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Chronic Total Occlusion: Collaterals and Myocardial Viability

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CHRONIC TOTAL OCLUSION: COLLATERALS AND MYOCARDIAL VIABILITY

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Abstract

Background: Cardiovascular disease is the main cause of death worldwide, with coronary disease behind the majority of these deaths. Coronary disease treatment is complex, particularly in chronic coronary syndromes. Chronic total occlusions are found in 18-35% of chronic coronary syndromes patients. Its treatment is a true challenge due to both procedure risk and lack of proven prognostic impact. Collateral circulation influence in determining the ischemic area and myocardial viability remains a controversial subject.

Objective: To establish the relation between coronary collateral circulation existence with myocardial viability and perfusion in chronic total occlusion patients.

Methods: Coronary collateral circulation was accessed by invasive coronary angiography. Angiographic semi-quantitative data was obtained with both Rentrop and Werner scores. Well-developed collaterals were defined as a concomitant Rentrop grade 3 and Werner collateral connection score 2 or 3, the remaining were considered poorly-developed collaterals. Myocardial perfusion and myocardial viability were evaluated with positron emission tomography.

Results: No significant differences were found in the Ischemia ($p = 0.808$) and Viability ($p = 0.263$) scores between well-developed and poorly-developed collateral patients. Ischemia score in both well-developed and poorly-developed collateral patients was 6.6 ± 4.2 and 6.9 ± 4.2, respectively. Viability score in well-developed collateral patients was 1.9 ± 1.9 and 2.9 ± 3.4 in poorly-developed collateral patients. Myocardial viability, according 18F-fluorodeoxyglucose uptake percentage, was present in the majority of patients with poorly-developed collaterals (72.2%), against 58.8% of patients with well-developed collaterals ($p = 0.404$).

Discussion: We found a poor correlation between chronically total occluded coronary collaterals angiographic characterization and myocardial ischemia and viability. Similar trials, using different imaging exams, reached different and conflicting conclusions, which encourage more studies about the predictive and protective effects of collateral circulation on the myocardium.

Conclusion: Angiographic evaluation of chronic total occlusion collateral function seems to have a poor association with myocardial perfusion and metabolism, so it should not be used as an assumption of the ischemic impairment and viability.

Keywords: Chronic Total Occlusion, Collateral Circulation, Myocardial Perfusion, Myocardial Viability, Positron Emission Tomography.

Abbreviations

CAD: Coronary Artery Disease

CTO: Chronic Total Occlusion

PCI: Percutaneous Coronary Intervention

CC: Collateral Circulation

PET-CT: 13N-NH3/18F-FDG Positron Emission Tomography - Computed Tomography

WD: Well-developed

PD: Poorly-developed

MI: Myocardial Infarction

J-CTO: Multicenter Chronic Total Occlusion Registry of Japan

SRS: Summed Rest Score

SSS: Summed Stress Score

SDS: Summed Difference Score

FDG: 18F-fluorodeoxyglucose

NH3: 13N-ammonia

OMT: Optical Medical Therapy

MACE: Major Adverse Cardiovascular Events

Background

Cardiovascular disease is the main cause of death worldwide, being that coronary artery disease (CAD) is responsible for 19% to 20% of those deaths.(1)

A chronic total occlusion (CTO) consists in the obstruction of 100% of the lumen of a coronary artery with TIMI (Thrombolysis in Myocardial Infarction) 0 flow for at least 3 months, based on angiographic evaluation. However, the exact period over which a CTO lesion is present is difficult to determine since serial coronary angiographies are not performed. It can be found on approximately 20% of patients submitted to an angiography and on 30% to 50% of patients with known CAD. Patients submitted to myocardial revascularization surgery are even more prone to developing a CTO in the future (50-55%).(2-4)

CTO treatment remains a controversial challenge. Although they share similar characteristics, patients with CTO present a different pathophysiology with the involvement of, usually, a single-vessel territory with collateral blood supply, making its evaluation even more challenging. Only 10 to 15% of CTO patients are submitted to percutaneous coronary intervention (PCI).(4, 5) Despite current guidelines recommend CTO revascularization in patients with symptoms or proven marked ischemic impairment, patient selection for CTO PCI is also focused on angiographic characteristics that predict the likelihood of procedural success as well as the presence of a well-formed collateral vessel circulation. Viability assessment plays an important role in the management of CTO patients. In patients who have viable myocardium, coronary revascularization limits the progression of myocardial damage and loss of regional contraction. However, neither angina nor the status of the coronary collateral circulation (CC) is sufficiently accurate in predicting viability.(6, 7)

The 13N-NH3/18F-FDG Positron Emission Tomography - Computed Tomography (PET-CT) is the gold standard for the assessment of myocardial ischemia and viability. Combining both myocardial perfusion and metabolism evaluation, it is possible to find 4 different patters which can predict if the myocardium is viable or not. Ischemic cardiomyopathy continues to be the most common aetiology for myocardial dysfunction in developed countries. The assessment of myocardial viability with PET-CT is based on its ability to distinguish between the two main pathogenic mechanisms for chronic myocardial dysfunction in ischemic cardiomyopathy: irreversible loss of myocardium due to prior myocardial infarction (scar), and, at least partially reversible loss of contractility as a result of chronic or repetitive ischemia (hibernating myocardium). The distinguishing feature of these two mechanisms is that revascularization has the potential to restore contractile function of hibernating myocardium but not scar.(8-12)

The establishment of CC nearby a CTO is frequent and the presence of well-developed (WD) collaterals was assumed to prevent ischemia in the CTO territory. However, some studies stated that in majority the collateral function during increased blood flow demand in viable myocardium is predominantly insufficient.(13, 14)

This study intends to find if the angiographic characterization of the collateral circulation is enough to assume perfusion and viability of a CTO dependent myocardium in order to help in therapeutic decision-making of these patients.

Methods

Study population and clinical assessment

This prospective, observational study included patients with a CTO who underwent PET-CT between 2017 and 2020. All patients were submitted to both invasive coronary angiography and PET-CT in a sequential way, after providing a written informed consent. The study was approved by the Ethical Committee.

Patients baseline clinical variables included hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, smoking history and previous myocardial infarction.

Invasive coronary angiography

Semi-quantitative assessment of CC angiographic data was performed applying both Rentrop classification and Werner collateral connection score. WD collaterals were defined as a concomitant Rentrop grade 3 and Werner collateral connection score 2 or 3. Werner grade < 2 or Rentrop score < 3 were considered poorly developed (PD) collaterals (Figure 1, Annexe I).

J-CTO (Multicenter CTO Registry of Japan) score was also calculated.

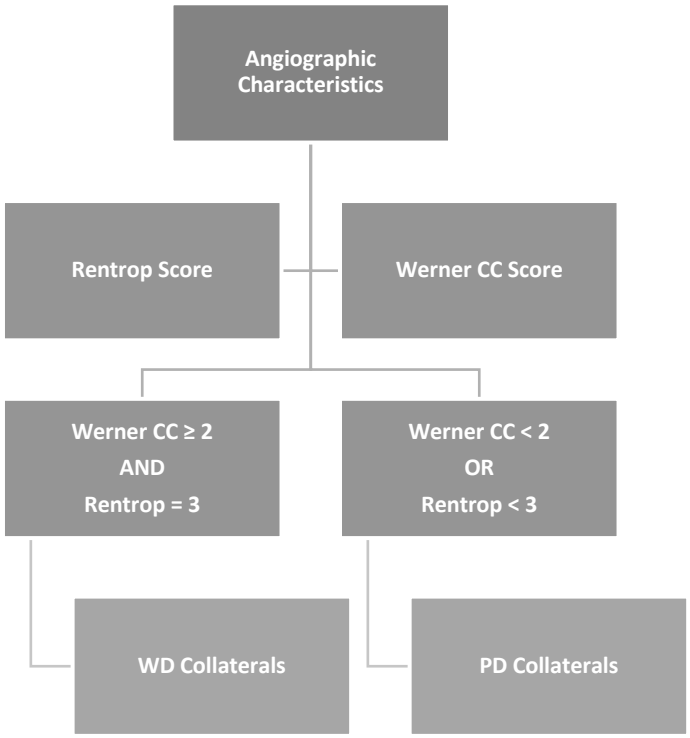

Figure 1 - Semi-quantitative evaluation of collateral circulation angiographic characteristics with Rentrop and Werner CC (collateral connection) scores

PET imaging and analysis

A standardized protocol for static 18F-fluorodeoxyglucose (FDG) PET-CT imaging was used. Patients without diabetes were studied in the postprandial state after a 50 g oral glucose load. Those patients with diabetes or glucose intolerance also received insulin according to a standardized protocol.

The left ventricle was divided into 17 segments and vascular territories according to the AHA (American Heart Association) segmentation model, accounting for coronary dominance. This 17-segments model was used for interpretation of the PET-CT study (Figure 2), and segments were graded for myocardial perfusion using a visual, semi-quantitative scale, from 0 (normal myocardium) to 4 (absence of radiotracer activity).(15, 16)

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.

The Ischemia Score or Summed Difference Score (SDS) was calculated as the difference between SSS and SRS.

The Viability Score was analyzed as the difference between SRS and the FDG score. The CTO territory was considered “viable” based on the established threshold of ≥ 50% FDG uptake compared with remote myocardium.

Only the segments of the 17-segments left ventricular model related with the respective CTO vessel were considered in the scores calculation.

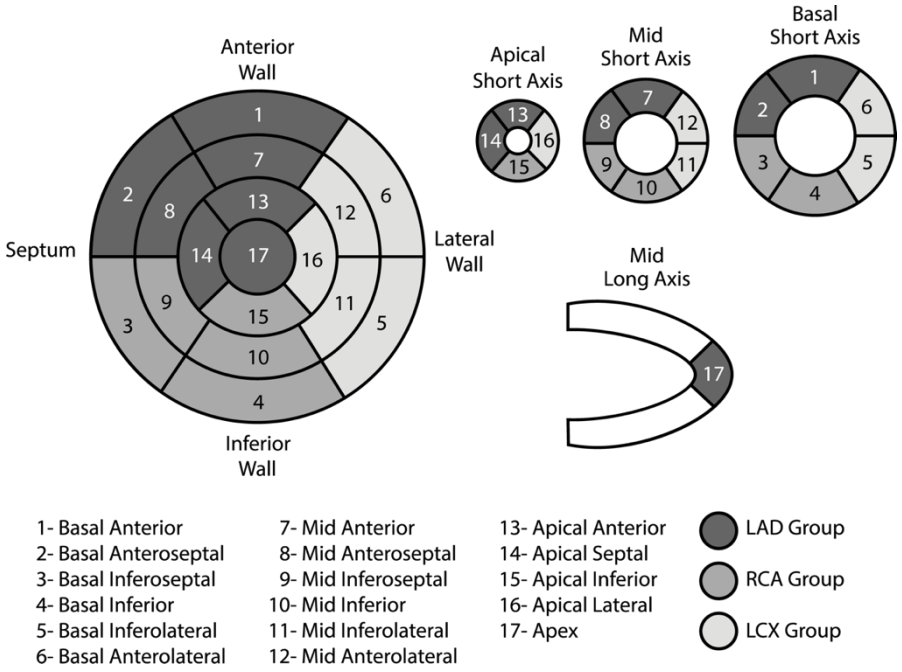

Figure 2 - Circumferential polar plot of the 17 myocardial segments divided according coronary artery supply. Recommended nomenclatures for imaging of the heart. Left anterior descending (LAD), right coronary artery (RCA) and left circumflex coronary artery groups of the 17-segments model of the left ventricle. Modified from reference 16.

Statistical analysis

It was performed using SPSS for MacOS version 25. Continuous variables were expressed as mean ± standard deviation or median [interquartile range] 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. For all tests, a two tailed $p < 0.05$ was considered statistically significant.

Results

Baseline clinical and angiographic characteristics

We recruited 58 patients (median age 62 [57-71]) with 59 CTOs. All patients underwent rest myocardial perfusion scans, stress scans were performed in 41 patients and only 38 patients complete a myocardial perfusion imaging with FDG.

With regard to clinical presentation, 23 patients were found to have a CTO in the framework of chronic coronary syndrome, 18 in the context of acute coronary syndrome, and 11 had their CTO diagnosis related to heart failure with preserved ejection fraction.

Most frequent CTO arteries were the right coronary (44.1%) and the left anterior descending artery (45.8%). Mean J-CTO Score was 1.4 ± 1.0.

WD collaterals were present in 31 (52.5%) patients and were more prevalent in right coronary artery CTOs (67.8% vs. 21.4%, $p < 0.001$).

Further patient baseline clinical and angiographic characteristics are found in Table 1.

Table 1 - Patient baseline clinical and angiographic characteristics. Values are expressed as mean ± SD, median [Q1-Q3], or numbers (%). For the "Other" remaining 7 patients CTO was found as follows: in a valvopathy study for 1 patient, in post-intervention angiographic evaluation of 3 patients, during the pre-kidney transplant study of 1 patient, and, in ventricular tachycardia management of 2 patients.

BASELINE CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS

	All patients (n = 59)	Well-developed collaterals (n = 31)	Poorly-developed collaterals (n = 28)	p value
Age	62 [57-71]	60 [56-71]	63 [58-71]	0.654
Sex				0.338
Man	58 (79.3)	20 (48.4)	28 (100.0)	
Woman	1 (1.7)	1 (3.2)	0	
Clinical characteristics				
Hypertension, medically treated	46/58 (79.3)	25/31 (48.4)	21/27 (77.8)	0.788
Dyslipidemia, medically treated	50/57 (87.7)	25/30 (83.3)	25/27 (92.6)	0.288
Diabetes mellitus, medically treated	28 (47.4)	14 (45.2)	14 (50.0)	0.154
Insulin dependent	13 (22.0)	4 (12.9)	9 (32.1)	0.075
Atrial fibrillation	8 (13.6)	6 (19.4)	2 (7.1)	0.171
Chronic kidney disease	6 (10.2)	1 (3.2)	5 (17.9)	0.063
Smoking history				0.433
Current smoker	20/47 (42.6)	14/26 (53.8)	6/21 (28.6)	
Former smoker (> 1 year)	17/47 (36.2)	9/26 (34.6)	8/21 (38.1)	
Chronic obstructive pulmonary disease	8/53 (15.1)	4/28 (14.3)	4/25 (16.0)	0.862
Clinical presentation				0.700
Chronic coronary syndrome	23 (39.0)	13 (41.9)	10 (35.7)	
Acute coronary syndrome	18 (30.5)	10 (32.3)	8 (28.6)	
Heart failure with preserved ejection fraction	11 (18.6)	4 (12.9)	7 (25.0)	
Other	7 (11.9)	4 (12.9)	3 (10.7)	
Medications				
Anti-platelet	34/57 (52.6)	16/30 (53.3)	18/27 (66.7)	0.306
Anticoagulants	9/57 (15.8)	7/30 (23.3)	2/27 (7.41)	0.100
Statin	44/56 (78.6)	24/30 (80)	20/26 (76.9)	0.780
Renin-angiotensin-aldosterone system inhibitors	42/57 (73.7)	22/30 (73.3)	20/27 (74.1)	0.949
Beta-blockers	38/56 (67.9)	19/29 (65.5)	19/27 (70.4)	0.698

BASELINE CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS

	All patients (n = 59)	Well-developed collaterals (n = 31)	Poorly-developed collaterals (n = 28)	p value
Angiographic characteristis				
	24 (40.7)	10 (32.3)	14 (77.8)	0.166
CTO vessel				
Left anterior descending	26 (44.0)	9 (29.0)	17 (60.7)	0.014
Left circumflex	6 (10.2)	1 (3.2)	5 (17.9)	0.063
Right coronary artery	27 (45.8)	21 (67.8)	6 (21.4)	< 0.001
CTO characteristics				
Ostial occlusion	9 (15.3)	4 (12.9)	5 (17.9)	0.597
Intra-stent occlusion	12 (20.3)	5 (16.1)	7 (25)	0.398
Blunt entry	25 (42.4)	12 (38.7)	13 (46.4)	0.549
Calcification	25 (42.4)	13 (41.9)	12 (42.9)	0.943
Tortuosity	3 (5.1)	3 (9.7)	0	0.091
Length (> 20 mm)	28 (47.5)	15 (48.4)	13 (46.4)	0.880
J-CTO score	1.39 ± 1.1	1.42 ± 1.0	1.36 ± 1.1	0.746

Myocardial perfusion and ischemia

No significant differences were found in the Ischemia Score (ischemia score in WD was 6.6 ± 4.2 vs. 6.9 ± 4.2 [p = 0.808]).

PD collateral CTO patients had numerically worse perfusion scores suggesting higher levels of ischemia (Figure 3).

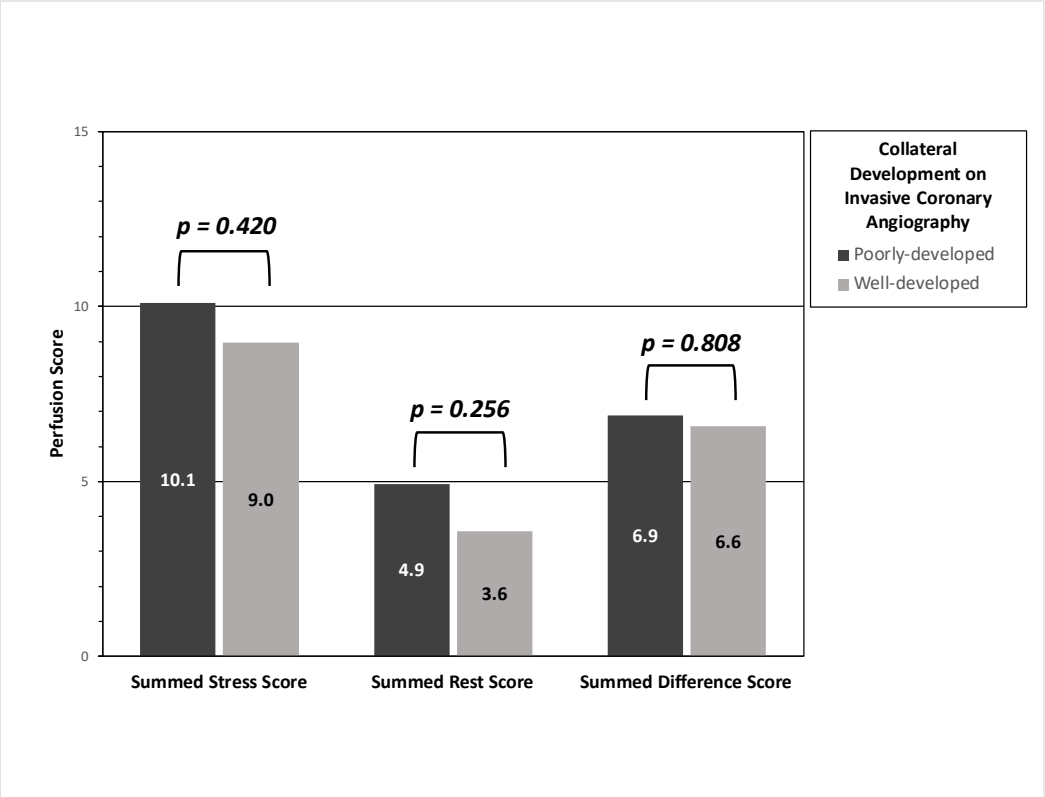

Figure 3 - Comparison of the SSS, SRS and SDS, in the CTO territory, between patients with PD and WD collaterals.

Myocardial viability

No significant differences were found in Viability Score (viability score in WD was 1.9 ± 1.9 vs. 2.9 ± 3,4 [p = 0.263]) (Figure 4).

Viability, according to FDG uptake percentage, was present in 72.2% of PD collateral CTO patients (vs. 58,8% in WD, p = 0.404) (Figure 4).

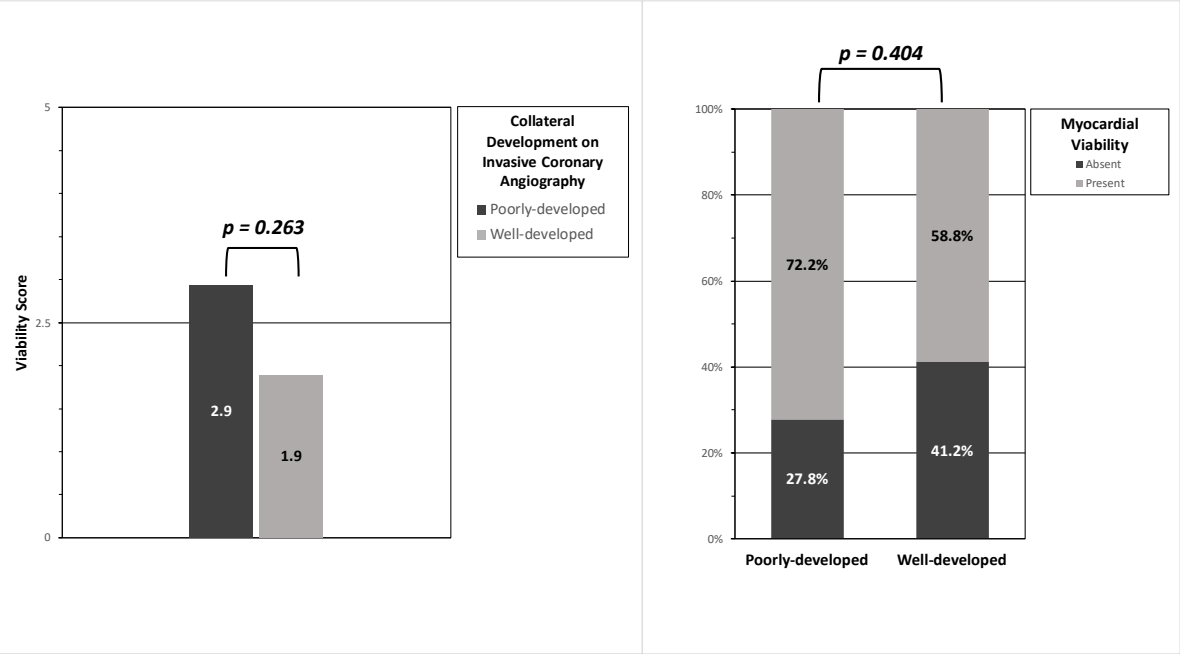

Figure 4 - Left: comparison of the Viability Score (SRS – FDG Score), in the CTO territory, between patients with PD and WD collaterals. Right: frequency of myocardial viability in the CTO territory, between patients with PD and WD collaterals, obtained through FDG uptake percentage.

Imaging examples

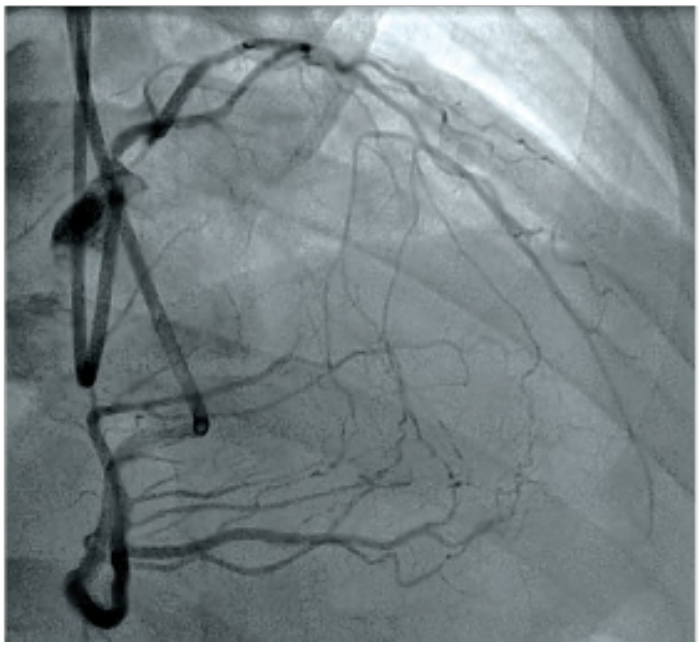

Figure 5 - Coronary angiographic evaluation of left descending artery CTO CC function with Rentrop 3 CC.

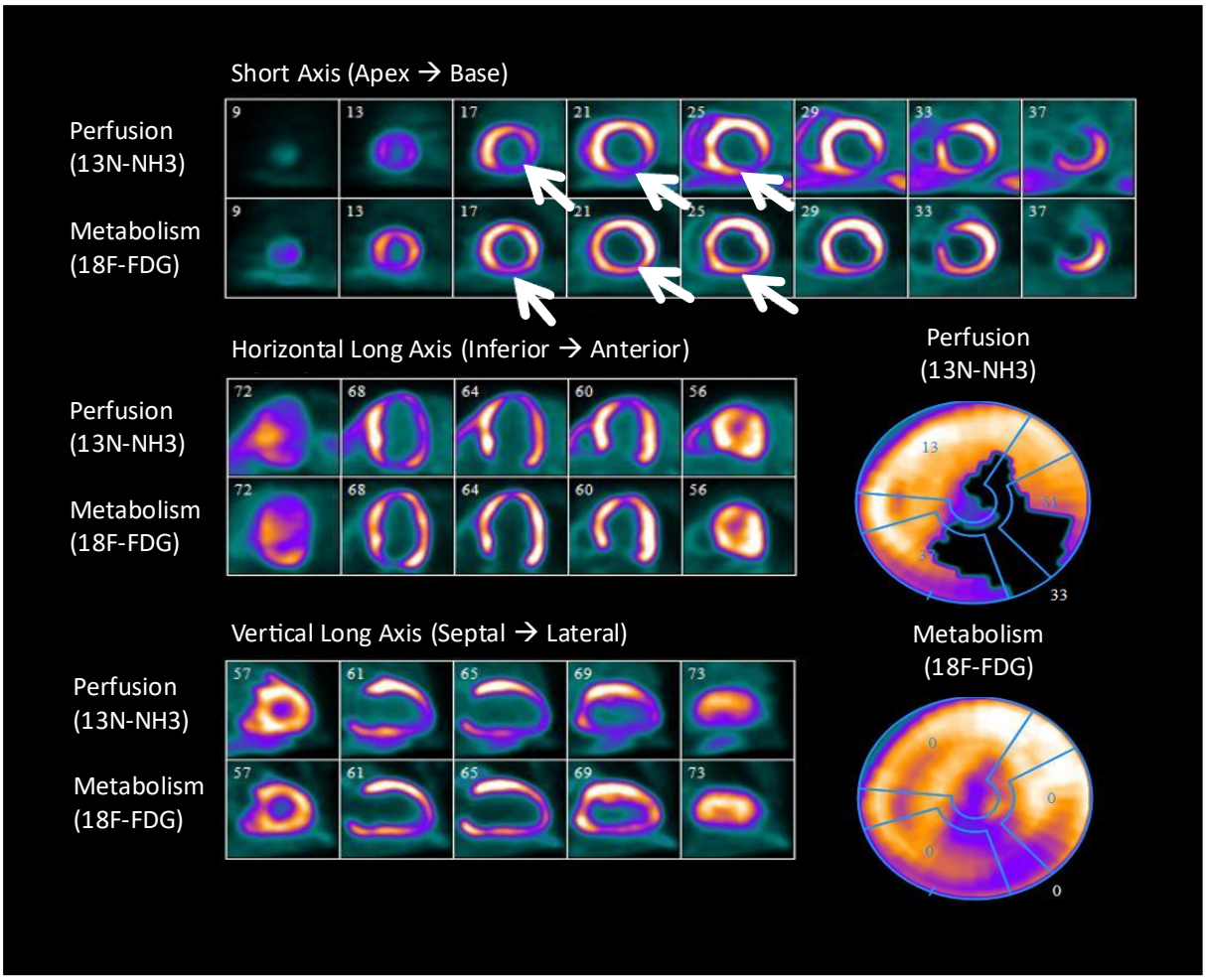

Figure 6 - Example of assessment of myocardial viability with PET-CT with fixed myocardial inferolateral perfusion defect but with 18F-FDG uptake (viable). Top rows: 13N-ammonia (13N-NH3) is used as a tracer of myocardial blood flow at rest in short axis images starting at the apex and moving toward the base of the heart (upper image), horizontal long axis (middle image) and vertical long axis (lower image). Myocardial perfusion is markedly decreased in the apical, inferior and inferolateral regions (white arrows). Bottom rows: 18F-fluorodeoxyglucose (18F-FDG) is used as a tracer of myocardial glucose metabolism. 18F-FDG uptake is enhanced relative to blood flow, demonstrating a pattern of perfusion-metabolism mismatch (white arrows) in the abnormally perfused myocardial regions, indicative of viable or hibernating myocardium. Polar map of viability study: the upper polar map plot displays the extent of the rest perfusion defect (black area). The lower polar map plot shows 18F-FDG uptake in the rest perfusion defect area indicating metabolic viability. Image source: ICNAS (Instituto das Ciências Nucleares Aplicadas à Saúde). Modified from reference 12.

Discussion

CTO treatment options and benefits

A CTO, as a chronic lesion (100% occlusion with TIMI 0 flow for at least 3 months, Annexe II), allows time for recruitment and development of CC. Therefore, a CC is often present in CTOs and its predictive and protective effects on myocardial viability remain an area of controversy, encouraging studies about its impact on the approach of these patients.

The decision to revascularize patients with CTOs is not clear and many factors, including cardiac imaging, play an important role for the patient selection who will benefit from intervention. It remains unclear how different imaging modalities can be related, incorporating both physiological and anatomical evaluation, in decision-making and planning.

Multiple scoring systems are available in order to predict technical success of these patients. For instance, the J-CTO score, is a 5 point scoring system (blunt stump, calcification, within lesion bending $> 45°$, occlusion length ≥ 20mm, and prior failed attempt to revascularize the CTO) to assess the difficulty of CTO crossing. (Annexe III).(2, 4, 17)

Treatment options for patients with a CTO include standard approach for stable CAD with medical therapy, as well as lifestyle and risk factor modifications. Current guidelines recommend CTO revascularization in patients with refractory symptoms or objective evidence of marked ischemic burden. It is possible that both angina or heart failure symptoms may improve after revascularization.(5, 18)

In EURO-CTO trial, a lower frequency of angina on the Seattle Angina Questionnaire with PCI + optimal medical therapy (OMT) over OMT alone was demonstrated, but 12-month major adverse cardiovascular events (MACE) rate was not reduced. In case of myocardial dysfunction, they performed a non-invasive imaging study to assess the myocardial viability of the CTO coronary territory dependence. In this study PCI was successful in 86.6% of revascularized patients.(19)

The results of the DECISION-CTO trial showed that routine PCI + OMT was not superior to OMT alone in reducing MACE at 3-years follow-up, neither in reducing angina class or quality of life. However, this study did not require the demonstration of ischemia or viability though imaging.(20)

PET-CT imaging in CTO patients

Cardiac imaging in CTO can be used not only to evaluate the predictors of recovery after intervention but also to provide planning and procedural assistance. The prediction for symptom improvement can be based on physiology evaluation, which includes viability and ischemia assessment. Planning evaluation also includes anatomy assessment, besides viability and ischemia testing.(5)

PET-CT is a very embracing imaging modality which allows the assessment of both viability and perfusion with myocardial FDG and 13N-ammonia (NH3) uptake imaging, respectively. PET-CT interpretation patterns can be used on predicting the recovery capacity of the CTO territory (Annexe IV). Only two PET-CT patterns are considered viable: the pattern with both perfusion and metabolism preservation which can be present in normal myocardium or myocardial stunning, and, the mismatch pattern, only with perfusion reduction which usually results from hibernating myocardium.(8, 9)

An accurate and reliable assessment of ischemia is imperative, as patients with coronary CTOs are in a chronic state of ischemia. Both non-invasive and invasive studies have demonstrated that even in patients with WD collaterals, there may be significant ischemia as rest.(15) In this study we used PET-CT imaging in order to determine if the invasive coronary angiography CC semi-quantitative analysis was sufficient to assume myocardial ischemia and viability in a CTO territory. After using proper statistical analysis, we found there is no strong relation between CC angiographic characterization and myocardial perfusion or viability. Angiographic characteristics should not be used as a single way of determining myocardial impairment and more relevance should be given to prior ischemia and viability documentation, namely with a PET-CT.

Similar studies

Some studies have tried to find a relation between CC and viable myocardium. However, there are few reports using PET-CT as an imaging modality: Di Carli *et al*. (1994) demonstrated that the CC development in CTOs does not assure a corresponding viable myocardium detected with PET-CT.(21) Dong *et al.* (2018) indicated that CC angiographic assessment in not an effective way of predicting myocardium viability and reported no significant difference between resting myocardial perfusion and CC grade in CTO patients.(22)

Other similar studies, used quantitative cardiac magnetic resonance imaging to access viability. Khaled *et al.* (2020) concluded that the presence of WD collaterals could translate a greater myocardial viability of a CTO territory in the magnetic resonance, as an independent predictor.(23) Similarly, Choi *et al.* (2013) shown an inverse relationship between the extent of transmural scar assessed by late gadolinium enhancement and the degree of CC development.(24) Ripley *et al.* (2014) demonstrated that a gradation of greater accessed viability was found with increase in CC Rentrop grade.(25) Malek *et al*. (2015) found that late gadolinium enhancement was significantly lower in CTO territories subtended by Rentrop grade 3 CC.(26) Schumacher *et al.* (2020) came to the conclusion that WD collaterals are associated with less myocardial scar and more preserved function with greater potential recovery. However, they also indicated that neither PD collaterals nor a myocardial infarction history in CTO patients exclude viability of the dependent territory.(27) Wang *et al.* (2019) found poor correlation between angiographic grade of CC and the transmural extent of myocardial scarring downstream of a CTO. (28)

Limitations

First, the sample size is not large enough to represent the population. Second, the analysis of the angiographic and PET-CT results was made by a single observer and there is some subjectivity in the semi-quantitative evaluation of the CC. We could still point the coronary anatomical variability that may not totally correspond to the 17-segment model for each territory used. The greatest variability occurs at the apical cap, segment 17, which can be supplied by any of the 3 arteries.

Conclusion

Angiographic evaluation of CTO collateral function seems to have a poor association with myocardial perfusion and metabolism, so it should not be used as an assumption of the ischemic burden and viability. Furthermore, myocardial viability was present in the majority of patients with PD collaterals which means PD collaterals related to the CTO territory should not be a reason to defer a patient from considerations for CTO revascularization.

It can thus be concluded that myocardial viability should not be presumed exclusively on the CC angiographic anatomical characteristics. The viable myocardium should be searched using different imaging modalities in both CTO patients with WD and PD collaterals. It is crucial that myocardial perfusion and viability evaluation are taken into account in the decision-making of these patients.

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Annexes

Annexe I - Rentrop and Werner Collateral Connection scores. Modified from reference 13.

COMPARISON OF RENTROP AND WERNER COLLATERAL CONNECTION SCORES

Rentrop		Werner	
Grade 0	No filling of any collateral channel	**CC 0**	No continuous connection
Grade 1	Filling of the side branches of the infarct-related artery	**CC 1**	Threadlike continuous connection
Grade 2	Partial filling of the epicardial vessel of the infarct-related artery	**CC 2**	Side branch-like connection (≥ 0,4 mm)
Grade 3	Complete collateral filling of the epicardial vessel	**CC 3**	> 1 mm diameter of direct connection

Annexe II - Thrombolysis in Myocardial Infarction Flow Grading System. Modified from reference 2.

THROMBOLYSIS IN MYOCARDIAL INFARCTION FLOW GRADING SYSTEM

Flow grade	Description	Meaning
TIMI 0 Flow	Absence of any forward flow beyond a coronary occlusion	**No perfusion** **Complete occlusion**
TIMI 1 Flow	Faint forward flow beyond the occlusion with an incomplete filling of the distal coronary bed	**Penetration without perfusion**
TIMI 2 Flow	Delayed forward flow with complete filling of the distal coronary bed	**Partial perfusion**
TIMI 3 Flow	Normal flow with complete filling of the distal coronary bed	**Full perfusion**

Annexe III - Japanese Chronic Total Occlusion Score. Modified from reference 17.

J-CTO SCORE

Variables	Category
Entry Shape Tapered: 0 points Blunt: 1 point	**Easy:** 0 points
Calcification Absence: 0 points Present: 1 point	**Intermediate:** < 2 points
Occlusion Length < 20 mm: 0 points ≥ 20 mm: 1 point	**Difficult:** 2 points
Re-try Lesion No: 0 points Yes: 1 point	**Very Difficult**: ≥ 3 points

Annexe IV - PET-CT interpretation patterns. Modified from references 9 and 11.

PET-CT INTERPRETATION PATTERNS

Category/Pattern	Perfusion	Glucose metabolism
Normal Normal myocardium Myocardial stunning Viable	Preserved	Preserved
Mismatch Hibernating myocardium Viable	Reduced	Preserved
Match Myocardial scar Non-viable	Reduced OR Proportionally reduced	Reduced OR Proportionally reduced
Reverse mismatch Non-ischemic cardiomyopathy Left bundle branch block Diabetes mellitus	Preserved	Reduced