterals (A) and
complete retrograde filling of the CTO vessel (B) does not guarantee sufficient myocardial perfusion
during resting conditions (C and D). PET, positron emission tomography; CTO, chronic total occlusion;
LAD, left descending artery.

Figure 2. Illustration hyperemic MBF in relation to CTO-vessel (A), J-CTO score (B), CC score (C), and
Rentrop grade (D). Hyperemic MBF was comparable among different CTO vessels, CC score, and
Rentrop grade. However, hyperemic MBF was significantly lower for a J-CTO score ≥ 2 as compared
to J-CTO 0-1. MBF, myocardial blood flow; J-CTO, Japanese chronic total occlusion; CC, collateral
connection; other abbreviations as in figure 1.

Figure 3. Four scenarios displaying the lacking relationship between the collateral state and stress myocardial perfusion. Panel A shows well-developed collaterals from LAD to RCA, preventing significant myocardial ischemia. Panel B illustrates that even without well-developed collaterals the myocardium during stress is not ischemic per see. An example of good visual collaterals with limited functional capacity resulting in myocardial ischemia during vasodilatation stress PET is displayed in panel C. The fourth scenario (D) demonstrates a patient with stress perfusion impairment on PET in the absence of well-developed collaterals. RCA, right coronary artery; other abbreviations as figure 1.

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1 Figure 1.







1 Figure 3.

