Heart Vessels (2000) 15:176–180

ORIGINAL ARTICLE

**Izuru Nakae · Masatoshi Fujita · Kunihisa Miwa
Koji Hasegawa · Yasuki Kihara · Ryuji Nohara
Shoichi Miyamoto · Kinzo Ueda · Shun-ichi Tamaki
Shigetake Sasayama**

Age-dependent impairment of coronary collateral development in humans

Received: September 30, 2000 / Accepted: January 12, 2001

Abstract The purpose of this study was to evaluate whether age influences collateral development in patients with coronary artery disease. The extent of collateral development to the area perfused by the infarct-related artery was graded, depending on the degree of opacification of the occluded infarct-related artery. We evaluated the extent of collateral development using coronary cineangiography in 102 patients with an acutely occluded infarct-related coronary artery within 12 h after the onset of the first acute myocardial infarction, and who had a history of long-standing effort angina. Well-developed collateral circulation was observed in 54 (53%) of the patients. The patients were divided into two groups based on their age. The prevalence of well-developed collateral circulation in the younger group (≤64 years, $n = 48$) was 69% (33 of 48), being significantly ($P = 0.003$) higher than 39% (21 of 54) in the older group (≥65 years, $n = 54$). We conclude that in the presence of stimuli for collateral development i.e., long-standing effort angina accompanied by severe coronary stenosis, the age of patients is a key determinant of collateral development.

Key words Age · Angina pectoris · Angiogenesis · Collateral development

Introduction

Several lines of evidence showed the functional significance of a well-developed collateral circulation in patients with coronary artery disease.[1,2] Although it is well appreciated that severe coronary luminal narrowing causes the growth of an effective collateral circulation,[3,4] it is unclear whether or not the extent of collateral development resulting from a high-grade coronary stenosis is different between younger and older patients with coronary artery disease. Thus, the purpose of this study was to elucidate any relation between the age of patients and the extent of collateral development.

Patients and methods

Study patients

The study subjects were selected from 303 consecutive patients undergoing emergency coronary cineangiography within 12 h after the onset of acute myocardial infarction documented by chest pain lasting longer than 30 min and ST segment elevation. From this group, we studied 102 patients who met the following inclusion criteria: (1) the presence of effort angina occurring for more than 1 week before the onset of acute myocardial infarction; (2) complete occlusion of the infarct-related coronary artery; (3) no previous percutaneous transluminal coronary angioplasty or coronary artery bypass grafting surgery; and (4) no prior myocardial infarction. They included 81 men and 21 women with a mean age of 65 ± 10 years. The study protocol was approved by the ethics committee of Takeda hospital, and written informed consent was obtained from all patients.

Clinical variables

The presence and duration of a history of preinfarction angina before acute myocardial infarction were documented. Preinfarction angina was defined as typical anginal chest pain occurring more than 1 week before the onset of acute myocardial infarction.[5] Patients were considered to have a history of hypertension if their systolic pressure was above 160 mmHg, diastolic pressure was above 95 mmHg,

M. Fujita (✉)
College of Medical Technology, Kyoto University, 53 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
Tel. +81-75-751-3932; Fax +81-75-751-3909
e-mail: mfujita@kuhp.kyoto-u.ac.jp

I. Nakae · S. Miyamoto · K. Ueda · S. Tamaki
Division of Cardiology, Takeda Hospital, Kyoto, Japan

K. Miwa · K. Hasegawa · Y. Kihara · R. Nohara · S. Sasayama
Department of Cardiovascular Medicine, Kyoto University, Graduate School of Medicine, Kyoto, Japan

or if they were currently undergoing treatment for hypertension. A diagnosis of diabetes mellitus was established on the basis of any one of the following three factors: a history of taking insulin or an oral hypoglycemic agent, abnormal preinfarction fasting glucose levels (≥120 mg/100 ml), and positive results on the 75-g oral glucose tolerance test. Hypercholesterolemia was defined as abnormal serum cholesterol levels of above 220 mg/100 ml. Smokers were limited to current smokers.

Coronary cineangiography

After 10 000 units of an intravenous bolus of heparin and a sublingual dose of 0.3 mg of nitroglycerin were administered, coronary cineangiography was performed using the Judkins technique. A nonionic contrast agent was manually injected with enough force and in sufficient quantity to provide good visualization of the coronary arteries through a 7-F catheter. The noninfarct-related artery was first visualized to evaluate the extent of collateral circulation to the area perfused by the completely occluded infarct-related coronary artery. The percent lumen diameter stenosis of the coronary artery was determined using a caliper on multiple projections of adequately magnified 35-mm cine frames taken at end-diastole. The projection showing the most severe coronary narrowing was selected. More than 50% narrowing of the artery diameter was defined as a significant degree of stenosis.

Collateral circulation was graded on a scale (collateral index) of 0–3, based on the injection that best opacified the occluded vessel: 0 = no opacification; 1 = filling of side branches of the artery perfused by way of collateral vessels without visualization of the epicardial segment; 2 = partial filling of the epicardial segment by way of collateral vessels; 3 = complete filling of the epicardial segment by way of collateral vessels.[6] Collateral circulation was then classified into none or poorly developed colltarals with collateral indices of 0 or 1 and well-developed collaterals with collateral indices of 2 or 3.

Patient subgroups

The 102 patients were separated into two major subgroups using the median value of age. The younger group comprised 48 patients (≤64 years, 42 men and 6 women, with a mean age of 55 years) and the older group, 54 patients (≥65 years, 39 men and 15 women, with a mean age of 73 years).

Statistical analysis

Results are expressed as mean ± standard deviation. Proportional data were analyzed by the chi-squared test, with Yates' correction if one of the frequencies in the 2-by-2 contingency table was less than 5. Unpaired Student's *t*-test was used to compare continuous variables between the two groups. Results were considered significant at the 5% critical level.

Results

Well-developed collateral circulation to the infarct-related artery at the onset of infarction was found in 54 (53%) of the 102 patients.

Classification of patients according to the collateral circulation

Characteristics of the 102 patients according to the presence or absence of well-developed collaterals are shown in Table 1. Patients with well-developed collaterals were younger than those without collaterals (62 ± 11 years vs 67 ± 11 years, $P = 0.003$). However, the two groups were comparable with respect to the other variables.

Classification of patients according to age

Clinical and angiographic characteristics of the younger and older groups are summarized in Table 2. The two groups were well-balanced with respect to sex, coronary angiographic characteristics, duration of anginal symptoms, and all cardiovascular risk factors except the prevalence of

Table 1. Characteristics of 102 patients with and without well-developed collateral circulation at the onset of acute myocardial infarction

	CI = 0,1 (n = 48)	CI = 2,3 (n = 54)	P value
Age (years)	67 ± 11	62 ± 11	0.003
Male	39 (81%)	42 (78%)	NS
LAD	25 (52%)	21 (39%)	NS
Multivessel disease	21 (44%)	17 (32%)	NS
Hypertension	20 (42%)	20 (37%)	NS
Diabetes mellitus	10 (21%)	11 (20%)	NS
Smoking	31 (65%)	40 (74%)	NS
Hypercholesterolemia	16 (33%)	14 (26%)	NS
Longer (≥1 year) history of angina	12 (25%)	19 (35%)	NS

CI, collateral index; LAD, left anterior descending coronary artery; NS, not significant

Table 2. Clinical and angiographic characteristics in the younger and older groups

	Younger group (n = 48)	Older group (n = 54)	P value
Male	42 (88%)	39 (72%)	NS
LAD	26 (54%)	20 (37%)	NS
Multivessel disease	14 (29%)	24 (44%)	NS
Hypertension	20 (42%)	20 (37%)	NS
Diabetes mellitus	10 (21%)	11 (20%)	NS
Smoking	40 (83%)	31 (57%)	0.004
Hypercholesterolemia	14 (29%)	16 (30%)	NS
Longer (≥1 year) history of angina	13 (27%)	18 (33%)	NS
Well-developed collaterals	33 (69%)	21 (39%)	0.003

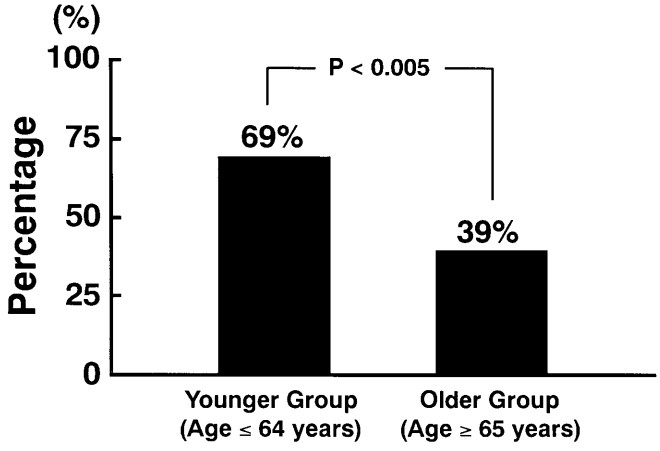

Fig. 1. Prevalence of well-developed collateral circulation to the infarct-related artery at the onset of acute myocardial infarction, which was more frequently observed in the younger than in the older group

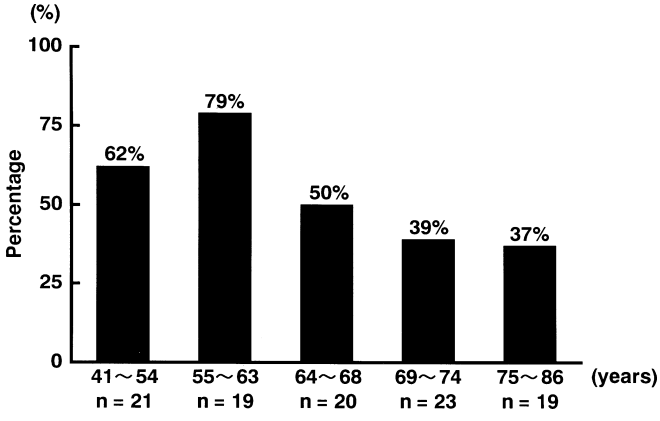

Fig. 2. Prevalence of well-developed collateral circulation in age quintiles. The incidence decreased as the age increased

cigarette smokers. The incidence of the presence of well-developed collateral circulation was significantly higher ($P = 0.003$) in the younger group (33 (69%) of 48) than in the older group (21 (39%) of 54) (Fig. 1). Figure 2 illustrates the prevalence of well-developed collaterals in quintiles of age. The incidence of collaterals decreased gradually as the age increased, although the difference was not statistically significant.

Discussion

The salient finding of this study was that the extent of collateral development is largely influenced by the age of the patients.

Although it is well known that the presence of well-developed collaterals at the time of acute myocardial infarction can limit infarct size and preserve myocardial function,[1,2] limited information is available regarding the conditions required to induce growth of collateral vessels in humans. It is well known that a high-grade coronary stenosis results in collateral vessel growth. Indeed, Cohen et al.[3] showed that a coronary stenosis of less than 80% luminal narrowing is rarely associated with angiographically demonstrable collateral circulation, whereas lesions of 95% or more narrowing nearly always are associated with good collateral filling. A high-grade coronary stenosis is accompanied by myocardial ischemia,[7,8] a transcollateral pressure gradient associated with increased wall and shear stresses at the site of preexistent small collateral vessels,[9,10] and an increase in several angiogenic growth factors,[11,12] which all are important stimuli for collateral vessel growth. Since long-standing stable effort angina before acute myocardial infarction results from a high-grade coronary stenosis, it is likely that this clinical condition will become a marker of the presence of stimuli for collateral development. Thus, in the present study only patients with chronic angina before acute myocardial infarction were evaluated regarding the extent of collateral development.

It is well recognized that patients with obstructive lesions as a sequela of Kawasaki disease have few episodes of angina pectoris and acute myocardial infarction.[13] It is tempting to speculate that collateral vessels develop more vigorously in children or adolescents than in adults. Indeed, a high prevalence of well-developed collateral vessels and their protective role in Kawasaki disease has been reported in several clinical observational studies.[14,15] Rivard et al.[16] demonstrated for the first time that angiogenesis responsible for collateral development is impaired with aging in rabbit and mouse hindlimb ischemia models. They ascribed the responsible mechanisms to age-related vascular endothelial dysfunction and reduced vascular endothelial growth factor expression. These clinical and basic reports support our hypothesis that the extent of collateral development is dependent on the age of patients with obstructive coronary artery disease.

It is well known that the degree of collateral development is mainly dependent on the severity of the underlying coronary artery disease.[17,18] Thus, patients with coronary collaterals appear to have a more extensive disease of the major coronary arteries. Usually, since older patients have more severe coronary atherosclerosis, which was the case in the present study, they should have well-developed collaterals. However, in the present study the prevalence of well-developed collaterals was paradoxically lower in the older than in the younger patients. The age-dependent impairment of collateral development would explain the paradox.

Our findings showed that only age was a determinant of collateral development in patients with long-standing effort angina before acute myocardial infarction. In an animal study, it has been demonstrated that collateral vessel development induced by hindlimb ischemia is severely attenuated in the Watanabe heritable hyperlipidemic rabbit.[19] In contrast, in our study the extent of collateral growth was comparable in patients with and without hypercholesterolemia. The disparity may be explained by the extremely high level of total plasma cholesterol (686 mg/dl in the

mean value) in the Watanabe rabbit. In this regard, more investigations are needed to evaluate whether collateral development is attenuated in patients with familial hypercholesterolemia. Recently, Abaci et al.[20] reported that patients with diabetes mellitus have a lesser ability to develop collateral blood vessels in the presence of coronary artery disease. In our study, there was no difference in the prevalence of diabetes mellitus between patients with and without well-developed collaterals. The disparity may be, at least in part, due to the different study protocol and patient characteristics.

There are some limitations to the present study. Firstly, not angina but myocardial ischemia resulting from a high-grade coronary stenosis is important for the development of collateral circulation. Therefore, myocardial ischemia, including the silent one that occurred before acute myocardial infarction, should have been evaluated.[21] Furthermore, it was difficult to confirm whether chest pain actually was associated with myocardial ischemia. Further prospective studies are needed to elucidate the relation between a high-grade coronary stenosis and collateral development. Secondly, since conventional coronary angiography fails to visualize collateral vessels with a diameter less than 100 μm, contrast echocardiography[22] or coronary wedge pressure measurement[23] may be more appropriate for evaluation of collateral circulation. However, the aim of this study was to delineate patients with well-developed collaterals, so that the angiographic approach seems sufficient for this purpose. Thirdly, it is postulated that in patients with multivessel disease, coronary arteries other than the infarct-related artery were responsible for angina before acute myocardial infarction. In these patients, collateral development to the infarct-related artery is not expected. However, the prevalence of multivessel disease was comparable between the younger and older groups (29% vs 44%). In this regard, a study of a large cohort of patients with single-vessel disease is warranted to confirm our findings reported here. Fourthly, in the present study the duration of angina before acute myocardial infarction was not precisely examined, since most patients were admitted to our hospital with the first symptom. However, we have previously shown that a relatively short period of stimuli is adequate for collateral development in experimental[24–26] and clinical[27,28] studies. Finally, further prospective studies are needed to determine whether there are any differences in collateral development between ages. Angiogenic therapy for coronary artery disease may be suitable for this kind of evaluation.

In conclusion, the findings reported here indicate that not only a high-grade coronary stenosis but also the age of patients is an important factor for collateral development in patients with coronary artery disease. This may explain, at least in part, the poor prognosis of the older patients with coronary artery disease.

Acknowledgments. This study was supported by the "Research for the Future" Program (JSPS-RFTF 99 I 00201) from the Japan Society for the Promotion of Science, and Grant-in-Aid for Scientific Research (b) 10557067 from the Ministry of Education, Science and Culture, Tokyo, Japan.

References

1. Sasayama S, Fujita M (1992) Recent insights into coronary collateral circulation. Circulation 85:1197–1204
2. Habib GB, Heibig J, Forman SA, Brown BG, Roberts R, Terrin ML, Bolli R, the TIMI Investigators (1991) Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I thrombolysis in myocardial infarction (TIMI) trial. Circulation 83:739–746
3. Cohen M, Sherman W, Rentrop KP, Gorlin R (1989) Determinants of collateral filling observed during sudden controlled coronary artery occlusion in human subjects. J Am Coll Cardiol 13:297–303
4. Rentrop KP, Thornton JC, Feit F, Buskirk MV (1988) Determinants and protective potential of coronary arterial collaterals as assessed by an angioplasty model. Am J Cardiol 61:677–684
5. Nakae I, Fujita M, Fudo T, Iwase T, Tanaka T, Tamaki S, Nohara R, Sasayama S (1996) Relation between preexistent coronary collateral circulation and the incidence of restenosis after successful primary coronary angioplasty for acute myocardial infarction. J Am Coll Cardiol 27:1688–1692
6. Rentrop KP, Cohen M, Blanke H, Phillips RA (1985) Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 5:587–592
7. Mohri M, Tomoike H, Noma M, Inoue T, Hisano K, Nakamura M (1989) Duration of ischemia is vital for collateral development: repeated brief coronary artery occlusion in conscious dogs. Circ Res 64:287–296
8. Chilian WM, Mass HJ, Williams SE, Layne SM, Smith EE, Scheel KW (1990) Microvascular occlusions promote coronary collateral growth. Am J Physiol 258:H1103–H1111
9. Schaper W (1967) Tangential wall stress as a molding force in the development of collateral vessels in the canine heart. Experientia 23:595–596
10. Symons JD, Pitsillides KF, Longhurst JC (1992) Chronic reduction of myocardial ischemia does not attenuate coronary collateral development in miniswine. Circulation 86:660–671
11. Kumar S, West D, Shahabuddin S, Arnold F, Haboubi N, Reid H, Carr T (1983) Angiogenesis factor from human myocardial infarcts. Lancet 2:364–368
12. Fujita M, Ikemoto M, Kishishita M, Otani H, Nohara R, Tanaka T, Tamaki S, Yamazato A, Sasayama S (1996) Elevated basic fibroblast growth factor in pericardial fluid of patients with unstable angina. Circulation 94:610–613
13. Shiraishi I, Onouchi Z, Hayano T, Hamaoka K, Kiyosawa N (1991) Asymptomatic myocardial infarction in Kawasaki disease: long-term prognosis. Pediatr Cardiol 12:78–82
14. Onouchi Z, Hamaoka K, Kamiya Y, Hayashi S, Ohmochi Y, Sakata K, Shiraishi I, Hayano T, Fukumochi H (1993) Transformation of coronary artery aneurysm to obstructive lesion and the role of collateral vessels in myocardial perfusion in patients with Kawasaki disease. J Am Coll Cardiol 21:158–162
15. Tatara K, Kusakawa S, Itoh K, Honma S, Hashimoto K, Kazuma N, Lee K, Asai T, Murata M (1991) Collateral circulation in Kawasaki disease with coronary occlusion or severe stenosis. Am Heart J 121:797–802
16. Rivard A, Fabre JE, Silver M, Chen D, Murohara T, Kearney M, Magner M, Asahara T, Isner JM (1999) Age-dependent impairment of angiogenesis. Circulation 99:111–120
17. Fulton WFM (1964) The dynamic factor in enlargement of coronary arterial anastomoses, and paradoxical changes in the subendocardial plexus. Br Heart J 26:39–50
18. Helfant RH, Kemp HG, Gorlin R (1970) Coronary atherosclerosis, coronary collaterals, and their relation to cardiac function. Ann Intern Med 73:189–193
19. Van Belle E, Rivard A, Chen D, Silver M, Bunting S, Ferrara N, Symes JF, Bauters C, Isner JM (1997) Hypercholesterolemia attenuates angiogenesis but does not preclude augmentation by angiogenic cytokines. Circulation 96:2667–2674
20. Abaci A, Oguzhan A, Kahraman S, Eryol NK, Ünal S, Arinç H, Ergin A (1999) Effect of diabetes mellitus on formation of coronary collateral vessels. Circulation 99:2239–2242

21. Ambepityia G, Kopelman PG, Ingram D, Swash M, Millis PG, Timmis AD (1990) Exertional myocardial ischemia in diabetes: a quantitative analysis of anginal perceptual threshold and the influence of autonomic function. J Am Coll Cardiol 15:72–77
22. Sabia PJ, Powers ER, Ragosta M, Saremobock IJ, Burwell LR, Kaul S (1992) An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. N Engl J Med 327:1825–1831
23. Probst P, Zangl W, Pachinger O (1985) Relation of coronary artery occlusion pressure during percutaneous transluminal coronary angioplasty to presence of collaterals. Am J Cardiol 55:1264–1269
24. Fujita M, McKown D, McKown M, Franklin D (1986) Changes in coronary flow following repeated brief coronary occlusion in the conscious dog. Heart Vessels 2:87–90
25. Fujita M, McKown DP, McKown MD, Hartley JW, Franklin D (1987) Evaluation of coronary collateral development by regional myocardial function and reactive hyperaemia. Cardiovasc Res 21:377–384
26. Fujita M, Yamanishi K, Araie E, Sasayama S, McKown DP, Franklin D (1994) Determinants of collateral development in a canine model with repeated coronary occlusion. Heart Vessels 9:292–299
27. Fujita M, Sasayama S, Asanoi H, Nakajima M, Sakai O, Ohno A (1988) Improvement of treadmill capacity and collateral circulation as a result of exercise with heparin pretreatment in patients with effort angina. Circulation 77:1022–1029
28. Araie E, Fujita M, Miwa K, Miyagi K, Sasayama S (1991) Heparin exercise treatment following percutaneous transluminal coronary angioplasty in a patient with effort angina. Heart Vessels 6:181–183