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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Combined analysis of myocardial function, viability, and stress perfusion in patients with chronic total occlusion in relation to collateral flow

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Abstract

Background: Indications for revascularisation in chronic total occlusion (CTO) of the coronary artery depend on the interplay between myocardial function, viability, and ischaemia. The technical feasibility of the procedure often relies on the collateral flow to the occluded artery.

Aim: To assess the relation between the degree of collateral flow and characteristics of the myocardium supplied by the occluded artery.

Methods: The study included 54 patients (mean age 62 years, 85% males) with CTO referred for cardiovascular magnetic resonance (CMR) to assess indications for revascularisation. The presence of well-developed collateral flow was defined as a collateral connection grade = 2 and Rentrop score = 3.

Results: The presence of well-developed collaterals (n = 24, 44%) was less likely to be related to systolic dysfunction of the segments supplied by the occluded artery (mean wall motion score index 1.31 ± 0.44 vs. 1.64 ± 0.67, p = 0.04) in comparison to a lack of well-developed collaterals. Patients with well-developed collaterals had a lower frequency of previous myocardial infarction of the CTO territory (38% vs. 67%, p = 0.03) with similar frequency of transmural infarctions (21% vs. 23%, p = 0.83). They less frequently presented perfusion deficits of the CTO area during hyperaemia (42% vs. 70%, p = 0.03) and the size of deficits was smaller (median 0.0% [interquartile range 0–12%] vs. 7.5% [0–15%], p = 0.04).

Conclusions: Myocardial segments supplied by CTO with well-developed collaterals are less prone to inducible ischaemia, have better systolic function, and are less likely to undergo myocardial infarction, in comparison to those supplied by CTO with poor collateral circulation. CMR is a non-invasive method that can be used for a comprehensive workup of patients being considered for CTO revascularisation.

Key words: chronic total occlusion, collateral circulation, cardiovascular magnetic resonance, viability, ischaemia

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INTRODUCTION

Technical developments in interventional cardiology over recent years have opened the way for more successful percutaneous restoration of blood flow in chronically totally occluded (CTO) coronary arteries [1]. Clinical studies have consistently demonstrated that revascularisation of the CTO leads to an improvement of the myocardial systolic function and a reduction of ischaemic burden, and may even improve prognosis [2–6]. Qualification for the procedure is based on clinical symptoms, and the assessment of ischaemia and viability of the myocardial area supplied by the occluded artery [7]. Although dedicated randomised clinical trials in patients with CTO are ongoing, extrapolation of data from the literature on patients with stable coronary artery disease suggests that revascularisation is warranted in those with at least moderate ischaemia [8]. Most of the studies in that area used single photon emission computed tomography (SPECT) [4, 7, 9, 10]. The number of studies with the use of cardiovascular magnetic resonance (CMR) allowing comprehensive assessment of myocardial function, viability, and ischaemia in these patients is far smaller [5].

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Technical feasibility of the CTO revascularisation relies on the angiographic picture of the occluded artery and often on the collateral flow to the artery segments distally to the site of occlusion [1, 7]. Many studies focused on the relation between the angiographic status of the CTO territory and the feasibility of the procedure by means of dedicated tools and various approaches (antegrade, retrograde, or combined) [1]. There are very few reports analysing the interplay between the status of collateral circulation development and myocardial function of the CTO territory [9–14]. The one CMR study addressing this issue focused on the relation between systolic myocardial function and the degree of irreversible injury (previous infarction of the CTO territory and angiographic collateral circulation), but it did not include the assessment of myocardial stress perfusion [13].

Therefore, the aim of this study was to comprehensively assess the relation between angiographic collateral flow to the CTO and functional status (systolic function, stress perfusion, and myocardial viability) of the CTO territory by means of CMR.

METHODS

Study group

The study retrospectively included 54 consecutive patients within our institution between the end of 2010 and the beginning of 2014 (mean age 62 years, 85% males). All of these patients had CTO and were referred for CMR to assess indications for revascularisation. CTO was defined as the presence of flow interruption in the epicardial coronary artery or minimal contrast penetration through the lesion without distal vessel opacification (Thrombolysis in Myocardial Infarction [TIMI] 0–1) [15]. Patients with documented acute coronary syndrome within three months preceding coronary angiography were excluded from the study. Patients after previous coronary artery by-pass grafting with patent grafts were excluded from the analysis.

Informed consent was obtained from each participating patient. The study was approved by the Local Ethics Committee.

Magnetic resonance

All patients underwent CMR scan with a 1.5 Tesla scanner (Magnetom Avanto, Siemens, Erlangen, Germany). Scout images and electrocardiographic gated breath-hold steady state free precession (SSFP) cine images in two- and four-chamber views were registered to set up final short axis imaging planes. Systolic function assessment was based on SSFP images from the mitral valve insertion point to the apex to encompass the entire left ventricle (LV). Imaging parameters were as follows: field of view 28 × 34 cm, matrix 416 × 512, effective repetition time 33 to 54 ms, echo time 1.2 ms, flip angle 64 to 79°, slice thickness 8 mm, gap 1.6 mm, in-plane image resolution 1.6 × 1.6 mm to 1.8 × 1.8 mm, and temporal resolution 25 to 40 phases per cardiac cycle.

This was followed by first-pass stress perfusion by means of a saturation-recovery echo gradient sequence registered in three short-axis slices (basal, mid-ventricular, peri-apical) after intravenous administration of 0.1 mmol/kg of gadolinium contrast agent at 3.5 mL/s (gadobutrol, Gadovist®, Bayer Schering Pharma AG, Berlin, Germany) and flushed with 30 mL of isotonic saline. Hyperaemia was obtained by 4-min infusion of 0.73 mg/kg of dipyridamole. Imaging parameters were as follows: field of view 27 × 36 cm, matrix 94 × 192, effective repetition time 165 ms, echo time 1.08 ms, flip angle 12°, slice thickness 10 mm, and in-plane image resolution 2.9 × 1.9 mm.

Delayed enhancement (DE) images were obtained with a breath-hold segmented inversion recovery sequence performed 10 min after contrast injection and acquired in the same orientation as the cine images. Imaging parameters were as follows: field of view 28 × 34 cm, matrix 154 × 256, effective repetition time 700 ms, echo time 4.9 ms, flip angle 30°, slice thickness 8 mm, gap 1.6 mm, and in-plane image resolution 1.7 × 1.3 mm. The inversion time was adjusted to completely null normal myocardium (typically between 250 and 350 ms).

All patients with exclusion criteria for contrast stress perfusion CMR, such as acute or chronic renal failure defined as estimated glomerular filtration rate < 30 mL/min, severe form of claustrophobia, second- or third-degree atrio-ventricular block, and the presence of temporary or permanent pacemakers, were excluded from the study.

Image analysis

Angiographic collateral flow to the CTO was defined by means of collateral connection grade (CC0 — no continuous connection, CC1 — continuous threadlike connection, CC2 — continuous small branchlike connection) and the Rentrop classification (class 0 — no visible filling of collaterals, class 1 — filling of side branches, class 2 — partial filling of epicardial segment of the occluded vessel, class 3 — total filling of epicardial segment) [16, 17]. The presence of well-developed collateral flow was defined as a collateral connection grade = 2 and Rentrop score = 3 [13]. The assessment was blinded to the results of the CMR study.

Assignment of LV segments to the vessel with CTO was based on the American Heart Association's scientific statement with six segments representative of left anterior descending artery, five of circumflex artery, and five of right coronary artery [18]. The apex was excluded from the analysis because it was not visible on the stress perfusion scans.

CMR cine images were analysed with the use of dedicated software (MASS 6.2.1, Medis, Leiden, the Netherlands). Initially, short-axis images were previewed from the base to the apex in a cinematic mode, and then endocardial and epicardial contours for end-diastole and end-systole were manually traced. Delineated contours were used for the quantification of end-diastolic and end-systolic volumes normalised to body surface area and ejection fraction.

Regional wall motion abnormalities for each CTO territory were defined as the wall-motion score index (WMSI) of that territory, where each segment was given 1 point for normal systolic function, 2 points for hypokinesis, 3 points for akinesis, 4 points for dyskinesis, and 5 points for aneurysm [18].

Stress perfusion deficit at first-pass of gadolinium contrast perfusion through the myocardium indicative of ischaemia was defined as a lack of perfusion in at least one myocardial segment, present for at least five dynamic cycles after maximal myocardial signal intensity increase, calculated using Mean Curve software on a Siemens workstation and not corresponding to the area of DE. Rest perfusion following stress perfusion was performed at the discretion of the physician and only in some patients, mainly for the differentiation of artefacts and true stress perfusion deficits. Stress perfusion deficits not corresponding directly to DE and below half of the segment thickness were calculated as 3% of the LV mass (LVM), and those above half of the segment thickness as 6% of the LVM [19]. The percentage of the LVM with stress perfusion deficits in the CTO territory was then summarised to receive the total size of the perfusion deficit.

Infarct size (IS) was defined as an area above 50% of the maximal signal intensity within DE (full-width at half maximum — FWHM) and expressed as a percentage of the LVM in correspondence to the CTO territory (relative infarct size) [20]. Infarction was labelled as transmural if infarct transmurality within at least one segment of the CTO territory exceeded 50%.

Statistical analysis

All results for categorical variables were presented as numbers and percentages and for continuous variables as means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the normality of distribution assessed with the use of the Kolmogorov-Smirnoff test. The χ^2 test or the Fisher exact test was used for comparison of categorical variables, when appropriate. The Student t-test or the Mann-Whitney test for unpaired samples was applied to compare continuous variables, depending on the normality of the distribution. Pearson's test or Spearman's test was applied to assess any correlations, depending on the normality of distribution. All tests were two-sided with a significance level of $p < 0.05$. Statistical analyses were performed with MedCalc statistical software 10.0.2.0 (MedCalc, Mariakerke, Belgium).

RESULTS

The presence of well-developed collaterals supplying CTO was found in 24 (44%) patients. There were no differences in baseline characteristics between patients with well-developed and poorly developed collaterals (Table 1).

There was a trend towards less frequent presence of systolic dysfunction of the CTO territory in patients with well-developed collaterals (Table 1). Semi-quantitative analysis demonstrated that the presence of good collaterals was less likely to be related to systolic dysfunction of the segments supplied by the occluded artery (mean WMSI 1.31 ± 0.44 vs. 1.64 ± 0.67, p = 0.04).

Patients with well-developed collaterals had a lower frequency of previous myocardial infarction (MI) of the CTO territory (38% vs. 67%, p = 0.03), but there was a similar frequency of transmural infarctions (21% vs. 23%, p = 0.83) and relative IS in that area (0.21% [IQR 0–4.52%] vs. 3.14% [IQR 0–6.91%], p = 0.12) in comparison to patients with poor collaterals.

The former also less frequently presented perfusion deficits of the CTO territory during hyperaemia (42% vs. 70%, p = 0.03), and the size of perfusion deficits was smaller (median 0.0% [IQR 0–12%] vs. 7.5% [IQR 0–15%] of the LVM, p = 0.04).

Representative images of relations between the degree of collateral circulation development to the CTO and systolic function, irreversible myocardial injury, and stress ischaemia are shown in Figure 1.

In the whole group, the WMSI of the segments supplied by the CTO correlated with the IS (rho = 0.586, p < 0.0001, Fig. 2). WMSI of the segments supplied by the CTO showed a very weak correlation with the size of the reversible perfusion deficit in that area (rho = 0.284, p = 0.04). There was no correlation between the size of reversible perfusion deficit and infarct size (rho = –0.074, p = 0.59).

DISCUSSION

The progress in percutaneous revascularisation of the CTO is parallel to technological developments in interventional cardiology [1, 7]. Apart from the technical feasibility, correct assessment of indications for the procedure and possible clinical benefits remain a key issue [7].

CMR is a non-invasive method that can be used for a comprehensive workup of patients being considered for CTO revascularisation. This study, along with SPECT and stress echocardiography, can be used for the detection of ischaemia, which is the main indication for revascularisation in this group of patients. However, unlike other routinely used methods, contrast enhanced CMR can be used to confirm the viability of myocardial segments supplied by the CTO. CMR can also be considered as a gold-standard method in the assessment of the left ventricular systolic function [21].

To our knowledge, this is the first study using means of CMR to comprehensively assesses the relation between collateral circulation to the CTO and functional status of the myocardial territory supplied by the occluded artery. Previous studies in that field used other methods of ischaemia detection (SPECT), while CMR and computed tomography (CT) studies were limited to the analysis of myocardial function and IS [9–14].

Table 1. Baseline characteristics of the studied groups

Variable	Poorly developed collaterals (n = 30)	Well-developed collaterals (n = 24)	P
Male sex	24 (80%)	22 (92%)	0.28
Mean age [years]	61.6 ± 6.0	61.2 ± 10.4	0.85
Hypertension	26 (87%)	20 (83%)	1.00
Diabetes mellitus	16 (53%)	9 (38%)	0.25
Hyperlipidaemia	19 (63%)	17 (71%)	0.38
Multivessel disease	14 (47%)	12 (50%)	0.75
Borderline or significant lesion in the artery providing collaterals to CTO	6 (20%)	7 (29%)	0.43
Peripheral artery disease	6 (20%)	3 (13%)	0.72
Previous MI	16 (53%)	12 (50%)	0.81
Angina class according to CCS:			0.08
0	14	7	
1–2	10	15	
3–4	6	2	
Occluded artery:*			0.21
Left anterior descending artery	19	9	
Circumflex artery	3	4	
Right coronary artery	11	13	
LVEDVI [mL/m^2]	99.9 ± 28.6	90.9 ± 21.6	0.22
LVESVI [mL/m^2]	49.3 ± 27.3	40.8 ± 19.9	0.22
LVEF [%]	53.6 ± 14.0	57.1 ± 12.2	0.34
Systolic dysfunction of the CTO territory	19 (63%)	9 (38%)	0.06
Delayed enhancement in the CTO territory	20 (67%)	9 (38%)	0.03
Reversible perfusion deficit of the CTO territory	21 (70%)	10 (42%)	0.03

*The location of CTO lesion was defined as the CTO supplying the largest vascular territory if there were multiple CTO lesions, observed in 9% of patients (n = 5); CCS — Canadian Cardiovascular Society; CTO — chronic total occlusion; LVEDVI — left ventricular end-diastolic volume index; LVEF — left ventricular ejection fraction; LVESVI — left ventricular end-systolic volume index; MI — myocardial infarction

Previous CMR and CT studies are in line with our findings demonstrating that poor collateral flow is related to worse systolic function and higher frequency of previous MIs [13, 14]. However, contrary to these reports we showed that the prevalence of previous MI in patients with CTO is generally smaller and there is no difference in terms of the size of previous MI between patients with good and poor collateral circulation. This may be, at least partially, related to differences in the imaging methods used or the means of delayed enhancement quantification (FWHM instead of six SD from the mean signal of the remote myocardium) [13]. It suggests that the percentage of patients with CTO who may potentially qualify for revascularisation may be larger than expected based on the previous report [13].

Until now there have been no CMR studies relating the degree of collateral circulation development and the presence and size of stress perfusion deficits in the CTO territory. Previous studies in that area using SPECT or fractional flow reserve (FFR) did not find any relation between these two parameters [9–12, 22]. However, a study with transthoracic coronary Doppler echocardiography with venous adenosine infusion showed that collateral flow reserve correlates well with Rentrop graded collateral flow [23]. One of the SPECT studies suggested that excellent angiographic collaterals may prevent rest regional motion abnormalities but do not appear to protect against stress-induced perfusion deficits [11].

According to the CMR protocol used in this study, not all patients underwent rest perfusion, and so we decided not to include this analysis in the study. However, contrary to the described studies using SPECT and FFR and in line with the echo Doppler study, we demonstrated that stress ischaemia was more likely to be found and was larger in patients with poorly developed collaterals. The discrepancies between these studies and our analysis may be explained by a different way of ischaemia induction (exercise stress for SPECT and hyperaemia with dipyridamole or adenosine for CMR and FFR/echocardiography, respectively), the less stringent definition of well-developed collateral circulation used in these

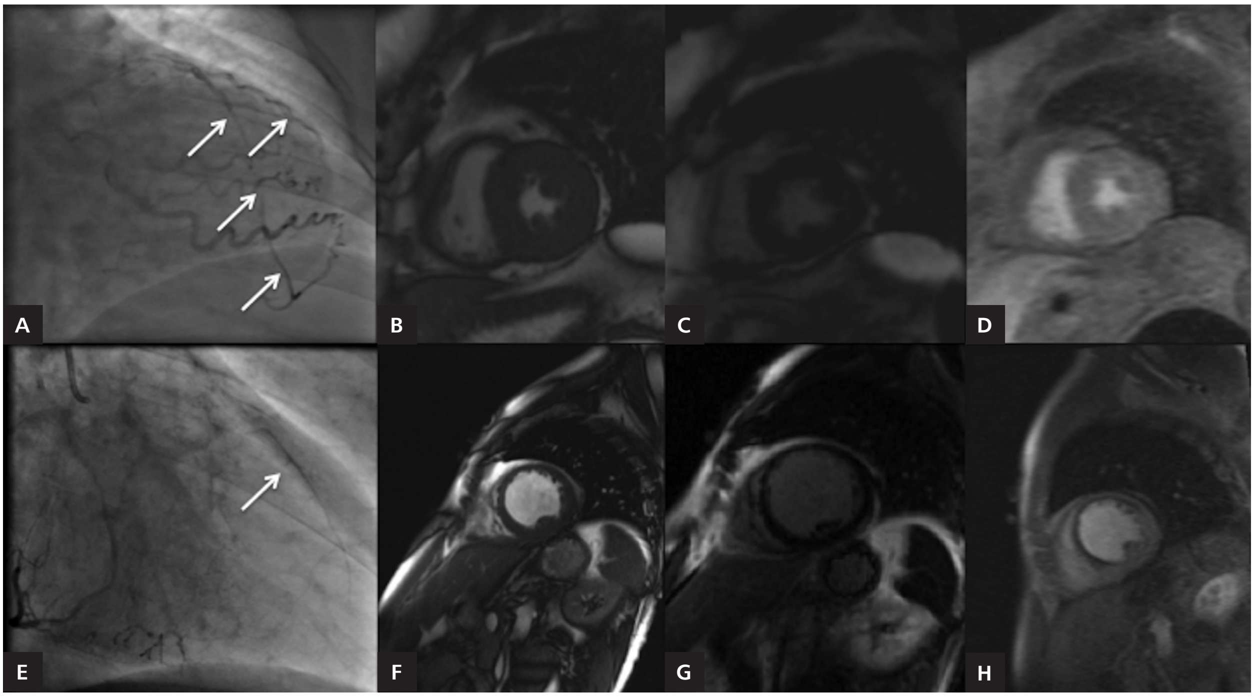

Figure 1. Representative images demonstrating relations between collateral circulation and functional status of the chronic total occlusion territory. Angiographic images show collateral circulation to the chronically occluded left anterior descending artery (**A** and **E**). Short-axis cardiovascular magnetic resonance images at mid-ventricular level of end-systole SSFP sequence (**B** and **F**), delayed enhancement (**C** and **G**) and stress first-pass myocardial perfusion (**D** and **H**); **A–D**. An example of a female patient with well-developed collateral circulation from the circumflex artery (white arrows), normal systolic function, and lack of irreversible myocardial injury or perfusion deficits during hyperaemia; **E–H**. An example of a male patient with poorly developed collateral circulation from the right coronary artery (white arrow), hypokinesis of the anterior and antero-septal segments, thin subendocardial delayed enhancement in the dysfunctional segments confirming previous myocardial infarction, and large perfusion deficit during hyperaemia in that territory

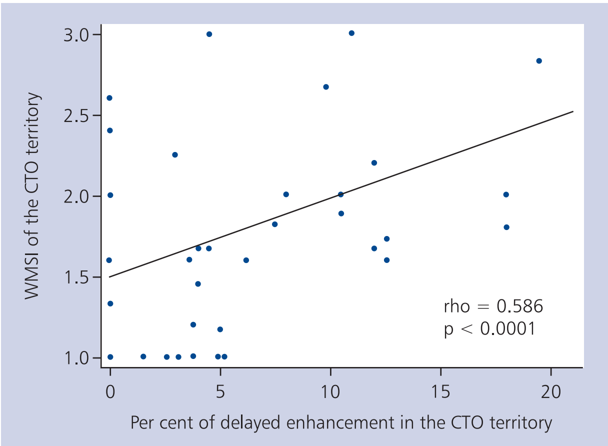

Figure 2. Correlation between wall motion score index (WMSI) of the chronic total occlusion (CTO) territory and relative infarct size

studies (based on the Rentrop scale or collateral connection grade alone), or different patient populations included into the studies. The latter hypothesis is based on the observation that stress ischaemia in the CTO territory was found in all patients undergoing FFR, in around 80% of patients undergoing SPECT, and only in around 60% of patients in our study [9–12, 22]. In one small study using CMR, stress perfusion deficits not matching the myocardial scar in patients with CTO were found in 11/16 patients (68%) [24]. Another CMR study, however, found ischaemia in 80% of patients with CTO [5].

There are other inconsistencies between different methods of ischaemia detection in patients with CTO. Rest ischaemia was observed in most patients undergoing FFR and in almost none of the patients subjected to SPECT [11, 22]. Moreover, contrary to previous CMR/CT studies and our findings, the SPECT studies did not demonstrate any differences in the prevalence of MI of the segments supplied by the CTO between patients with well-developed and poor collaterals [10, 11]. These facts suggest that inherent features of each method may influence the results [25]. Unfortunately, there is only one CMR study that can be used as a comparison to our findings [13].

Our results are further supported by the demonstration that systolic dysfunction is related not only to irreversible injury (due to previous MI) but also, although the correlation is very weak, to reversible injury (due to ischaemia) [11].

Limitations of the study

There are some limitations of this study. One of them is the relatively small sample size. Secondly, as described previously, we were unable to analyse rest myocardial perfusion in all patients. Furthermore, the presence of stress perfusion deficits might have been to some extent influenced by stealing phenomenon from the collaterals in case of borderline/significant lesions in arteries providing collateral circulation to the CTO. Finally, because of the retrospective nature of the study, patients qualified for revascularisation did not undergo a second CMR scan after the procedure to analyse changes in functional status of the CTO territory.

CONCLUSIONS

In conclusion, LV segments supplied by CTO with well-developed collaterals are less prone to inducible ischaemia, have smaller size of ischaemia, better systolic function and were less likely to undergo MI in comparison to those supplied by CTO with poor collateral circulation. Only a minority of patients with CTO have transmural MI in that territory.

Conflict of interest: *none declared*

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Ocena czynności skurczowej, żywotności i perfuzji mięśnia sercowego w trakcie hiperemii u chorych z przewlekle niedrożną tętnicą wieńcową w zależności od krążenia obocznego

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Streszczenie

Wstęp: Wskazania do rewaskularyzacji przewlekle niedrożnej tętnicy wieńcowej zależą od czynności skurczowej, żywotności i niedokrwienia mięśnia zaopatrywanego przez zamkniętą tętnicę. Techniczne możliwości wykonania zabiegu często zależą od krążenia obocznego do strefy za miejscem zamknięcia tętnicy.

Cel: Celem pracy była ocena zależności między stopniem rozwoju krążenia obocznego a charakterystyką mięśnia sercowego zaopatrywanego przez zamkniętą tętnicę.

Metody: Do badania włączono 54 chorych (średni wiek 62 lata, 85% mężczyzn) z przewlekle niedrożną tętnicą wieńcową, skierowanych na rezonans magnetyczny serca w celu oceny wskazań do rewaskularyzacji. Obecność dobrze rozwiniętego krążenia obocznego definiowano jako stopień połączeń obocznych = 2 i wskaźnik Rentropa = 3.

Wyniki: Obecność dobrze rozwiniętego krążenia obocznego (n = 24, 44%) była rzadziej związana z dysfunkcją skurczową segmentów zaopatrywanych przez zamkniętą tętnicę (punktowy wskaźnik kurczliwości 1,31 ± 0,44 *vs*. 1,64 ± 0,67; p = 0,04) w porównaniu z chorymi bez dobrze rozwiniętych kolaterali. Pacjenci z dobrze rozwiniętym krążeniem obocznym rzadziej przybyli zawał serca za zamkniętą tętnicą (38% *vs*. 67%; p = 0,03), przy porównywalnej częstości zawałów pełnościennych w tym obszarze (21% *vs*. 23%; p = 0,83). W grupie tej rzadziej występowały także ubytki perfuzji w trakcie hiperemii w rejonie zaopatrywanym przez zamkniętą tętnicę (42% *vs*. 70%; p = 0,03), a wielkość ubytków była mniejsza (mediana 0,0% [przedział międzykwartylowy 0–12%] *vs*. 7,5% [0–15%]; p = 0,04).

Wnioski: Segmenty mięśnia sercowego zaopatrywane przez zamkniętą tętnicę wieńcową z dobrze rozwiniętym krążeniem obocznym są mniej podatne na niedokrwienie, cechują się lepszą czynnością skurczową i rzadziej stwierdza się przebyty zawał serca w tej lokalizacji w porównaniu z segmentami zaopatrywanymi przez zamkniętą tętnicę wieńcową ze słabo rozwiniętymi kolateralami. Rezonans magnetyczny serca jest metodą nieinwazyjną, którą można zastosować w celu kompleksowej oceny pacjentów z przewlekle niedrożną tętnicą wieńcową pod kątem ewentualnej rewaskularyzacji.

Słowa kluczowe: przewlekle niedrożna tętnica wieńcowa, krążenie oboczne, rezonans magnetyczny serca, żywotność, niedokrwienie

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