ORIGINAL PAPER

Can the degree of coronary collateralization be used in clinical routine as a valid angiographic parameter of viability?

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Abstract

The success rate of percutaneous coronary artery intervention (PCI) of chronic total occlusion (CTO) lesions have increased in the recent years. However, improvement of function is only possible when significant myocardial viability is present. One of the most important factors of maintaining myocardial viability is the opening and development of collaterals. Our hypothesis was that with a higher degree of collaterals more viable myocardium is present. In 38 patients we compared the degree of collaterals, evaluated with a conventional coronary angiogram (CCA) and graded by the Rentrop classification to transmural extent of the scar obtained in a viability study with magnetic resonance (MRI). We found a statistically significant association of the degree of collaterals determined with Rentrop method and transmural extent of the scar as measured by CMR ($p = 0.001$; Tau = -0.144). Additionally, associations showed an increase in the ratio between viable vs. non-viable myocardium with the degree of collaterals. Our study suggests that it may be beneficial to routinely grade the collaterals at angiography in patients with CTO as an assessment of myocardial viability.

Keywords Myocardial viability · Collateral grade · CMR · CCA · Rentrop method · Viability parameters

Introduction

During the last decade, techniques for percutaneous coronary artery intervention (PCI) of chronic total occlusion (CTO) have developed significantly, leading to the success rate of 85–90% in hands of dedicated operators [1]. Although PCI of CTO does not reduce major adverse cardiovascular events (MACE), there may be significant improvement in the quality in life [2]. However, such benefits of PCI CTO are likely only if significant myocardial viability is present in the CTO territory. The evaluation of myocardial viability before PCI is therefore of interest.

Various factors may modify the natural course and size of myocardial infarction in the acute stage: duration of ischemia, size, and location of occlusion, coronary cardioprotective medication and coronary artery anatomy [3]. The extent and duration of reduced or total stoppage of blood flow and oxygen supply are determinants of partial (chronic) or total ischemia. The development and/or opening of pre-performed collateral coronary vasculature (arteriogenesis) are thought to be one of the very important factors limiting chronic ischemia [4], and through this keeping the myocardium viable [3–9].

Various clinical studies have demonstrated results in support of a close relationship between the presence of collateral coronary circulation and myocardial viability [10–18], whereas several other studies could not confirm this hypothesis [19, 20].

We addressed the relationship between extent of collateral supply in the CTO territory assessed with conventional coronary angiogram (CCA) and myocardial viability using magnetic resonance imaging (MRI), which is a gold standard

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for myocardial viability imaging, although different modalities are being used for the evaluation [21, 22].. The goal of this prospective study was to elucidate using sophisticated imaging methods the positive relationship between the presence of functioning coronary collateral circulation and the amount of viable myocardium in patients with CTO as defined by the consensus document from the Euro CTO club [23].

Methods

Study population

Forty-two patients were recruited for our study between 2011 and 2018 after an elective CCA revealed a CTO. Within 1 month of diagnosis all patients were studied by Cardiac Magnetic Resonance (CMR) using a standard protocol using intravenous contrast agent (Gadovist, Bayer). In conjunction with the patient's informed consent form, patient history data was obtained using a questionnaire. Questions about smoking, diabetes, hypertension, statins therapy, a positive family history of coronary heart disease, regular exercise and angina pectoris were answered with a yes/no answer option. Late gadolinium enhanced images were obtained 10 min after contrast administration and used for evaluation of myocardial viability defined as less than 50% transmural enhancement. Two of the patients revealed late enhancement patterns suggestive of infiltrative cardiomyopathy. In two patients the re-evaluation of CCA could not confirm a CTO lesion. These four patients were excluded from further analysis with a final number of 38 patients enrolled in the study. The study was approved by the National ethics committee of Slovenia.

CCA

In the clinical setting CCA is used as gold standard for depicting coronary collaterals. For comparative angiographic assessment of visible coronary collateral vessels, Rentrop grading system was used [24, 25] (Table 1). The grading was performed by an experienced interventional cardiologist.

CMR

The CMR images were obtained using a 1,5 T scanner (Signa Excite, GE Waukesha, USA). The CMR protocol consisted of cine imaging steady-state free precession (SSFP) in two, four chamber and short axis views. A slice thickness of 8 mm with 2 mm spacing was used. Late gadolinium enhancement (LGE) images were obtained 10 min after contrast administration using a segmented gradient echo inversion recovery LGE sequence. Short axis views with a slice thickness of 8 mm without spacing were obtained. Long axis images were obtained in every of the 17 segments and additional images if delayed enhancement was present.

Left ventricular parameters as EDV, ESV, SV, EF, LVMM were determined using Medis Suite Cardiovascular MR software (the Netherlands). EDV, ESV, SV and CO have been indexed to body surface area (BSA). As the reference for normal values we took the EACVI consensus paper on normal values of cardiac chamber size ECS guidelines [26]. Since the patients were predominantly male (87%), we opted for the reference values of males. In addition, rate pressure product (RPP) and systemic vascular resistance (SVR) have been calculated. The end diastolic wall thickness (EDWT) was measured on cine images at the end of diastole and reported in millimeters and compared to normal values [27].

Gadolinium contrast agent was administered intravenously with a flow of 3,5 ml/s and a dose of 0,2 mmol/kg. Left ventricular wall enhancement 10 min after contrast agent administration was evaluated. Due to the interest of CTO, we analyzed only segments that were referred to the CTO vessel territory. Segmentation was based on the AHA 17-segment model. Two hundred and ninety of the total 684 segments were included into analysis.

Scar tissue was assessed by the presence of late gadolinium enhancement by the grading approached introduced by Kim [28]–(Table1). The scar tissue was measured in millimeters perpendicular to the subendocardial layer at maximum scar level in the segment and then divided by the thickness

Table 1 The grading system used in our study

Transmural extent of the scar	Rentrop classification
Grade 0–no scar present	Grade 0–no visible filling of the collaterals
Grade 1–transmural extent of the scar 1–25%	Grade 1–filling of the side branches, but no visibility of the epicardial vessel
Grade 2–transmural extent of the scar 26–50%	Grade 2–partial filling of the epicardial vessel via collaterals
Grade 3–transmural extent of the scar 51–75%	Grade 3–complete filling of the epicardial vessel
Grade 4–transmural extent of the scar 76–100%	

of the whole myocardial wall in this segment. The number obtained was multiplied by 100 and presented as percentage.

Statistical analysis

Data were analyzed using IBM SPSS software version 25.0 (IBM Inc., Armonk, New York) and R (R Core Team 2017, Vienna, Austria). Differences of continuous or ordinal variables between categorical nominal groups were determined using Mann–Whitney U-Test and Kruskal–Wallis H-Test with applied pairwise comparisons. Ordinal by continuous correlations and ordinal by ordinal associations were determined using Spearman's rank and Kendall's Tau b or c correlations, respectively. Differences

between nominal categorical variables were determined using Chi-square statistics. A receiver operating characteristic (ROC) curve analysis was applied to determine area under curve (AUC) for predictors. Alpha level was set to 5% and p value < 0.05 was considered statistically significant.

Results

Patient's characteristics

Table 2 is showing essential patient's characteristics of 33 male and 5 female patients included in this study. 21 (55%) were smokers, 18 (47%) had diabetes type 2 and all of them were on glycemic control therapy, no patients had type 1 diabetes. 27 patients were treated for hypertension and 30 patients (79%) were on statins. Only 11 patients (28%) had a positive family history with a parent or sibling having a cardiac event under the age of 55 for males and 65 for females [29]. Twenty patients were taking regular time for physical activity referred by them as exercise (at least 30 min of walking or cycling). 13 patients (34%) were experiencing angina on exertion.

Volumetric parameters

The mean values of the ejection fraction in our patient selection were reduced by 26% of normal values accompanying by an increase of the LV end diastolic volume index of 31.6 ml/m^2 from normal values. Rate pressure product

Table 2 Patient characteristics

	N (38)	%
Gender (male/female)	33/5	
Age (years)	61.6 ± 10.3	
Weight (kg)	87.5 ± 17,4	
Height (cm)	170.2 ± 17.2	
Body mass index	29.1 ± 4.6	
Systolic blood pressure (mmHg)	131.3 ± 20	
Diastolic blood pressure (mmHg)	77.9 ± 13.5	
Smokers	21	55
Diabetes mellitus type 2	18	47
Statin therapy	30	79
Hypertension	27	71
Positive family history	11	28
Angina pectoris on exertion	13	34
Excersise	20	52

Table 3 Patient Left Ventricular Volumes and hemodynamic parameters

	AVG ± SD	Min	Max	Normal values
EF (%) ejection fraction	43.1 ± 18.6	10	83	F 57–77 M 57–77
EDV/BSA (ml/m^2) end diastolic volume	104.8 ± 39.4	97	410	F 56–96 M 57–105
ESV/BSA (ml/m^2) end systolic volume	63.3 ± 40.4	16	330	F 14–34 M 14–38
SV/BSA (ml/m^2) stroke volume	41 ± 15	13,67	174	F 42–62 M 43–67
CO/BSA (l/min/m^2) cardiac output	2.904 ± 0.95	1,6	13	
Myocardial mass (g)	133.1 ± 41.1	74	262	F 56–140 M 92–176
Heart Rate (/min)	70.4 ± 13.2	45	101	60–70
EDWT	6.1 ± 2.6	1	11	F 4–7 mm M 5–8 mm
Rate pressure product	9170 ± 260	5200	13,200	6000–10.125 (mmHg × HR)
Systemic vascular Resistance(mmHg/min/l)	20.1 ± 17.0	6	110	9–20 wood units (mmHg × min/l)

was within low normal values. Systemic vascular resistance was at the upper normal level (Table 3).

Dominance

Only CTO related territories were evaluated using the AHA (American Heart Association) 17-segment model [28, 30]. We assigned 7 segments to the LAD territory, 5 to RCA and 5 to LCX territory in case of right dominating system. In case of a left dominating system, RCA had only 3 segments and LCX had 7. In total 290 CTO segments were evaluated. On average 7, 6 CTO segments were identified per patient.

Right dominant system was present in 34 patients, left dominant system in 2 patients and a codominant system also in 2 patients. In both codominant cases RCA was the CTO vessel. In one case the degree of collaterals was rated as Rentrop grade 3 and the other as Rentrop grade 1. We analyzed all the segments as being a CTO territory (Table 4).

Site of occlusion

Proximal coronary vessel occlusion was found in 86 segments and mid/vessel occlusion was found in 204 segments. No distal occlusion was seen.

Collateral grade

Collateral Grade 0 was found in 10 segments, Grade 1 in 31 segments, Grade 2 in 56 segments and Grade 3 in 123 segments (Table 5)

Transmural extent of the scar

Transmural extent of the scar of 1–25% (Grade 1) was present in 26 segments (8,9%), transmural extent of the scar of 26–50% (Grade 2) in 69 segments (23,8%), a transmural extent of the scar of 51–75% (Grade 3) was present in 33 segments (11,4%) and a transmural extent of the scar of 76–100% (Grade 4) in 24 segments (8,3%). 138 CTO segments (47%) were without a scar present (Grade 0) (Table 6)

Table 5 Number of segments within collateral groups

Collateral grade	0	1	2	3
Number of segments (290)	10	31	56	123

Relationship between scar thickness and degree of collaterals

We found statistically significant difference of the percent of transmural scar extent between different Rentrop collateral grades (p = 0.016) (Fig. 1 a, b). With subsequent pairwise comparisons the results have shown statistically significant decrease of the transmural scar extent in the group with grade 3 collaterals (21.98 ± 29.16; median: 0) in comparison with grade 2 (30.89 ± 31.97; median 25; p = 0.013) or grade 1 (38.90 ± 34.81; median 42.33; p = 0.008) collaterals (Fig. 1 a). No statistically significant difference was observed in comparison of grade 1 and grade 2 collaterals. Group of grade 0 collaterals couldn't be assessed due to low number of cases (N = 10). Additionally ordinal correlation confirmed a negative association between Rentrop collateral grade and ordinally classified transmural extent of the scar (p = 0.001; Tau = − 0.144).

In addition, scar thickness was classified into dichotomous groups below and including 50% and more than 50% to represent viable and non-viable myocardium, respectively. Our results show that the degree of collaterals is statistically significant higher in the group with scar thickness below and including 50% (mean 2.31 ± 0.78) as compared to the group with scar thickness above 50% (mean 1.98 ± 0.74; p = 0.001) (Fig. 2). The ratio between viable vs. non-viable myocardium was also increased with the degree of collaterals and was found to be significantly different (p = 0.006) between grades of collaterals (Fig. 3).

Influence of risk factors

Influence of risk factors was assessed using a questionnaire and clinical data of present weight, cholesterol, and diabetes

Table 4 Frequency of coronary vessel dominance in our group of patients

Dominance	N = 38	Segments 290	Percent (%) 100
Right dominant	34	259	89,3
Left dominant	2	20	6,9
Codominant	2	11	3,8

Table 6 Differentiation of patients and segments according to transmural extent of the scar

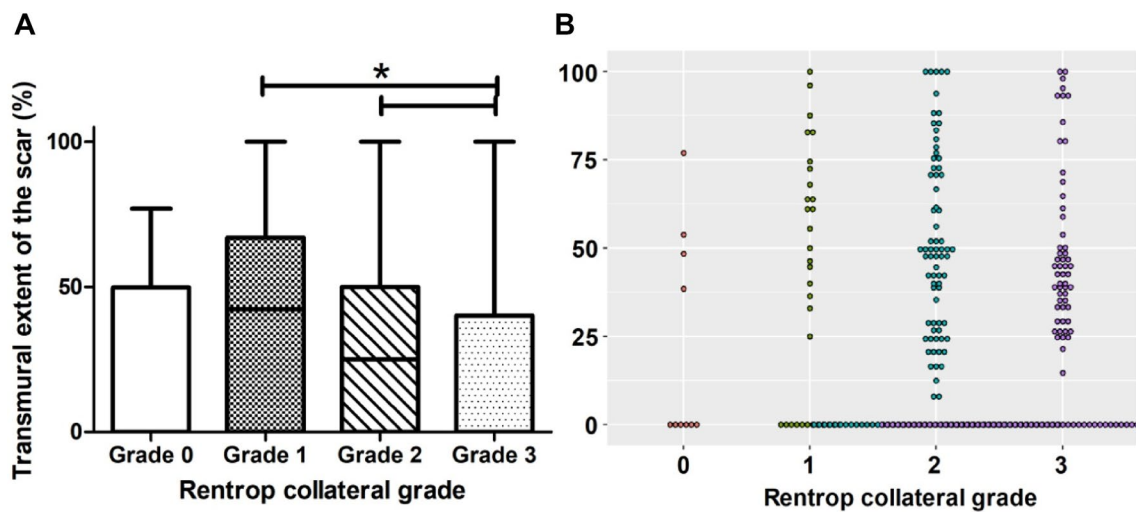|	Patients	Segments	Percentage
Transmural extent of the scar	N = 38	290	100
0–(No scar)	18	138	47,6
1–(1–25%)	4	26	8,9
2–(26–50%)	9	69	23,8
3–(51–75%)	6	33	11,4
4–(76–100%)	1	24	8,3

Fig. 1 Transmural extent of the scar across Rentrop collateral grades. **a** Data are presented as raw percent median, interquartile ranges, min and max. **b** Data are presented as raw values. Differences between groups were determined using Kruskal–Wallis pairwise comparison. * indicates $p < 0.05$

Fig. 2 Degree of collaterals in scar thickness groups. Data are presented as mean $\pm$ standard deviation. Differences between groups were determined using Mann–Whitney U-Test. * indicates $p < 0.05$
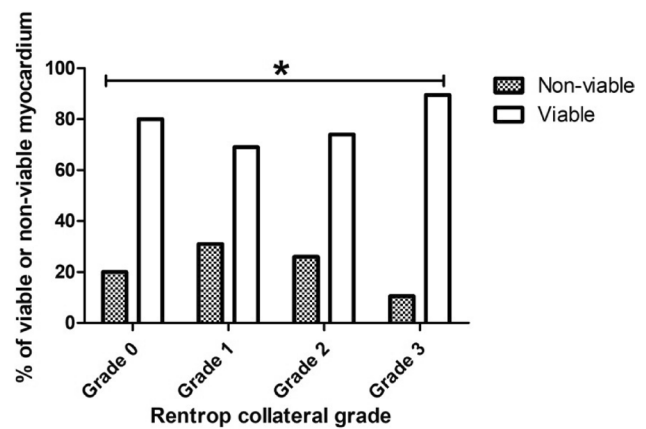
Fig. 3 Ratio of viable myocardium vs non-viable CTO segments across grades of collaterals. Data are presented as % myocardium assigned to CTO. Differences between grades were determined using chi-square statistics. * indicates $p < 0.05$

status of enrolled patients. We found statistically significant difference of contractility level between patients with hypercholesterolemia, but no statistical difference was observed for degree of collaterals, transmural extent of the scar or EDWT. We found that patients with hypercholesterolemia exhibit lower level of contractility (mean 1.45 ± 1.06) in comparison with the patients without hypercholesterolemia (mean: 1.95 ± 0.83; $p < 0.001$). Regarding the presence of diabetes, we observed statistically significant lower level of transmural extent of the scar in patients with diabetes (mean: 1.00 ± 1.24) in comparison with the patients without diabetes (mean 1.48 ± 1.45; $p = 0.007$). EDTW was statistically significant higher in patients with diabetes (mean

7.06 ± 2.49) in comparison with the patients without diabetes (mean: 5.83 ± 2.53; $p < -0.001$), but no statistically significant difference was found for degree of collaterals and contractility. Transmural extent of the scar level was also statistically significant higher in patients who smoke (mean 1.53 ± 1.41) in comparison with non-smokers (mean 0.84 ± 1.23; $p < 0.001$), but no statistically significant difference was observed for degree of collaterals, contractility or EDTW. No statistically significant difference was found in relation with the aforementioned parameters and BMI.
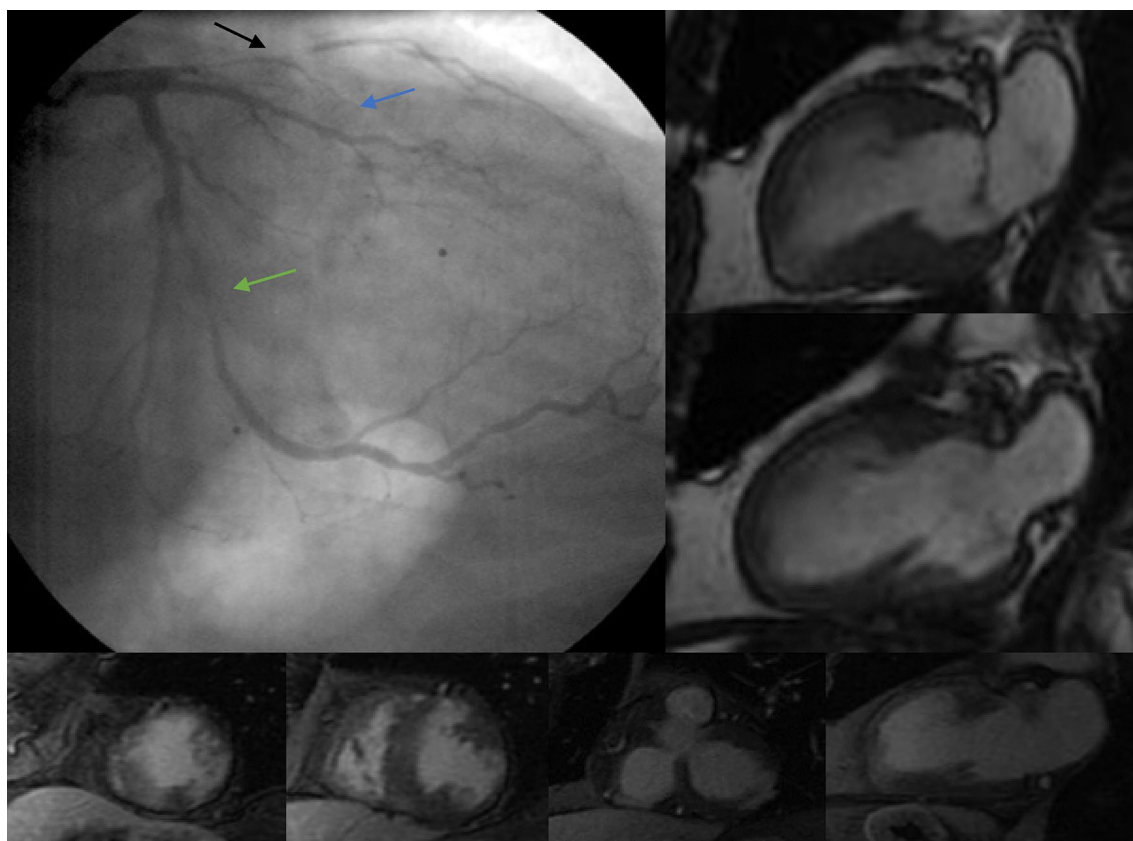
Fig.4 Patient A: (upper left) angiography showing a proximal CTO LAD (black arrow) with very weak auto-collaterals (blue arrow) (Rentrop 0–1) which fill mainly ramus intermedius and not mid-distal LAD (Rentrop 0–1). There were no right to left collaterals to LAD; (on the right) SSFP 2CH image in systole **a** and diastole **b** with an ejection fraction of 30% as well as no thickening of the myocardium in the anterior wall; (bottom row) delayed enhancement images in short axis view (apical, mid-ventricular, basal slice) show a more than 75% extend of the scar in segments 7,13 and 14. The 2CH long axis confirms the thin anterior wall in the mid and apical segments (bottom right). Additional subendocardial scar after an LCX infarct, that was spontaneously recanalized (green arrow)

Discussion

Our results confirm a positive relationship between the presence of functioning coronary collateral circulation and the amount of viable myocardium in patients with CTO. Figure 4 illustrates a case of insufficient collaterals with subsequent lower ejection fraction and a scar of > 75% of the anterior wall (Fig. 4). Figure 5 illustrates a case of well-developed left to right collaterals, a good ejection fraction and no fibrosis (Fig. 5).

Our study confirms that with the increasing degree of collaterals, the amount of viable myocardium increases. The inverse correlation is supported by an increasing ratio between viable and non-viable myocardium which we used to decrease the bias due to different sample sizes amongst the collateral groups.

Our results are in concordance with the study performed by Ripley et al. [17] and Choi et al. [18], but not in concordance with the recent study by Wang et al. [19]. Unlike our study, Wang el al did not find a correlation between the degree of collaterals and amount of viable myocardium. This may be due to our inclusion criteria being the same as for the Choi's study whereas the Wang study excluded patients with a preserved systolic function (EF%). Preserved EF is, from our point of view, a clinical feature of well-developed collateral system and a consequence of preserved contractility.

The degree of collateralization was recently reported to be predictive of procedural success of CTO-PCI in a recent study by Allahvala et al. [31] and Schumacher et al. [32] in support of our observations.

In a previous study He et al. [20] attempted to avoid other parameters that might influence collateral development and myocardial perfusion by excluding patients with multi vessel disease, severe stenosis, or previous myocardial infarction. We only excluded patients for which a CTO could not be confirmed. We also did not exclude patients who had two CTO lesions or severe atherosclerosis. There is a possibility that coronary steal from the CTO territory affects the remote myocardium and contributes to lower ejection fraction. However, we therefore only focused on
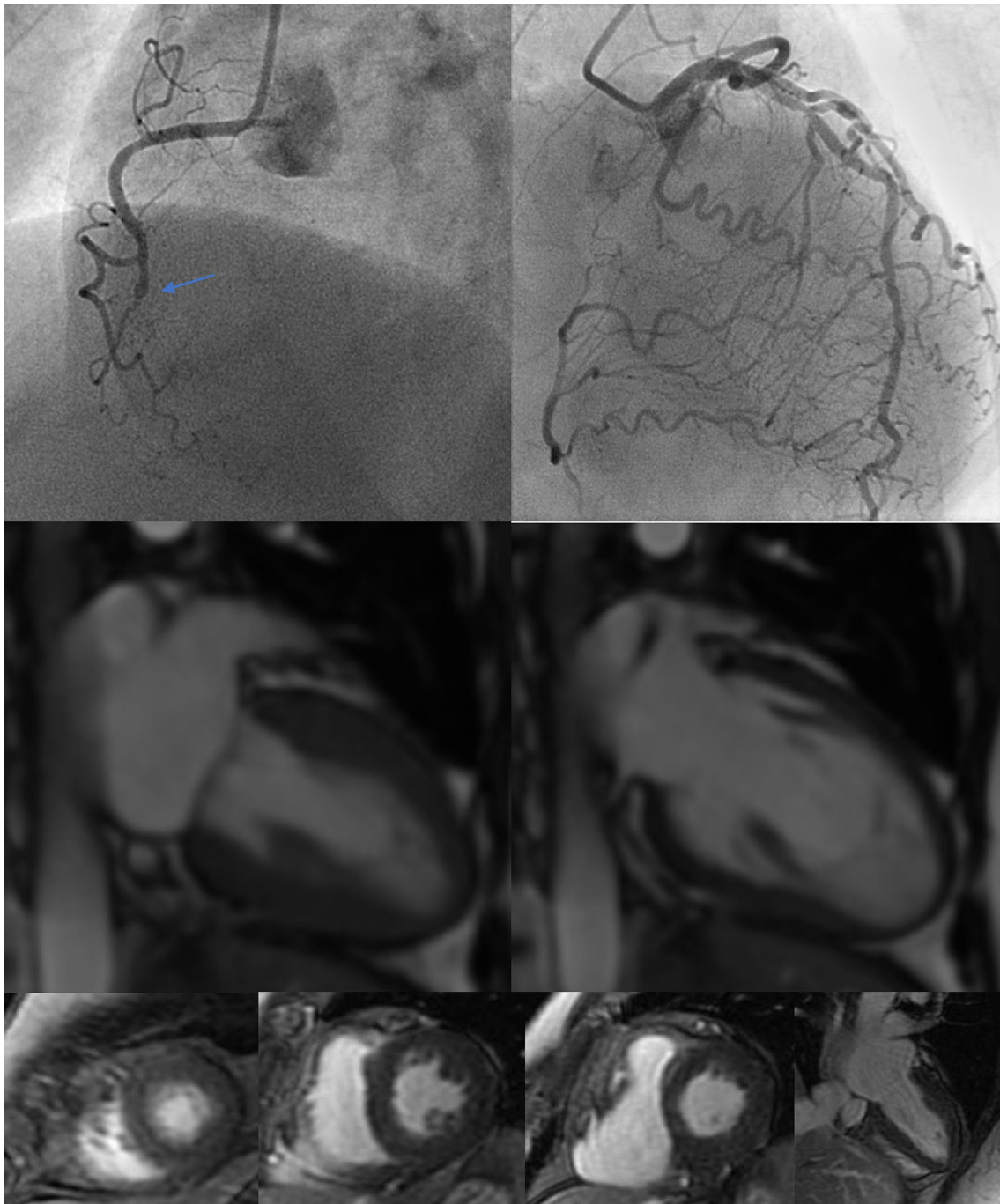
Fig.5 Patient B: (upper left) angiography showing a CTO RCA (black arrow) and (upper right); well-developed collaterals (Rentrop 3) from LAD to distal (PDA,PLV) and mid RCA (mid row left) SSFP images in systole and diastole (mid row right) with good ejection fraction (70%); (bottom row) delayed enhancement images in SA (apical, mid-ventricular, basal) and 2CH showing no fibrosis

the correlation of transmural extend of the scar and the degree of collaterals, exclusively in a CTO territory. The non-CTO territories were not evaluated. In He's study the degree of collaterals was not graded therefore a correlation was not evaluated. However, they did confirm that collateral circulation influences viability and the lack of collateral circulation does not exclude viability. The latter was also our finding, since despite a strong overall correlation among contractility and transmural extent of the scar with the collateral degree, we also had a few viable segments in the group where no collaterals were present. The number of these segments was too low to make a statement

in the statistical analyses. However, from a clinical point of view, the reason for having viable myocardium with no visible collaterals might be the limit to the size of the vessel we can depict (> 100 μm) [33]. Also, a human error while measuring the extent of the scar with values around 50% is possible.

On the other hand, some segments with transmural extent of the scar of > 50% (non-viable) were present in the groups with the 2 or 3 grades of collaterals. These segments were studied in a territory manner/on a patient basis. For example, if the segment was evaluated by MR as not viable, but the collateral vessel grading for the assigned CTO lesion as Grade 2 or 3, we looked at all segments that part of the CTO territory. The evaluated segments were assigned to 17 patients. Nine of those patients had at least 70% and one had 60% of viable segments within the affected vessel territory. The presence of nonviable segments within a viable territory could be explained with the downregulation of the collateral development after the sheer stress pressure falls to normal. By this the main trigger for arteriogenesis is not present and the collateral development stops [33–39]. Another reason could be that the reference standard of transmurality is imperfect, as shown in a study by Nagel [40]. All nine patients with segments where the transmural extent of the scar was > 50% and had collateral grade of 2 or 3 were male, but no correlation with other factors was found.

Four of the remaining patients with good collaterals but transmural extent of the scar > 50% were smokers. Three were male and one patient was female. In our study the only significant difference of smoking as a risk factor was with transmural extent of the scar. Patients who smoked had an increase in transmural extent of the scar than non-smokers. The effects of smoking [41] and gender [42] on the micro-circulation have been well-documented.

By analyzing influence of risk factors in addition to smoking we found a difference in contractility in patients who were on statins. Those on statin therapy had less wall motion abnormalities. The positive effect of statins on the endothelium has been previously documented [43]. The important difference in patients on glycemic control therapy was that their EDWT was higher and the scar was thinner than in the group without diabetes, respectively. The effects on LV mass in diabetic people has also been confirmed by other studies [44]. Whether reduced infarct size is a consequence of glycemic control therapy or better collateral development remains unclear in our study.

Finally, we looked at the site of occlusion. There was a suggestion of better collateral development in the case of a mid-vessel occlusion when compared with a proximal occlusion. None of our patients had a distal occlusion.

Our study was a single center retrospective study and it is therefore exploratory. Recovery of function following opening the CTO would be the best parameter to support our conclusions, but no MR follow-up study to evaluate the improvement after opening the CTO lesion was made. It has been shown that opening a CTO lesion improves the quality of life and relieves symptoms [2]. It would also be interesting to see, whether the improvement is greater with a higher degree of collaterals. The relatively low number of patients is another limitation to the study. With the increasing number there might also be a significant difference between the site of occlusion and degree of collaterals, which would be also interesting to see in future studies. Another limitation to our study is Rentrop grading being assessed by one interventional cardiologist, therefore reproducibility remains questionable.

Conclusion

Different imaging modalities use different parameters to evaluate for viability. Echocardiography enables us to evaluate contractility, EDWT as well as volumetric analysis CMR contractility, EDWT and transmural extent of the scar (also perfusion and stress perfusion) in addition to volumetric analyses, whereas angiography is limited by 2D views to contractility and depiction of collaterals. As for now the best evaluation of viability is obtained with a MR study, but not every center has an MR available. Our study suggests that there is a correlation between collaterals at angiography in patients with CTO and myocardial viability but the importance of this observation requires follow-up data. In the caseof a CTO lesion with good collaterals (Rentrop Garde 2 or 3) this information could guide the decision making on opening a CTO lesion.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

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