Properties of myocardial microcirculation in patients with different pathomorphological substrates, before and after recanalization of coronary artery chronic total occlusion

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BACKGROUND

Chronic total occlusion (CTO) is defined as a complete occlusion of the coronary artery without blood flow (TIMI 0) in the occluded segment, which lasts longer than 3 months (1). In various published series, the prevalence of CTO lesions in patients with coronary artery disease is between 20-30% (2-4). In a large Canadian registry with over 16,000 subjects, the prevalence of CTO lesions on diagnostic coronary angiography was 18.4% of all angiographically significant coronary stenoses (5).

This coronary lesion group is especially recognized as technically most complex coronary lesion subset for percutaneous revascularization. The success of percutaneous revascularization of these lesions has been only 60-70% until recently, which is significantly lower than the revascularization of non-occlusive lesions, which is successful in as many as 98% of cases (5,6). Over the past decade, significant advances have been made in the technology, equipment, and techniques of percutaneous revascularization procedures for the treatment of CTOs, which, with increasing operator experience, have resulted in procedural success rates of about 90% (7-9).

The particular functional characteristics of CTO lesions are the existence of collateral blood vessels, and smaller or larger amount of viable myocardium in the area of its vascularization. The complex interplay of these two factors depends on the overall coronary physiology and influence the clinical manifestations in the patient.

Collaterals are interarterial connections that allow blood flow from the donor artery to the vascular territory that belongs to the occluded epicardial artery. In this manner, the integrity of the myocardium supplied by the occluded coronary artery can be preserved partially or even completely (10). However, although at rest collateral blood flow can provide preservation of the viability and even contractile capacity of the myocardium, it is considered that collateral flow during exertion is not sufficient in up to 90% of cases (11).

Collaterals develop in the process of arteriogenesis through the "recruitment" of preformed and preexisting interarterial connections, in a process that depends largely on the hemodynamic shear stress along the pressure gradient (between the unoccluded and occluded artery) that occurs in the case of coronary artery occlusion, and the presence of a viable myocardium is not necessary for the development of collaterals (10,12).

Numerous studies have been published to date that examined the functional parameters of occluded (and recanalized) coronary artery microcirculation (10,11,13–18), while data on the potential effects of CTO recanalization on collateral flow and collateral donor physiology are scarce. In the presence of CTO, if the myocardium in the area of the occluded artery is perfused with significant blood flow through the collateral bloodstream, the CTO recanalization and the establishment of normal antegrade flow results in a rapid decrease or termination of the collateral flow, and decrease flow in the donor artery, which may alter circulatory parameters of donor artery itself (e.g. fractional coronary flow reserve - FFR, coronary flow reserve - CFR, etc.). *Werner* and co-workers have elegantly demonstrated that collateral flow provides about 50% of

the antegrade flow that is established after CTO recanalization (17). The collateral function decreases rapidly after opening the CTO, and practically after a little more than 30 minutes after the establishment of antegrade flow reaches the lowest level that is maintained even after 24 hours from the intervention (17,19). It is not yet clear enough and there is insufficient published data on the contribution of collateral flow to coronary artery donor physiology. Thus, *Werner et al* showed that the FFR in the artery donating collateral for CTO was 0.82 ± 0.11 in 18 patients who did not have angiographically significant stenosis on the donor artery (15). In this way, they showed that small angiographic irregularities or mild diffuse coronary disease in the case of large coronary flow (caused by developed collateral blood flow) can give a significant drop in pressure in the arterial tree near the border defined for the existence of ischemic lesions. Furthermore, several cases have been reported in the literature in which there were significant changes in the FFR value in the donor artery after successful CTO recanalization, which in some cases led to a change in the indication for revascularization by moving from a FFR value <0.80 to values ≥0.80 (20-24). It is unclear to what extent these cases represent the broader population of CTO patients and whether they can be generalized. "Publication bias" where relatively rare occurrences that show major changes in the expected direction are more likely to be published than smaller ones or changes in the unexpected direction (25, 26). To our knowledge, only two studies to date have been published on a large number of patients examining the impact of CTO reanalysis on FFR in the non-occluded arteries. In a study of 14 subjects who had a CTO recanalized, 6 of 9 patients with initial ischemic FFR in the donor artery experienced a change in FFR to the non-ischemic range (FFR before PCI 0.76 ± 0.04 and after PCI 0.86 ± 0.03) (27). Recently, the largest and most important study was published with 34 patients examining the impact of CTO recanalization on the functional parameters of non-occluded vessels (28). This study confirmed that after successful CTO recanalization, there is a modest increase in FFR (0.810 versus 0.782) in the collateral donor artery, as well as a reduction in coronary flow therein (28). Recently, a group of Japanese authors also proposed an in vitro model to test the effect of collateral flow on the circulation of the donor artery and the recipient of the collateral flow, with a complex mathematical model and formulas describing the effect of the collateral recipient's blood vessel revascularization on the function of the collateral donor blood vessel (29). Non-invasive measurement of coronary flow reserve before and after CTO reanalysis has been reported in only one study so far, which in a series of 24 patients showed that after successful recanalization of the CTO of the right coronary artery, there was an increase in coronary flow reserve (CFR) after 3 months of intervention (2.3 ± 0.3 vs 1.8 ± 0.3; p <0.001), whereas in the immediate postprocedural period (within 24h of PCI), the CFR value through the LAD artery did not increase (1.8 ± 0.3 vs 1.8 ± 0.2, p = 0.89).

Previous studies have not sufficiently examined the relationship between collateral flow changes after PCI for CTO and changes in functional parameters of the donor artery with the amount of viable myocardium and segmental function of the left ventricle after revascularization. Also, the association of the phenomenon of coronary theft with the viability and occurrence of inducible myocardial ischemia has not been sufficiently investigated.

WORKING HYPOTHESIS

1. Following successful recanalization of chronic total coronary artery occlusion, the hemodynamic microcirculatory parameters (CFR, FFR, HMR) in the non-occluded (collateral donor) coronary artery will change as compared to the values before the procedure.
2. The magnitude of change in these parameters depends on the size of the collateral blood flow to the territory of the occluded coronary artery and the amount of viable myocardium in the vascularization zone of the occluded artery.

OBJECTIVES OF THE RESEARCH

1. The primary goal of the study is to determine the magnitude and direction of change in the functional parameters of microcirculation in collateral donor coronary artery after the successful opening of the chronic total occlusion.
2. The secondary goals of the study are:

a) determination of the factors on which the change in hemodynamic parameters of the non-occluded arteries depend,
b) determining the factors that influence the improvement of segmental kinetics of the left ventricle after six months from the recanalization of the occluded artery,
c) determination of correlation of functional parameters of microcirculation with ischemia, viability and segmental kinetics of the left ventricle,
d) determining the correlation (change) of microcirculatory functional parameters with the quality of life determined by the Seattle Angina Questionnaire.

STUDY PROTOCOL

A. Data collection before intervention

In all patients, the following tests will be performed in the period before the intervention:
- Electrocardiogram,
- Echocardiographic examination,
- Stressechocardiographic test,
- Measurement of coronary flow reserve for collateral donor artery (RCA or LAD) by non-invasive transthoracic Doppler echocardiography,
- Scintigraphy (SPECT) for detection of viable myocardium in the CTO area,
- Seattle Angina Questionnaire

B. Data collection during PCI for CTO

At the beginning of the procedure, after administration of nitroglycerin intracoronary (200 μg), angiography will be performed with optimal visualization of epicardial coronary circulation and collateral blood flow to the area vascularized by the occluded artery. Angiographic quantification of collateral and collateral flow will be performed according to Rentrop and CC classifications

(16,30). Quantitative coronary angiography (QCA) will be used to quantify all coronary stenoses except CTO, which by definition is 100% stenosis.
Before the CTO recanalization, after adequate heparinization of the patient (by administration of 100 IU / kg heparin intravenously), the following functional parameters will be measured in each of the two non-occluded coronary arteries using a coronary wire with pressure and flow sensor (Combowire; Volcano Corp, San Diego, CA):
- Basal blood flow velocity
- Hyperemic blood flow velocity
- Coronary flow reserve (CFR)
- Mean blood pressure in the aorta (Pa) and at the sensor position (Pd)
- Fractional flow reserve (FFR)
- Hyperemic microvascular resistance (HMR)
Hyperemia will be caused by the administration of an intravenous infusion of adenosine (140μg / kg / min).
Following this, the CTO will be opened, using standard contemporary strategies and materials. After passage of the occlusion with the antegrade wire, a coronary wire with pressure and flow sensor will be introduced distally to the occlusion, and hyperemia will be induced by administering adenosine intravenously. After measuring the above functional parameters at this location, CTO dilatation and stent implantation will be initiated. Successful percutaneous coronary intervention (procedural success) is defined as the establishment of TIMI 3 flow with a residual stenosis of less than 30% after stent implantation or balloon dilatation. In the case of procedural success, the previously described functional parameters will be measured in the recovered coronary artery using the coronary wire with pressure and flow sensors when administered adenosine intravenously.
Finally, to evaluate the effect of CTO opening on the physiological parameters of the non-occluded arteries, all the functional measurements mentioned above will be repeated with the same (or closest possible) sensor positions in both non-occluded arteries, as described in detail above.

C. Data collection in the procedure
The following examinations will be performed in all patients who have achieved procedural success:
- *Within the first 24 hours of intervention*: measurement of coronary flow reserve for LAD and RCA artery by non-invasive Doppler echocardiography,
- *6 months after the intervention:*
- Electrocardiogram
- Echocardiographic examination
- Measurement of coronary flow reserve for LAD and RCA artery by non-invasive Doppler echocardiography
- Seattle Angina Questionnaire
- Information on possible adverse cardiovascular events from intervention to follow-up (MACE)
- Catheterization of the heart if clinically indicated

MEASUREMENT AND DEFINITION

- The procedural success of recanalizing chronic total occlusion.
Successful percutaneous coronary intervention (procedural success) is defined as the establishment of TIMI 3 flow with residual stenosis of less than 30% after stent implantation or balloon dilatation.
- TIMI flow is a scale that semi-quantifies antegrade flow through the coronary artery as follows: TIMI 0 - no antegrade flow behind occlusion; TIMI 1 - there is a flow behind the occlusion site with incomplete filling of the distal coronary artery; TIMI 2 - slow antegrade flow that completely fills the distal artery; TIMI 3 - Normal coronary flow with complete filling of distal artery (31).
- Rentrop classification of collateral flow (30) is a widely used angiographic system that does not describe the characteristics of collateral blood vessels themselves, but their effect on filling the occluded artery distal to the site of occlusion. There are 4 grades of collateral flow according to this classification: Rentrop 0 - no filling of the occluded vessel via collateral blood flow, Rentrop 1 - filling only the lateral branches of the occluded vessel without filling the main epicardial blood vessel, Rentrop 2 - partial filling of the main epicardial blood vessel, and Rentrop 3 - completely filling the major epicardial blood vessel.
- Semi-quantitative classification of collateral vessels (collateral connections) (16): CC0 - no continuous connections, CC1 - continuous collateral threadlike connections, CC2 - lateral branches (diameter ≥0.4mm). CC3 - Direct connections ≥1mm in diameter.
- The Seattle Angina Questionnaire is a modern and validated instrument for assessing the quality of life in patients with coronary disease (32). This questionnaire is based on five different domains that are assessed in patients: physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception.
- Myocardial scintigraphy - All patients will have a 740 MBq 99mTc-MIBI myocardial scintigraphy given intravenously 10-15 minutes after sublingual administration of 0.5mg nitroglycerin (33) before attempting to recanalize the occlusion. The recording will take place 45-60 minutes after the administration of the radiopharmaceuticals, in a supine position, with a single gamma camera equipped with a high-resolution low energy collimator. 64 projections will be taken in the 180-degree range (starting from 45 degrees from the right front oblique to 45 degrees from the left rear position). After the reconstruction of the image, semi-quantification of myocardial perfusion and function will be done software. The size and severity of the perfusion defect will be calculated based on a 17-segment radiopharmaceutical uptake model and based on a guide from the European Nuclear Medicine Association and the European Association of Cardiologists for radionuclide imaging of cardiac function (34). The total download score of MIBI radiopharmaceuticals (SRS) will be calculated. The size and severity of the perfusion defect will also be indicated according to each of the three major vascular territories: anterior descendant, circumflex, and right coronary artery. Assessment of regional left ventricular wall thickness will be assessed by visual inspection in the Chinese mode of SPECT perfusion images (34). The presence of viable myocardium in the infarct zone will be considered as the absorption of radiopharmaceuticals ≥55% of normal perfusion, with left-wall wall thickness gain (35–37). Also, the left ventricular ejection fraction, end-diastolic volume, and end-systolic volume will be evaluated using an automated algorithm (38).
- Echocardiography - Transthoracic echocardiographic examination will be performed in all subjects. All standard echocardiographic sections will be made. Measurements from orthogonal apical sections ("two and four cavities") will be used to estimate the global function of the left ventricle, with the simulation fraction calculated using the Simpson method. A 17-segment

model will be used to calculate the wall motion score index of the left ventricular segment, while segmental kinetics will be constructed as follows: 1-normal segment kinetics, 2-hypokinesia, 3-akinesia, and 4- dyskinesia. This score will be calculated by dividing the sum of the mobility levels of the individual segments by the total number of visualized segments (39).

Stressechocardiographic test - a submaximal, symptom-limited stress-echocardiographic test on a Bruce protocol will be performed in all subjects. Before the test, at the end of each load step, and after the test is completed, arterial blood pressure and SF will be measured. The criteria for discontinuation of the test are: onset of anginal problems, fatigue, reaching submaximal frequency, the onset of ST depression greater than 1 mm, and the onset of hypertensive reaction (blood pressure greater than 240/130 mmHg). According to the protocol of the stressechocardiographic test, an echocardiographic examination in the left decubital position will be done to everyone before and immediately after the test. The test was defined as positive for the presence of inducible myocardial ischemia if there was a deterioration of left ventricular segmental kinetics at the EHO after the test.
- Measurement of coronary flow reserve for LAD artery - Transthoracic Doppler echocardiographic examination will record blood flow velocities in the LAD artery, at rest and after induction of hyperemia by administering adenosine intravenously (0.14 mg/kg/ min). Coronary flow reserve will be calculated as the ratio of maximum hyperemic and maximum basal flow rate (40).
- The following invasive functional parameters will be determined for all subjects where technically feasible:
- Basal blood flow velocity
- Hyperemic blood flow velocity
- Mean blood pressure in the aorta (Pa) and at the sensor position (Pd)
- Coronary flow reserve (CFR)
- Fractional flow reserve (FFR)
- Hyperemic microvascular resistance (HMR)
- Procedural complications - All patients will be monitored for the occurrence of periprocedural complications, including myocardial infarction, coronary perforation, cardiac tamponade, emergency cardiac surgery, complications at the site of vascular access.
- Adverse cardiovascular events during the follow-up period - All patients will be monitored for adverse cardiovascular events during the follow-up period: cardiovascular death, non-fatal myocardial infarction, and any recurrent myocardial revascularisation.

SAMPLE SIZE

Based on the primary goal of the study, the required number of subjects was calculated according to the appropriate formula for Student's t-test for related samples using the following assumptions and data from previous published research: statistical power (1-β) = 0.80; statistical significance (α) = 0.05; expected change (increase) of coronary flow reserve (CFR) in the donor artery after opening of chronic total occlusion of 0.5 (41-43), expected standard deviation for invasive Doppler CFR in the reference artery of 0.85 (44).

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \cdot \sigma^2}{\delta^2} = \frac{(1{,}960 + 0{,}842)^2 \cdot 0.85^2}{0{,}5^2} = 22{,}7 \approx 23$$

The sample size we calculated to be 23 patients, based on the above assumptions. Taking into account that the success of the procedure of opening a chronic total occlusion at the Cardiology Clinic of the Clinical Center of Serbia is 90% and that 15% of the respondents will be unavailable for a six-month follow-up, a total of 30 patients should be included.

STATYSTICAL ANALYSIS

- The following statistical methods will be used for data description:
Mean, median, standard deviation, interquartile range
- The following methods of analytical statistics will be used:
chi-square test, Student's t-test for independent and related samples, correlation, linear regression, logistic regression, The ROC curve and C-statistics will be used to determine the cut-off values. All tests will be realized as two-way. A p-value of <0.05 will be considered statistically significant. Data analysis will be done in the SPSS statistical software package (version 19 or above).

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