Table 6
Association between combination of best uric acid cut-off concentration with Killip's classes and all-cause mortality

Group	Total Death	Unadjusted			Adjusted		
		OR	95% CI	p Value	OR	95% CI	p Value
1 (n = 772)*	16 (2%)	1.000	—	—	1.000	—	—
2 (n = 219)†	12 (5%)	2.664	1.260–5.632	0.0103	3.465	1.555–7.720	0.0024
3 (n = 76)‡	15 (20%)	10.431	5.156–21.105	<0.0001	8.573	3.822–19.230	<0.0001
4 (n = 57)§	24 (42%)	27.005	14.328–50.896	<0.0001	22.473	10.802–46.754	<0.0001

Hazard ratios compared with quartile 1 with regard to long-term mortality after nonadjustment and adjustment for independent factors that were closely associated with all-cause mortality in multivariate analysis (age and peak creatine phosphokinase level).

* Killip's classes I and II plus serum UA levels ≤447 μmol/L.

† Killip's classes I and II plus serum UA levels >447 μmol/L.

‡ Killip's classes III and IV plus serum UA levels ≤447 μmol/L.

§ Killip's classes III and IV plus serum UA levels >447 μmol/L.

Appendix

JACSS Principal Investigators: H. Ogawa (chair; Kumamoto University), Y. Asada (Miyazaki Medical College), C. Tei (Kagoshima University), K. Kimura (Yokohama City University Medical Center), K. Tsuchihashi (Sapporo Medical University), M. Ishihara (Hiroshima City Hospital), S. Miyazaki, M. Yamagishi, Y. Ikeda (National Cardiovascular Center), M. Shirai (Yamaguchi University), H. Hiraoka (Osaka University), N. Shimoyama (Oita National Hospital), and M. Sonoda (National Hospital Kyushu Cardiovascular Center).

JACSS Clinical Investigators (Participating Institutions): Y. Ogata (Japanese Red Cross Kumamoto Hospital), T. Honda (Social Welfare Organization Imperial Gift Foundation Inc., Saiseikai Kumamoto Hospital), Y. Hokamura (Kumamoto City Hospital), T. Saito (Kumamoto Central Hospital), Y. Mizuno (Kumamoto Kinoh Hospital), H. Miyagi (Kumamoto National Hospital), T. Matsumura (Labor Welfare Corp., Kumamoto Rosai Hospital), T. Tabuchi (Yatsushiro Health Insurance General Hospital), N. Sakaino (Amakusa Medical Center), K. Kimura (Arao City Hospital), K. Obata (Health Insurance Hitoyoshi General Hospital), H. Shimomura (Fukuoka Tokushukai Medical Center), K. Matsuyama (Social Insurance Ohmuta-Tenryoh Hospital), N. Nakamura (Shinbeppu Hospital), N. Yamamoto (Miyazaki Prefectural Nobeoka Hospital), M. Hase (Sapporo Medical University School of Medicine), T. Matsuki (Shinnittetsu Muroran General Hospital), A. Hashimoto (Kushiro City General Hospital), M. Abiru (Oji General Hospital), T. Matsuoka (National Hospital Kyusyu Cardiovascular Center), H. Toda, S. Ri (Kagoshima City Hospital), Y. Toyama, H. Yamaguchi, S. Toyoshima (Nanpuh Hospital), H. Torii (Kagoshima Medical Association Hospital), Y. Atuchi, A. Miyamura (Tenyokai Chuo Hospital), S. Hamasaki (Kagoshima University Faculty of Medicine), and K. Miyahara (Shinkyo Hospital).

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Beneficial Effect of Preinfarction Angina on In-Hospital Outcome is Preserved in Elderly Patients Undergoing Coronary Intervention for Anterior Acute Myocardial Infarction

Masami Kosuge, MD; Kazuo Kimura, MD; Sunao Kojima, MD*; Tomohiro Sakamoto, MD*; Masaharu Ishihara, MD**; Yujiro Asada, MD†; Chuwa Tei, MD††; Shunichi Miyazaki, MD‡; Masahiro Sonoda, MD‡‡; Kazufumi Tsuchihashi, MD§; Masakazu Yamagishi, MD‡; Yoshihiko Ikeda, MD§§; Mutsunori Shirai, MD¶; Hisatoyo Hiraoka, MD¶¶; Takeshi Inoue, MD#; Fumio Saito, MD##; Hisao Ogawa, MD*
on behalf of the Japanese Acute Coronary Syndrome Study (JACSS) Investigators

Background Preinfarction angina improves survival after acute myocardial infarction (AMI) in nonelderly but not elderly patients in the thrombolytic era. However, it remains unclear whether preinfarction angina has a beneficial effect on clinical outcome in elderly patients undergoing percutaneous coronary intervention (PCI).
Methods and Results The study group comprised 484 anterior AMI patients who were admitted within 24 h of onset and underwent emergency PCI. Patients were divided into 2 groups: those aged <70 years (nonelderly patients, n=290) and those aged ≥70 years (elderly patients, n=194). Angina within 24 h before AMI was present in 42% of nonelderly patients and in 37% of elderly patients. In nonelderly patients, preinfarction angina was associated with a lower in-hospital mortality rate (1% vs 7%, p=0.02). Similarly, in elderly patients, preinfarction angina was associated with a lower in-hospital mortality rate (6% vs 16%, p=0.03). Multivariate analysis showed that the absence of preinfarction angina was an independent predictor of in-hospital mortality in both nonelderly (odds ratio 4.20; 95% confidence interval (CI) 1.20–10.6; p=0.04) and elderly patients (odds ratio 3.04; 95%CI 1.06–18.1; p=0.04).
Conclusions Angina within the 24 h before AMI is associated with better in-hospital outcomes in elderly and nonelderly patients. (*Circ J* 2005; **69:** 630–635)

Key Words: Aging; Angina pectoris; Myocardial infarction; Reperfusion

Brief episodes of ischemia before sustained coronary artery occlusion protect the heart by delaying lethal injury and significantly limiting the size of the infarct, an effect known as ischemic preconditioning[1,2] Clinical studies have confirmed that angina shortly before the onset of acute myocardial infarction (AMI) is associated with a smaller infarct size and better short- and long-term outcomes[3–6] However, it has been reported that in the thrombolytic era preinfarction angina limits infarct size and improves clinical outcome in nonelderly, not elderly, patients with AMI[7,8] and it remains unclear whether preinfarction angina has a beneficial effect on clinical outcome in elderly patients undergoing percutaneous coronary intervention (PCI). In this study, we assessed the relation of preinfarction angina to in-hospital outcome in nonelderly and elderly patients with anterior AMI who underwent PCI.

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*Division of Cardiology, Yokohama City University Medical Center, Yokohama, *Department of Cardiovascular Medicine, Kumamoto University School of Medicine, Kumamoto, **Department of Cardiology, Hiroshima City Hospital, Hiroshima, †First Department of Pathology, Miyazaki University School of Medicine, Miyazaki, ††The First Department of Internal Medicine, Kagoshima University Faculty of Medicine, Kagoshima, ‡Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, ‡‡The Second Department of Cardiology, National Hospital Kyusyu Cardiovascular Center, Kagoshima, §Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, §§Department of Pathology, National Cardiovascular Center, Suita, ¶Department of Microbiology, School of Medicine, Yamaguchi University, Ube, ¶¶Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Suita, #Division of Cardiology, Oita National Hospital, Oita, ##Department of Cardiology, Nihon University Surugadai Hospital, Tokyo, Japan*
Mailing address: Kazuo Kimura, MD, The Division of Cardiology, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan. E-mail: c-kimura@urahp.yokohama-cu.ac.jp

Methods

Patients

The Japanese Acute Coronary Syndrome Study (JACSS) is a retrospective, observational multicenter trial[9] involving 484 patients with anterior AMI who fulfilled the following inclusion criteria: (1) admission within 24 h of symptom onset; (2) coronary angiography performed immediately after admission; (3) emergency percutaneous transluminal coronary angioplasty, stenting or both of the left anterior descending coronary artery (LAD); and (4) availability of a detailed clinical history. The diagnosis of anterior AMI was based on typical chest pain lasting more than 30 min, ST-segment elevation of at least 1 mm in 2 contiguous precordial leads, and a subsequent increase in the serum creatine

Table 1 Clinical Characteristics and Coronary Angiographic Findings in Nonelderly (<70 Years Old) and Elderly (≥70 Years Old) Patients

	Nonelderly (n=290)	*Elderly (n=194)*	*p value*
Age (years)	*58±8*	*77±5*	*0.000*
Preinfarction angina (%)	*123 (42)*	*71 (37)*	*0.201*
Men (%)	*243 (84)*	*109 (56)*	*0.000*
Killip ≥2 on admission (%)	*41 (14)*	*54 (28)*	*0.000*
Risk factors			
Smoking (%)	*164 (57)*	*51 (26)*	*0.000*
Hyperlipidemia (%)	*109 (38)*	*49 (25)*	*0.005*
Diabetes mellitus (%)	*82 (28)*	*46 (24)*	*0.265*
Hypertension (%)	*139 (48)*	*127 (66)*	*0.000*
Prior infarction (%)	*29 (10)*	*25 (13)*	*0.323*
Time to admission (h)	*4.0±4.7*	*5.4±5.0*	*0.003*
Multivessel disease (%)	*91 (31)*	*81 (42)*	*0.019*
TIMI flow grade 0 at initial CAG (%)	*205 (71)*	*124 (64)*	*0.118*
Final TIMI flow grade ≥2 (%)	*280 (97)*	*190 (98)*	*0.372*
Final TIMI flow grade 3 (%)	*258 (89)*	*170 (88)*	*0.652*
Stent implantation (%)	*224 (77)*	*156 (80)*	*0.405*
Peak creatine kinase (IU/L)	*3,803±3,064*	*3,305±2,412*	*0.045*
In-hospital mortality (%)	*12 (4)*	*24 (12)*	*0.001*

Data are presented as mean±standard deviation or number (%) of patients.
TIMI, Thrombolysis in Myocardial Infarction; CAG, coronary angiography.

Table 2 Clinical Characteristics and Coronary Angiographic Findings in Nonelderly (<70 Years Old) Patients According to the Presence or Absence or Preinfarction Angina

	No angina (n=167)	*Angina (n=123)*	*p value*
Age (years)	*58±8*	*57±8*	*0.355*
Men (%)	*139 (83)*	*104 (85)*	*0.763*
Killip ≥2 on admission (%)	*26 (15)*	*15 (12)*	*0.415*
Risk factors			
Smoking (%)	*90 (54)*	*74 (60)*	*0.287*
Hyperlipidemia (%)	*62 (37)*	*47 (38)*	*0.850*
Diabetes mellitus (%)	*56 (34)*	*26 (21)*	*0.021*
Hypertension (%)	*83 (50)*	*56 (46)*	*0.482*
Prior infarction (%)	*19 (11)*	*10 (8)*	*0.362*
Time to admission (h)	*3.6±4.2*	*4.5±5.3*	*0.103*
Multivessel disease (%)	*52 (31)*	*39 (32)*	*0.918*
TIMI flow grade 0 at initial CAG (%)	*126 (75)*	*79 (64)*	*0.038*
Final TIMI flow grade ≥2 (%)	*160 (96)*	*120 (98)*	*0.419*
Final TIMI flow grade 3 (%)	*139 (83)*	*119 (97)*	*0.000*
Stent implantation (%)	*126 (75)*	*98 (80)*	*0.396*

Data are presented as mean±standard deviation or number (%) of patients.
TIMI, Thrombolysis in Myocardial Infarction; CAG, coronary angiography.

kinase concentration to more than twice the upper limit of normal. Preinfarction angina was defined as the presence of typical chest pain occurring at rest or during exercise and persisting for less than 30 min within 24 h before the onset of AMI[3,6] The study protocol was reviewed and approved by the ethics committee of each participating hospital.

Coronary Angiography and Coronary Intervention

Coronary angiography was performed immediately after admission to assess the perfusion status of the LAD according to the Thrombolysis in Myocardial Infarction (TIMI) study classification[10] The recanalization method was left to the attending physician's discretion. Final TIMI flow grade was assessed on the final angiograms. Multivessel disease was defined as ≥75% stenosis in 1 or more vessels remote from the LAD.

Statistical Analysis

Data are expressed as mean±SD. Categorical data were compared by chi-square analyses. Student's t-test was used to compare continuous variables. A probability value <0.05 was considered to indicate a statistically significant difference. Multiple logistic regression analysis was used to examine the determinants of in-hospital mortality. Variables used for analysis included age, sex, time to admission, prior infarction, Killip class on admission, preinfarction angina, initial occlusion status in the LAD, multivessel disease, stent implantation, final TIMI flow grade, hypertension, diabetes mellitus, hyperlipidemia, and smoking. Odds ratios and 95% confidence intervals were calculated. Analyses were done using SPSS PC software (Chicago, IL, USA).

Results

Patient Characteristics

There were 290 patients aged <70 years (nonelderly patients, mean age 58 years, range 29–69) and 194 patients

Table 3 Clinical Characteristics and Coronary Angiographic Findings in Elderly (≥70 Years Old) Patients According to the Presence or Absence of Preinfarction Angina

	No angina (n=123)	Angina (n=71)	p value
Age (years)	77±5	78±6	0.519
Men (%)	75 (61)	34 (48)	0.077
Killip ≥2 on admission (%)	41 (33)	13 (18)	0.025
Risk factors			
Smoking (%)	32 (26)	19 (27)	0.910
Hyperlipidemia (%)	29 (24)	20 (28)	0.478
Diabetes mellitus (%)	29 (24)	17 (24)	0.954
Hypertension (%)	84 (68)	43 (61)	0.275
Prior infarction (%)	17 (14)	8 (11)	0.609
Time to admission (h)	5.1±4.6	5.8±5.6	0.392
Multivessel disease (%)	54 (44)	27 (38)	0.424
TIMI flow grade 0 at initial CAG (%)	78 (63)	46 (65)	0.848
Final TIMI flow grade ≥2 (%)	121 (98)	69 (97)	0.574
Final TIMI flow grade 3 (%)	107 (87)	63 (89)	0.723
Stent implantation (%)	100 (81)	56 (79)	0.682

Data are presented as mean±standard deviation or number (%) of patients.
TIMI, Thrombolysis in Myocardial Infarction; CAG, coronary angiography.

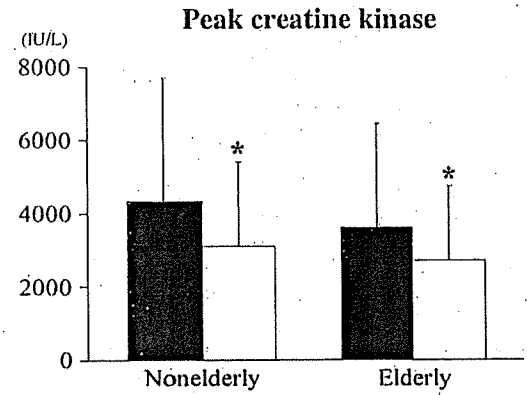

Fig 1. In both nonelderly (age <70 years) and elderly patients (age ≥70 years), the peak creatine kinase concentration was significantly lower in those with (white bar) than in those without (black bar) preinfarction angina. *p<0.05 vs patients without preinfarction angina.

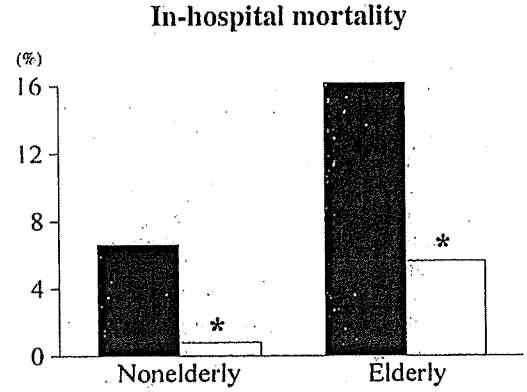

Fig 2. In both nonelderly patients (age <70 years) and elderly patients (age ≥70 years), in-hospital mortality was significantly lower in those with (white bar) than in those without (black bar) preinfarction angina. *p<0.05 vs patients without preinfarction angina.

aged ≥70 years (elderly patients, mean age 77 years, range 70–95). Overall, stent implantation was performed in 380 patients (79%). The final TIMI flow grade was ≥2 in 470 patients (97%) and 3 in 428 (89%). The baseline characteristics of all the patients are presented in Table 1. The nonelderly and elderly patient groups differed with regard to age, sex, Killip class on admission, smoking, hyperlipidemia, hypertension, time to admission, and multivessel disease. However, there were no differences in diabetes mellitus, prior infarction, the prevalence of initial or final TIMI flow grade, or stent implantation. Preinfarction angina was slightly but not significantly less frequent in elderly patients.

The baseline characteristics of the nonelderly patients with and without preinfarction angina are presented in Table 2. These groups were similar with regard to age, sex, Killip class on admission, coronary risk factors other than diabetes, prior infarction, time to admission, the prevalence of multivessel disease, final TIMI flow grade ≥2, and stent implantation. The prevalence of both diabetes mellitus and an initial TIMI flow grade of 0 was significantly lower and the prevalence of final TIMI flow grade 3 was significantly higher in patients with preinfarction angina.

The baseline characteristics of the elderly patients with and without preinfarction angina are presented in Table 3. These groups were similar with regard to age, sex, coronary risk factors, prior infarction, time to admission, the prevalence of multivessel disease, initial and final TIMI flow grades, and stent implantation. The prevalence of Killip class ≥2 on admission was significantly lower in patients with preinfarction angina.

Peak Creatine Kinase (CK) Concentration (Fig 1)

The peak CK concentration was significantly lower in elderly patients than in nonelderly patients, but in both groups, preinfarction angina was associated with a lower peak CK.

In-Hospital Mortality (Fig 2)

During hospitalization (mean 14 days), 36 patients (7.4%) died; 86% of in-hospital deaths were related to cardiac causes. In-hospital mortality was significantly higher in elderly patients than nonelderly patients. In both groups, preinfarction angina was associated with lower in-hospital mortality. Multivariate analysis revealed that the absence of preinfarction angina was an independent

Table 4 Multivariate Analysis of Factors Associated With In-Hospital Mortality in Nonelderly (<70 Years Old) and Elderly (≥70 Years Old) Patients According to the Presence or Absence of Preinfarction Angina

Variable	Nonelderly (<70 years old)		Elderly (≥70 years old)	
	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Age	1.03 (0.93–1.13)	0.603	1.19 (1.04–1.37)	0.008
Female	0.84 (0.12–5.72)	0.858	1.70 (0.38–7.64)	0.489
Time to admission	0.95 (0.77–1.19)	0.673	0.96 (0.81–1.15)	0.680
Prior infarction	7.20 (1.44–36.0)	0.016	4.96 (1.02–24.2)	0.048
Killip class ≥2	4.82 (1.12–20.8)	0.035	32.2 (7.38–49.4)	<0.001
Absence of preinfarction angina	4.20 (1.20–10.6)	0.037	3.04 (1.06–18.1)	0.044
TIMI flow grade 0 at initial CAG	1.63 (0.34–7.75)	0.537	3.46 (0.66–18.1)	0.141
Multivessel disease	1.10 (0.19–2.00)	0.264	1.05 (0.21–1.68)	0.220
Stent implantation	1.58 (0.31–8.00)	0.584	0.61 (0.12–3.05)	0.551
Final TIMI flow grade	0.86 (0.36–2.10)	0.752	0.09 (0.02–0.38)	0.001
Hypertension	4.77 (0.96–22.6)	0.058	1.53 (0.37–6.34)	0.561
Diabetes mellitus	2.92 (0.76–11.3)	0.120	1.02 (0.16–1.77)	0.191
Hyperlipidemia	0.67 (0.16–2.72)	0.571	0.26 (0.08–1.74)	0.164
Smoking	1.01 (0.25–4.02)	0.995	0.58 (0.10–4.30)	0.592

95%CI, 95% confidence interval; TIMI, Thrombolysis in Myocardial Infarction; CAG, coronary angiography.

predictor of in-hospital death in both nonelderly and elderly patients (Table 4).

Discussion

In the present study preinfarction angina occurring within 24 h of the onset of anterior AMI was associated with a lower peak CK concentration and lower in-hospital mortality after PCI in elderly and nonelderly patients. Multivariate analysis showed that the absence of preinfarction angina was an independent predictor of in-hospital mortality in both groups of patients. These findings suggest that the beneficial effects of preinfarction angina on in-hospital outcome is preserved independenty of age in patients undergoing PCI for anterior AMI.

Preinfarction Angina

Clinical studies have reported that in the thrombolytic era the presence of preinfarction angina is associated with a smaller infarct and better survival[3–6] Andreotti et al have shown that thrombolytic therapy results in more rapid recanalization in patients with preinfarction angina than in those without it![11] Ishihara et al found that after thrombolytic therapy, recanalization of an occluded infarct-related artery is more frequently achieved in patients with preinfarction angina than in those without it[6] Experimentally, brief antecedent ischemia has been shown to enhance recombinant tissue plasminogen activator-induced thrombolysis![12] Taken together, these findings suggest that early implementation of thrombolytic therapy may partly contribute to better outcomes in patients with preinfarction angina who undergo this treatment. The beneficial effects of preinfarction angina may also be explained by other mechanisms, including ischemic preconditioning, collateral circulation, and intermittent occlusion![13] Ischemic preconditioning is a cardioprotective phenomenon in which short periods of myocardial ischemia make the myocardium more resistant to subsequent episodes![1,2] In the present study we showed that preinfarction angina per se, apart from the perfusion status of the infarct-related artery before and after recanalization, was related to improved in-hospital survival. These findings suggest that the beneficial effects of preinfarction angina on clinical outcome may be related to the cardioprotective effect of ischemic preconditioning.

Ischemic Preconditioning and Aging

Experimental studies have demonstrated that the effects of ischemic preconditioning are attenuated with age[14,15] and several mechanisms have been proposed for this phenomenon, including decreased adenosine triphosphate concentrations or superoxide dismutase activity, reduced production of stress-induced proteins, reductions in norepinephrine release and α-adrenergic receptor stimulation, increased intracellular calcium concentrations, increased vulnerability of myocardium to ischemia, and attenuated activation of the K_{ATP} channels![14–18] On the other hand, Przyklenk et al have shown that ischemic preconditioning reduces infarct size in both middle-aged and old rabbits independently of morphologic and functional cardiovascular aging, characterized by myocyte hypertrophy, increased myocardial fibrosis, and attenuated responsiveness to α-adrenergic stimulation![19] These findings are supported by studies done by Loubani et al[20] demonstrating in experimental models that necrosis induced by severe ischemic insults to the human myocardium is not exacerbated by increasing age and that ischemic preconditioning equally protects the myocardium in both elderly and younger patients. Thus, the relation between aging and the implications of ischemic preconditioning remain a matter of debate.

Preinfarction Angina and Aging

In contrast to previous studies![7,8] our observational multicenter study found that the presence of angina within 24 h of infarction was associated with a smaller infarct and a better in-hospital outcome in elderly and nonelderly patients. Several reasons may account for inconsistencies with the results of prior studies. First, in the study by Abete et al[7] coronary angiography was not performed in most of the patients. Second, only 34% of elderly patients with preinfarction angina received thrombolytic therapy in their study, which might have contributed to a poorer outcome. Preinfarction angina has been shown to provide no benefit in the absence of reperfusion![21] In our study, a final TIMI flow of grade ≥2 was achieved in 97% of the patients. The study by Ishihara et al demonstrated that preinfarction angina is associated with better short- and long-term outcomes in nonelderly patients than in elderly patients who underwent emergency cardiac catheterization[8] Their study was performed between 1981 and 1994, whereas our study

period was in 2001. The recent improvements in cardiac catheterization including PCI,[22] treatment and patient care may partially explain the discrepancy between their findings and ours. Another likely reason for the inconsistent results is the definition of "elderly", which seems to have changed over time. Indeed, over the past 20 years, the definition of "elderly" in studies of outcome in patients undergoing cardiac surgery and related procedures has gradually increased from ≥65 years old to ≥80 years old.[23–25] Unspecified or unmeasured baseline characteristics of patients aged ≥70 years may also have differed our study and previous investigations. We limited our study group to patients undergoing emergency PCI, a decision that might be at least in part related to the patients' daily activities. Elderly patients in our study may have thus had a relatively high level of physical activity. Experimental studies have shown that exercise training restores the protective effect of ischemic preconditioning in the aging heart by increasing norepinephrine release.[26]

Study Limitations

This was a small, retrospective, observational, nonrandomized study. Furthermore, the subjects were limited to those with anterior AMI who underwent PCI because we recently showed that preinfarction angina improves in-hospital outcome after PCI in patients with anterior AMI, but not in those with nonanterior AMI.[27] The inclusion of these latter patients would have confounded assessment of the effect of preinfarction angina on in-hospital outcome. Another major limitation is the quantification of ischemic episodes. Because episodes of preinfarction angina were ascertained on the basis of patient history, silent ischemia was not taken into account. Silent ischemia has been shown to occur frequently in elderly patients.[28] In our study, preinfarction angina was slightly less frequent in elderly patients, but if we had taken silent ischemia into account, the benefits of preinfarction angina may have become clearer in elderly patients. Further prospective studies are needed to confirm whether the beneficial effects of preinfarction angina are preserved in elderly patients.

Conclusion

The presence of angina within 24 h of an anterior AMI is associated with a smaller infarct and better in-hospital outcome in elderly and nonelderly patients undergoing PCI.

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Appendix I

JACSS Principal Investigators

Ogawa H (Chairperson; Kumamoto University), Asada Y (Miyazaki Medical College), Tei C (Kagoshima University), Kimura K (Yokohama City University Medical Center), Tsuchihashi K (Sapporo Medical University), Ishihara M (Hiroshima City Hospital), Miyazaki S, Yamagishi M, Ikeda Y (National Cardiovascular Center), Shirai M (Yamaguchi University), Hiraoka H (Osaka University), Inoue T (Oita National Hospital), Sonoda M (National Hospital Kyusyu Cardiovascular Center), and Saito F (Nihon University Surugadai Hospital).

JACSS Participating Institutions and Clinical Investigators

Honda T (Social Welfare Organization Imperial Gift Foundation Incorporated Saiseikai Kumamoto Hospital), Ogata Y (Japanese Red Cross Kumamoto Hospital), Saito T (Kumamoto Central Hospital), Hokamura Y (Kumamoto City Hospital), Mizuno Y (Kumamoto Kinoh Hospital), Miyagi H (Kumamoto National Hospital), Matsumura T (Labor Welfare Corporation Kumamoto Rosai Hospital), Tabuchi T (Yatsushiro Health Insurance General Hospital), Sakaino N (Amakusa Medical Center), Kimura K (Arao City Hospital), Obata K (Health Insurance Hitoyoshi General Hospital), Shimomura H (Fukuoka Tokushukai Medical Center), Matsuyama K (Social Insurance Ohmuta-Tenryoh Hospital), Nakamura N (Shinbeppu Hospital), Yamamoto N (Miyazaki Prefectural Nobeoka Hospital), Hase M (Sapporo Medical University School of Medicine), Matsuki T (Shinnittetsu Muroran General Hospital), Hashimoto A (Kushiro City General Hospital), Abiru M (Oji General Hospital), Matsuoka T (National Hospital Kyusyu Cardiovascular Center), Toda H, Ri S (Kagoshima City Hospital), Toyama Y, Yamaguchi H, Toyoshima S (Nanpuh Hospital), Torii H (Kagoshima Medical Association Hospital), Atuchi Y, Miyamura A (Tenyokai Chuo Hospital), Hamasaki S (Kagoshima University Faculty of Medicine), and Miyahara K (Shinkyo Hospital).

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Effects of Glucose Abnormalities on In-Hospital Outcome After Coronary Intervention for Acute Myocardial Infarction

Masami Kosuge, MD; Kazuo Kimura, MD; Sunao Kojima, MD*; Tomohiro Sakamoto, MD*; Kunihiko Matsui, MD*; Masaharu Ishihara, MD**; Yujiro Asada, MD†; Chuwa Tei, MD††; Shunichi Miyazaki, MD‡; Masahiro Sonoda, MD‡‡; Kazufumi Tsuchihashi, MD§; Masakazu Yamagishi, MD‡; Yoshihiko Ikeda, MD§§; Mutsunori Shirai, MD***; Hisatoyo Hiraoka, MD††; Takeshi Inoue, MD‡‡‡; Fumio Saito, MD§§§; Hisao Ogawa, MD* on behalf of the Japanese Acute Coronary Syndrome Study (JACSS) Investigators

Background The effects of glucose abnormalities on outcomes after percutaneous coronary intervention (PCI) remain unclear. We examined the association between glucose abnormalities and in-hospital outcome in patients undergoing PCI for acute myocardial infarction (AMI).

Methods and Results A total of 849 patients with AMI who were admitted within 12 h after symptom onset and underwent emergency PCI were classified according to the presence or absence of admission hyperglycemia, defined as a blood glucose level on admission of >11 mmol/L and whether they had a history of diabetes mellitus: group 1 (n=504), non-diabetic patients without admission hyperglycemia; group 2 (n=111), diabetic patients without admission hyperglycemia; group 3 (n=87), non-diabetic patients with admission hyperglycemia; and group 4 (n=147), diabetic patients with admission hyperglycemia. Among groups 1, 2, 3 and 4, in-hospital mortality was 2.6, 2.7, 11.5 and 8.8%, respectively ($p<0.01$). Multivariate analysis showed that compared with group 1 patients, the odds ratio (95%confidence interval) for in-hospital mortality among those in groups 2, 3, and 4 were 0.80 (0.24–2.60, p=0.708), 2.29 (1.10–5.49, p=0.039), and 2.14 (1.14–4.69, p=0.048), respectively.

Conclusions In-patients undergoing PCI for AMI, admission hyperglycemia, irrespective of the presence or absence of diabetes, is associated with increased in-hospital mortality, whereas diabetes without admission hyperglycemia is not. (*Circ J* 2005; **69**: 375–379)

Key Words: Glucose; Myocardial infarction; Reperfusion; Stent

Patients with diabetes have been established to have poorer outcomes after acute myocardial infarction (AMI) than non-diabetic patients[1,2] Furthermore, hyperglycemia itself on admission (admission hyperglycemia) is also associated with an increased risk of adverse events, including heart failure, cardiogenic shock, and death after AMI, irrespective of whether diabetes was previously diagnosed[3–6] Recently, Wahab et al report that diabetes, admission hyperglycemia, or both were associated with adverse outcomes after AMI during the thrombolytic era[6]

Thrombolytic therapy has been established to significantly reduce mortality among both diabetic and non-diabetic patients with AMI[7] Despite substantial benefits, thrombolytic therapy is less likely to be given to diabetic patients, which might contribute to their poorer outcome[6,8] Recently, percutaneous coronary intervention (PCI) is increasingly used for reperfusion therapy, improving the outcome of patients with AMI. In diabetic patients with AMI, primary angioplasty is associated with fewer and less severe adverse events than thrombolytic therapy[9] suggesting that PCI might have a beneficial effect on survival in diabetic patients. The aim of this study was to examine the relations of glucose abnormalities to infarct size and in-hospital mortality in patients with AMI who underwent PCI.

Methods

Study Population

The Japan Acute Coronary Syndrome Study (JACSS) was a retrospective, observational multicenter trial. Between January and December 2001, patients with AMI admitted to 35 participating hospitals in Japan were studied.

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*Division of Cardiology, Yokohama City University Medical Center, Yokohama, *Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kurume, **Department of Cardiology, Hiroshima City Hospital, Hiroshima, †First Department of Pathology, Miyazaki University School of Medicine, Miyazaki, ††The First Department of Internal Medicine, Kagoshima University Faculty of Medicine, Kagoshima, ‡Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, ‡‡The Second Department of Cardiology, National Hospital Kyusyu Cardiovascular Center, Kagoshima, §Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, §§Department of Pathology, National Cardiovascular Center, Suita, ***Department of Microbiology, School of Medicine, Yamaguchi University, Ube, †††Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Suita, ‡‡‡Division of Cardiology, Oita National Hospital, Oita and §§§Department of Cardiology, Nihon University Surugadai Hospital, Tokyo, Japan*

Mailing address: Kazuo Kimura, MD, The Division of Cardiology, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan. E-mail: c-kimura@urahp.yokohama-cu.ac.jp

Table 1 Baseline Characteristics

	Group 1 (n=504)	Group 2 (n=111)	Group 3 (n=87)	Group 4 (n=147)	p value
Age (years)	65±12	66±10	71±12	66±13	<0.01
Male	77%	79%	68%	65%	<0.01
Time from symptom onset to admission (h)	3.6±2.8	3.2±2.4	3.0±2.2	3.3±2.5	NS
Killip >1 on admision	14%	14%	25%	27%	<0.01
Previous infarction	10%	18%	10%	14%	NS
Previous angina	40%	40%	38%	29%	NS
Blood glucose level on admission (mmol/L)	7.5±1.7	8.4±1.7	13.9±3.2	16.1±4.6	<0.01
HbA_{1c} (%)†	5.3±0.6 (n=209)	6.9±1.2 (n=78)	5.7±0.9 (n=31)	8.1±1.8 (n=102)	<0.01
Diabetes mellitus	0	100%	0	100%	
Hyperlipidemia	28%	45%	23%	41%	<0.01
Hypertension	53%	63%	53%	62%	NS
Smoking	52%	55%	45%	46%	NS
Serum creatinine on admission (mg/d)	0.9±0.9	1.1±1.1	1.0±0.8	1.2±1.2	NS
Medication before AMI					
Oral hypoglycemic drug	0	35%	0	45%	<0.01
Insulim	0	9%	0	22%	<0.01
Aspirin	8%	16%	7%	15%	<0.01
β-blocker	4%	7%	6%	5%	NS
ACE inhibitor	5%	12%	6%	10%	<0.05
HMG CoA	4%	15%	7%	14%	<0.01
Anterior AMI	51%	40%	56%	43%	NS
ST-segment elevation	91%	90%	95%	91%	NS
3-vessel disease	10%	19%	12%	21%	<0.01
TIMI flow grade 0 at initial CAG	68%	61%	75%	63%	NS
Final TIMI flow grade ≥2	97%	97%	97%	95%	NS
Final TIMI flow grade 3	90%	87%	87%	88%	NS
Stent implantation	79%	73%	83%	78%	NS

AMI, acute myocardial infarction; ACE, angiotensin-converting enzyme; CAG, coronary angiography; HbA_{1c}, glycosylated homoglobin; HMG CoA, hydroxymethylglutaryl-coenzyme A reductase inhibitors.
†HbA_{1c} was measured during hospitalization in only 420 patients.
Group 1, Non-diabetic patients without admission hyperglycemia; Group 2, Diabetic patients without admission hyperglycemia; Group 3, Non-diabetic patients with admission hyperglycemia; Group 4, Daibetic patients with admission hyperglycemia.
Data are presented as mean values±SD or percentages of patients.

A diagnosis of AMI required at least 2 of the following characteristics: typical chest pain persisting for 30 min or longer, ischemic electrocardiographic changes, and a peak creatine kinase level equivalent to more than twice the upper limit of normal. The study protocol was reviewed and approved by the ethical committee of each participating hospital. A total of 849 patients who met the following entry criteria were studied: (i) admission within 12 h from the onset of AMI; (ii) coronary angiography performed immediately after admission; (iii) percutaneous transluminal coronary angioplasty, stenting, or both of the infarct-related artery; (iv) measurement of blood glucose level on admission; and (v) availability of a detailed clinical history. Data from all subjects, excluding information that could be used to identify patients, such as names and identification numbers, were transmitted to a central data collection center, located in the Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, for analysis.

Coronary Angiography and Coronary Intervention

Written informed consent for coronary catheterization was obtained from all patients at each hospital. Coronary angiography was performed immediately after admission. The perfusion status of the infarct-related artery was assessed according to the Thrombolysis in Myocardial Infarction (TIMI) study classification.[10] The recanalization method was left to the physicians' discretion. Final TIMI flow grade was assessed on the basis of final angiograms obtained on admission.

Data Analysis

Previous angina was defined as the presence of typical chest pain occurring at rest or during exercise and persisting for less than 30 min, within 24 h before the onset of AMI. Diabetes mellitus was considered present if this diagnosis and antidiabetic treatment, including drugs or insulin, had been given to the patient, if the fasting glucose level was found to be ≥126 mg/dl (7.0 mmol/L) on the previous occasion or if the results of an oral glucose tolerance test were abnormal. Patients who did not meet these criteria were considered not to have diabetes mellitus. Blood samples for measurement of blood glucose level were obtained on admission. Admission hyperglycemia was defined as a blood glucose level on admission of >198 mg/dl (11 mmol/L).[6,11] Glycosylated hemoglobin (HbA_{1C}) was measured in 420 patients (49%) within 14 days after admission. Patients were classified into 4 groups, based on their history of diabetes and their blood glucose level on admission:

Group 1 (n=504): Non-diabetic patients without admission hyperglycemia;
Group 2 (n=111): Diabetic patients without admission hyperglycemia;
Group 3 (n=87): Non-diabetic patients with admission hyperglycemia;
Group 4 (n=147): Diabetic patients with admission hyperglycemia.

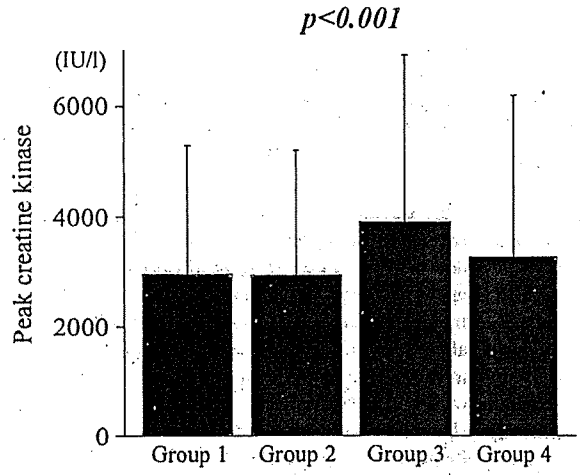

Fig 1. Peak creatine kinase level was higher in group 3, and infarct sizes were similar in the other 3 groups.

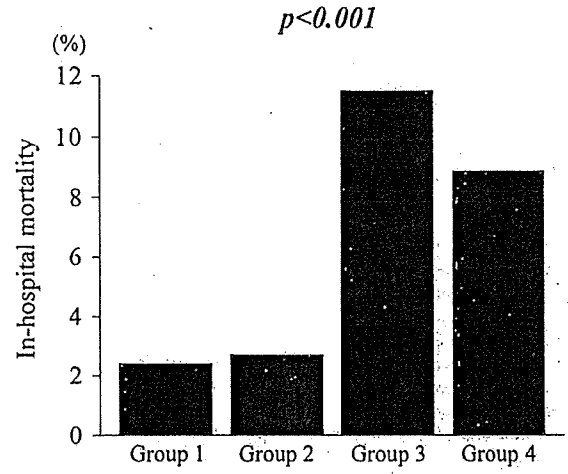

Fig 2. In-hospital mortality was highest in group 3 and second highest in group 4.

Statistical Analysis

Data are expressed as mean values±standard deviation for continuous variables and as percentages for categorical variables. We made comparisons by one-way analysis of variance for continuous variables, and the statistical significance of differences was calculated by using the Scheffe F test. Chi-squared analysis or Fisher's exact test was used to compare categorical variables. A two-tailed p value of <0.05 was considered to indicate statistical significance. Multiple logistic regression analysis was used to examine determinants of in-hospital mortality. Variables used for analysis included an age of >70 years,[12] sex, time to admission, Killip >1 on admission, previous infarction, serum creatinine level on admission, ST-segment elevation, anterior infarction, absence of previous angina within 24 h before symptom onset, occlusion status at the culprit lesion, 3-vessel disease, stent implantation, final TIMI flow grade ≤2, and glycemic status. The strength of association of glycemic status was assessed by comparison of the 3 groups with a disordered blood glucose profile to the normal (group 1) patients who had no diagnosis of diabetes without admission hyperglycemia. Analyses were conducted with the use of SPSS PC software.

Results

Patient Characteristics

The overall prevalence of diabetes in the study group was 30%. Patients' characteristics in the 4 study subgroups are presented in Table 1. Non-diabetic patients with admission hyperglycemia were likely to be oldest. Patients with admission hyperglycemia were likely to be female and to be in the Killip class >1 on admission, and independent of a diabetic status. The prevalence of previous infarction was slightly but not significantly higher in the diabetic patients than in the non-diabetic patients. Diabetic patients with admission hyperglycemia had the highest blood glucose level on admission and the highest HbA1c value. In general, diabetic patients were more likely to have hyperlipidemia and hypertension than non-diabetic patients. Diabetic patients were more likely to be receiving aspirin, angiotensin-converting enzyme inhibitors, and hydroxymethylglutaryl-coenzyme A reductase inhibitors. There were no differences in the 4 groups with regard to time from symptom onset to admission, infarct location, serum creatinine level on admission, and prevalence of ST-segment elevation.

Coronary Angiographic Findings

The coronary angiographic findings of the patients are presented in Table 1. Stent implantation was performed in 665 patients (78%). Diabetic patients were more likely to have 3-vessel disease than non-diabetic patients. There were no significant differences in the 4 groups with respect to the prevalences of TIMI flow grade 0 at initial coronary angiography, a final TIMI flow grade ≥2, a final TIMI flow grade of 3, or stent implantation.

Peak Creatine Kinase Level

Non-diabetic patients with admission hyperglycemia had a higher peak creatine kinase level than the other 3 groups, which had similar levels (Fig 1).

In-Hospital Mortality

During hospitalization (mean 14 days), 39 patients (4.5%) died (38 of cardiac causes and one of multiple organ failure). In-hospital mortality was higher in non-diabetic and diabetic patients with admission hyperglycemia, especially in the former (Fig 2). Multivariate analysis showed that patients who were >70 years of age, had Killip >1 on admission, serum creatinine on admission, anterior infarction, final TIMI grade ≤2, and admission hyperglycemia, irrespective of the presence or absence of diabetes (groups 3 and 4), were independent predictors of in-hospital death (Table 2).

Discussion

Our findings suggest that in-patients undergoing PCI for AMI, and the presence of admission hyperglycemia with or without diabetes significantly contributed to in-hospital mortality. Diabetes without admission hyperglycemia did not increase in-hospital mortality.

Non-Diabetic Patients With Admission Hyperglycemia

The poor outcome in non-diabetic patients with admission hyperglycemia may arise from a larger infarct size. Hyperglycemia has been shown to increase intercellular adhesion molecule-1, which increases the leukocyte plug-

Table 2 Multivariate Analysis of Factors Associated With In-Hospital Mortality

Variable	Odds ratio (95%CI)	p value
Group 1	1.00 (–)	–
Group 2	0.80 (0.24–2.60)	0.708
Group 3	2.29 (1.10–5.49)	0.039
Group 4	2.14 (1.14–4.69)	0.048
Age >70 years	3.09 (1.08–9.81)	0.049
Sex	0.90 (0.32–2.55)	0.636
Time to admission	1.07 (0.75–1.16)	0.519
Killip >1 on admission	5.49 (1.88–16.0)	0.002
Previous infarction	2.49 (0.73–8.45)	0.143
Serum creatinine on admission	1.82 (1.13–2.93)	0.014
ST-segment elevation	0.49 (0.11–2.29)	0.336
Anterior infarction	5.45 (1.68–17.7)	0.005
Absence of previous angina	1.15 (0.37–3.64)	0.280
TIMI flow grade 0 at initial CAG	3.67 (0.96–14.0)	0.057
3-vessel disease	2.93 (0.95–8.98)	0.061
Stent implantation	1.10 (0.32–3.02)	0.976
Final TIMI flow grade ≤2	3.53 (1.06–11.7)	0.039

CAG, coronary angiography.
Group 1, Non-diabetic patients without admission hyperglycemia; Group 2, Diabetic patients without admission hyperglycemia; Group 3, Non-diabetic patients with admission hyperglycemia; Group 4, Daibetic patients with admission hyperglycemia.

ging of capillaries[13] augments platelet-dependent thrombus formation[14] and attenuates endothelium-dependent vasodilation[15] Although these mechanisms may contribute to a larger infarct size, we cannot rule out the possibility that hyperglycemia was caused by severe myocardial damage[16] The poor outcome in non-diabetic patients with admission hyperglycemia might also be related to undiagnosed diabetes. Unrecognized diabetes or impaired glucose tolerance may increase endothelial damage due to untreated glucose abnormalities. Two recent studies show that abnormal glucose metabolism is very common in patients with AMI: approximately two-thirds of patients with no previous diagnosis of diabetes have undetected diabetes or impaired glucose tolerance[17,18]

Diabetic Patients With or Without Admission Hyperglycemia

Diabetic patients with admission hyperglycemia had a very high blood glucose level on admission. Nonetheless, these patients had a relatively small infarct size, similar to those in patients without admission hyperglycemia. Diabetic patients with admission hyperglycemia had a higher rate of insulin treatment and a higher HbA1c value, suggesting a longer duration of severe diabetes. Diabetic patients who have impaired islet responses to glucose, especially those with insulin-dependent diabetes, are particularly prone to the development of marked hyperglycemia during stress states[19,20] Marked hyperglycemia in these patients may therefore not correlate with infarct size. However, diabetic patients with admission hyperglycemia had higher in-hospital mortality than did patients in the other groups without admission hyperglycemia. Our findings suggest that the poor outcome in diabetic patients with admission hyperglycemia is primarily related to the deleterious effects of diabetes on myocardial function rather than to infarct size. One explanation is the existence of a specific form of heart muscle disease associated with diabetes. Clinically, this disease manifests itself as left ventricular dysfunction or failure[21] The higher prevalence of Killip class >1 on admission in diabetic patients with admission hyperglycemia, despite a similar infarct size as compared with patients without admission hyperglycemia, may reflect increased susceptibility to the deleterious effects of diabetes. Such effects might be most obvious in patients with a prolonged history of severe diabetes. Hyperglycemia itself may directly impair left ventricular function[6] Furthermore, poorly controlled diabetes may relate to microvascular dysfunction[22] Moreover, coronary atherosclerosis may be more severe and diffuse in diabetic patients with admission hyperglycemia[23] as indicated by the higher incidence of 3-vessel disease. Severer ischemia in the non-infarcted myocardium might increase the risk of heart failure.

Diabetic patients without admission hyperglycemia had a smaller infarct size and a better in-hospital outcome than did patients with admission hyperglycemia, regardless of whether they had a history of diabetes. These findings do not support the results of a recent study by Wahab et al, who showed that diabetic patients, irrespective of admission hyperglycemia, have higher mortality after AMI than non-diabetic patients[9] In-hospital mortality in their diabetic patients was much higher than that in the patients of the present study. These disparate findings may relate to the different treatment strategies used. Patients in the study by Wahab et al, especially those who were diabetic, were less likely to receive thrombolysis or PCI. The worse outcome in their diabetic patients might thus be related, at least in part, to inadequate reperfusion therapy, as suggested previously[6,8] In contrast, we studied only patients who received PCI, and our final success rate was high. The better in-hospital outcome of diabetic patients without admission hyperglycemia in the present study suggests that a higher rate of reperfusion by PCI might improve survival in such patients, compared with that of previous studies. Another important distinction between the 2 studies involves the baseline characteristics of diabetic patients without admission hyperglycemia. In the present study, a smaller proportion of patients were receiving insulin treatment, and the mean HbA1c value was 6.9%, suggesting relatively good glycemic control. Our subjects most likely had milder or a shorter duration of diabetes than those studied by Wahab et al[6] Experimental studies have shown that the heart in the early phase of diabetes is more resistant to ischemia than the non-diabetic heart[24] Another study has reported that a shorter duration of diabetes is associated with a better outcome after AMI! These findings suggest that the duration and severity of diabetes are important determinants of outcome.

Study Limitations

This was a retrospective, observational and non-randomized study. However, we included approximately two-thirds of all patients who were admitted to JACSS-affiliated hospitals within 12 h from the onset of AMI. Therefore, we believe that our results serve to demonstrate the effect of glucose abnormalities on in-hospital outcome in patients who receive PCI. In the present study, diabetes mellitus was diagnosed on the basis of whether patients were receiving antidiabetic treatment, blood glucose levels were measured before admission, and the results of oral glucose tolerance tests were available. However, diabetes may have not been diagnosed with the use of these general criteria in some "non-diabetic" patients. The inclusion of such patients may have substantially affected the study results. The inability to exclude such patients from this multicenter retrospective investigation represents an important limitation of our

study design. Nonetheless, the proportion of our subjects who had diabetes (approximately 30%) was consistent with that of previous studies of patients?[25] Furthermore, we evaluated infarct size on the basis of peak creatine kinase level, but peak creatine kinase level may not accurately reflect infarct size. Other techniques that allow direct examination of infarct size, such as radioisotopes, are needed to more objectively evaluate infarct size and provide important additional information. Further prospective studies involving larger numbers of patients are required to confirm the effect of admission hyperglycemia for patients on outcome after PCI for AMI.

Conclusions

Our findings suggest that in-patients undergoing PCI for AMI, and admission hyperglycemia, irrespective of the presence or absence of diabetes, is associated with increased in-hospital mortality, whereas diabetes without admission hyperglycemia is not.

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Appendices

*JACSS Principal Investigators (*chairperson)*

*Ogawa H (Kumamoto University), Asada Y (Miyazaki Medical College), Tei C (Kagoshima University), Kimura K (Yokohama City University Medical Center), Tsuchihashi K (Sapporo Medical University), Ishihara M (Hiroshima City Hospital), Miyazaki S, Yamagishi M, Ikeda Y (National Cardiovascular Center), Shirai M (Yamaguchi University), Hiraoka H (Osaka University), Inoue T (Oita National Hospital), Sonoda M (National Hospital Kyusyu Cardiovascular Center), and Saito F (Nihon University Surugadai Hospital).

JACSS Participating Institutions and Clinical Investigators

Honda T (Social Welfare Organization Imperial Gift Foundation Incorporated Saiseikai Kumamoto Hospital), Ogata Y (Japanese Red Cross Kumamoto Hospital), Saito T (Kumamoto Central Hospital), Hokamura Y (Kumamoto City Hospital), Mizuno Y (Kumamoto Kinoh Hospital), Miyagi H (Kumamoto National Hospital), Matsumura T (Labor Welfare Corporation Kumamoto Rosai Hospital), Tabuchi T (Yatsushiro Health Insurance General Hospital), Sakaino N (Amakusa Medical Center), Kimura K (Arao City Hospital), Obata K (Health Insurance Hitoyoshi General Hospital), Shimomura H (Fukuoka Tokushukai Medical Center), Matsuyama K (Social Insurance Ohmuta-Tenryoh Hospital), Nakamura N (Shinbeppu Hospital), Yamamoto N (Miyazaki Prefectural Nobeoka Hospital), Hase M (Sapporo Medical University School of Medicine), Matsuki T (Shinnittetsu Muroran General Hospital), Hashimoto A (Kushiro City General Hospital), Abiru M (Oji General Hospital), Matsuoka T (National Hospital Kyusyu Cardiovascular Center), Toda H, Ri S (Kagoshima City Hospital), Toyama Y, Yamaguchi H, Toyoshima S (Nanpuh Hospital), Torii H (Kagoshima Medical Association Hospital), Atuchi Y, Miyamura A (Tenyokai Chuo Hospital), Hamasaki S (Kagoshima University Faculty of Medicine), and Miyahara K (Shinkyo Hospital).

Atherosclerosis Found on Carotid Ultrasonography Is Associated With Atherosclerosis on Coronary Intravascular Ultrasonography

Toshiyasu Ogata, MD, Masahiro Yasaka, MD, Masakazu Yamagishi, MD, Osamu Seguchi, MD, Kazuyuki Nagatsuka, MD, Kazuo Minematsu, MD

Objective. Little has been reported on the relationship between left main coronary artery atherosclerosis and carotid ultrasonographic results. We evaluated the association between carotid and coronary atherosclerosis assessed by coronary intravascular ultrasonography (IVUS) in 45 patients. ***Methods.*** We counted the number of plaques with intima-media thickness (IMT) greater than or equal to 1.1 mm and calculated a plaque score by summing all plaque thicknesses. With the use of IVUS, the percent plaque area was calculated at the proximal, middle, and distal sites of the left main coronary artery. The maximum percent plaque area and mean percent plaque area of the 3 sites were also calculated. Relationships among the degree of left main coronary artery atherosclerosis and carotid atherosclerosis and vascular risk factors were evaluated. ***Results.*** The mean percent plaque area and maximum percent plaque area were increased in men and in patients with hypertension compared with women and those without hypertension ($P < .1$). Both the average of the maximum common carotid IMT and plaque number were correlated with both the mean percent plaque area and maximum percent plaque area ($P < .05$). Men, the presence of hypertension, and the average of the maximum common carotid IMT were correlated with both the mean percent plaque area and maximum percent plaque area by multiple linear regression analysis ($P < .05$). ***Conclusions.*** The average of the maximum common carotid IMT was significantly correlated with left main coronary artery atherosclerosis evaluated by IVUS. ***Key words:*** atherosclerosis; carotid arteries; coronary disease; ultrasonography.

Abbreviations
CAD, coronary artery disease; IMT, intima-media thickness; IVUS, intravascular ultrasonography

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Address correspondence and reprint requests to Toshiyasu Ogata, MD, Department of Medicine and Clinical Science, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail: togata@intmed2.med.kyushu-u.ac.jp

Several studies have identified a relationship between the presence of carotid artery disease and coronary artery disease (CAD). An autopsy study showed a strong correlation between the extent of carotid and coronary atherosclerosis.[1,2] Both arterial beds share risk factors that contribute to the progression of atherosclerosis.[3,4] Ultrasonography is used to assess the presence and extent of atherosclerosis in the carotid and coronary arteries. The carotid intima-media thickness (IMT) has been shown to be a good index of the presence and extent of CAD.[5–8] Also, there is evidence of a strong relationship between the presence of carotid plaques and coronary lesions.[9–12]

Patients with severe left main CAD are known to have a poor long-term prognosis.[13–15] Although coronary angiography is considered the criterion standard for the diagnosis of left main CAD, the degree of atherosclerosis is often underestimated by this method. In contrast, intravascular ultrasonography (IVUS) has been shown to be more accurate and sensitive than coronary angiography in identifying left main coronary artery lesions.[16] Although increased IMT on carotid ultrasonography has been used as a noninvasive marker for CAD, there have been few reports assessing the relationship between left main coronary artery atherosclerosis and carotid ultrasonographic results directly.

The aim of this study was to determine whether atherosclerosis detected in the carotid arteries by carotid ultrasonography was related to the extent of left main coronary artery atherosclerosis evaluated by IVUS.

Materials and Methods

Between November 1, 2000, and December 31, 2002, carotid ultrasonography was performed on 45 Japanese patients (40 men and 5 women; mean age ± SD, 60.8 ± 10.7 years; median age, 62 years) with CAD who also underwent coronary angiography. This study was approved by the Ethics Committee of our hospital. We obtained informed consent about coronary angiography and IVUS from all patients or their families. Coronary angiography was performed by a standard technique to assess the number of involved vessels.

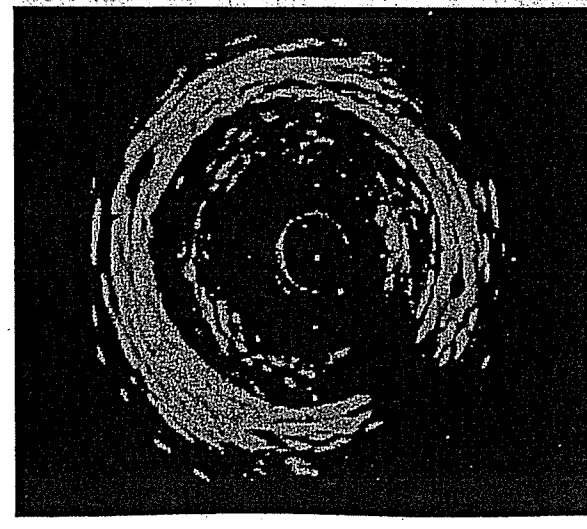
If CAD of more than 1 vessel was detected on coronary angiography, IVUS studies were performed with a single-element 30-MHz, 2.9F or 3.2F intracoronary ultrasonographic catheter (Hewlett-Packard Company, Palo Alto, CA) (Figure 1). The IVUS transducer (30-40 MHz, 1800 rpm) was carefully advanced to the distal site of the patient's left main coronary artery, and the transducer was automatically pulled back (0.5 or 1.0 mm/s) by a motorized pullback device (Cardiovascular Imaging Systems/Boston Scientific, Natick, MA). Special care was taken to visualize the vessel lumen circularly rather than elliptically. If the lumen appeared elliptical, the transducer was repositioned as centrally as possible in the vessel. All images were recorded on super VHS videotape for subsequent analysis.

Ultrasonographic measurements were performed with an offline computer. The vessel lumen area was determined by tracing the leading edge of the intima. The external elastic membrane area was determined by tracing the leading edge of the second bright echo.[17] The percent plaque area was calculated as {(external elastic membrane area – lumen area)/external elastic membrane area} × 100. It was measured at proximal, middle, and distal sites. The maximum percent plaque area and mean percent plaque area of the 3 measurements were used in this study. Calcification of the left main coronary artery was considered present if there was high echo density with acoustic shadowing of the plaque.[12]

Carotid ultrasonography was carried out by experienced clinicians (T.O. and M.Yas.) using an Ultramark 9 HDI unit (Philips Medical Systems, Bothell, WA) with a linear array pulsed wave transducer operating at 5.0 to 10.0 MHz. Neither of them knew about the results of the IVUS study. The pulse repetition frequency was primarily 5000 Hz, and the low-pass filter was 50 Hz. Imaging was performed while the patients were lying in a supine position with their head turned away from the side being scanned and neck extended. The origin of the internal carotid artery was examined in longitudinal and transverse planes.

The IMT was evaluated by 2 calipers on the frozen frame of a suitable longitudinal image as the distance between the luminal-intimal interface and the medial-adventitial interface of the artery. We measured the maximum IMT of each

Figure 1. Representative IVUS image of the left main coronary artery.



side of the common carotid artery and calculated their average (the average of the maximum common carotid IMT). We also measured the maximum IMT from the common carotid artery to the internal carotid artery on each side and averaged the results (the average of the maximum IMT). An atheromatous plaque was defined as a lesion with an IMT greater than or equal to 1.1 mm. We calculated plaque number by counting the numbers of plaques in both carotid arteries. To assess the severity of atherosclerosis, we used plaque score, which was calculated by summing all plaque thicknesses in both carotid systems.[18]

To examine the influence of patients' age on the percent plaque area, we divided them into 2 groups in the boundary of their median age (>62 and <62 years old). Hypertension was defined as systolic blood pressure greater than 140 mm Hg, diastolic blood pressure greater than 90 mm Hg, or current use of antihypertensive agents. Diabetes mellitus was defined as a hemoglobin A1C concentration greater than 6.5% or current use of hypoglycemic medications. Hypercholesterolemia was defined as total cholesterol concentration greater than 220 mg/dL or current use of cholesterol-lowering agents. Patients were categorized as smokers if they were current smokers.

The relationship between left main coronary artery atherosclerosis and carotid atherosclerosis was evaluated by simple linear regression analysis. Data were analyzed by StatView for Windows, version 5.0 (SAS Institute Inc, Cary, NC). The association between age, sex, presence of vascular risk factors, and percent plaque area in the left main coronary artery was examined by an unpaired *t* test. Multiple linear regression analyses were performed to determine atherosclerotic risk factors and carotid artery measurements that were significantly related to left main coronary artery atherosclerosis.

Results

The numbers of patients with hypertension, diabetes mellitus, and hypercholesterolemia and who were current smokers were 27 (60%), 21 (46.7%), 26 (57.8%), and 21 (46.7%), respectively. According to coronary angiography, 1-vessel disease was observed in 18 patients; 2-vessel disease was observed in 15 patients; and 3-vessel disease was observed in 12 patients. The mean percent plaque area ± SD was 34.1% ± 15.0%, and maximum percent plaque area was 37.5% ± 16.0%. The average of the maximum common carotid IMT, the average of the maximum IMT, plaque score, and plaque number were 0.98 ± 0.36 mm, 1.53 ± 0.88 mm, 4.26 ± 2.74 mm, and 2.4 ± 1.7, respectively. Significant differences in carotid ultrasonographic results were not observed among groups of patients with 1-, 2-, and 3-vessel disease.

There was no significant relationship between the mean percent plaque area, maximum percent plaque area, and patient's age (Table 1). The mean percent plaque area and maximum percent plaque area in men were increased significantly compared with those in women. The mean percent plaque area and maximum percent plaque area in patients with hypertension were also higher than those without hypertension. The mean percent plaque area and maximum percent plaque area did not differ statistically according to the presence of diabetes mellitus, hypercholesterolemia, or current smoking.

The average of the maximum common carotid IMT was correlated with both the mean percent plaque area and maximum percent plaque area on the basis of simple regression analysis (Table 2 and Figure 2). However, the average of the maximum IMT and plaque score did not significant-

Table 1. Mean and Maximum Percent Plaque Area by Patients' Clinical Characteristics

Characteristic	Mean %PA		Max %PA	
	Mean	*P*	Mean	*P*
Age				
<62 y	33.6		36.9	
>62 y	34.5	.85	37.9	.84
Sex				
Male	35.7		39.2	
Female	20.9	.036	23.5	.037
Hypertension				
Presence	38.3		40.9	
Absence	27.6	.017	32.3	.077
Diabetes mellitus				
Presence	31.0		34.4	
Absence	36.8	.20	40.2	.23
Hypercholesterolemia				
Presence	33.4		37.3	
Absence	34.9	.75	37.6	.95
Smoking habit				
Presence	34.6		39.0	
Absence	32.9	.73	32.9	.33

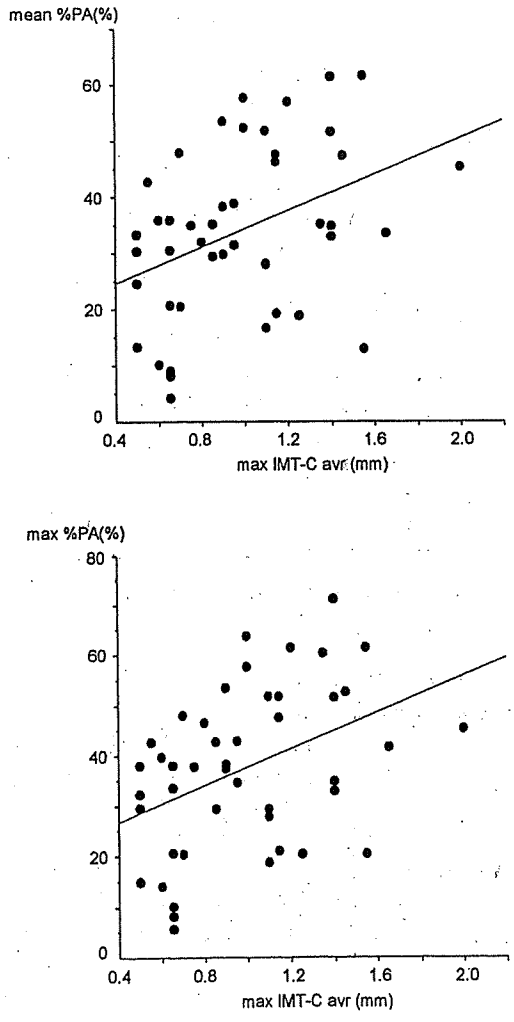
Max %PA indicates maximum percent plaque area; and Mean %PA, mean percent plaque area.

Table 2. Mean and Maximal Percent Plaque Area by Carotid Ultrasonographic Parameters

Parameter	Mean %PA		Max %PA	
	r	*P*	*r*	*P*
Max IMT-C avg, mm	0.39	.007	0.41	.005
Max-IMT avg, mm	0.14	.36	0.16	.30
PS, mm*	0.18	.22	0.22	.15
PN*	0.32	.034	0.35	.021

Max-IMT avg indicates average maximum IMT from the common carotid artery to the internal carotid artery on each side; Max IMT-C avg, average maximum IMT of each side of the common carotid artery; Max %PA, maximum percent plaque area; Mean %PA, mean percent plaque area; PN, plaque number; and PS, plaque score.
*Spearman rank correlation.

Figure 2. Scattergram of mean percent plaque area (mean %PA) and maximum percent plaque area (max %PA) by average maximum IMT of each side of the common carotid artery (max IMT-C avg). The max IMT-C avg was correlated with both mean %PA and max %PA on the basis of simple regression analysis (mean %PA: $r = 0.39$; $P = .007$; max %PA: $r = 0.41$; $P = .005$).



ly correlate with the mean percent plaque area or maximum percent plaque area. Plaque number was correlated with the mean percent plaque area and maximum percent plaque area (Figure 3). The average of the maximum common carotid IMT, average of the maximum IMT, plaque score, and plaque number of patients with calcifications in the left main coronary artery did not differ from those without calcifications.

All clinical and carotid ultrasonographic parameters with a significant relationship with the mean percent plaque area and maximum percent plaque area were tested with multivariate analysis (Table 3). Male sex, patients with hypertension, and the average of the maximum common carotid IMT were correlated with both the mean percent plaque area and maximum percent plaque area.

Figure 3. Scattergram of mean percent plaque area (mean %PA) and maximum percent plaque area (max %PA) by plaque number (PN). The PN was correlated with both mean %PA and max %PA on the basis of Spearman rank correlation (mean %PA: $r = 0.32$; $P = .034$; max %PA: $r = 0.35$; $P = .021$).

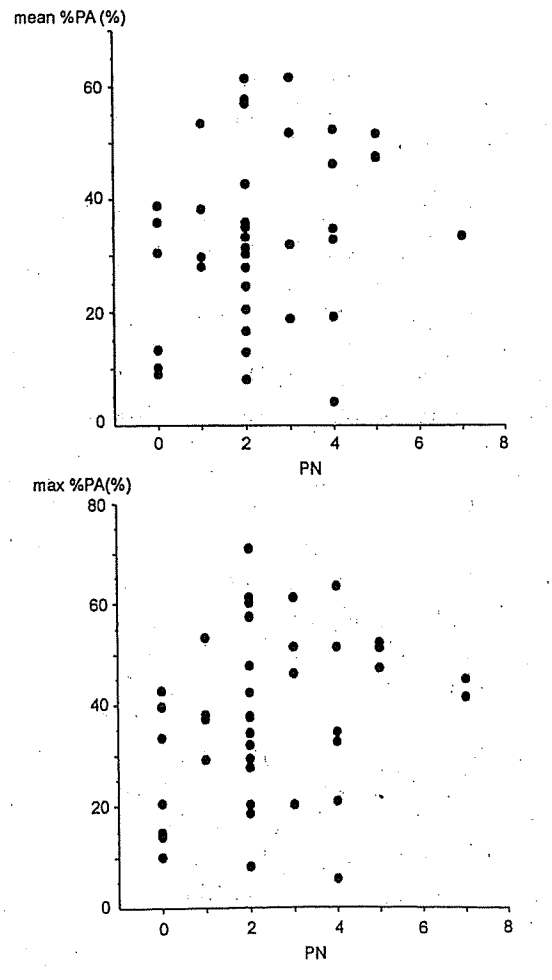


Table 3. All Clinical and Carotid Ultrasonographic Parameters and Relationship With Mean and Maximum Percent Plaque Area in the Multivariate Analysis

Parameter	Mean %PA		Max %PA	
	β	*P*	β	*P*
Male	0.37	.005	0.35	.010
Hypertension	0.46	.003	0.36	.021
Max IMT-C avg	0.50	.006	0.51	.008
PN	−0.24	.21	−0.21	.30

Max IMT-C avg indicates average maximum IMT of each side of the common carotid artery; Max %PA, maximum percent plaque area; Mean %PA, mean percent plaque area; and PN, plaque number.

Discussion

It has been reported that the IMT of the carotid artery is related not only to the presence of CAD but also to the occurrence of coronary events[5–8,19,20] There have been few reports concerning the relationship between carotid and left main coronary artery stenosis in patients undergoing coronary angiography.[21] Coronary angiography significantly underestimates the presence of atherosclerotic stenosis in the left main coronary artery because of coronary remodeling and methodological limitations.[16,22–24] Conversely, because IVUS permits detailed, high-quality cross-sectional imaging of the coronary arteries in vivo, we can evaluate the precise extent of left main coronary artery atherosclerosis. This study showed that the average of the maximum common carotid IMT, a parameter of carotid ultrasonographic findings, was correlated with accurate measurements of left main coronary artery atherosclerosis. It is well known that left main CAD is related to a patient's prognosis. Therefore, this carotid ultrasonographic finding may be associated with long-term prognosis. However, more research is needed on the correlation between the degree of carotid atherosclerosis and long-term prognosis.

A limitation of this study was that all patients had CAD. This selection bias meant that our findings regarding the relationship between carotid disease and left main CAD are relevant only to this specific group of patients and may not be applied to the general population.

Hypercholesterolemia and diabetes mellitus are known as important risk factors for the development of coronary atherosclerosis in Japan. In this study, however, male sex and hypertension were independent predictive factors rather than hypercholesterolemia and diabetes mellitus because all patients had CAD.

In conclusion, left main coronary artery atherosclerosis seems to be correlated with the average of the maximum common carotid IMT assessed by carotid ultrasonography as well as with men and the presence of hypertension. The average of the maximum common carotid IMT is the most important carotid ultrasonographic factor associated with left main coronary artery atherosclerosis.

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Intravascular Shear Stress Imaging Based on Ultrasonic Velocity Vector Measurement

Naotaka Nitta[1)], Kazuhiro Homma[1)] and Tsuyoshi Shiina[2)]

1)National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba 305-8564, Japan
2)Graduate School of Systems and Information Engineering, Univ. of Tsukuba, Tsukuba 305-8573, Japan

Abstract - It has been reported that the wall shear stress affects the biochemical function of endothelial cell and the development of arteriosclerosis plaque. Therefore, the quantitative estimation of the wall shear stress has possibilities to be useful for the prevention of arteriosclerosis. In this paper, a novel method for the real-time and quantitative estimation of intravascular shear stress distribution is proposed based on the estimates of the viscosity and the shear rate distribution.

Experimental investigation, in which two types of fluids with different viscosity coefficient (water, and water mixed by PVA) flowed at a constant flow rate in a silicone tube with a simulated arteriosclerosis plaque, was performed. After estimating the viscosity coefficient and the shear rate distribution based on the ultrasonic measurements of the velocity vector distribution in the tube, the shear stress distributions were obtained. The averaged value of the shear stress distribution estimated in the higher viscosity fluid (water mixed by PVA: 0.3 Pa) became larger than that in the lower viscosity fluid (water: 0.1 Pa). These results reveal that the proposed method is technically valid for the quantitative shear stress estimation.

I. INTRODUCTION

Relationships between the intravascular wall shear stress, which is controlled by both viscosity of blood and flow dynamics, and the development of arteriosclerosis plaque have been clarified by various researches. Some evidences, which support the hypothesis that the arteriosclerosis plaque occurs frequently at the intimal regions stimulated by the low shear stress or the oscillatory shear stress, are reported [1]. Furthermore, the influences of the shear stress to the vulnerable plaque rupture are also reported [2]. On the other hand, it is also reported that the wall shear stress affects the biochemical function of endothelial cell such as the production of nitric oxide (NO) which has an anti-arteriosclerosis effect [3]. Therefore, various researches have been investigated the shear stress assessment since it might be useful for the prevention of arteriosclerosis.

The methods for assessing the wall shear stress noninvasively are classified by two methodologies. One method is based on the computational mechanics, in which the 3-D vascular reconstruction using various modalities (X-ray CT, MRI, IVUS and angiography) and the computational fluid dynamics (CFD) are combined for obtaining the intravascular shear stress distribution [4]. The other method is based on the velocity profile measurements by MRI and ultrasound, in which the shear rate is evaluated by spatially differentiating the velocity profile along the radial direction [5], or the shear stress is obtained by the multiplication of the calculated shear rate and the predetermined viscosity coefficient, in which the viscosity coefficient is preliminarily measured by using blood sample after the drawing [6]. Most techniques evaluate the shear rate or the shear stress with the predetermined viscosity because the viscosity coefficient changes due to non-Newtonian property of blood. However, when the shear stress is defined by the Newton's law of viscosity, the local variation of viscosity coefficient might affect the quantitative shear stress estimation. Therefore, if a novel technique for the local shear stress assessment can be established by considering the viscosity assessment, it is expected to be a more quantitative shear stress assessment technique.

So far, in order to evaluate the blood characteristics as typified by its viscosity, we have investigated a method for estimating the kinematic viscosity coefficient based on the ultrasonic blood flow measurement [7]. In this study, by extending the method for kinematic viscosity estimation to the shear stress estimation, a novel method for the real-time and quantitative estimation of intravascular shear stress distribution is proposed.

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