



Original Article

Do Myocardial Blush Grade Following Chronic Total Occlusion Recanalization Improve Clinical Outcome of Chronic Coronary Syndromes Patients?

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ABSTRACT

Background : Myocardial blush grade (MBG) is an angiographic parameter to describe the adequacy of myocardial reperfusion. The correlation between myocardial blush and the clinical outcome following chronic total occlusion (CTO) recanalization is still unclear. Our study aimed to investigate the impact of myocardial blush after CTO recanalization on the clinical outcome of CCS patients.

Design : A retrospective cohort study was conducted. Patients who underwent CTO recanalization were divided into two groups based on the myocardial blush. Patients were classified as having good myocardial blush (MBG category 2 to 3 or QUBE 0 to 10.2) and poor myocardial blush (MBG category 0 to 1 or QUBE 10.2 to 36.4). The outcome measured was the improvement of angina measured using the Seattle Angina Questionnaire (SAQ) and the reduction of antianginal drug regimens.

Results : The follow-up period was ranging from 2 to 24 months following the CTO recanalization procedure. The SAQ for physical limitation (83.86 ± 16.11 vs. 77.92 ± 3.44 ; $p = 0.247$), angina frequency (85.27 ± 17.44 vs. 74.76 ± 22.05 ; $p = 0.105$), and quality of life (73.24 ± 3.41 vs. 72.82 ± 3.56 ; $p = 0.932$) between the two groups was not significantly different. Good myocardial blush was not correlated with the reduction of antianginal drug regimens ($10 (52.6)$ vs. $8 (40)$; $p = 0.639$).

Conclusion : Myocardial blush post-CTO recanalization was not associated with the improvement of angina symptoms and the reduction of antianginal drug regimens among patients with CCS.

1. Introduction

CTO in coronary arteries was identified in about 15% to 30% of patients who underwent invasive diagnostic coronary angiography.¹ Until now, the revascularization strategy of CTO remains the main problem and is a common cause for a patient's referral for coronary artery bypass graft (CABG) surgery.² Some studies revealed that CTO recanalization could provide some advantages, including improving left ventricular systolic function, symptoms, and quality of life. Moreover, better tolerance of subsequent ischemic events, possibly improved long-term survival, arrhythmia burden reduction, and long-term health care costs reduction also could be achieved by CTO recanalization.^{3,4} The revascularization strategy in multivessel disease with concomitant CTO may be challenging. The existence of CTO remains the largest and most significant technical challenge to achieve complete revascularization by percutaneous coronary intervention

(PCI) approach.⁵

The primary goal of revascularization is not only to return the epicardial coronary artery blood flow but also to ensure and maintain adequate myocardial perfusion.⁶ A simple clinical equipment described the myocardial reperfusion effectiveness is lacking. So far, noninvasive approaches have not been applicable in daily clinical practice and the abroad used angiographic parameter, Thrombolysis In Myocardial Infarction (TIMI) flow grade, depicts the epicardial blood flow instead of myocardial.⁷ MBG is an angiographic parameter to describe the adequacy of myocardial reperfusion. An open-source software program named The Quantitative Blush Evaluator (QuBE) provides a feasible, practical, and reproducible method to measure myocardial perfusion.⁸ The correlation between myocardial blush and the clinical outcome following CTO recanalization is still unclear. Our study aimed to investigate the impact of myocardial blush after CTO

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recanalization on the clinical outcome of CCS patients.

2. Method

2.1. Study Design

We conducted a retrospective cohort study in the catheterization laboratory of Saiful Anwar General Hospital Malang from August to November 2016. The study protocol conformed to the 1975 Declaration of Helsinki's ethical guidelines. The study protocol was recognized and approved by the ethical committee of Saiful Anwar General Hospital.

2.2. Patient Selection

Patients who underwent PCI between January 2014 and August 2016 were identified retrospectively from our database. The inclusion criteria included: (1) CCS patient receiving optimal medical treatment; (2) CCS patient who had CTO in at least one coronary artery in an angiographic examination; and (3) CCS patient aged at least 40 years. The exclusion criteria included: (1) Patient with non-cardiac comorbid with a life expectancy of <1 year; (2) Patients with the barrier to underwent a medical examination and study follow-up at the cardiology outpatient clinic of Saiful Anwar General Hospital; (3) Patients with severe physical limitations that were not allowed to do daily physical activities; and (4) Patients with routine medications from the psychiatrist. Data on their current health conditions were obtained either from the phone call or from their last office visit in November 2016.

2.3. Procedural Aspect

Before the procedure, all patients were treated with a loading dose of aspirin and clopidogrel. CTO recanalization procedures were mainly conducted through the femoral artery access and antegrade approach with 7 Fr guiding catheters. For each patient, the

CTO recanalization procedure was performed under the GE Healthcare Innova 2100 Cardiovascular Imaging system. The angiographic sequence was recorded using standardized projections until the visual confirmation of the myocardial washout phase. At the beginning of the procedure, patients received a single bolus of unfractionated heparin. Procedural success is defined as the successful CTO recanalization and dilation of ≥ 1 CTO/patient with or without stent implantation, residual stenosis of < 50%, and TIMI flow grade > 1 without major adverse cardiovascular events (MACE).^{9,10}

2.4. Exposure and Outcomes

CTO is defined as the total (100%) occlusion of the coronary artery with TIMI 0 flow for at least three months.¹¹ Patients who underwent CTO recanalization were divided into two groups based on the myocardial blush. Patients were classified as having good myocardial blush if they had the MBG category 2 to 3 (QUBE 0 to 10.2). However, patients were classified as having poor myocardial blush if they had the MBG category 0 to 1 (QUBE 10.2 to 36.4). The QUBE program needs an angiogram recorded immediately after PCI only. Moreover, quantitative blush assessment limits intra- and inter-observer variability, a typical phenomenon in visually assessed myocardial blush grading.^{8,12} Following PCI, all patients got dual antiplatelet treatment, including aspirin and clopidogrel. The outcome measured was the improvement of angina measured using the Seattle Angina Questionnaire (SAQ), which has been extensively studied and validated in cardiac patients.^{4,13} The outcome measured also included the reduction of antianginal drug regimens, including isosorbide dinitrate or nitroglycerine. The follow-up duration was ranging from 2 to 24 months.

2.5. Statistical analysis

All data obtained were analyzed using IBM SPSS 24 software. Numerical data were presented as mean and standard deviation, while categorical data were presented as number and percentage. Data normality assessment was conducted using the

Table 1. Baseline characteristic

Variable	Good myocardial blush (MBG 2-3) (n = 19)	Poor myocardial blush (MBG 0-1) (n = 21)	Total (n = 40)	p-Value
Age, year	54.8 \pm 10	58.3 \pm 7.2	57 \pm 8	0.211
Sex, male	19 (100)	17 (81)	36 (90)	0.108
BMI, kg/m ²	24.2 \pm 4.1	25.1 \pm 3.2	24 \pm 3	0.405
Hypertension	10 (52.6)	11 (52.4)	21 (52.5)	1.000
Diabetes	5 (26.3)	11 (52.4)	16 (40)	0.175
Dyslipidemia	4 (21.1)	4 (20)	8 (20)	1.000
Cigarette smoking	10 (52.6)	12 (57.1)	22 (55)	1.000
Family history of CAD	3 (15.8)	5 (23.8)	8 (20)	0.698
History of ACS	8 (42.1)	10 (47.6)	18 (45)	0.975
Heart failure	7 (36.8)	10 (47.6)	17 (42.5)	0.713
Stroke	1 (5.3)	3 (14.3)	4 (10)	0.607
CKD	6 (31.6)	11 (52.4)	17 (42.5)	0.313
LVEF	46.4 \pm 17	37.1 \pm 13.5	43 \pm 10	0.190
ACE inhibitor	10 (52.6)	10 (47.6)	20 (50)	1.000
ARB	6 (31.6)	6 (28.6)	12 (30)	1.000
Statin	19 (100)	19 (100)	40 (100)	-
Antiplatelet	19 (100)	19 (100)	40 (100)	-
β -blocker	14 (73.7)	15 (71.4)	29 (72.5)	1.000
CCB	5 (26.3)	4 (20)	9 (22.5)	0.716
Nitrate	15 (78.9)	19 (95)	34 (85)	0.182

ACE inhibitor = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin ii receptor blockers; BMI = Body mass index; CCB = calcium channel blockers; CKD = chronic kidney disease; CVD = cardiovascular diseases; LVEF = left ventricular ejection fraction; MBG = myocardial blush grade.

Shapiro Wilk test. Statistical analysis used for categorical variables was the Chi-Square test. While continuous variables were analyzed using the T-Test test. The confidence interval was 95%. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristic

In the beginning, we had successfully identified 149 patients who have CTO proved to be the primary lesions. A total of 42 patients underwent percutaneous coronary intervention in CTO lesions. However, two of them were excluded because of medication non-compliance. Finally, 40 patients underwent CTO recanalization included in the statistical analysis. The baseline characteristics of the patients between both groups were not significantly different (Table 1). The patient's age was $57 \pm$ eight years. Most of them were male (90%). About 56% of patients suffered from hypertension, 40% had diabetes mellitus, 20% had dyslipidemia, 55% were smokers, and 20% had the familial history for coronary artery disease. All patients received optimal medical treatment for stable angina pectoris, including antiplatelet, statin, and one or more anti-angina.

On angiographic analysis and procedural aspects (table 2), 7

(18%) patients had one vessel disease, 8 (20%) had a two-vessels disease, 24 (60%) had three vessels disease, and 1 (3%) had left main disease. The chronic total occlusion percutaneous coronary intervention (PCI CTO) procedures were conducted for the left anterior descending artery, the left circumflex artery, the right coronary artery in 45%, 12,5%, and 10% patients, respectively. The wire crossing time < 30 minutes was achieved in 85% of patients. About 80% of patients received drug-eluting stent (DES) implantation, and 20% received bare-metal stent (BMS). The PCI CTO procedures needed <200 mL contrast in 32 patients. The patients' angiographic and procedural aspects were not significantly different, except for the dose area product (DAP).

3.2. Outcomes

The follow-up period was ranging from 2 to 24 months following the CTO recanalization procedure. The SAQ includes physical limitation, angina frequency, and quality of life. The SAQ for physical limitation between the two groups was not significantly different (83.86 ± 16.11 vs. 77.92 ± 3.44 ; $p = 0.247$). The SAQ on angina frequency (85.27 ± 17.44 vs. 74.76 ± 22.05 ; $p = 0.105$) and SAQ for quality of life (73.24 ± 3.41 vs. 72.82 ± 3.56 ; $p = 0.932$) also revealed the similar results. Our results also revealed that good myocardial blush was not correlated with the reduction of antianginal drug regimens (10

Table 2. Angiographic characteristics and procedural aspects

Variable	Good myocardial blush (MBG 2-3) (n = 19)	Poor myocardial blush (MBG 0-1) (n = 21)	Total n = 40	p-Value
Number of significant lesions				0.384
1 vessel disease	4 (21.1)	3 (14.3)	7 (18)	
2 vessels disease	5 (26.3)	3 (14.3)	8 (20)	
3 vessels disease	9 (47.4)	15 (71.4)	24 (60)	
Left main disease	1 (5.3)	0 (0.0)	1 (2.5)	
SYNTAX score				0.911
Skor < 22	6 (31.6)	6 (28.6)	12 (30)	
Skor 22 – 32	7 (36.8)	7 (33.3)	14 (35)	
Skor >33	6 (31.6)	8 (38.1)	14 (35)	
CTO location				0,175
Left main artery	1 (5.3)	0 (0.0)	1 (2.5)	
Left anterior descending artery	11 (57.9)	7 (33.3)	18 (45)	
Left circumflex artery	2 (10.5)	3 (14.3)	5 (12.5)	
Right coronary artery	0 (0.0)	4 (19.0)	4 (10)	
Multivessel CTO	5 (26.3)	7 (33.3)	12 (30)	
Bridging collateral	3 (15.8)	3 (14.3)	6 (15)	0,619
Contralateral collateral	9 (47.4)	11 (52.4)	18 (45)	0,500
Wire crossing time				0.398
<30 minutes	15 (78.9)	19 (90.5)	34 (85)	
>30 minutes	4 (21.1)	2 (9.5)	6 (15)	
Contrast				0.241
<200 mL	17 (89.5)	15 (71.4)	32 (80)	
>200 mL	2 (10.5)	6 (28.6)	8 (20)	
DAP (Cgy.cm ²)				0,042
<10.000	4 (21.1)	0 (0.0)	4 (10)	
>10.000	15 (78.9)	21 (100)	36 (90)	
Stent				0.654
BMS	3 (15.8)	5 (23.8)	8 (20)	
DES sirolimus	8 (42.1)	6 (28.6)	14 (35)	
DES everolimus	6 (31.6)	9 (42.9)	15 (38)	
DES paclitaxel	2 (10.5)	1 (4.8)	3 (8)	
Complete revascularization	8 (42.1)	8 (38.1)	16 (40)	1.000

BMS = bare metal stent; CTO = chronic total occlusion; DAP = dose area product; DES = drug eluting stent; MBG = myocardial blush grade; SYNTAX = synergy between percutaneous coronary intervention with taxus and cardiac surgery

Table 3. Outcome

Variable	Good myocardial blush (MBG 2-3) (n = 19)	Poor myocardial blush (MBG 0-1) (n = 21)	p-Value
SAQ - physical limitation	83.86 ± 16.11	77.92 ± 3.44	0.247
SAQ - angina frequency	85.27 ± 17.44	74.76 ± 22.05	0.105
SAQ - quality of life	73.24 ± 3.41	72.82 ± 3.56	0.932
Reduction of antianginal drug regimens	10 (52.6)	8 (40)	0.639

SAQ = Seattle Angina Questionnaire; MBG = myocardial blush grade

(52.6) vs. 8 (40); p = 0.639).

4. Discussion

In patients with severe coronary artery disease, CTO and non-CTO patients' signs and symptoms cannot be distinguished. Several parameters were correlated with the clinical presentation of CTO, including the number of the coronary arteries involved, the existence of other concomitant coronary lesions, the presence of collateral blood flow, myocardial viability, and the degree of myocardial ischemia.^{1,5} Lesson learned from the Flow Cardia's approach to chronic total occlusion recanalization (FACTOR) trial suggests that two-thirds of the patients referred for the trial had angina, which significantly impaired their quality of life.¹⁴ However, all patients included in our study suffered from angina. A study by Safley et al. revealed that dyspnea is the most common anginal equivalent symptom among CTO patients. That study also showed similar alleviation in both dyspnea and angina following PCI in CTO and non-CTO group.⁴

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial showed that CABG has lower major adverse cardiac and cerebrovascular events (MACCE) than PCI for three vessels disease and left main disease during three years follow up period.¹⁵ The final decision on PCI or CABG remains individual and depends on the operator and the patient. The main advantages of CTO PCI are improved symptoms, improved left ventricular function, the reduction of the need for late CABG.^{14,16} The revascularization strategy in multivessel disease with concomitant CTO might be challenging. In multivessel disease as the first revascularization step, PCI CTO might be a rational approach. In case of failure, a complete CABG multivessel disease revascularization might be an acceptable strategy.¹⁷

Total Occlusion Angioplasty Study-Società Italiana di Cardiologia Invasiva (TOAST-GISE) study revealed that the successful CTO PCI was related to the reduction of the one-year incidence of cardiovascular mortality or myocardial infarction (MI), the reduction of the need for CABG, and the improvement of angina freedom in most patients.¹⁸ CTO PCI should be conducted electively and not ad hoc. Separating diagnostic coronary angiography and CTO PCI allows for a detailed discussion with the patient about the indication, targets, risk, and alternatives to PCI, including optimal medical treatment or CABG. The risk that more specific to CTO PCI warrant discussion. These include the risk of donor vessel injury, perforation, tamponade, and radiation exposure.

Myocardial blush is an angiographic parameter that represents the adequacy of myocardial reperfusion. The previous study from Gai et al. revealed that higher post PCI MBG was associated with the improvement of total blush and ejection fraction (EF).¹⁹ At first, we assumed that the better myocardial blush is associated with better improvement of angina symptoms. However, our study failed to prove that hypothesis. In our study, we found that myocardial blush was not correlated with the improvement of angina symptoms. The SAQ for physical limitation, angina frequency, and quality of life were not

significantly different between both groups. Our study also revealed that myocardial blush was not correlated with and the reduction of antianginal drug regimens. CTO recanalization restores coronary blood flow to the myocardium. If the CTO recanalization is accompanied by optimal medical treatment, the myocardial perfusion will gradually improve even though the MBG after the CTO PCI procedure is not good enough. The reduction in antianginal drug regimens between both groups had no significant difference. The ischemic burden of incomplete revascularization was the reason for nitrate administration as an antianginal in our study. The existing data showed that 57.5% of the total study participants were still incomplete revascularization. They were patients with multivessel lesions and required subsequent PCI procedures.

As far as we are concerned, our study was the only study to investigate the impact of post-CTO recanalization MBG on the clinical outcomes of CCS patients, including the improvement of angina symptoms and the reduction of antianginal drug regimens. By using the QuBE, we could limit intra- and inter-observer variability in evaluating the myocardial blush. Several limitations were found in our study. First, this study was a retrospective study. Second, unequal follow-up period among the participants. It could be a significant potential for bias. Third, we included patients with incomplete revascularization. The residual angina symptoms could be the effect of the incomplete revascularization. Fourth, we conducted a study with a small number of participants. However, our sample number was higher than the study by Gai et al.¹⁹ Last, the baseline SAQ among the participants was not assessed. A study with a better design and larger participants was needed to obtain good quality evidence.

5. Discussion

Our study provided a preliminary overview of myocardial blush following the CTO PCI procedure. Myocardial blush post-CTO recanalization was not associated with the improvement of angina symptoms and the reduction of antianginal drug regimens among patients with CCS.

6. Declarations

6.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication

Not applicable.

6.3. Availability of data and materials

Data used in our study were presented in the main text.

6.4. Competing interests

Not applicable.

6.5. Funding source

Not applicable.

6.6. Authors contributions

Idea/concept: IH. Design: IH. Control/supervision: MSR, DH, DS YW. Data collection/processing: IH, FR, AGP. Extraction/Analysis/interpretation: IH, FR, AGP. Literature review: MSR, DH, DS, YW. Writing the article: IH. Critical review: MSR, DH, DS, YW. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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