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Angiographically Demonstrated Coronary Collaterals Predict Residual Viable Myocardium in Patients With Chronic Myocardial Infarction: A Regional Metabolic Study

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Abstract

Angiographical demonstration of coronary collateral circulation may suggest the presence of residual viable myocardium. The development of coronary collaterals was judged according to Rentrop's classification in 37 patients with old anteroseptal myocardial infarction and 13 control patients with chest pain syndrome.

The subjects with myocardial infarction were divided into 2 groups: 17 patients with the main branch of the left coronary artery clearly identified by collateral blood flow from the contralateral coronary artery [Coll(+)group, male/female 10/7, mean age 56.6 years] and 20 patients with obscure coronary trunk [Coll(−)group, male/female 16/4, mean age 54.9 years]. Thallium-201 myocardial scintigraphy and examination of local myocardial metabolism were carried out by measuring the flux of lactic acid under dipyridamole infusion load. Coronary stenosis of 99% or total occlusion was found in only 5 of 20 patients (25%) in the Coll(−)group but in 16 of 17 patients (94%) in the Coll(+)group ($p < 0.001$). Redistribution of myocardial scintigraphy was found in 11 of 15 patients (73%) in the Coll(+)group, but only 3 of 18 patients (17%) in the Coll(−)group ($p < 0.01$). The myocardial lactic acid extraction rate was $-13.2 \pm 17.0\%$ in the Coll(+)group, but $9.1 \pm 13.2\%$ in the Coll(−)group ($p < 0.001$).

These results suggest that coronary collateral may contribute to minimizing the infarct area and to prediction of the presence of viable myocardium.

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Key Words

■ Collateral circulation ■ Myocardial infarction (pathophysiology)
■ Myocardial viability ■ Angiography

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INTRODUCTION

Coronary collaterals are the result of neovascularization following various stimuli such as perfusion pressure gradient[1,2] and myocardial ischemia[3,4] and contribute to the preservation of cardiac performance[5,6] and the prolongation of anginal threshold[7]. Coronary collaterals minimize the infarcted area in acute coronary events[8] and, therefore, most cardiologists consider that viable myocardium remains in the infarcted area and that the tissue is nourished through the well-developed collaterals to revascularize these occluded vessels.

In this study, we tested whether or not angiographically-demonstrated collaterals predict the presence of residual viable myocardium by examining regional myocardial metabolism.

METHODS

Study population

This study was approved by the Institutional Review Board for Human Experimentation at Osaka Medical College and written informed consents were obtained from all participants.

The study population consisted of 37 patients who had old anteroseptal infarction with a history of 1 to 5 months (mean 2.1 months), and had enzymatic abrormality and ST deviation in precordial electrocardiogram. All patients had angiographical stenotic lesions ($\geq 90\%$) in the left anterior descending artery or in other vessels. Thirteen patients with chest pain syndrome who were angiographically normal constituted the control group (male/female 7/6, mean age 58.7 years).

The patients with a history of infarction were subdivided into 2 groups based on the development of coronary collaterals by Rentrop's classification: Coll (−) group; 0° = no collaterals and I° = only septal branches detectable ($n = 20$, male/female 16/4, mean age 54.9 years.); and Coll (+) group; II° = anterior descending artery detectable and III° = main branch clearly detectable ($n = 17$, male/female 10/7, mean age 56.6 years; **Table 1**).

Thallium-201 scintigraphy with dipyridamole infusion

A rotatable camera (ELZ-7500, Siemens) equipped with a low-energy, high-resolution collimator and interfaced with a digital computer (Scintipack 2400, Shimazu) was used for all studies.

Three min after the intravenous infusion of 0.568 mg/kg of dipyridamole over 4 min, 2 mCi of thallium-201 was injected. Cardiac images were generated by oblique angle reconstruction, which produced short-axis, vertical long-axis and horizontal long-axis slices from apex to base.

Thallium-201 uptake in the anteroseptal wall, corresponding to the anterior descending coronary artery, was estimated on initial and delayed images (3 hr after injection of dipyridamole) and judged as complete redistribution, partial redistribution or persistent defect by 3 independent reviewers.

Diagnostic catheterization

Standard left heart catheterization was performed using Judkins' technique after fasting and following the discontinuation of all cardiovascular agents for 24 hr. Left ventriculography was performed at right anterior oblique 30° projection and wall motion abnormality was assessed. Coronary angiography was performed with intra-aortic administration of 2 mg isosorbide dinitrate and multiple views were obtained. Angiographical findings were assessed using the American Heart Association classification by a few independent reviewers.

Coronary collaterals to the left anterior descending artery (via the right coronary system on right anterior oblique 30° projection) were graded using Rentrop's classification[1].

Coronary circulation and metabolic study

Within an one-week period following the diagnostic catheterization, a 19G elastic needle was punctured into the right radial artery and a 7F multithermister thermodilution catheter (Wilton Webster Inc) was inserted into the great cardiac vein by incision of the right cubital vein after discontinuation of cardiovascular agents for 24 hr. Great cardiac venous flow (GCVF, m*l*/min) was then measured by the thermodilution technique, taking care that the catheter tip remained stable without baseline drift of the thermodilution signal.

Arterial (A) and great cardiac venous (C) blood samples were obtained simultaneously for measurement of lactic acid content (mg/d*l*, Diagluca, Toyobo Inc). All flow and metabolic measurements were performed at resting state (R) and following 0.568 mg/kg intravenous dipyridamole infusion (DP) over 4 min.

Calculations were performed using the following formulas;

Table 1 Patient profiles

Group	Case	Gender (M/F)	Age (yr)	PMI	Q wave
Control	1	M	60	−	−
(n=13)	2	F	58	−	−
	3	M	61	−	−
	4	M	43	−	−
	5	F	66	−	−
	6	M	65	−	−
	7	M	61	−	−
	8	F	63	−	−
	9	F	55	−	−
	10	F	63	−	−
	11	F	74	−	−
	12	M	50	−	−
	13	M	44	−	−
	Mean±SD	7/6	58.7±8.8	0/13	0/13
Coll (−)	1	M	57	+	+
(n=20)	2	M	57	+	+
	3	F	46	+	+
	4	M	33	+	+
	5	M	60	+	+
	6	M	59	+	−
	7	M	54	+	+
	8	M	57	+	+
	9	M	51	+	+
	10	F	56	+	−
	11	M	62	+	+
	12	M	65	+	+
	13	F	55	+	+
	14	M	46	+	+
	15	M	63	+	−
	16	M	49	+	+
	17	F	67	+	+
	18	M	52	+	+
	19	M	64	+	+
	20	M	45	+	+
	Mean±SD	16/4	54.9±8.3	20/0	17/3
Coll (+)	1	F	52	+	−
(n=17)	2	M	58	+	+
	3	M	57	+	+
	4	M	49	+	+
	5	M	61	+	+
	6	M	51	+	+
	7	F	75	+	+
	8	F	56	+	+
	9	F	78	+	+
	10	M	48	+	−
	11	M	34	+	−
	12	F	68	+	−
	13	F	68	+	−
	14	M	42	+	−
	15	F	58	+	−
	16	M	68	+	+
	17	M	39	+	+
	Mean±SD	10/7	56.6±12.3	17/0	10/7

Coll (+) group: patients with anterior descending artery and main branch clearly detectable by Rentrop's classification.
Coll (−) group: patients with no collaterals or only septal branches detectable by Rentrop's classification.
M=male; F=female; PMI=prior myocardial infarction.

Coronary flow reserve (%)

$$= \frac{DP - R}{R} \times GCVF \times 100$$

Myocardial lactic acid extraction rate (LER, %)

$$= \frac{(A) - (C)}{(A)} \times 100$$

Statistical analysis

Coronary hemodynamics and lactic acid extraction rate were calculated as mean ± SD. Data for the 2 groups were compared using Student's t-test. Data for the 3 groups were compared by one-way analysis of variance. Data for each group were compared using Scheffe's multiple-comparison test for significance at the $p < 0.05$ level. Collateral development, scintigraphical findings and severity of coronary stenosis were analyzed using the chi-square test.

RESULTS

Angiographical findings (Table 2)

Wall motion abnormality in the Coll (−) group tended to be more severe than that in the Coll (+) group, which included 3 patients with normal wall motion. Only 5 of 20 patients (25%) in the Coll (−) group had 99% luminal stenosis of the left anterior descending artery, but 16 of 17 patients (94%) in the Coll (+) group exhibited ≥ 99% luminal stenosis ($p < 0.001$).

Thallium-201 scintigraphical findings (Table 3)

Complete redistribution in the anteroseptal region was found in only 3 patients (17%) in the Coll (−) group, but in 11 patients (73%) in the Coll (+) group ($p < 0.01$). Persistent defect was found in 9 patients (50%) in the Coll (−) group but only 2 patients (14%) in the Coll (+) group.

Coronary hemodynamics (Table 4)

GCVF did not differ at rest nor during dipyridamole infusion between the 3 groups [at rest: control group 62.0 ± 20, Coll (−) group 63.0 ± 17, Coll (+) group 67.6 ± 39 ml/min; dipyridamole infusion: control group 172 ± 42, Coll (−) group 161 ± 92, Coll (+) group 150 ± 100 ml/min]. Coronary flow reserve tended to be lower in both Coll (−) and Coll (+) groups than in the control group, but not to a significant extent [control group 197 ± 103%, Coll(−)group 138 ± 102%, Coll(+) group 131 ± 98%; **Fig. 1**].

Table 2 Angiographical findings

Group	Case	LVG	CAG	Coll
Control	1	N	N	−
(n=13)	2	N	N	−
	3	N	N	−
	4	N	N	−
	5	N	N	−
	6	N	N	−
	7	N	N	−
	8	N	N	−
	9	N	N	−
	10	N	N	−
	11	N	N	−
	12	N	N	−
	13	N	N	−
Coll (−)	1	3A	#6:90	0
(n=20)	2	2A,3A	#6:90	0
	3	2H,3H	#6:90	0
	4	3D	#7:90	0
	5	2A,3A	#7:90	0
	6	2A,3A	#7:90	0
	7	2H,3D	#7:90	0
	8	2A,3A	#6:90	0
	9	2H,3D	#6:90	0
	10	2A,3A	#6:90	0
	11	2D,3D	#6:99	0
	12	2H,3A	#7:90	0
	13	2A,3D	#7:99	I°
	14	2H,3A	#6:90	I°
	15	2H,3H	#6:90	I°
	16	2A,3A	#6:90	I°
	17	2A,3A	#7:99	I°
	18	2A,3D	#6:99	I°
	19	2A,3A	#7:90	I°
	20	2H,3A	#7:99	I°
Coll (+)	1	2H,3H	#6:99	II°
(n=17)	2	2H,3H	#7:100	II°
	3	2H,3D	#6:99	II°
	4	3D	#7:99	II°
	5	3H	#6:99	II°
	6	3H	#7:99	II°
	7	2D,3D	#6:100	II°
	8	2H,3H	#6:99	III°
	9	N	#7:100	III°
	10	N	#6:100	III°
	11	N	#7:100	III°
	12	2H	#7:90	III°
	13	2H,3H	#6:100	III°
	14	2H,3H	#7:100	III°
	15	2H	#7:99	III°
	16	2H,3A	#6:99	III°
	17	2H,3H	#7:99	III°

Area 2, area 3 and #6, #7: American Heart Association classification of CAG and LVG (H=hypokinesis, A=akinesis, D=dyskinesis). 0−III°: collateral grade by Rentrop's classification.
CAG=coronary angiography; LVG=left ventriculography; N=normal.
Explanation of the groups as in Table 1.

Table 3 Thallium-201 myocardial scintigraphy (dipyridamole infusion load)

Group	n	Finding		
		Complete redistribution	Partial redistribution	Persistent defect
Coll (−)	18	3(17)	6(33)	9(50)
Coll (+)	15	11(73)*	2(13)	2(14)

( ): %. *$p<0.01$.
Explanation of the groups as in Table 1.

Severity of coronary stenosis and myocardial lactic acid metabolism

LER following dipyridamole infusion (an index of myocardial anaerobic metabolism) was significantly lower in patients with ≥ 99% stenosis than in patients with 90% stenosis (LER = 10.2 ± 14.7% in 90% stenosis, and −9.7 ± 16.8% in 99% stenosis, $p < 0.001$; **Fig. 2**).

Coronary collaterals and myocardial lactic acid metabolism (Table 5)

LER at rest did not differ significantly between the 3 groups, but LER following dipyridamole infusion in the Coll (+) group was significantly lower than in the control and Coll (−) groups [control group 6.0 ± 5.5%, the Coll (−) group 9.1 ± 13.2%, Coll (+) group − 13.2 ± 17.0%, $p < 0.001$; **Fig. 3**].

DISCUSSION

Evaluation of residual viable myocardium perfused by the occluded coronary vessels is important in patients undergoing coronary revascularization such as percutaneous transluminal coronary angioplasty or coronary artery bypass grafting for old myocardial infarction. Myocardial stress scintigraphy, dobutamine stress echocardiography and myocardial contrast echocardiography have had some limitation in the diagnosis of viability. This study examined myocardial metabolism based on the assumption that the coronary collaterals are responsible for myocardial ischemia and perfuse the occluded coronary artery in myocardial infarction.

The significance of the coronary collaterals at the onset of infarction has been much discussed. Habib *et al.*[9] reported that a low peak creatine kinase value and slight wall motion abnormality were found in patients with good collaterals among 125

Table 4 Coronary hemodynamics

Group	Case	GCVF(R) (ml/min)	GCVF(DP)	CFR(%)
Control	1	50	151	201
(n=13)	2	40	166	315
	3	76	182	139
	4	52	179	244
	5	60	164	173
	6	48	157	227
	7	64	115	80
	8	40	218	445
	9	50	154	208
	10	59	182	208
	11	111	272	145
	12	79	188	138
	13	77	105	36
	Mean±SD	62±20	170±42	197±103
Coll (−)	1	52	193	271
(n=20)	2	79	139	76
	3	89	179	101
	4	67	360	437
	5	54	56	4
	6	64	105	64
	7	63	103	64
	8	37	129	249
	9	54	106	96
	10	42	71	69
	11	53	97	83
	12	42	180	164
	13	65	150	131
	14	94	174	85
	15	60	128	113
	16	87	177	103
	17	47	112	138
	18	49	78	59
	19	78	419	249
	20	85	257	202
	Mean±SD	63±17	161±92	138±102
Coll (+)	1	64	82	28
(n=17)	2	62	138	123
	3	43	128	198
	4	67	167	149
	5	59	76	29
	6	64	275	330
	7	84	65	−23
	8	69	161	133
	9	39	98	151
	10	51	219	329
	11	41	121	195
	12	164	240	46
	13	49	62	27
	14	37	68	84
	15	61	134	120
	16	166	449	170
	17	29	68	134
	Mean±SD	67.6±39	150±100	131±98

GCVF=great cardiac venous flow; R=rest; DP=dipyridamole; CFR=coronary flow reserve.
Explanation of the groups as in Table 1.

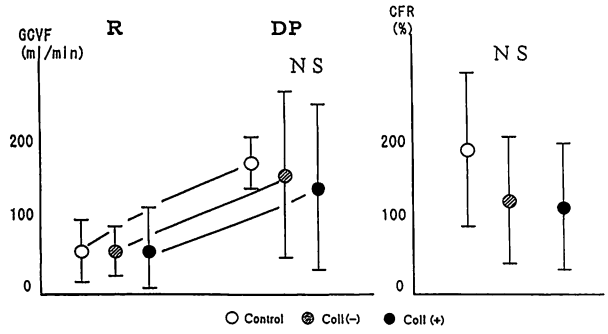

Fig. 1 Coronary hemodynamics
Explanation of the groups and abbreviations as in Tables 1, 4.

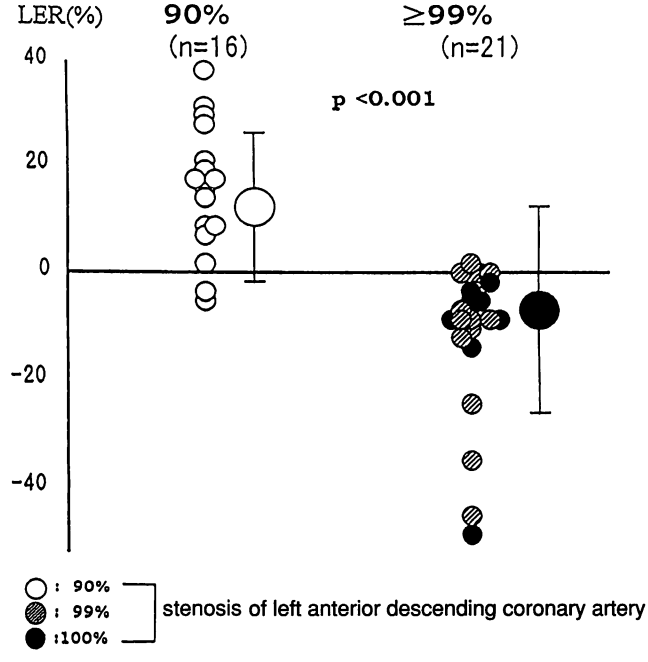

Fig. 2 Severity of coronary stenosis and myocardial lactic acid metabolism
LER = lactic acid extraction rate.

patients who did not undergo recanalization in the Thrombolysis in the Myocardial Infarction (TIMI) Study. According to Freedman *et al.*[10], the coronary collaterals were found in all patients with non Q wave infarction, but only 76% patients with Q wave infarction. In our results also, 17 of 20 patients (85%) in the Coll (−) group showed infarctional Q waves in electrocardiogram, but only 10 of 17 patients (59%) in the Coll (+) group. These results suggest that in the Coll (−) group, atheromatous rupture and formation of fibrin-rich thrombi were the main causes for sudden coronary occlu-

Table 5 Myocardial lactic acid metabolism

Group	Case	LER(R)(%)	LER(DP)(%)
Control	1	27.6	20.0
(n=13)	2	6.5	1.7
	3	9.9	3.4
	4	24.6	4.5
	5	17.6	5.2
	6	32.9	8.5
	7	27.0	5.3
	8	14.3	4.4
	9	10.8	2.9
	10	0.0	0.0
	11	31.7	14.3
	12	−8.5	5.6
	13	13.9	2.3
	Mean±SD	16.0±12.5	6.0±5.5
Coll (−)	1	15.6	−6.5
(n=20)	2	−2.1	−6.5
	3	23.0	2.9
	4	47.6	27.0
	5	28.9	19.0
	6	21.7	5.4
	7	42.9	24.3
	8	37.5	28.9
	9	50.0	6.9
	10	31.4	3.3
	11	14.3	5.2
	12	19.7	37.6
	13	28.1	1.8
	14	42.5	−5.9
	15	18.9	12.8
	16	21.4	17.8
	17	31.9	9.5
	18	11.1	0.0
	19	25.0	11.1
	20	15.2	−5.4
	Mean±SD	26.2±13.2	9.1±13.2
Coll (+)	1	24.0	0.0
(n=17)	2	25.4	−2.0
	3	32.6	−13.0
	4	25.4	−6.8
	5	−20.3	−34.4
	6	33.3	−8.3
	7	15.4	−15.2
	8	22.3	−1.0
	9	7.4	−5.5
	10	17.8	−7.0
	11	20.4	−6.8
	12	10.9	−8.9
	13	17.3	−51.4
	14	7.4	−4.3
	15	15.7	−46.5
	16	12.8	−25.6
	17	29.4	12.9
	Mean±SD	17.5±12.6	−13.2±17.0

Explanation of the groups and abbreviations as in Tables 1, 4, Fig. 2.

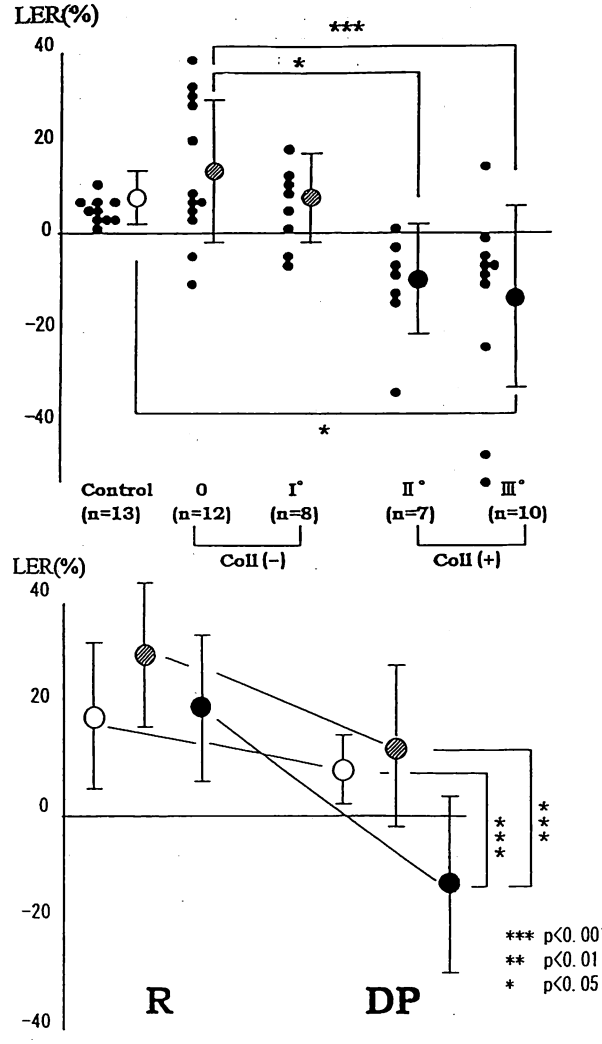

Fig. 3 Angiographically demonstrated collaterals and myocardial lactic acid metabolism following dipyridamole infusion
Explanation of the groups and abbreviations as in Tables 1, 4, Fig. 2.

sion. In the Coll(+)group, coronary stenosis had gradually progressed to develop these good collaterals. Thus, acute coronary occlusion due to the formation of platelet-rich thrombi minimized the infarcted area.

There may be a relationship between the severity of coronary stenosis and the coronary collaterals, Gensini *et al.*[11] reported in 1969 that the development of the coronary collaterals required luminal stenosis at more than 50% in the recipient coronary artery. However, after advances in imaging equipment, Goldberg *et al.*[12] in 1983 stated that coronary collaterals were not found in any case of coronary stenosis at less than 90%, 39% of the subtotally

occluded cases and 84% of the totally occluded cases. Cohen *et al.*[13] also reported that the rate of development of coronary collaterals toward occluded blood vessels via the contralateral artery in percutaneous transluminal coronary angioplasty showed good positive correlation with the severity of preoperative coronary stenosis. In our results 15 of 20 patients showed 90% stenosis and only 5 patients showed 99% stenosis in the Coll(−) group, whereas in the Coll(+) group, subtotal or total occlusion was found in 16 of 17 patients. These results indicate that the difference in the coronary perfusion pressure between the contralateral and recipient arteries is important for the development of coronary collaterals and at least subtotal coronary stenosis is required for the recipient artery.

Fujita *et al.*[14] reported a relationship between the myocardial viability and the coronary collaterals in patients with chronic myocardial infarction using scintigraphy, and detected more residual viable myocardium in patients with good collaterals. In our study, thallium-201 myocardial scintigraphy under dipyridamole loading showed that complete redistribution, a sign of residual viable myocardium, was more frequently found in the Coll(+) group than in the Coll(−) group (73% vs 17%, $p < 0.01$) and these results indicate that good collaterals can minimize the infarcted area at the time of any cardiac event.

To assess clinically the coronary flow reserve, the thermodilution method had been used until quite recently but the Doppler flow wire method is widely employed. Comparison of the absolute value of coronary flow by these 2 methods shows a lower value by the former than the latter method, but the thermodilution method gives some useful information concerning coronary flow reserve and metabolic condition. When coronary luminal stenosis is more than 75%, flow reserve is restricted and cardiac release of lactic acid is induced by a "steal phenomenon"[15]. Thus, flow and metabolic study by dipyridamole gives useful information concerning the myocardium perfused by occluded vessels.

Lambert *et al.*[16] reported that coronary collateral can contribute sufficiently to flow reserve in the resting state, but Goldberg *et al.*[17] and Sim *et al.*[18] described limitations during exercise and the inability to prevent myocardial ischemia. Also in our results, coronary flow reserve tended to be lower in the infarcted groups than in the control group, but there was no difference concerning the degree of collateral development [Coll(+) group 150 ± 100%, Coll(−) group 161 ± 92%]. These results suggest that good collaterals have certain limitations for coronary flow reserve and cannot protect myocardial ischemia in the loading state.

Even if critical stenosis is presented in the infarct-related artery, myocardial ischemia is not induced as far as the perfused myocardium is replaced by necrotic tissue and no longer participates in the metabolism. In contrast, when viable myocardium is present in the peri or the infarcted area, cardiac flux of lactate will show a negative value, so lactate release will occur. In our study, obvious induction of lactate release was found in the Coll(+) group and those may be responsible for the presence of the remaining viable myocardium.

Study limitation

In this study, evaluation of coronary stenosis and scintigraphical finding were not performed with a quantitative method such as the quantitative coronary arteriography method or washout rate. Therefore, a lack of objectivity cannot be denied. To study the relationship between the development of collaterals and remaining viable myocardium in the infarcted area, concordance of coronary stenosis that is 90% or ≥ 99% may be necessary. However, our main purpose was to elucidate whether or not the coronary collaterals toward the infarcted area may predict the presence of remaining viable myocardium, especially concerning the cardiac metabolism. This study will provide clinically useful information in the application of coronary revascularization.

CONCLUSION

We examined whether angiographically demonstrated collaterals predict the presence of myocardial viability in patients with old myocardial infarction, especially the cardiac lactate flux.

In the well-developed collateral group (grade Ⅱ/Ⅲ in Rentrop's classification), many patients showed redistribution on thallium-201 scintigraphy, severe coronary stenosis of more than 99% or total occlusion and induction of myocardial lactate release on dipyridamole infusion load. These results suggest that well-developed collaterals predict the residual viable myocardium in patients with old infarction.

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要　約

陳旧性心筋梗塞症における冠側副血行と残余心筋との関連：心筋代謝面よりの検討

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陳旧性心筋梗塞症において冠動脈造影上みられる冠側副路が残存心筋の存在を示唆するか否かを，ジピリダモール静注負荷^{201}Tl心筋シンチグラム所見と局所心筋乳酸代謝の面より検討した．

対象は発症1ヵ月以上経過した前壁中隔梗塞37例で，Rentrop分類により冠側副路未発達群（20例，男性16例，女性4例，平均年齢54.9歳），冠側副路発達群（17例，男性10例，女性7例，平均年齢56.6歳）に分け，胸痛症候群を対照群（13例）として比較検討した．その結果，発達群は未発達群に比べ99%以上の高度冠狭窄例（94% vs 25%，$p<0.001$）や^{201}Tl心筋シンチグラム上再分布所見を呈する例（73% vs 17%，$p<0.01$）が有意に多く，また心筋乳酸代謝も強い嫌気性傾向にあった（$-13.2\pm17\%$ vs $9.1\pm13.2\%$，$p<0.01$）．

以上の結果より，嫌気性心筋乳酸代謝と冠動脈造影上確認される冠側副路は梗塞巣の縮小効果，すなわち残存心筋の存在を示唆するものと思われた．諸条件が許すなら積極的に血行再建術の施行が望まれる．

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