

Effect of coronary collateral circulation on the prognosis of elderly patients with acute ST-segment elevation myocardial infarction treated with underwent primary percutaneous coronary intervention

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Abstract

Investigate the effect of coronary collateral circulation (CCC) on the prognosis of elderly patients with acute ST-segment elevation myocardial infarction (STEMI) and acute total occlusion (ATO) of a single epicardial coronary artery.

Three hundred forty-six advanced-age patients (age ≥ 60 years) with STEMI and ATO who underwent primary percutaneous coronary intervention (PCI) were enrolled in this study. According to the Rentrop grades, the patients were assigned to the poor CCC group (Rentrop grade 0–1) and good CCC group (Rentrop grade 2–3).

Multivariate logistic regression analysis revealed that poor coronary collateral circulation was an independent factor for Killip class ≥ 2 (odds ratio [OR]: -1.559 ; 95% confidence interval [CI]: 1.346 – 2.378 ; $P = .013$), the use of an intra-aortic balloon pump (IABP) (OR: -1.302 ; 95% CI: 0.092 – 0.805 ; $P = .019$), and myocardial blush grade (MBG) 3 (OR: 1.516 ; 95% CI: 2.148 – 9.655 ; $P < .001$). We completed a 12-month follow-up, during which 52 patients (15.0%) were lost to follow-up and 19 patients (5.5%) died. Univariate analysis (Kaplan–Meier and log-rank tests) suggested that poor CCC had a significant effect on all-cause mortality ($P = .046$), while multivariate analysis (Cox regression analysis) indicated that CCC had no statistically significant effect on all-cause mortality ($P = .089$) after the exclusion of other confounding factors. After excluding the influence of other confounding factors, this study showed that the mortality rate increased by 26.9% within 1 year for every 1-hour increment of time of onset. The mortality rate in patients with Killip class ≥ 2 was 8.287 times higher than that in patients with Killip class 0 to 1. The mortality rate in patients over 75 years was 8.25 times higher than that in patients aged 60 to 75 years. The mortality rate in patients with myocardial blush grade 3 (MBG 3) was 5.7% higher than that in patients with MBG 0–2.

The conditions of CCC in the acute phase had no significant direct effect on all-cause mortality in patients, but those with good CCC had a higher rate of MBG 3 after primary PCI and a lower rate of Killip ≥ 2 .

Abbreviations: AMI = acute myocardial infarction, ATO = acute total occlusion, CABG = coronary artery bypassing grafting, CCC = coronary collateral circulation, CI = confidence interval, CTO = total coronary artery occlusion, DAPT = dual anti-platelet therapy, FPG = fasting blood glucose, HDL = high-density lipoprotein cholesterol, IABP = intra-aortic balloon pump, LDL = low-density lipoprotein cholesterol, MBG = myocardial blush grade, OR = odds ratio, ORT = onset-to-reperfusion time, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction, TC = total cholesterol, TG = triglyceride, TIMI = thrombolysis in myocardial infarction.

Keywords: acute total occlusion, coronary collateral circulation, prognosis, ST-segment elevation myocardial infarction

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1. Introduction

Percutaneous coronary intervention (PCI) has been the best treatment option for patients with acute ST-segment elevation myocardial infarction (STEMI). Although epicardial blood flow has been successfully restored after primary PCI, myocardial reperfusion and left ventricular function recovery are usually not ideal.^[1–6] Studies have shown that the degree of myocardial damage before the reperfusion of epicardial blood flow is an important determinant of myocardial reperfusion,^[7,8] that is, adequate preoperative myocardial protection appears to be important to obtain satisfactory reperfusion results. Coronary collateral circulation (CCC) is a self-preservation of blood supply during myocardial ischemia. Therefore, the presence of CCC after acute coronary occlusion may play a key role in preoperative myocardial protection and may also affect the prognosis in STEMI patients. However, previous studies have suggested that the effects of CCC on the prognosis of acute

myocardial infarction (AMI) are debatable.^[9] The reason may be related to the heterogeneity of the subjects and different definitions of the primary endpoint. In our precious study,^[10] we investigated the association between triglyceride (TG)/high-density lipoprotein (HDL) ratio and development of CCC in elderly population with STEMI and acute total occlusion (ATO), and considered that TG/HDL ratio is an independent risk factor for the poor development of CCC. This study was designed to investigate the effects of CCC on in-hospital clinical status all-cause mortality in elderly STEMI patients with single epicardial vascular occlusion who underwent successful primary PCI with no >12 hours after onset.

2. Subjects and methods

2.1. Research subjects

Three hundred forty-six elderly patients (age ≥ 60 years) with STEMI and acute coronary occlusion (ATO) who were admitted to the Department of Cardiology, the First Hospital of Lanzhou University, China from September 2014 to March 2017 were enrolled in this study. Moreover, these patients underwent coronary angiography and successful primary PCI within 12 hours after onset. All patients were either treated directly at the emergency chest pain center of our hospital or transferred from the local county hospital. According to Rentrop grade, the patients were assigned to the poor CCC group (Rentrop grade 0–1) and good CCC group (Rentrop grade 2–3). Left main coronary occlusion, combined with occlusion of non-culprit vessel verified by angiography, previous myocardial, history of PCI or coronary artery bypass grafting, peripheral artery disease, stroke, abnormal status including chronic inflammatory or autoimmune disease, etc., were excluded.

According to the Rentrop grades, a total of 346 patients were assigned to the poor CCC group (Rentrop grade 0–1) and good CCC group (Rentrop grade 2–3).

This retrospective study was approved by the Ethics Committee of the First Hospital of Lanzhou University. All patients have signed the informed consent form.

2.2. Data collection

The highly trained researchers retrospectively reviewed the medical records of all patients. All blood samples were collected before procedures and processed within half an hour. Biochemical indicators including fasting blood glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglyceride (TG) were tested by a hospital clinical laboratory using an automated biochemical analyzer (Beckman coulter UniCel D \times 800 Synchron, USA). NT-proBNP was tested by specialists in the CCU ward using a bedside meter (Roche Cobas e411, Switzerland).

2.3. Assessment of Killip classification, TIMI blood flow grade, myocardial blush grade (MBG), the Gensini scoring, and the Rentrop grading

Killip classification^[11] is used to assess the cardiac function of patients with AMI and includes 4 categories: Class I, no rales or crackles in the lungs and no S3; Class II, rales or crackles in the

lungs, but the range of the rales is $< 1/2$ of the lung field; Class III, the range of rales in the lung is $> 1/2$ of the lung field (pulmonary edema); and Class IV, shock.

TIMI blood flow grade^[12] (range, 0–3) reflects the degree of coronary blood flow during coronary angiography, as follow: TIMI 0, no perfusion, or the absence of any antegrade flow beyond a coronary occlusion; TIMI 1, penetration without perfusion, of faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed; TIMI 2, partial reperfusion, or delayed or sluggish antegrade flow with complete filling of the distal territory; and TIMI 3, normal flow, filling the distal coronary bed completely.

MBG^[13] was grade by evaluating myocardial reperfusion during coronary angiography. Grade 0: no myocardial blush or contrast density; grade 1: minimal myocardial blush or contrast density; grade 2: moderate myocardial blush or contrast density, but less than myocardial blush or contrast density in the ipsilateral or contralateral non-infarct-related angiography; grade 3 normal myocardial blush or contrast density, comparable myocardial blush or contrast density in the ipsilateral or contralateral non-infarct-related angiography. MBG 0–1, no perfusion of the myocardium; MBG 2, partial reperfusion of myocardium; MBG 3, complete reperfusion of myocardium.

Rentrop grade^[14] is used to assessing the level of coronary circulation based on coronary angiography. Grade 0, no fillings; grade 1, filling of side branches of the occluded artery, with no dye reaching the epicardial segment; grade 2, partial filling of the epicardial vessel; grade 3, complete filling of epicardial vessel by collateral vessels. We defined Rentrop grade 0–1 as poor coronary collateral circulation and Rentrop grade 2–3 as good coronary collateral circulation.

The Gensini scoring system^[15] is derived from the American Heart Association's criteria for the evaluation of coronary artery image scores: the degree of stenosis is defined as the degree of stenosis at the most severe stenosis site. A percent diameter stenosis $< 25\%$ is defined as 1 point, $\geq 25\%$ to $< 50\%$ as 2 points, $\geq 50\%$ to $< 75\%$ as 4 points, $\geq 75\%$ to $< 90\%$ as 8 points, $\geq 90\%$ to $< 99\%$ as 16 points, and $\geq 99\%$ as 32 points. According to the different coronary artery branches, the above scores were multiplied by a corresponding coefficient: 5 for the left main branch lesions, 2.5 and 1.5 for the proximal and middle segment lesions of the left anterior descending branch, respectively, 1 and 0.5 for D1 and D2 in the diagonal branches, respectively, 2.5 and 1 for the proximal and distal segment lesions of the left circumflex, respectively, and 1 for the proximal, middle, distal, and posterior descending branch lesions of the right coronary. The sum of the scores of each lesion is the total score of the degree of coronary artery stenosis in a patient. Meanwhile, according to the total score, the degree of coronary artery stenosis was divided into mild (< 50 points), moderate (≥ 50 to < 80 points) and moderate (≥ 80 points).

2.4. Clinical endpoints and follow-up

The cardiovascular medical professionals completed the follow-up phone calls in all patients at scheduled time-points. Adverse events, mainly all-cause death, were documented. The follow-up was performed in all patients at 1, 3, 6, and 12 months after discharge from the hospital over the phone call. Early or delayed follow-up was within a week of the scheduled time point.

2.5. Statistical analysis

All statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL). The quantitative variables were expressed as the means ± standard deviation. The categorical variables were expressed as percentages. Chi-square test was used to compare the difference in the categorical variables between the groups. The *t* test was used to compare the quantitative variables with normal distribution between groups. The Mann–Whitney *U* test was used to compare the data without normal distribution. The Kolmogorov–Smirnov test was used to test the normal distribution of the quantitative variables. Multivariate logistic regression analysis was performed to evaluate the effect of collateral circulation on the treatment outcomes and measures. Univariate analysis (Kaplan–Meier and log-rank tests) was used to screen for factors affecting death, and Cox regression analysis was used to evaluate factors with significant effects on mortality. *P* < .05 was considered statistically significant.

3. Results

3.1. Baseline

The baseline characteristics of patients based on the assessment of poor or good coronary collateral circulation are shown in Table 1. No significant differences were found between the 2 groups in angiographic features, including coronary arterial dominance and the Gensini score. There was no significant difference in the type and duration of dual anti-platelet therapy between the 2 groups. No significant differences were found between the 2 groups in the length and number of stents, antithrombotic therapy, and the number of coronary artery vessel lesion. However, significant differences were noted in the time of onset, preoperative intravenous thrombolysis, triglyceride (TG) level, high-density lipoprotein (HDL) level, and acute occlusion of the coronary arteries. Statistical differences were also detected in Killip grading and the use of IABP, MBG, and death between the groups.

Table 1
Baseline characteristics.

	Poor collateral circulation group (n=238)	Good collateral circulation group (n=108)	P value
Age, y	68.2 ± 6.2	66.7 ± 5.1	.03
Male (n, %)	186 (78.2)	88 (81.5)	.48
Time of onset, h	4.10 ± 2.66	6.73 ± 2.19	<.001
History of previous angina (n, %)	106 (44.5)	50 (46.3)	.76
History of diabetes (n, %)	34 (14.3)	18 (16.7)	.57
History of hypertension (n, %)	80 (33.6)	42 (38.9)	.34
History of hyperlipidemia (n, %)	11 (3.2)	2 (1.9)	.34
Currently smoking (n, %)	136 (57.1)	62 (57.4)	.96
Family history of premature coronary heart disease (n, %)	6 (2.5)	2 (1.9)	.70
Preoperative systolic blood pressure, mmHg	116.1 ± 23.15	114.0 ± 27.2	.46
Preoperative diastolic blood pressure, mmHg	95.0 ± 16.8	90.3 ± 21.5	.50
BMI, kg/m ²	25.87 ± 6.68	26.07 ± 6.10	.80
eGFR, mL/min-1.73 m ²	103.2 ± 32.0	98.6 ± 32.8	.22
Blood glucose, mmol/L	8.95 ± 3.84	8.88 ± 4.14	.87
TC, mmol/L	4.83 ± 1.00	4.76 ± 1.19	.54
LDL, mmol/L	3.19 ± 0.80	3.09 ± 0.95	.33
HDL, mmol/L	1.04 ± 0.23	1.11 ± 0.25	.02
TG, mmol/L	2.74 ± 1.65	1.88 ± 1.09	<.001
Preoperative intravenous thrombolysis therapy (n, %)	4 (1.7)	12 (11.1)	<.001
DAPT duration			.117
Program 1(m, n)	10.91 ± 2.73(71)	11.31 ± 2.15(30)	.413
Program 2(m, n)	11.22 ± 2.81(145)	11.57 ± 2.33(67)	.387
Program 3(m, n)	10.11 ± 3.21(22)	10.47 ± 1.73(11)	.255
Stent			
Length, mm	21.23 ± 7.21	22.31 ± 8.95	.233
Number	1.51 ± 0.74	1.65 ± 0.96	.140
Coronary artery vessel lesion			.194
1-vessel lesion (n, %)	47(19.75)	17(15.74)	
2-vessel lesion (n, %)	143(60.08)	60(55.56)	
3-vessel lesion (n, %)	48(20.17)	31(28.70)	
Circumflex occlusion (n, %)	52 (21.8)	6 (5.6)	<.001
Right coronary occlusion (n, %)	74 (31.1)	58 (53.7)	<.001
Anterior descending branch occlusion (n, %)	112 (47.1)	44 (40.7)	.27
Preoperative NT-proBNP, pg/mL	545.2 ± 301.7	512.8 ± 281.5	.08
Killip classification ≥2 (n, %)	29 (12.2)	4 (3.7)	.01
Use of IABP (n, %)	45 (18.9)	6 (5.6)	<.001
Postoperative MBG 3 (n, %)	45 (21.6)	38 (27.8)	.001
Postoperative LVEF (%)	43.9 ± 11.3	45.7 ± 10.5	.08
Death (n, %)	17 (7.1)	2 (1.9)	.046

BMI = body mass index, DAPT = dual anti platelet therapy, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, IABP = intra-aortic balloon pump, LDL = low-density lipoprotein, LVEF = cardiac left ventricular ejection fraction, m = month, MBG = myocardial blush grade, Program 1 = Aspirin (100 mg qd) + Clopidogrel (75 mg qd), Program 2 = Aspirin (100 mg qd) + Tigrilo (90 mg Bid), Program 3 = Aspirin + Clopidogrel, replace clopidogrel with ticagrelor 1 month later, TC = total cholesterol, TG = triglyceride.

Table 2
Effect of collateral circulation on the treatment outcomes and measures by multivariate logistic regression analysis.

	<i>B</i> value	Std. Error	<i>P</i> value	Exp(<i>B</i>)	95% CI for Exp(<i>B</i>)
Killip Class ≥ 2 (1=yes; 0=no)	-1.559	0.631	.013	0.210	0.061–0.724
Use of IABP (1=yes; 0=no)	-1.302	0.553	.019	0.272	0.092–0.805
Postoperative MBG 3 (1=yes; 0=no)	1.516	0.383	<.001	4.554	2.148–9.655

IABP=intra-aortic balloon pump, MBG=myocardial blush grade.

3.2. Multivariate logistic regression analysis to evaluate the effect of collateral circulation on the treatment outcomes and measures

Killip class ≥ 2 , the use of IABP, and postoperative MBG 3 were the dependent variables, while age, occlusion of the corresponding coronary artery, the time of onset, preoperative thrombolysis, the TG level, the HDL level, and the selection of a good collateral circulation group (1=yes, 0=no) were independent variables in the multivariate logistic regression analysis. The effect of the good or poor collateral circulation group on the dependent variable was evaluated (Table 2).

3.3. Univariate analysis (Kaplan–Meier and log-rank tests) and multivariate analysis (Cox regression analysis) of coronary collateral circulation for all-cause mortality

We completed the 12-month follow-up, during which 52 patients (15.0%) were lost to the follow-up, and 19 patients (5.5%) died. Univariate analysis (Kaplan–Meier and log-rank tests) suggested that poor coronary collateral circulation had a significant effect on all-cause mortality ($P=.046$), while multivariate analysis (Cox regression analysis) indicated that coronary collateral circulation had no statistically significant effect on all-cause mortality ($P=.089$) after adjustment for the time of onset, Killip grade, MBG, age, and LVEF (see Fig. 1).

3.4. Identified factors affecting all-cause mortality by Cox regression analysis

After excluding the influence of other confounding factors, including HDL, TG, preoperative intravenous thrombolysis and LVEF, this study showed that the mortality rate increased by 26.9% within 1 year for every 1-hour increment of the time of onset. The mortality rate in patients with Killip grade ≥ 2 was 8.287 times higher than that in patients with Killip grade 0–1. The mortality rate in patients over 75 years was 8.25 times higher than that in patients aged 60 to 75 years. The mortality rate in the patients with MBG 3 was 5.7% higher than that in the patients with MBG 0–2 (Table 3).

4. Discussion

The enrolled patients in this study were elderly patients with STEMI and aged over 60 years. The time of onset was no more than 12 hours, and single major epicardial coronary artery occlusion was identified. The degrees of stenosis of the culprit vessels were consistent (100%). Moreover, we performed Kaplan–Meier and log-rank tests showing that the Gensini scores (including mild, medium, and severe groups) were not significantly different, indicating that the degree of stenosis of the entire coronary system was consistent. We defined the criteria for successful primary PCI as a postoperative thrombolysis. In

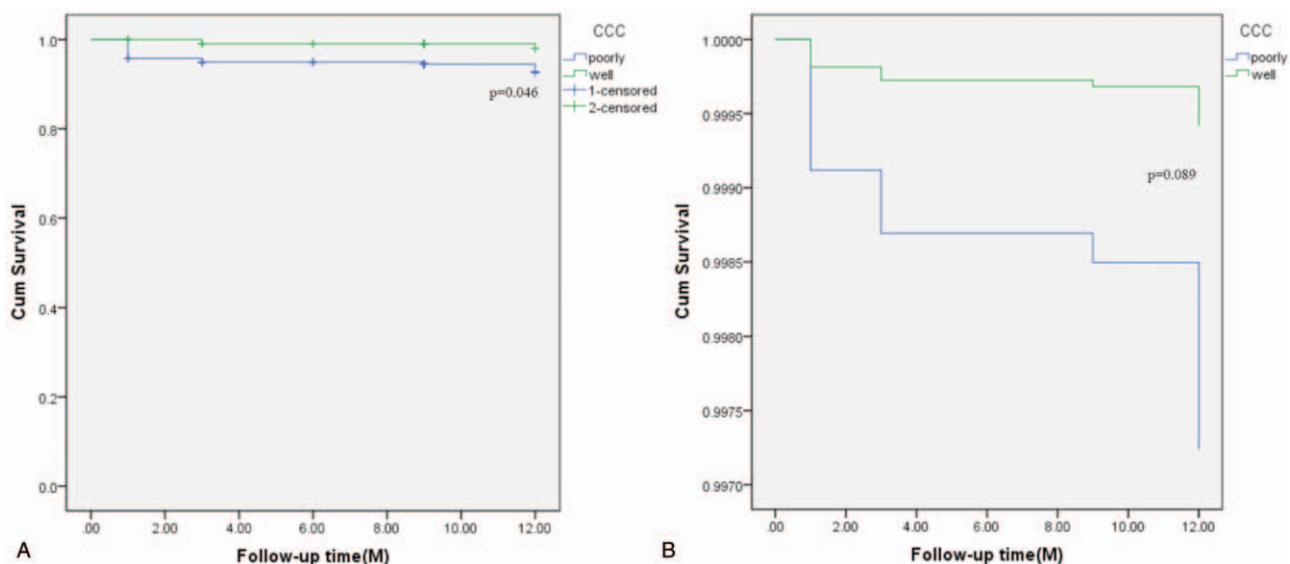


Figure 1. Effect of collateral circulation on death by univariate and multivariate analyses. Panel A. Univariate analysis (Kaplan–Meier and log-rank tests) to assess the effect of coronary collateral circulation (good group vs poor group) on death. Panel B. Multivariate analysis (Cox regression analysis) to assess the effect of coronary collateral circulation on death with adjustment for the time of onset, Killip grade, MBG, age, and LVEF. LVEF=cardiac left ventricular ejection fraction, MBG=myocardial blush grade.

Table 3
Cox regression analysis for death.

	B	SE	Wald	P	Exp(B)	95.0% CI for Exp(B)
Time of onset, h	0.239	0.089	7.206	.007	1.269	1.066–1.511
Killip class ≥ 2 (1 = yes; 0 = no)	2.115	0.598	12.484	<.001	8.287	2.564–26.780
Postoperative MBG3 (1 = yes; 0 = no)	-2.870	1.098	6.827	.009	0.057	0.007–0.488
Age (1 = >75 years; 0 = 60–75 years)	2.110	0.514	16.863	<.001	8.250	3.013–22.588

Statistically significant outcomes ($P < .05$) were obtained from the Cox regression model by including variables (collateral circulation grade, time of onset, Killip classification, postoperative MBG and age) that were statistically significant ($P < .1$) in the univariate analysis and LVEF.

myocardial infarction (TIMI) blood flow level >3 but not between 2 and 3. The above-depicted inclusion criteria make the research population highly homogeneous with better comparability.

Previous studies have shown that MBG, which describes the effectiveness of myocardial reperfusion, is an independent predictor of long-term mortality after reperfusion therapy in patients with AMI. A higher MBG is associated with a lower incidence of major adverse cardiac events, including reinfarction and sudden cardiac death.^[13,16] Significant variables, including the level of TG and HDL, the rate of preoperative intravenous thrombolysis, circumflex occlusion and right coronary occlusion, and the percentage of postoperative MBG 3, Killip ≥ 2 , and use of IABP were determined after univariate analysis. But the multivariate logistic regression analysis showed that patients with good coronary collateral circulation had a higher rate of postoperative MBG 3 (4.554 times) and a lower rate of Killip ≥ 2 (0.21 times) and a lower rate of the use of IABP (0.272 times) than patients with poor coronary collateral circulation; this result indicated that good coronary collateral circulation can improve myocardial perfusion after primary PCI, thereby protecting cardiac function and reducing the use of IABP. These results are consistent with those in previous studies.^[13,16,17]

The long-term impact of coronary collateral circulation on death in patients with AMI has been debated. Boehrer et al^[18] studied 146 patients with AMI who had complete occlusion of the culprit vessels but no significant stenosis in the non-culprit vessels for >12 years. These patients were divided into 2 groups according to whether there was infarct-related collateral circulation. No significant difference was found in the mortality between the groups after the 12-year follow-up (16% for those with collateral circulation and 19% for those without collateral circulation). Antoniucci et al^[19] compared 1164 patients with AMI who underwent primary PCI within 6 hours after onset. These patients were divided into 2 groups according to the existence of infarct-related collateral circulation. After a 6-month follow-up, multifactorial Cox regression analysis showed no correlation between collateral circulation and death. Elsmann et al^[17] also completed a 1-year follow-up in 1059 patients with AMI who underwent primary PCI within 6 hours after onset. The patients were divided into 3 groups according to Rentrop grading (Grade 0, 1, and 2–3); the survival rates of the 3 groups after 1 year (95%, 96%, and 97%, respectively) were not significantly different. Meier et al^[20] analyzed patients with acute coronary syndrome who underwent primary PCI and found no statistically significant difference in the mortality of patients with or without coronary collateral circulation. A meta-analysis has shown that the risk of death in patients with coronary heart disease and good collateral circulation is 36% lower ($P = .005$) than that in patients with poor collateral circulation. Subgroup analysis of this study

showed statistical significance of the risk of death in patients with stable coronary heart disease but not in patients with subacute myocardial infarction and AMI.^[21] In another study,^[22] patients with subacute myocardial infarction within 3 to 28 days after onset were followed up for 60 months, and the mortality of the patients with good collateral circulation was significantly reduced ($P = .009$).

Although controversial, we found through literature analysis that, for patients with AMI, especially those who developed the condition less than 6 hours after onset and underwent primary PCI, no significant relationship was detected between coronary collateral circulation and death. This finding is consistent with our results. However, the largest difference between our and other studies is that our selected subjects were more comparable because they were elderly patients with STEMI who had a single epicardial vascular occlusion and underwent successful PCI within 12 hours after onset. Additionally, the Gensini scores were similar in both groups, and we defined the successful criteria for primary PCI as postoperative blood flow at TIMI level 3, while the criteria in other related studies were postoperative blood flow at TIMI level 2–3. Furthermore, there was no significant difference in the type and duration of dual anti-platelet therapy (DAPT) between the 2 groups. The PLATO study demonstrated superiority of ticagrelor over clopidogrel in the prevention of ischemic events in patients with acute coronary syndromes.^[23] In the PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy, Ticagrelor achieves greater antiplatelet than clopidogrel in patients with acute coronary syndromes, both in the first hours of treatment and during maintenance therapy.^[24] The 12-month duration of DAPT was implemented in our study, which was recommended by the European and American guidelines.^[25,26] Thus, the research population was within the ideal range as much as possible in this study, reducing the interference of other factors on the research results; therefore, our research results are more reliable.

Previous studies concerning total coronary artery occlusion (CTO) have basically shown that patients with stable angina combined with CTO^[27] or patients with AMI combined with CTO^[28] can improve the survival rate of patients with good coronary collateral circulation compared with those with CTO-related poor collateral circulation. The survival rate was increased by 66.7% in the former group^[27] and by 50% in the latter.^[28] However, this study suggests that the effects of coronary collateral circulation on ATO are different than those on CTO. The causes may be the following: the blood flow of the collateral circulation in the acute phase provides insufficient perfusion to the myocardial infarction area, that is, the blood supply of the collateral circulation is quantitatively different from the blood supply of the occluded large coronary artery and is not sufficient to reverse the effects of coronary occlusion and

reperfusion. A study^[19] has shown that, in the initial 6 hours after AMI, only the collateral circulation associated with the infarcted area is visible in 48% patients and reaches 92% in 1 to 14 days, but the magnitude of these collateral circulation blood flows is relatively lower (Rentrop grade 0–1) in the acute phase. Our study has shown that, within 12 hours after AMI, the composition ratios of the collateral circulation with Rentrop grades 0, 1, 2, and 3 are 45.7%, 23.1%, 27.2%, and 4.0%, respectively. Rentrop grade 0–1 accounted for 68.9% of all grades. The low flow has a limited protective effect on the myocardium. Although the mortality was higher in patients without reperfusion therapy, that is, 16% in patients with collateral circulation and 19% in patients with collateral circulation, no significant difference was observed between the groups.^[29] Furthermore, the mortality rate of patients with AMI who underwent primary PCI was lower. The mortality rates in patients with Rentrop grades 0, 1, and 2–3 were 5%, 4%, and 3%, respectively, but there was still no significant difference between them.^[30] This result indicates that the presence of good collateral circulation in the acute phase of myocardial infarction has a limited impact on death, and the most influential factor for death is whether the culprit vessel is recanalized quickly^[21]; thus, it is related to the dynamic changes in coronary collateral circulation. Time is an important factor for the formation of collateral circulation. As long as stenosis or complete occlusion exists, the degree of good collateral circulation is eventually increased over time. On the other hand, if the occluded blood vessels have been recanalized, the collateral circulation will gradually subside over time, and good collateral circulation can become poor collateral circulation. In the current study, there was significant differences in the time of onset and preoperative intravenous thrombolysis between poor coronary collateral circulation group and good coronary collateral circulation group. In a retrospective analysis of clinic and imaging data of 554 consecutive patients, Kim et al^[31] proved that earlier successful recanalization was strongly associated with good outcome in poor collateral group; however, this association was weak during the tested time window in good collateral group. This suggests that the onset-to-reperfusion time (ORT) window for good outcome can be adjusted according to collateral status. Recently, Toumpoulis et al^[32] compared the long-term survival of patients subjected to coronary artery bypassing grafting (CABG) after thrombolysis to those without thrombolysis, and demonstrated increased long-term survival of patients after thrombolysis. Therefore, we speculated that the onset time and preoperative intravenous thrombolysis may have an impact on the prognosis, which requires us to be more rigorous in subsequent studies. The subjects in this study are those who underwent successful primary PCI. During the 1-year follow-up, in theory, good collateral circulation in most patients will gradually become poor collateral circulation. Based on the abovementioned 2 points, for patients with ATO who have undergone successful primary PCI, good collateral circulation for myocardial protection only exists before the vascular recanalization forms an effective perfusion. This phenomenon may explain why many studies have shown significant differences in the effect of coronary collateral circulation on the prognosis of acute AMI (especially within 6 hours after onset) and that of stable coronary heart disease (e.g., CTO).

MBG represents an indicator of effective myocardial perfusion after reperfusion therapy for AMI. Previous studies have shown that MBG not only affects left ventricular function in patients with AMI but also has a significant impact on death.

For patients with AMI who have undergone primary PCI, studies by Hoffmann et al^[33] and Hamdan et al^[34] showed that patients with lower MBG had more severe impairment of left ventricular function than those with higher MBG. The study by Zeng et al^[35] showed that, for patients with AMI who have undergone primary PCI, the incidence of major adverse events was also higher in those with lower MBG during the follow-up. Our study suggests that MBG has a significant effect on patient mortality. Patients with good coronary collateral circulation have a postoperative ratio of MBG3 that is 4.554 times higher than that in patients with poor coronary collateral circulation. This finding indicates that effective reperfusion forms after recanalization of the culprit vessel has a significant impact on the prognosis. The results are consistent with previous findings. Therefore, in these patients, timely and effective reperfusion therapy can reduce mortality to a maximum amount. The criteria for successful reperfusion therapy are to achieve not only a TIMI blood flow level 3 but also MBG 3, that is, to form effective reperfusion.

This study also found that the 1-year mortality rate in patients with Killip class ≥ 2 after the exclusion of other confounding factors was 8.287 times higher than that of patients with Killip class 1. This result is basically consistent with previous studies. In STEMI patients who underwent primary PCI, Vicent et al^[36] found that the in-hospital mortality rates were 1.5%, 3.7%, 16.7%, and 36.7% for patients with Killip class 1, 2, 3, and 4, respectively. A higher Killip classification is associated with a higher mortality. The abovementioned 2 studies found that Killip classification was significantly associated with in-hospital death. However, we found that, even if the patients were discharged from the hospital after improvement, the Killip classification during hospitalization was related to the long-term prognosis and that its trend was consistent with that of the short-term prognosis.

We also found that patients over 75 years had a mortality rate 8.25 times higher than that of patients aged 60 to 75 years. This result is consistent with the findings of previous studies.^[37,38] Weaver et al^[37] studied the relationship between age and in-hospital mortality in 3256 patients with AMI and found that the mortality rates of patients aged ≤ 54 years, 55–64 years, 65–74 years, and ≥ 75 years were 2%, 4.6%, 12.3%, and 17.8%, respectively. Advanced age is associated with a higher mortality rate. Singh et al^[38] analyzed the relationship between age and prognosis in 1597 patients with AMI who underwent primary PCI. These patients were divided into 4 groups according to age: 55 to 59 years, 60 to 69 years, 70 to 79 years, and ≥ 80 years. Patients aged 80 years or older had more adverse baseline characteristics, including risk factors and comorbidities, than younger patients. In-hospital mortality was significantly higher in patients over 80 years than that in the other 3 groups (the mortality rates in patients aged 80 years or older, 70–79 years, 60–69 years, and 50–59 years were 21%, 13%, 9%, and 4%, respectively; $P < .001$). During the follow-up, the mortality rate of the patients in the highest age group who underwent successful primary PCI was significantly higher than that in the other 3 groups. This finding indicates that both the in-hospital and out-hospital mortality rates of elderly patients are significantly increased.

This study also demonstrated that the mortality rate increased by 26.9% within 1 year for every 1-hour increment of the time after onset. A large-scale study in the United States^[39] revealed that the shorter time from onset to the revascularization is associated with a better prognosis: compared with patients

undergoing revascularization >2 hours after onset, patients undergoing revascularization within 2 hours after onset have a better postoperative blood flow and lower mortality rate after the 3-year follow-up. It is generally believed that within 12 hours after the onset of AMI, a longer vascular occlusion time is associated with a larger area of myocardial necrosis and a worse prognosis.

5. Conclusion

In summary, for elderly STEMI patients with single epicardial coronary artery occlusion who successfully underwent primary PCI with no >12 hours after onset, good or poor coronary collateral circulation in the acute phase does not affect the 12-month all-cause death. However, patients with good coronary collateral circulation had a higher rate of MBG 3 and a lower rate of Killip class ≥ 2 after primary PCI. Postoperative MBG 3 and Killip class ≥ 2 were independent negative and positive factors of all-cause death, respectively. This result indicates that good coronary collateral circulation still has an indirect beneficial effect on the prognosis. Moreover, a longer time after onset and a more advanced age are associated with higher mortality.

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References

- [1] Stone GW, Peterson MA, Lansky AJ, et al. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. *J Am Coll Cardiol* 2002;39:591–7.
- [2] Kastrati A, Mehilli J, Dirschinger J, et al. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. *Lancet* 2002;359:920–5.
- [3] Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;346:957–66.
- [4] Henriques JP, Zijlstra F, van't Hof AW, et al. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. *Circulation* 2003;107:2115–9.
- [5] Costantini CO, Stone GW, Mehran R, et al. Frequency, correlates, and clinical implications of myocardial perfusion after primary angioplasty and stenting, with and without glycoprotein IIb/IIIa inhibition, in acute myocardial infarction. *J Am Coll Cardiol* 2004;44:305–12.
- [6] Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1999;341:1949–56.
- [7] Wong CK, French JK, Krucoff MW, et al. Slowed ST segment recovery despite early infarct artery patency in patients with Q waves at presentation with a first acute myocardial infarction. Implications of initial Q waves on myocyte reperfusion. *Eur Heart J* 2002;23:1449–55.
- [8] Uyarel H, Cam N, Okmen E, et al. Level of Selvester QRS score is predictive of ST-segment resolution and 30-day outcomes in patients with acute myocardial infarction undergoing primary coronary intervention. *Am Heart J* 2006;151:1239.e1–7.
- [9] Seiler C, Meier P. Historical aspects and relevance of the human coronary collateral circulation. *Curr Cardiol Rev* 2014;10:2–16.
- [10] Liu GY, Meng XX, Zhang Z. Triglyceride to HDL-cholesterol ratio as an independent risk factor for the poor development of coronary collateral circulation in elderly patients with ST-segment elevation myocardial infarction and acute total occlusion. *Medicine (Baltimore)* 2018;97:e12587.
- [11] Killip T3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 1967;20:457–64.
- [12] Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879–88.
- [13] van't Hof AW, Liem A, Suryapranata H, et al. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation* 1998;97:2302–6.
- [14] Seiler C. Assessment and impact of the human coronary collateral circulation on myocardial ischemia and outcome. *Circ Cardiovasc Interv* 2013;6:719–28.
- [15] Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol* 1983;51:606.
- [16] Kaya MG, Arslan F, Abaci A, et al. Myocardial blush grade: a predictor for major adverse cardiac events after primary PTCA with stent implantation for acute myocardial infarction. *Acta Cardiol* 2007;62:445–51.
- [17] Elsmann P, van't Hof AW, de Boer MJ, et al. Role of collateral circulation in the acute phase of ST-segment-elevation myocardial infarction treated with primary coronary intervention. *Eur Heart J* 2004;25:854–8.
- [18] Boehrer JD, Lange RA, Willard JE, et al. Influence of collateral filling of the occluded infarct-related coronary artery on prognosis after acute myocardial infarction. *Am J Cardiol* 1992;69:10–2.
- [19] Antoniucci D, Valenti R, Moschi G, et al. Relation between preintervention angiographic evidence of coronary collateral circulation and clinical and angiographic outcomes after primary angioplasty or stenting for acute myocardial infarction. *Am J Cardiol* 2002;89:121–5.
- [20] Meier P, Lansky AJ, Fahy M, et al. The impact of the coronary collateral circulation on outcomes in patients with acute coronary syndromes: results from the ACUITY trial. *Heart* 2014;100:647–51.
- [21] Meier P, Hemingway H, Lansky AJ, et al. The impact of the coronary collateral circulation on mortality: a meta-analysis. *Eur Heart J* 2012;33:614–21.
- [22] Steg PG, Kerner A, Mancini GB, et al. Impact of collateral flow to the occluded infarct-related artery on clinical outcomes in patients with recent myocardial infarction: a report from the randomized occluded artery trial. *Circulation* 2010;121:2724–30.
- [23] James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATElet inhibition and patient Outcomes (PLATO) trial. *Am Heart J* 2009;157:599–605.
- [24] Storey RF, Angiolillo DJ, Patil SB, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol* 2010;56:1456–62.
- [25] Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119–77.
- [26] O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2013;82:E1–27.
- [27] Meier P, Gloekler S, Zbinden R, et al. Beneficial effect of recruitable collaterals: a 10-year follow-up study in patients with stable coronary

- artery disease undergoing quantitative collateral measurements. *Circulation* 2007;116:975–83.
- [28] Elias J, Hoehers LPC, van Dongen IM, et al. Impact of collateral circulation on survival in st-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention with a concomitant chronic total occlusion. *JACC Cardiovasc Interv* 2017;10:906–14.
- [29] Goldberg RJ, Gore JM, Gurwitz JH, et al. The impact of age on the incidence and prognosis of initial acute myocardial infarction: the Worcester Heart Attack Study. *Am Heart J* 1989;117:543–9.
- [30] Turi ZG, Stone PH, Muller JE, et al. Implications for acute intervention related to time of hospital arrival in acute myocardial infarction. *Am J Cardiol* 1986;58:203–9.
- [31] Kim BM, Baek JH, Heo JH, et al. Collateral status affects the onset-to-reperfusion time window for good outcome. *J Neurol Neurosurg Psychiatry* 2018;89:903–9.
- [32] Toumpoulis IK, Anagnostopoulos CE, Katritsis DG, et al. The impact of preoperative thrombolysis on long-term survival after coronary artery bypass grafting. *Circulation* 2005;112:1351–7.
- [33] Hoffmann R, Haager P, Arning J, et al. Usefulness of myocardial blush grade early and late after primary coronary angioplasty for acute myocardial infarction in predicting left ventricular function. *Am J Cardiol* 2003;92:1015–9.
- [34] Hamdan A, Kornowski R, Lev EI, et al. Impact of myocardial blush on left ventricular remodeling after first anterior myocardial infarction treated successfully with primary coronary intervention. *Isr Med Assoc J* 2010;12:211–5.
- [35] Zeng Y, Huang CL, Shang LH, et al. [Myocardial blush grade, ST-segment elevation resolution and prognosis in acute myocardial infarction patients with or without diabetes mellitus post primary percutaneous coronary intervention]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2007;35:439–42.
- [36] Vicent L, Velasquez-Rodriguez J, Valero-Masa MJ, et al. Predictors of high Killip class after ST segment elevation myocardial infarction in the era of primary reperfusion. *Int J Cardiol* 2017;248:46–50.
- [37] Weaver WD, Litwin PE, Martin JS, et al. Effect of age on use of thrombolytic therapy and mortality in acute myocardial infarction. The MITI Project Group. *J Am Coll Cardiol* 1991;18:657–62.
- [38] Singh M, Mathew V, Garratt KN, et al. Effect of age on the outcome of angioplasty for acute myocardial infarction among patients treated at the Mayo Clinic. *Am J Med* 2000;108:187–92.
- [39] Prasad A, Gersh BJ, Mehran R, et al. Effect of ischemia duration and door-to-balloon time on myocardial perfusion in st-segment elevation myocardial infarction: an analysis from HORIZONS-AMI Trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction). *JACC Cardiovasc Interv* 2015;8:1966–74.