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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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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 $[^{15}O]H_2O$ positron emission tomography (PET).

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

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

ABBREVIATIONS LIST

CTO, chronic coronary total occlusions

CAD, coronary artery disease

PET, positron emission tomography

LVEF, left ventricular ejection fraction

MBF, myocardial blood flow

ICA, invasive coronary angiograms

CC, collateral connection score

RFR, relative flow reserve

CFR, coronary flow reserve

J-CTO, Japanese CTO score

SPECT, single photon emission computed tomography

INTRODUCTION

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

METHODS

Study design and participants

All CTO-patients considered for percutaneous revascularization at the VU University Medical Center are analyzed in a dedicated program with two experienced CTO operators. Invasive coronary angiograms, myocardial viability, ischemia, and cardiac symptoms of all patients were analyzed to determine indication for revascularization and a prospective database of all patients is maintained. Symptomatic as well as asymptomatic patients are included in this database. Patients with a documented CTO referred for $[^{15}O]H_2O$ PET to assess myocardial blood flow (MBF) were included in the present study. Inclusion criteria were a documented CTO of a native coronary artery and a preserved LVEF (≥ 50%) on echocardiography or magnetic resonance imaging to guarantee viable myocardium of the downstream myocardial territory of the CTO. Exclusion criteria were symptomatic asthma, pregnancy, high degree AV-block, and three-vessel disease. The study was approved by the institutional ethics committee.

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 (CC0), 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)

Positron emission tomography

PET studies using [^{15}O]H_2O were performed as described previously.(19) Briefly, patients were scanned on an Ingenuity TF 128 PET/CT scanner (Philips Healthcare, Best, The Netherlands). All patients were asked to refrain from any caffeine or xanthine containing products for 24 hours prior to scanning. After a scout-CT for patient positioning, a dynamic emission scan was performed at rest followed by an identical scan during intravenous adenosine (140 $\mu \cdot kg^{-1} \cdot min^{-1}$) induced hyperemia. Parametric MBF images were generated and analyzed quantitatively by an experienced analyst using Cardiac VUer.(20) MBF during baseline and hyperemia was calculated according to standard segmentation procedures for each of the following three vascular territories, left anterior descending (LAD), circumflex (Cx), and right coronary artery (RCA).(21) CFR was calculated as the ratio of hyperemic MBF to baseline MBF and relative flow reserve (RFR) was calculated as the ratio of hyperemic MBF of the downstream myocardial area of a CTO (target) to hyperemic MBF of a normal reference vascular territory (remote). Remote area was defined as four adjacent segments supplied by a non-obstructive vessel with the highest hyperemic perfusion values. Parametric hyperemic MBF polar maps were visually assessed to delineate defect areas. Quantitative MBF values of CTO vessels were obtained for the perfusion defect only as opposed to entire vascular territories.

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

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

RESULTS

Clinical characteristics

Seventy-six consecutive patients with a documented CTO and preserved LVEF who underwent [^{15}O]H_2O cardiac PET to determine indication for revascularization were included. Baseline patient characteristics are shown in table 1. Seventeen patients (22%) were asymptomatic at time of cardiac PET, whilst the majority of patients were analyzed for stable angina (n=43, 57%), dyspnea (n=13, 17%), or unstable angina (n=3, 4%). Asymptomatic patients were analyzed to determine indication for PCI CTO after PCI for (Non-)ST-elevated myocardial infarction (n=12), staged PCI for stable angina (n=3), cardiovascular screening (n=1), or an episode of ventricular arrhythmia (n=1). CTOs were predominantly located in the RCA (n=52, 68%) and less frequently in the LAD (n=15, 20%), or Cx (n=9, 12%). The majority of the included patients had single vessel disease (CTO), whilst seventeen patients (22%) had an additional obstructive lesion in a non-CTO vessel. Medical history exposed 34 (45%) patients with prior myocardial infarction, 53 (70%) patients with previous PCI, and in 5 (7%) patients coronary artery bypass grafting was performed previously. In 6 (8%) patients, with prior myocardial infarction, pathologic Q-waves of the downstream CTO-territory were observed on electrocardiogram. In all these six patients myocardial viability of the CTO territory was confirmed with late gadolinium enhanced magnetic resonance imaging (<50% transmurality). CTO characteristics are listed in table 2.

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).

Baseline myocardial blood flow

Global MBF was 0.95 ± 0.22 $mL \cdot min^{-1} \cdot g^{-1}$, whereas MBF of the target area during baseline was significantly lower as compared to the remote area (0.89 ± 0.25 vs. 0.98 ± 0.23 $mL \cdot min^{-1} \cdot g^{-1}$, $p < 0.001$). A high J-CTO score (≥ 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.

Hyperemic myocardial blood flow

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

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

Coronary flow reserve

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

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.

CTO characteristics

Well-developed collateral arteries preserve left ventricular function in the manifestation of a coronary occlusion.(22) In the present cohort of CTO patients with a preserved LVEF, predominantly well-developed collateral arteries were observed. Almost all patients displayed a CC score ≥1 and Rentrop grade ≥2, which is in line with previous studies in patients without prior Q-wave myocardial infarction.(15;16) However, intracoronary flow and pressure measurements allow for a more accurate estimation of the functional capacity of the collateral circulation than coronary angiography.(23) These invasive measurements have demonstrated the inability of the collateral arteries to comply with increased oxygen demand, which is confirmed by the present data.(16;24) Also, van der Hoeven et al. showed that when using invasive pressure measurements, the mean collateral flow index (CFI) in CTO patients is only 0.39, pointing at limited functional collateral capacity in the majority of patients, albeit with a large heterogeneity.(25) Interestingly, baseline and hyperemic perfusion were significantly lower in patients with unfavorable occlusion characteristics as expressed by higher J-CTO. It could be hypothesized that a high J-CTO represents more pronounced CAD, which is correlated with increased myocardial perfusion impairment. In addition, collateral supply to the CTO territory could be hampered by obstructive or diffuse disease of the donor vessels. Two-vessel disease was observed in seventeen patients (22%) in the present study, possibly altering 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).

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 collateral-depending myocardium or represent downregulation of flow as an early sign of hibernation.(26)

Hyperemic myocardial perfusion

Multiple studies have shown that hyperemic invasive fractional flow reserve of CTOs is severely reduced, and that hyperemic Doppler flow distal to the CTO is impaired in a significant proportion of patients (> 90%).(15;16;24) Also, studies using SPECT showed extensive relative stress perfusion 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 downstream CTO area, and a reduction of almost 50% as compared to remote perfusion. (29;30) Furthermore, 96% of the patients displayed a perfusion target to remote perfusion difference ≥ 25% (RFR ≤ 0.75). This would be comparable with a fractional flow reserve ≤ 0.75 in the co-existence of completely normal remote perfusion(31), although, the presence of a CTO is associated with a lower FFR of the contralateral vessel due to donor collateral supply.(16;32) This suggest that remote perfusion in CTO patients is an unsuitable reference standard for RFR calculation as it would underestimate the relative perfusion impairment.

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

Coronary flow reserve

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

Limitations

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

Conclusions

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

Funding and Conflict of interest statement

None

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.

Reference List

(1) Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol 2012 Mar 13;59(11):991-7.

(2) Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. Am Heart J 1993 Sep;126(3 Pt 1):561-4.

(3) Werner GS, Gitt AK, Zeymer U, Juenger C, Towae F, Wienbergen H, et al. Chronic total coronary occlusions in patients with stable angina pectoris: impact on therapy and outcome in present day clinical practice. Clin Res Cardiol 2009 Jul;98(7):435-41.

(4) Sianos G, Werner GS, Galassi AR, Papafaklis MI, Escaned J, Hildick-Smith D, et al. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. EuroIntervention 2012 May 15;8(1):139-45.

(5) Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. Circulation 2005 Oct 11;112(15):2364-72.

(6) Zidar FJ, Kaplan BM, O'Neill WW, Jones DE, Schreiber TL, Safian RD, et al. Prospective, randomized trial of prolonged intracoronary urokinase infusion for chronic total occlusions in native coronary arteries. J Am Coll Cardiol 1996 May;27(6):1406-12.

(7) Prasad A, Rihal CS, Lennon RJ, Wiste HJ, Singh M, Holmes DR, Jr. Trends in outcomes after percutaneous coronary intervention for chronic total occlusions: a 25-year experience from the Mayo Clinic. J Am Coll Cardiol 2007 Apr 17;49(15):1611-8.

(8) George S, Cockburn J, Clayton TC, Ludman P, Cotton J, Spratt J, et al. Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central Cardiac Audit Database. J Am Coll Cardiol 2014 Jul 22;64(3):235-43.

(9) Patel VG, Brayton KM, Tamayo A, Mogabgab O, Michael TT, Lo N, et al. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. JACC Cardiovasc Interv 2013 Feb;6(2):128-36.

(10) Stuijfzand WJ, Raijmakers PG, Driessen RS, van Royen N, Nap A, van Rossum AC, et al. Value of Hybrid Imaging with PET/CT to Guide Percutaneous Revascularization of Chronic Total Coronary Occlusion. Curr Cardiovasc Imaging Rep 2015;8(7):26.

(11) Galassi AR, Brilakis ES, Boukhris M, Tomasello SD, Sianos G, Karmpaliotis D, et al. Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. Eur Heart J 2015 Aug 7.

(12) Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and

Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008 Mar 11;117(10):1283-91.

(13) Danad I, Raijmakers PG, Harms HJ, Heymans MW, van Royen N, Lubberink M, et al. Impact of anatomical and functional severity of coronary atherosclerotic plaques on the transmural perfusion gradient: a [15O]H2O PET study. Eur Heart J 2014 Aug 14;35(31):2094-105.

(14) Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009 Jan 15;360(3):213-24.

(15) Werner GS, Ferrari M, Heinke S, Kuethe F, Surber R, Richartz BM, et al. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. Circulation 2003 Apr 22;107(15):1972-7.

(16) Werner GS, Surber R, Ferrari M, Fritzenwanger M, Figulla HR. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. Eur Heart J 2006 Oct;27(20):2406-12.

(17) Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985 Mar;5(3):587-92.

(18) Morino Y, Abe M, Morimoto T, Kimura T, Hayashi Y, Muramatsu T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. JACC Cardiovasc Interv 2011 Feb;4(2):213-21.

(19) Danad I, Raijmakers PG, Appelman YE, Harms HJ, de Haan S, van den Oever ML, et al. Coronary risk factors and myocardial blood flow in patients evaluated for coronary artery disease: a quantitative [15O]H2O PET/CT study. Eur J Nucl Med Mol Imaging 2012 Jan;39(1):102-12.

(20) Harms HJ, de Haan S, Knaapen P, Allaart CP, Lammertsma AA, Lubberink M. Parametric images of myocardial viability using a single 15O-H2O PET/CT scan. J Nucl Med 2011 May;52(5):745-9.

(21) Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Int J Cardiovasc Imaging 2002 Feb;18(1):539-42.

(22) Schwartz H, Leiboff RH, Bren GB, Wasserman AG, Katz RJ, Varghese PJ, et al. Temporal evolution of the human coronary collateral circulation after myocardial infarction. J Am Coll Cardiol 1984 Dec;4(6):1088-93.

(23) van Royen N, Piek JJ, Schaper W, Fulton WF. A critical review of clinical arteriogenesis research. J Am Coll Cardiol 2009 Dec 29;55(1):17-25.

(24) Sachdeva R, Agrawal M, Flynn SE, Werner GS, Uretsky BF. The myocardium supplied by a chronic total occlusion is a persistently ischemic zone. Catheter Cardiovasc Interv 2014 Jan 1;83(1):9-16.

(25) van der Hoeven NW, Teunissen PF, Werner GS, Delewi R, Schirmer SH, Traupe T, et al. Clinical parameters associated with collateral development in patients with chronic total coronary occlusion. Heart 2013 Aug;99(15):1100-5.

(26) Sambuceti G, Parodi O, Giorgetti A, Salvadori P, Marzilli M, Dabizzi P, et al. Microvascular dysfunction in collateral-dependent myocardium. J Am Coll Cardiol 1995 Sep;26(3):615-23.

(27) Aboul-Enein F, Kar S, Hayes SW, Sciammarella M, Abidov A, Makkar R, et al. Influence of angiographic collateral circulation on myocardial perfusion in patients with chronic total occlusion of a single coronary artery and no prior myocardial infarction. J Nucl Med 2004 Jun;45(6):950-5.

(28) Safley DM, Koshy S, Grantham JA, Bybee KA, House JA, Kennedy KF, et al. Changes in myocardial ischemic burden following percutaneous coronary intervention of chronic total occlusions. Catheter Cardiovasc Interv 2011 Sep 1;78(3):337-43.

(29) Danad I, Uusitalo V, Kero T, Saraste A, Raijmakers PG, Lammertsma AA, et al. Quantitative assessment of myocardial perfusion in the detection of significant

coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H2O PET imaging. J Am Coll Cardiol 2014 Oct 7;64(14):1464-75.

(30) Stuijfzand WJ, Uusitalo V, Kero T, Danad I, Rijnierse MT, Saraste A, et al. Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease. Circ Cardiovasc Imaging 2015 Jan;8(1).

(31) De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation 1994 Mar;89(3):1013-22.

(32) Ladwiniec A, Cunnington MS, Rossington J, Mather AN, Alahmar A, Oliver RM, et al. Collateral donor artery physiology and the influence of a chronic total occlusion on fractional flow reserve. Circ Cardiovasc Interv 2015 Apr;8(4).

(33) Galassi AR, Werner GS, Tomasello SD, Azzarelli S, Capodanno D, Barrano G, et al. Prognostic value of exercise myocardial scintigraphy in patients with coronary chronic total occlusions. J Interv Cardiol 2010 Apr;23(2):139-48.

(34) Simonsen JA, Johansen A, Gerke O, Mickley H, Thomassen A, Hess S, et al. Outcome with invasive versus medical treatment of stable coronary artery disease: influence of perfusion defect size, ischaemia, and ejection fraction. EuroIntervention 2016 Feb 20;11(10):1118-24.

(35) Heijne M, Raijmakers PG, Harms HJ, Lubberink M, Halbmeijer R, Appelman YE, et al. Coronary steal: revealing the diagnosis with quantitative cardiac PET/CT. J Nucl Cardiol 2010 Dec;17(6):1118-21.

Table 1. Baseline patient characteristics (n = 76)

Characteristic	N (%) or mean ± SD
Age (years)	62 ± 10
Male	60 (79%)
Body Mass Index ($kg \cdot m^{-2}$)	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%)
CX	9 (12%)

SD, standard deviation; CAD, coronary artery disease; RCA, right coronary artery; LAD, left anterior descending; Cx, circumflex; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery

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^{o})	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

Table 3. Hemodynamic conditions during PET at baseline and hyperemia

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

PET, positron emission tomography; bpm, beats per minute

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)	0.85 ± 0.25	1.21 ± 0.33	1.75 ± 1.39	0.47 ± 0.15
CX (n=9)	0.88 ± 0.23	1.57 ± 0.31	1.89 ± 0.55	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)	0.97 ± 0.24$^{\mu}$	1.50 ± 0.39†§	1.63 ± 0.60	0.55 ± 0.14
2 (n=25)	0.86 ± 0.25	1.28 ± 0.28	1.59 ± 0.56	0.55 ± 0.12
≥ 3(n=15)	0.75 ± 0.20	1.20 ± 0.35	1.91 ± 1.39	0.47 ± 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)	0.94 ± 0.20	1.37 ± 0.44	1.53 ± 0.65	0.50 ± 0.15
2 (n=56)	0.88 ± 0.26	1.36 ± 0.36	1.70 ± 0.87	0.54 ± 0.13
p-value	p = 0.73	p = 0.97	p = 0.79	p = 0.44
Rentrop grade				
0-1(n=3)	0.87 ± 0.31	1.38 ± 0.45	1.75 ± 0.80	0.46 ± 0.09
2 (n=19)	0.94 ± 0.21	1.38 ± 0.39	1.51 ± 0.47	0.56 ± 0.14
3 (n=54)	0.87 ± 0.26	1.37 ± 0.37	1.67 ± 0.80	0.54 ± 0.13
p-value	p = 0.56	p = 0.98	p = 0.61	p = 0.38

$^{\mu}$ p < 0.01 vs. J-CTO ≥ 3; † p < 0.05 vs. J-CTO 2; § p = 0.02 vs. J-CTO ≥ 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.

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

Variable	Hyperemic MBF				CFR			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	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	–	–

MBF, myocardial blood flow; CFR, coronary flow reserve; CAD, coronary artery disease; J-CTO, Japanese chronic total occlusion; CTO, chronic total occlusion; CC, collateral connection

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.

Figure 1.

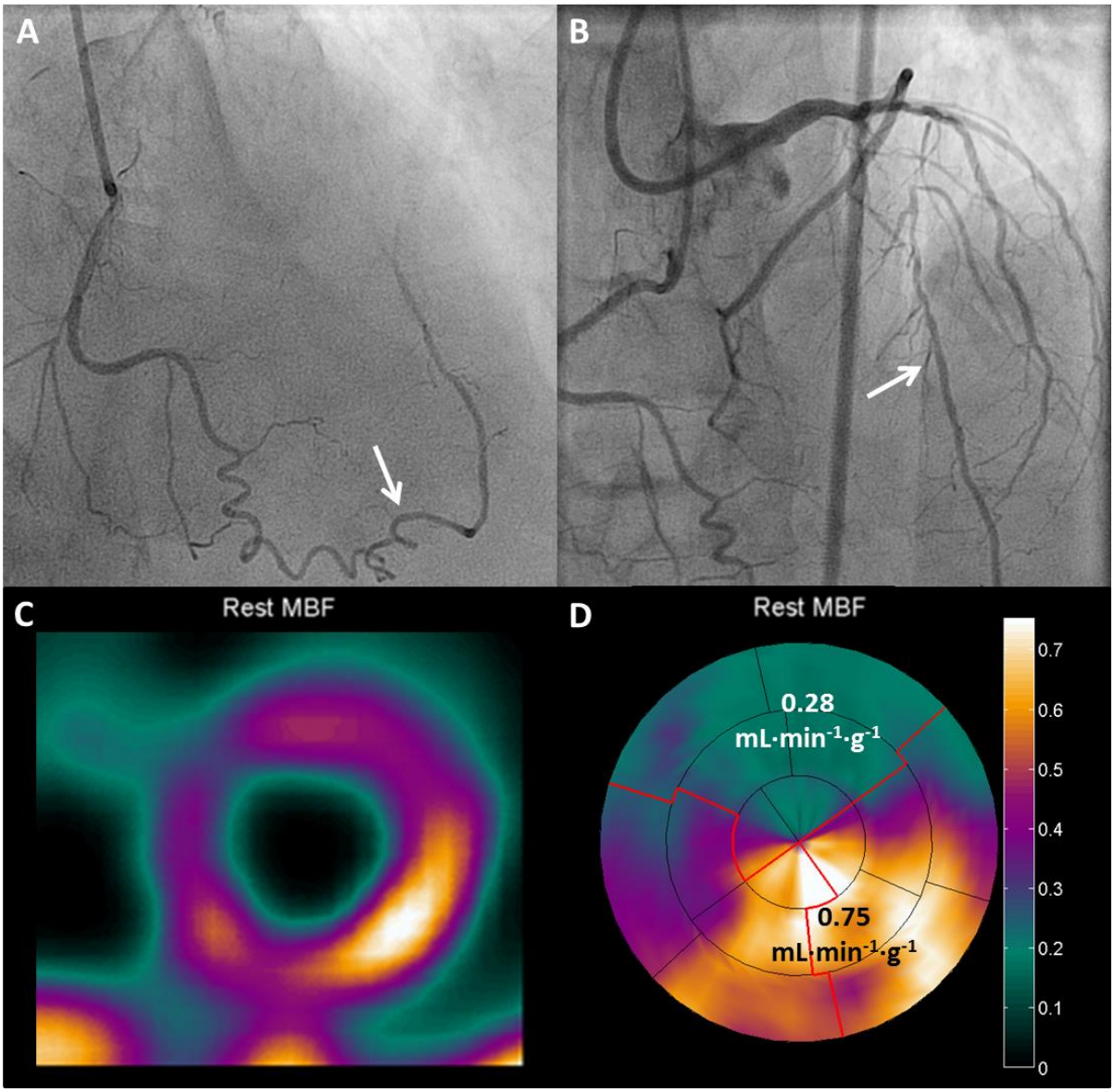

A
B
C
Rest MBF
D
Rest MBF
0.28
mL·min-1·g-1
0.75
mL·min-1·g-1
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0

Figure 2.

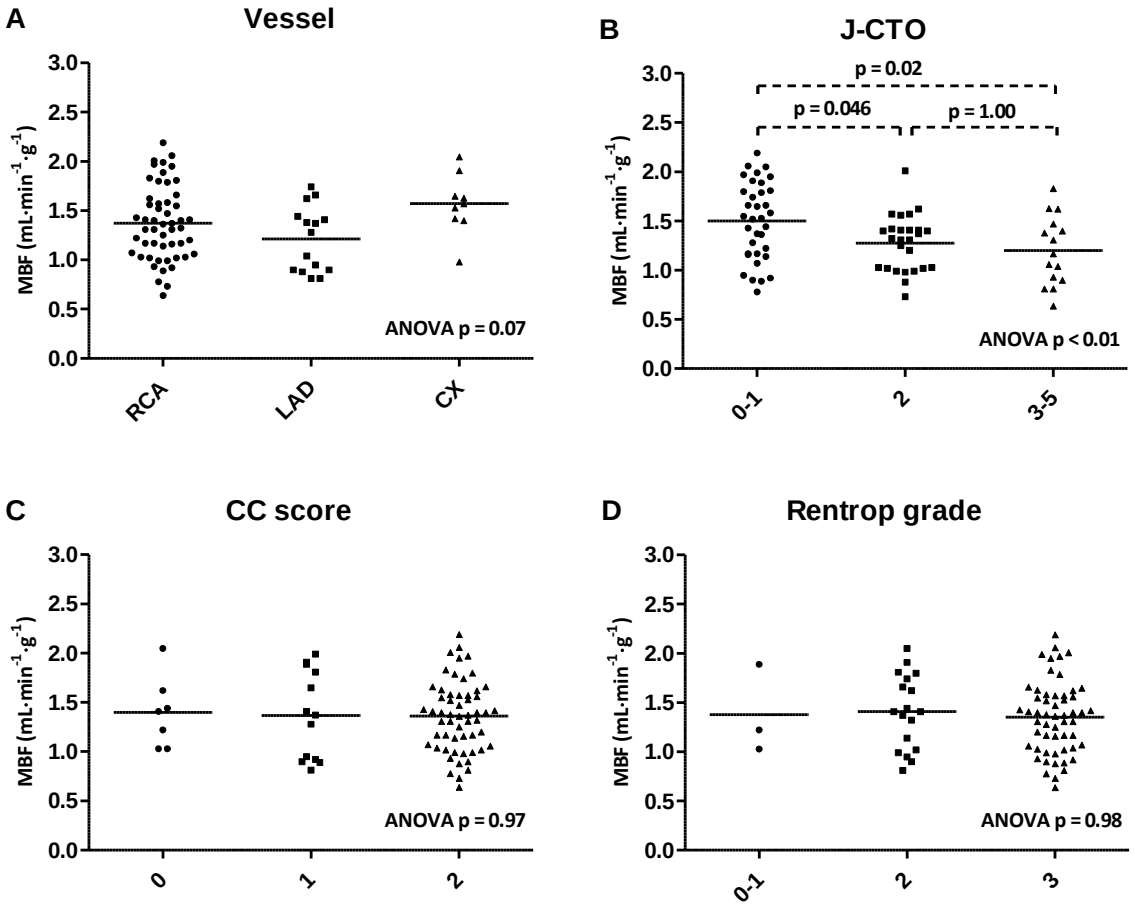
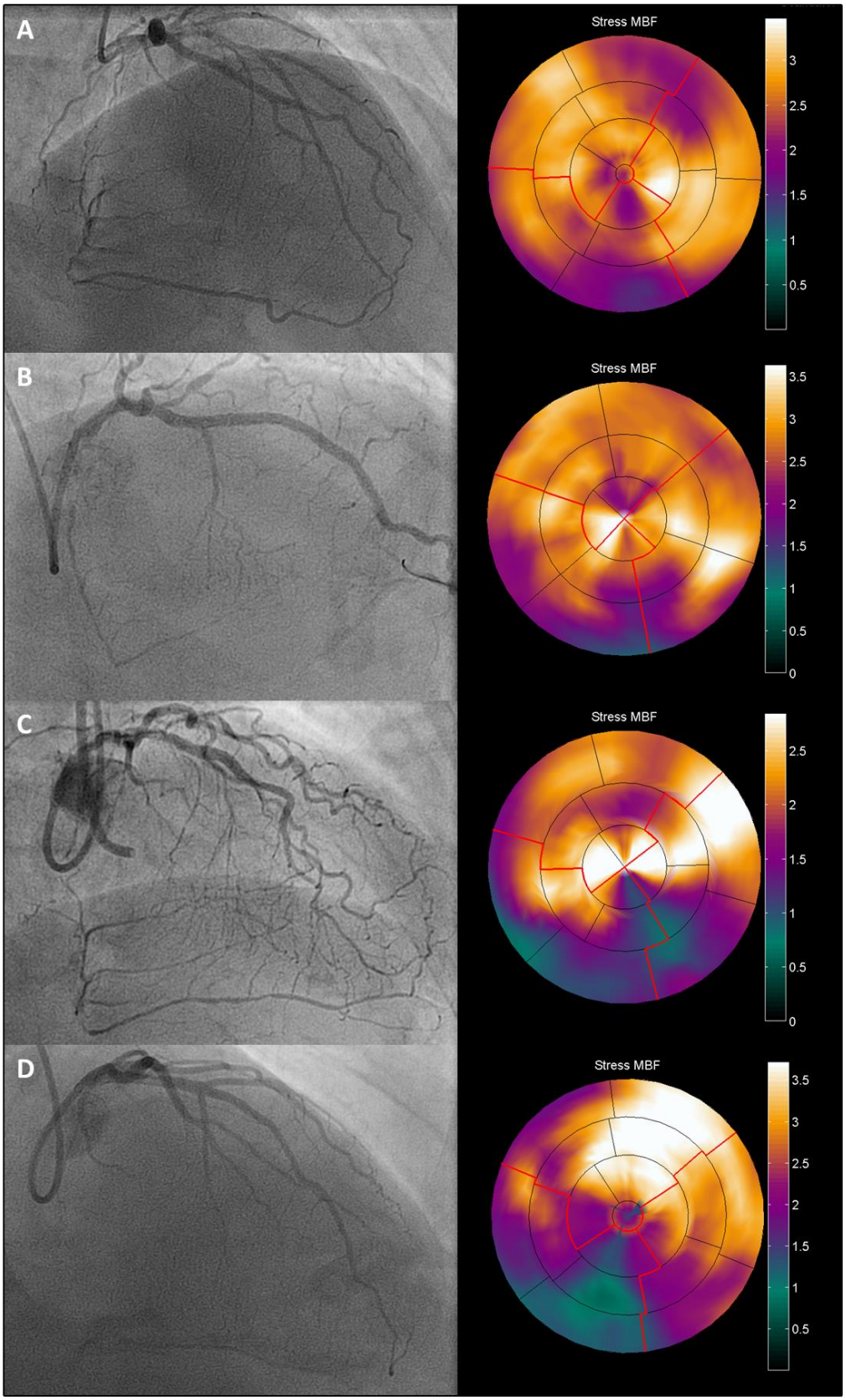

A
Vessel
MBF (mL·min-1·g-1)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ANOVA p = 0.07
RCA
LAD
CX
B
J-CTO
p = 0.02
p = 0.046
p = 1.00
ANOVA p < 0.01
0-1
2
3-5
C
CC score
ANOVA p = 0.97
0
1
2
D
Rentrop grade
ANOVA p = 0.98
0-1
2
3

Figure 3.


A
Stress MBF
3
2.5
2
1.5
1
0.5
B
Stress MBF
3.5
3
2.5
2
1.5
1
0.5
0
C
Stress MBF
2.5
2
1.5
1
0.5
0
D
Stress MBF
3.5
3
2.5
2
1.5
1
0.5