

# Gender Differences in Clinical Confidence: A Nationwide Survey of Resident Physicians in Japan

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## Abstract

### Purpose

The number of women physicians is increasing in Japan. The authors investigated gender differences in self-perceptions of clinical confidence.

### Method

This cross-sectional study was conducted in March 2007 by using a stratified random sample of 1,124 second-year resident physicians. Residents' confidence levels were assessed, using four-point Likert scales (e.g., 1 for "not at all" to 4 for "very much"), in four competency sets: physical exams, procedural skills, interpretations of clinical tests, and physician-patient relationships and social service

application. Gender effect was investigated for clinical confidence levels by general linear models adjusting for age, types of hospitals, number of clinical experiences, satisfaction with residency conditions, future career, and perspectives on life and work.

### Results

The overall mean confidence scores in the four sets ranged between 2.9 and 3.1. Compared with men, women were younger ( $P = .001$ ), more likely to be oriented more to life than to work ( $P < .001$ ), less interested in doctor of medical science degrees ( $P = .001$ ), and less likely to be satisfied with residency conditions ( $P = .020$ ). A significantly greater

proportion of women chose "family" (70% versus 54% for men) as "the most important thing in life." Compared with men, women were less confident in the majority of competency areas even after adjusting for the number of clinical experiences.

### Conclusions

This nationwide resident survey demonstrated gender differences in clinical confidence levels. Future studies require careful monitoring of self-confidence and its impact on physicians' professional development.

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**T**oday in Japan, women constitute approximately 30% of all medical students (except at Tokyo Women's Medical College, which has only women students) and nearly half of the young physicians in some specialties such as obstetrics, gynecology, and pediatrics. In spite of the increasing number of women in medicine, one study reported a marked decline in workforce participation, especially among women physicians in their late 20s and 30s.<sup>1</sup> Not limited to

Japan, low participation rates among women physicians have also been reported in Western countries.<sup>2</sup> Women are more likely to work fewer hours and to be in part-time practice.<sup>2-4</sup> Thus, it is anticipated that the increase in number of women physicians may lead to a decrease in the full-time workforce.

Because women physicians may also have the social roles of housewives and mothers, they may devote more of their time to family responsibilities rather than to work. However, their low participation rates may not simply be accounted for by family constraints. On the contrary, Heiliger and Hingstman<sup>5</sup> reported that home domain characteristics did not predict a part-time preference in women physicians. McMurray et al<sup>6</sup> reported that the presence of children was associated with less work-related stress for women under the age of 45, and Frank et al<sup>7</sup> reported that physicians with children were more interested in again working as physicians. These studies suggest that multiple roles may bring benefits that mitigate work strain.

Nevertheless, many reports agree that women physicians work fewer hours than

do their male colleagues.<sup>2-4</sup> Several studies reported that women physicians were more likely to receive fewer rewards for their work, both in academic advancement and monetary compensation.<sup>3,4,8-12</sup> Such gender inequity favoring men may undermine women's self-esteem and result in difficulty in developing their potential competencies. For example, McMurray et al<sup>6</sup> reported that women physicians were more likely to have a lower level of work control in hospital practice than men, and this was significantly associated with burnout in women. Frank et al<sup>7</sup> also reported that women with work stress, lack of work control, and experience of harassment had a lower likelihood of being satisfied with their careers and of wishing to become physicians again even if given the choice.

The purposes of our study were (1) to determine whether a difference exists between men and women in levels of confidence about clinical competency among second-year residents in Japan and (2) to investigate the effect of gender on confidence levels after adjusting for basic resident characteristics, satisfaction,

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future career, and perspectives on life and work. The workplace in Japanese medicine is a male-dominated society, and there are still very few women professors in university settings or hospital director positions. Studying gender differences in self-perceptions of clinical confidence may reflect the impact of a male-oriented society on career development among women physicians. The results of our study may have important implications for potential involvement and retention of women physicians in the workforce.

## Method

### Japanese postgraduate medical education

In Japan, according to the Japanese Medical Practitioners Law, medical residents are not allowed to perform medical procedures independently until they have completed a six-year undergraduate program at a medical school and passed the National Board Examination to obtain a doctor's license. Therefore, the new Japanese postgraduate medical education (PGME) was designed to provide various clinical opportunities that allow residents to obtain primary care skills and knowledge.<sup>13</sup> In this regard, the Japanese PGME may be equivalent to the clinical rotation program for third- and fourth-year medical students in the United States.

### Study participants

During fiscal years 2005 through 2007, the Ministry of Health, Labor, and Welfare (the Ministry) organized a scientific study committee to evaluate the new, two-year, variable rotation PGME program. In each of the three years, the committee conducted surveys of residents and hospitals; scientific papers based on the surveys in 2006 and 2005 have already been published.<sup>14,15</sup>

The data from our study were obtained from the second-year survey conducted in March 2007. We sent the questionnaire to the 813 teaching hospitals accredited by the Ministry that year, asking the program directors to recruit one out of five of the 7,495 second-year residents (i.e., every fifth resident from the top of the roster in sequence). When fewer than five residents were listed on a roster, the first resident on the roster was asked to

answer the questionnaire. As a result, 1,880 residents became our target sample. Because the academic calendar in Japan starts on April 1 and ends on March 31 of the following year, our study participants were about to complete the two-year PGME program. The Ministry gave ethical approval for the study, and all participants provided informed consent.

### Questionnaire

The questionnaire consisted of 16 sections with a total of 23 questions. Sections included basic characteristics, hospital information, rotation schedule, on-call information, number of patients experienced, satisfaction, consultation, course after PGME, specialties, intention to obtain DMSc and specialist qualification, areas of interest, whether one is work- or life-oriented, the most important thing in life, clinical confidence, and clinical experience (including basic skills and knowledge, and medical documents). Of these, the variables we investigated in this study were basic characteristics including age, gender, and types of hospitals (i.e., university or community hospital); clinical experience; clinical competency; residents' satisfaction with residency conditions ("satisfied"/"not satisfied"/"do not know"); attributes related to satisfaction; future career, including areas of interest and an intention to obtain a DMSc and specialist qualification; and perspective on life and work (i.e., "work- or life-oriented" and "the most important thing in life").

Residents were queried regarding the number of cases they had encountered for 82 conditions, including the most common disorders and symptoms such as headache, infection, edema, difficulty breathing, hypertension, cardiopulmonary arrest, abdominal pain, liver and kidney disease, genital organ disease, trauma, burn, and suicide. Each item had four choices (1 = none, 2 = 1–5 cases, 3 = 6–10 cases, 4 = 11 or more cases), and the average of the 82 items was defined as the "clinical experience."

The clinical competency confidence scale included 99 items and measured residents' confidence levels based on a four-point Likert scale (i.e., 1 = "not confident at all/cannot perform at all," 2 = "not very confident/cannot perform independently," 3 = "somewhat

confident/may be able to perform independently," and 4 = "very confident/able to perform independently").

Residents were asked to rate satisfaction with residency conditions (options provided). Attributes included educational opportunities (i.e., excellence in teaching, clinical opportunities, teaching resources, and consultation system) and working conditions (i.e., workplace atmosphere, distasteful work, salary, cooperation among departments, and coordination with paramedical staff). Questions regarding areas of interest allowed the following options: "clinical practice," "education," "research," "administration," "others," and "do not know." Residents were asked whether they were work- or life-oriented using the question, "Which are you oriented to, work or life?" with the five-point Likert scale (1 = "very much work-oriented" to 5 = "very much life-oriented"). Options for the most important thing in life included "professional commitment," "academic records," "income," "skill improvement," and "family."

### Data analyses

Responses to the clinical experience items were further divided into two groups according to their respective medians and treated as binary variables. The clinical competency confidence scale was developed into a questionnaire to reflect the theoretical concepts of the new PGME. The new PGME<sup>13</sup> had three guiding principles: (1) to improve basic skills and knowledge of primary care and build core clinical competency in evaluating a patient as a whole, (2) to improve salary, and (3) to cultivate physicianship. Consequently, irrelevant items were excluded. The excluded items were those related to orthopedic surgery and radiology, because these subjects were not core requirements, and those related to pediatrics, psychiatry, and obstetrics-gynecology, because items in these areas are skewed on a specific domain of content. We grouped the remaining items into four skill categories: physical exams (8 items), procedural skills (8 items), interpretation of clinical tests (11 items), and physician-patient relationships and social service application (7 items).

Each score, as well as overall scores, in the four clinical skill sets were assessed for gender by a *t* test. The internal

**Table 1**  
**Characteristics of 1,120 Second-Year Residents, Comparing Men and Women, Residency Survey in Japan, 2007\***

Characteristic	Men (n = 776) n (%)	Women (n = 344); n (%)	P value
<b>Basic characteristics</b>			
Age, mean (SD)	28 (0.1)	27 (0.2)	.001
Type of hospitals			.03
University hospitals	276 (36)	146 (42)	
Community hospitals	500 (64)	198 (58)	
Clinical experience			.64
Higher group	558 (72)	252 (73)	
Lower group	218 (28)	92 (27)	
<b>Satisfaction</b>			
Overall satisfaction with residency conditions			.02
Satisfied	465 (61)	177 (53)	
Not satisfied	194 (25)	96 (28)	
Do not know	105 (14)	64 (19)	
Attributes—overall satisfaction (multiple answers)			
Educational opportunities			
Excellence in teaching	405 (52)	187 (54)	.50
Clinical opportunities	353 (45)	151 (44)	.62
Teaching resources	165 (21)	65 (19)	.37
Consultation system	144 (19)	53 (15)	.20
Working conditions			
Atmosphere at workplace	377 (49)	194 (56)	.02
Scut work	215 (28)	100 (29)	.64
Salary	218 (28)	70 (20)	<.01
Cooperation among departments	190 (24)	66 (19)	.05
Coordination with paramedical staff	243 (31)	98 (28)	.34
<b>Future career</b>			
Area interested (multiple answer)			
Clinical practice	732 (94)	331 (96)	.18
Education/research/administration	166 (21)	45 (13)	.001
Others/do not know	30 (4)	13 (4)	.94
Intention to obtain specialist qualification			.18
Yes	719 (93)	326 (95)	
No	20 (3)	3 (1)	
Do not know	34 (4)	15 (4)	
Intention to obtain doctor of medical science			
Yes	306 (40)	96 (28)	.000
No	215 (28)	127 (37)	
Do not know	250 (32)	119 (35)	
<b>Perspectives on life and work</b>			
Work- or life-oriented			<.0001
Life-oriented	120 (16)	109 (32)	
Work-oriented	231 (30)	45 (13)	
Between	415 (54)	190 (55)	
The most important thing in a life			<.0001
Family	361 (54)	211 (70)	
Academic records/income/skill improvement	129 (20)	36 (12)	
Professional commitment	173 (26)	54 (18)	

\* Missing data: sex (4), satisfaction (19), specialist qualification (3), doctor of medical science (7), work- or life-oriented (10), the most important thing (156).

consistency reliability of the confidence questionnaire was calculated using item-total correlation and Cronbach alpha. The content validity of the questionnaire was assessed by 10 PGME experts. These experts were asked whether each item (1) reflected the theoretical concepts of PGME, (2) evaluated basic skills and knowledge in primary care, and (3) was clearly understandable. The expert group consisted of a professor at a national university, a professor at a private university, two deans of teaching hospitals, two PGME program directors at teaching hospitals, two medical officers from the Ministry's Office for Clinical Training Medical Professions, and two primary care physicians. Residents' basic characteristics, satisfaction, future career, and perspectives on life and work were assessed between men and women by chi-square tests for categorical variables and *t* tests for continuous variables. The details of each variable are shown in Table 1. Finally, to investigate the effect of gender on resident confidence levels, we used general linear regression models, adjusting for age, types of hospitals, clinical experience, and satisfaction with residency conditions. We computed beta coefficients that reflected an increase or decrease in a unit of clinical confidence levels in the four skill areas.

We conducted analyses using SAS version 8.12 for Windows (SAS Institute, Cary, North Carolina). All tests were two sided, with a significance level of 0.05 using the Wald chi-square test.

## Results

A total of 1,124 residents agreed to participate in this study (a response rate of 60%). Nevertheless, we were unable to determine the sex of four of the residents, and therefore the number of the study participants for analyses was 1,120.

### Scores for confidence levels in the four skill sets between men and women

The scores of the responding 1,120 residents are reported in Table 2. The internal consistency values of the four skill sets for measures of clinical competency were adequate:  $\alpha = 0.83$  in physical exams,  $\alpha = 0.86$  in procedural skills,  $\alpha = 0.88$  in interpretation of clinical tests, and  $\alpha = 0.87$  in physician-patient relationships and social service application. The item-total correlations were all positive and ranged from 0.41 to

Table 2

**Scores of 1,120 Second-Year Residents' Confidence Levels in Four Skill Groups of Clinical Competency, Residency Survey in Japan, 2007\***

	Mean		Mean difference (95% CI)
	Men	Women	
<b>Physical exam skills (<math>\alpha = 0.83</math>)<sup>†</sup></b>			
Overall	3.11	3.00	0.11 (0.06 to 0.17)
History taking	3.32	3.31	0.01 (-0.06 to 0.07)
Vital sign	3.59	3.58	0.02 (-0.05 to 0.09)
Thyroid	2.80	2.76	0.03 (-0.06 to 0.11)
Heart auscultation	3.01	2.88	0.13 (0.05 to 0.21)
Lung auscultation	3.19	3.06	0.13 (0.06 to 0.20)
Heart apex beat palpation	3.16	3.10	0.07 (-0.02 to 0.15)
Resistance on abdomen	3.30	3.16	0.16 (0.09 to 0.24)
Digital prostate exam	2.55	2.18	0.38 (0.27 to 0.48)
<b>Procedural skills (<math>\alpha = 0.86</math>)<sup>†</sup></b>			
Overall	3.40	3.27	0.12 (0.06 to 0.18)
Technique for drawing venous blood	3.64	3.66	-0.02 (-0.09 to 0.04)
Technique for drawing arterial blood	3.65	3.64	0.01 (-0.06 to 0.08)
Lumbar puncture technique	3.22	2.97	0.26 (0.16 to 0.36)
Urinary catheterization	3.50	3.53	-0.03 (-0.11 to 0.04)
Chest compressions	3.54	3.47	0.06 (-0.01 to 0.14)
Intubation	3.39	3.23	0.16 (0.08 to 0.24)
Lung ventilation	3.05	2.76	0.29 (0.20 to 0.39)
Electric defibrillator	3.20	2.92	0.28 (0.19 to 0.37)
<b>Interpretation of clinical tests (<math>\alpha = 0.88</math>)<sup>†</sup></b>			
Overall	3.06	2.94	0.11 (0.05 to 0.17)
Urinalysis	2.36	2.33	0.02 (-0.10 to 0.15)
Stool test for occult blood	3.05	2.98	0.06 (-0.04 to 0.16)
Arterial blood gas	3.33	3.21	0.12 (0.05 to 0.19)
Complete blood count	3.39	3.31	0.09 (0.02 to 0.16)
A battery of blood chemistry tests	3.37	3.27	0.10 (0.03 to 0.17)
Coag panel	3.27	3.14	0.13 (0.05 to 0.20)
Immunology tests	2.98	2.88	0.10 (0.01 to 0.19)
Endocrine tests	2.71	2.61	0.11 (0.02 to 0.20)
Cerebral fluid tests	2.91	2.69	0.22 (0.13 to 0.31)
ECG	3.13	2.92	0.21 (0.13 to 0.29)
Spirometry	3.13	3.01	0.13 (0.05 to 0.21)
<b>Physician-patient relationship and social service application (<math>\alpha = 0.87</math>)<sup>†</sup></b>			
Overall	2.92	2.86	0.06 (-0.01 to 0.12)
Patients' interpretative models	3.30	3.27	0.03 (-0.04 to 0.09)
Nonverbal communication	3.24	3.20	0.04 (-0.04 to 0.11)
Psychosocial care of patients	2.93	2.90	0.03 (-0.06 to 0.11)
Medical fees and social welfare service	2.63	2.54	0.08 (-0.02 to 0.18)
Collaboration with social workers	2.75	2.69	0.06 (-0.04 to 0.15)
Health education	2.92	2.85	0.07 (-0.01 to 0.15)
Social service application	2.64	2.54	0.11 (0.01 to 0.20)

\* Confidence levels were based on a four-point Likert scale (1 = "not confident at all/cannot perform at all"; 2 = "not very confident/cannot perform independently"; 3 = "somewhat confident/may be able-perform independently"; and 4 = "very confident/able-perform independently").

<sup>†</sup> Cronbach alpha coefficients.

0.70 for physical exams, 0.55 to 0.73 for procedural skills, 0.40 to 0.73 for interpretations of clinical tests, and 0.48 to 0.70 for physician-patient relationships and social service application. Because the deletion of any item would not result in an increase in Cronbach alpha of more than 0.01, we decided to retain all items in each group of competency skills. The content validity of the questionnaire was confirmed by the independent decision of all 10 PGME experts. Each expert felt that every question for each item reflected the theoretical concepts of PGME, evaluated basic skills and knowledge in primary care, and was clearly understandable.

The overall mean confidence scores in the four skill sets ranged between 2.9 and 3.1. When stratified by gender, the scores were generally higher in men than in women in physical exam skills, procedural skills, and interpretation of clinical tests. In contrast, the gap of scores between men and women narrowed in physician-patient relationships and social service application.

#### Basic characteristics, satisfaction, future career, and perspectives on life and work between men and women

Basic characteristics of the responding residents, comparing men and women, are shown in Table 1. The mean age of the residents was 28 years, and the majority of the participants were male ( $n = 776$ , 69%) and chose community hospitals ( $n = 706$ , 63%). The mean level of clinical experience was 3.15 on an ordinal scale where 3 indicated "6-10 cases" and 4 indicated "11 or more cases."

Women were found to be younger than men ( $P = .001$ ) and more likely to choose university hospitals for their residency ( $P = .029$ ). Men were more likely than women to be satisfied with residency conditions ( $P = .020$ ), and their attribution for their satisfaction was significantly different in the areas of workplace atmosphere, salary, and cooperation between departments. Both men and women chose clinical practice as area of interest, but men were found to be more interested than women in education/research/administration ( $P = .001$ ). Similarly, more men than women reported that they intended to obtain a DMSc degree ( $P = .001$ ). On the other

hand, with regard to perspectives on life and work, nearly half of both men and women reported that they value both their personal lives and work; among the others, 30% of men ( $n = 231$ ) versus only 13% of women ( $n = 45$ ) reported that they were more work-oriented ( $P < .001$ ). A markedly greater proportion of women than men chose "family" (70% versus 54%) as "the most important thing in life," followed by "professional commitment" (18% versus 26% for women and men, respectively,  $P < .0001$ ).

#### General linear model results of the gender effects on residents' confidence levels

Table 3 presents general linear model results of the gender effects on residents' confidence levels. After adjusting for age, clinical experience, types of hospitals, satisfaction with residency conditions, future career, and perspectives on life and work, women were found to be less confident compared with men about all skill sets except for physician-patient relationship and social service application (all  $P < .05$ ). Although identification as "life- or work-oriented" was not a significant contributor to confidence levels, designation of "the most important thing in life" was marginally significant (data not shown); compared with residents who reported "academic records," "income," or "skill improvement" as most important, residents reporting "family" were found to be less confident about their interpretation of clinical tests ( $P = .086$ ). No significant interaction of confidence levels with gender and other factors was found.

#### Discussion

Our results demonstrate that women were less likely than men to be confident about the majority of clinical skill sets except for physician-patient relationships and social service application, even after adjusting for number of clinical opportunities experienced. Gender differences were also identified in the basic characteristics of residents' satisfaction with residency conditions, future career, and perspectives on life and work. We discuss our results in light of their strengths and limitations while referring to the previous literature.

Previous studies both at clinical practice settings<sup>16,17</sup> and at research settings<sup>18</sup> reported that women tend to underestimate their abilities, although they perform better than men.<sup>16-18</sup> Such lower self-perceptions of competency among women may be accounted for by psychological vulnerability in women. Two studies reported that such vulnerability starts during medical school. Moffat et al<sup>19</sup> reported that female students had greater stress about workload and personal competence, and Dahlin and Runeson<sup>20</sup> reported that women worried about their future workload, citing issues like long working hours and responsibility in their careers. Gude et al<sup>21</sup> suggested that the role of the doctor is traditionally more male than female in its characteristics of being active, dominating, and responsible as opposed to passive, submissive, and dependent, and women may therefore have a lower level of role identification than do men. Alternatively, such vulnerability may result from gender inequity in the workplace. For example,

McMurray et al<sup>6</sup> reported that women had less work control than men, which significantly contributed to burnout among women physicians. A few studies investigating gender inequity reported that women receive less institutional support for research,<sup>9</sup> fewer mentoring opportunities,<sup>22</sup> and fewer academic resources<sup>23</sup> than men. In this regard, our study showed that women seemed to be less satisfied with residency conditions than were men. However, no gender difference was found in educational opportunities. Women seemed to be more satisfied than men with the "workplace atmosphere," and this relationship contradicted the idea that gender climate favors male physicians. These findings may be explained by the characteristics of our study subjects; they were second-year residents who were not yet eligible to do research and who were in a rotation period too short for them to yet perceive the gender climate in the workplace that might create specific obstacles to professional development.

Lower levels of clinical confidence among women residents were observed in the majority of clinical skill sets; however, the gap between men and women narrowed in the area of the physician-patient relationship (i.e., understanding of patients' interpretative models, nonverbal communication performance, psychosocial care of patients, and health education in compliance with the levels of patient knowledge and interests). Although the scores for confidence in physician-patient relationship seemed lower among men than those of other skill groups, such narrowed differences between men and women may be explained by the findings of previous studies that women physicians are good at listening and counseling, that is, at skills that build trusting relationships between physicians and patients.<sup>24-26</sup> Women physicians facilitate patient participation in the medical exchange more effectively than do men and are more likely to engage their patients in discussions of their social and psychological contexts and to deal more often with feelings and emotions. This is consistent with the results of previous studies, most of which were conducted in Western countries, verifying the clinical advantage of women physicians in this domain.

Table 3

#### General Linear Model Results of Gender Effect on Confidence Levels of 1,120 Second-Year Residents in Four Skill Sets of Clinical Competency, Residency Survey in Japan, 2007

The four clinical skill sets	Women versus men					
	Univariate			Multivariate*		
	$\beta$	SE	P	$\beta$	SE	P
Physical exam skills	-.114	.028	<.0001	-.093	.030	<.01
Procedural skills	-.123	.030	<.0001	-.084	.032	<.01
Interpretation of clinical tests	-.113	.030	.000	-.083	.033	.01
Physician-patient relationship and social service application	-.059	.033	.07	-.012	.036	.73

\* Adjusting for age, clinical experience, types of hospitals, satisfaction with residency conditions, future career, and perspectives on life and work.

The strength of this study is that it is a nationwide survey with a relatively large sample size, but several study limitations need to be discussed. First, the gender differences we observed might be accounted for by a selection bias. Overconfident residents may have been preferentially selected among male peers relative to their female peers. However, this scenario is unlikely because the study is a nationwide resident survey with a random sampling method. According to the Ministry,<sup>27</sup> 5,019 (66%) men and 2,549 (34%) women passed the National Board Examination for a doctor's license in 2005 and started residency. Although the number of responses by gender was not available in our dataset, the gender ratio in 2005 was comparable with that of our study subjects. Second, our study showed that only 13% of women residents reported they were more work-than life-oriented; a significant proportion of women residents chose "family" as "the most important thing in life." These findings might have been due to generational differences. The Women Physicians Health Study<sup>7</sup> reported that older women physicians in the United States attained greater job satisfaction and had only vague recall of training's rigor, showed "pioneer pride," or belonged to a cohort of "survivors." By contrast, our study participants were limited to young residents, a fact that requires careful interpretation. Third, although one of our hypotheses included the possibility that lower confidence levels may have a negative impact on career development, the findings indicated that perspectives on life and work were not significantly associated with confidence levels. In this regard, it is suggested that a more precise and direct measure to assess the negative impacts of lower confidence levels needs to be developed. Finally, because of the cross-sectional nature of this study, a causal relationship is difficult to determine. Our results might not truly demonstrate definite relationships but, rather, reflect surrogate indicators of unknown factors.

In spite of these limitations, our study demonstrated that women residents in Japan are less likely to be confident about some basic skills and knowledge than are men, even adjusting for the number of clinical experiences. Previous studies suggested that lower confidence levels

may have negative impacts on career satisfaction and even on decision making about continuing in the profession. The gender difference in clinical confidence may thus indicate an additional barrier women face in academic career development. Given that the number of women entering medicine is increasing, to attract and retain more women into the physician workforce, studies in this area require careful monitoring of self-confidence and further assessments. In this regard, quantitative research is useful for investigating the impact of lower confidence levels among women on their professional development, whereas qualitative research is useful for unveiling factors that influence the underestimation of self-confidence. In addition, an education program incorporated into the residency program that addresses gender difference is also important for helping young women physicians overcome barriers to career development in their future.

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Hitoshi Nakagawa, Yoshinobu Morikawa, Yuji Mizuno, Eisaku Harada, Teruhiko Ito, Kunihiro Matsui, Yoshihiko Saito and Hirofumi Yasue

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# Coronary Spasm Preferentially Occurs at Branch Points

## An Angiographic Comparison With Atherosclerotic Plaque

Hitoshi Nakagawa, MD; Yoshinobu Morikawa, MD; Yuji Mizuno, MD; Eisaku Harada, MD; Teruhiko Ito, MD; Kunihiko Matsui, MD, MPH; Yoshihiko Saito, MD; Hirofumi Yasue, MD

**Background**—Coronary spasm plays an important role in the pathogenesis of ischemic heart disease. However, similarities and differences between coronary spasm and atherosclerosis are not known. We examined the angiographic characteristics of coronary spasm in comparison with those of atherosclerosis.

**Methods and Results**—Thirty-two left anterior descending arteries, 11 left circumflex arteries, and 23 right coronary arteries with spasm and atherosclerotic plaque were analyzed for the localization of spasm in comparison with that of plaque in 47 patients (38 men and 9 women, mean age  $66.8 \pm 10.3$  yrs). Spasm predominantly occurred at the branch point as compared with plaque in each of the 3 arteries (76.7% versus 23.3%,  $P < 0.0001$ ; 72.7% versus 9.1%,  $P < 0.039$ ; and 60.0% versus 10.0%,  $P = 0.002$ , in the left anterior descending, left circumflex, and right coronary arteries, respectively). Spasm involved the proximal segment less frequently as compared with plaque in each of the 3 arteries (56.7% versus 93.3%,  $P < 0.0001$ ; 18.2% versus 81.8%,  $P = 0.016$ ; and 15.0% versus 75.0%,  $P < 0.0001$  in the left anterior descending, left circumflex, and right coronary arteries, respectively). Most spasms occurred at the nonplaque site in each of the 3 arteries (73.3%,  $P = 0.018$ ; 100%,  $P < 0.0001$ ; and 75.0%,  $P = 0.041$  in the left anterior descending, left circumflex, and right coronary arteries, respectively).

**Conclusion**—Coronary spasm preferentially occurred at branch points and nonplaque sites, whereas the atherosclerotic lesion was predominantly localized at the nonbranch points of the curved proximal segments. Coronary spasm may thus be a manifestation of a distinct type of arteriosclerosis different from the lipid-laden coronary atherosclerosis. (*Circ Cardiovasc Intervent.* 2009;2:97-104.)

**Key Words:** atherosclerosis ■ coronary spasm ■ endothelium ■ nitric oxide ■ vasoconstriction

Coronary spasm is not only the cause of variant angina but also participates in the pathogenesis of unstable angina, acute myocardial infarction, and sudden death, particularly in Japan.<sup>1-3</sup> However, precise mechanisms by which coronary spasm occurs are not fully understood. We have shown that endothelial nitric oxide (NO) activity is deficient and endothelial function is impaired in the coronary arteries involved in spasm.<sup>4</sup> Endothelial NO enhances vascular functions, including vessel relaxation, survival of vascular endothelial cells, inhibition of platelet aggregation, and attenuation of leukocyte infiltration.<sup>5,6</sup> Impaired NO activity has been suggested as the earliest pathophysiological events contributing to atherosclerosis.<sup>7,8</sup>

shear stress reduces it.<sup>5,9,10</sup> Although the entire vasculature is exposed to the atherogenic effect of systemic risk factors, atherosclerotic lesions form at specific arterial regions such as curvatures or branch sites where flow is disturbed.<sup>9,10</sup> Thus, local hemodynamic factors play a major role in the regional localization of atherosclerosis. It is, therefore, possible that coronary spasm also may preferentially occur at the sites of coronary arterial tree where flow is disturbed. However, no previous studies have examined this possibility and the relationship between coronary spasm and atherosclerosis is not clear. This study was designed to examine whether there are predilection sites for spasm in the coronary arteries and, if there are, whether these sites are similar to those of atherosclerosis.

### Clinical Perspective see p 104

Flow-generated shear stress is an important physiological stimulus that enhances the production of NO and high shear stress augments the bioavailability of NO, whereas disturbed

### Methods

#### Patients

Ninety-eight (67 men and 31 women, with a mean age of  $65.5 \pm 10.1$  years ranging from 35 to 86) Japanese patients in whom coronary

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**Table 1. Clinical Characteristics of the Study Subjects**

Variables	Normal Angiogram Group (n=51)	Atherosclerosis Group (n=47)
Age, yr	64.2±9.5	66.8±10.3
Gender (male/female)	29/22	38/9
Body mass index, kg/m <sup>2</sup>	24.3±3.8	24.2±3.4
Hypertension	19/51 (37%)	25/47 (53%)
Diabetes mellitus	8/51 (16%)	17/47 (36%)
History of smoking	32/51 (63%)	28/47 (60%)
Leukocyte, per $\mu$ L	6,160±1,668	6925±1944
Hemoglobin, g/dL	13.6±1.7	14.0±2.1
Platelet, $\times 10^4/\mu$	24.1±8.0	24.8±7.5
CRP, mg/L*	0.99 (0.32–2.81)	2.00 (0.48–3.52)
Total protein, g/dL	6.6±0.4	6.8±0.6
Albumin, g/dL	3.9±0.3	3.9±0.4
Fast plasma glucose level, mmol/L	5.86±1.51	5.69±1.01
AST, u/L	25.2±11.0	26.1±8.6
ALT, u/L	22.6±14.5	23.8±11.8
CK, u/L	105.4±71.8	106.7±71.3
Total cholesterol, mmol/L	5.11±0.81	5.35±1.00
LDL cholesterol, mmol/L	2.98±0.74	3.32±0.84
HDL cholesterol, mmol/L	1.54±0.40	1.32±0.38
Triglyceride, mmol/L	1.52±0.70	1.71±0.65

\*Median (25th and 75th percentile). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

spasm was induced by intracoronary injection of acetylcholine (ACh; Daiichi-Sankyo Co, Tokyo, Japan) were the subjects of this study. They had been admitted to our hospital because of chest pain or ECG abnormalities suspected of ischemic heart disease between January 2003 and January 2009. The study consisted of the 2 parts: the first part of the 51 patients with normal or almost normal coronary angiogram (<25% stenosis of luminal diameter) in whom the confounding effect of organic stenosis on coronary flow could be excluded (normal angiogram group) and the second part of the 47 patients with organic stenosis (25% to 90% stenosis of luminal diameter) (atherosclerosis group) based on the consensus of 3 to 4 investigators. We defined coronary spasm as a total or subtotal occlusion or severe diffuse constriction of an angiographically demonstrable coronary artery associated with transient ischemic ST segment changes on ECG. In each spasm artery, we defined the site of spasm as that of total or subtotal occlusion or as that of the most severe and proximal constriction in the case of segmental diffuse or multifocal spasm and the site of atherosclerotic lesion (plaque) as the most narrowed based on the consensus of 3 to 4 investigators. Patients with recent myocardial infarction, acute coronary syndrome, left main trunk disease, severe organic stenosis of >90%, multivessel coronary disease with >75% organic stenosis, heart failure, liver disease, creatinine level >1.5 mg/dL, acute inflammation, malignant diseases, and cholesterol lowering medication within a month were excluded from the study. None of the study patients were on statins or other lipid-lowering drugs. The clinical characteristics of the study patients are presented in Table 1. Hypertension was defined as >140/90 mm Hg and diabetes mellitus as fasting plasma glucose level >7 mmol/L (126 mg/dL) or 2-hour postload glucose level >11.1 mmol/L (200 mg/dL).

The protocol of this study was approved by the institutional review board and each patient provided written informed consent.

## Induction of Coronary Spasm

Ca-channel blockers and other vasodilators, if they had been administered, were stopped for at least 5 days. Coronary spasm was induced by intracoronary injection of ACh (Daiichi-Sankyo Co) after diagnostic catheterization in the morning. The details of the method were previously reported.<sup>11</sup> Briefly, ACh was injected in incremental doses of 20, 50, and 100  $\mu$ g into the left coronary artery and then 20 and 50  $\mu$ g into the right coronary artery (RCA) in 20 seconds under continuous monitoring of ECG and blood pressure. Coronary spasm induced by this method usually disappeared spontaneously within 1 to 2 minutes and both the left coronary artery and RCA could be examined separately unless severe spasm occurred in the left coronary artery and necessitated the prompt injection of isosorbide dinitrate (ISDN) into the arteries. After the end of the test, ISDN (0.1 mg) was injected into the coronary artery and angiography was again performed. The specificity of this test for variant or resting angina was 99%.<sup>12</sup> The test did not induce coronary spasm in any of the patients with normal coronary angiogram and without ischemic heart disease.<sup>12,13</sup> The specificity of this test for spasm arteries was also confirmed in the *in vitro* study.<sup>14</sup>

## Assessment of Coronary Artery Diameter and Length

We quantitatively measured the diameter of the coronary arteries and the distance from the branch point. An end-diastolic frame was digitized and the diameter of the index vessel was measured by CAAS II software (PIE Medical). We defined the branch point segment as that within 5-mm distal from the apex of the flow divider because the median distance between each adjacent branch was 14.3 mm (interquartile range was 9.1 to 21.1 mm). We divided the left anterior descending (LAD) artery, the left circumflex (LCx) artery, and the RCA into the proximal segments (segments 6, 7, and 9 in the LAD; segments 11 to 13 in the LCx; and segments 1 to 2 in the RCA) and the distal segments (segments 8 and 10 in the LAD; segments 14 and 15 in the LCx; and segments 3 and 4 in the RCA) according to the AHA coronary segment reporting system<sup>15</sup> and compared the incidence of spasm between the proximal and distal segments. The coronary diameter was expressed as percent narrowing in luminal diameter after ISDN injection. Total or subtotal obstruction or severe coronary spasm with a lumen diameter <0.4 mm could not be accurately quantified because of technical limitations of the computer-assisted quantitative coronary angiography.<sup>16</sup>

## Laboratory Methods

Fasting blood samples were drawn by venipuncture 1 to 2 days before coronary angiography and the hematologic and biochemical analyses were done using standard laboratory procedures.

## Statistical Analysis

Each of the 3 coronary arteries (LAD, LCx, and RCA) was separately analyzed. Discrete variables were expressed as counts and percentages and were compared using McNemar or binomial exact test between the paired data of the same artery. Probability value of <0.05 was considered to be statistically significant. Continuous data were expressed as mean±SD. However, when the variable was significantly skewed, the median (25th to 75th percentile) was reported. Statistical analysis was performed by using commercially available software (SPSS STATISTICS 17.0 BASE WIN, SPSS Japan Inc, Tokyo, Japan). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

## Results

Table 2 shows the coronary angiographic findings of the 2 groups. In the normal angiogram group, spasm was induced in 106 (45, 28, and 33 in the LAD, LCx, and RCA, respectively) arteries. Of these, 9 (8.5%) were total occlusion, 18 (17.0%) subtotal occlusion, 50 (47.2%) segmental diffuse

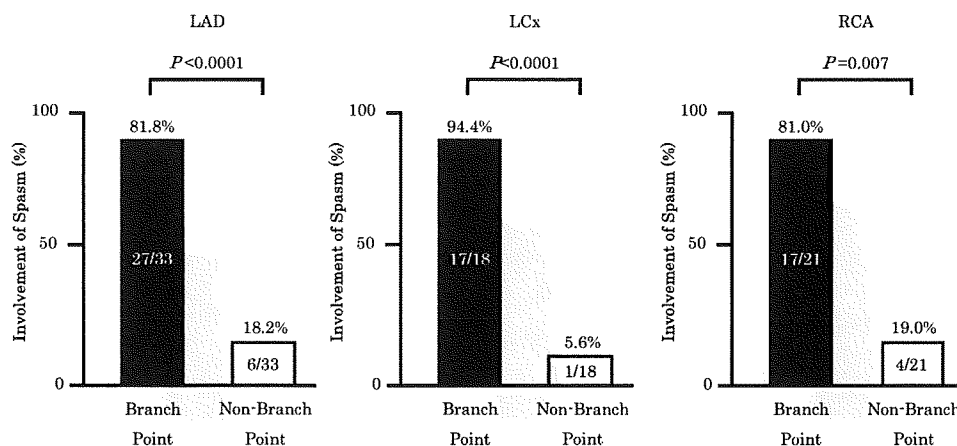
**Table 2. Coronary Angiographic Findings**

	Normal Angiogram Group Spasm Site (n=106)	Atherosclerosis Group Spasm Site (n=66)	P	Plaque Site (n=66)
<b>Entire artery spasm</b>				
LAD, n	12	2		2
LCX, n	10	0		0
RCA, n	12	3		3
Total, n	34	5		5
<b>LAD, n</b>				
LAD, n	33	30		30
Proximal segment, n (%)	23 (69.7)	17 (56.7)	<0.0001	28 (93.3)
<b>LCX, n</b>				
LCX, n	18	11		11
Proximal segment, n (%)	12 (66.7)	2 (18.2)	0.016	9 (81.8)
<b>RCA, n</b>				
RCA, n	21	20		20
Proximal segment, n (%)	4 (19.0)	3 (15.0)	<0.0001	15 (75.0)
Total, n	72	61		61

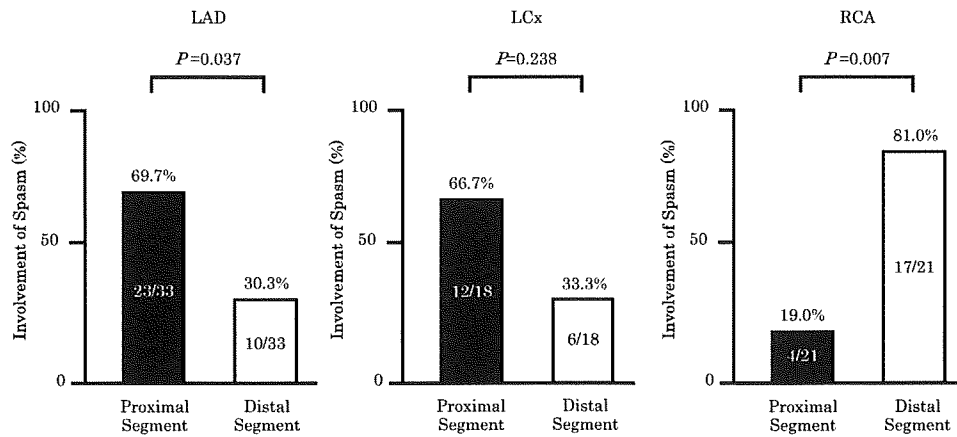
LAD indicates left anterior descending artery; LCA, left coronary artery; LCX, left circumflex artery; RCA, right coronary artery.

spasm involving the branch site and 29 (27.4%) diffuse and extensive spasm involving the entire arterial tree affecting the proximal and distal epicardial vessels and their branches. Five shifted from entire artery spasm into total occlusion. Accordingly, 34 (32.1%) of the 106 spasms involved the entire arterial tree in this group. Spasm of 1 vessel, 2 vessels, and 3 vessels was demonstrated in 16, 15, and 20 patients, respectively. Of the 44 patients in whom ACh was injected into both the left coronary artery and RCA, 15 had 1-vessel, 9 had 2-vessel, and 20 had 3-vessel spasm, and thus most (65.9%) patients had multivessel coronary spasm demonstrated. For the analysis of the localization of spasm at branch or nonbranch point, 34 (12 LAD, 10 LCx, and 12 RCA) entire artery diffuse spasms were excluded and the remaining 72 arteries (33 LAD, 18 LCx, and 21 RCA) were analyzed. Spasm occurred at the branch point in 27 (81.8%) of 33 LAD, 17 (94.4%) of 18 LCx, and 17 (81.0%) of 21 RCA. Coronary spasm thus preferentially occurred at the branch point in all of the 3 arteries (Figure 1). Spasm involved the proximal segment in 23 (69.7%) of the 33 LAD, 12 (66.7%) of the 18 LCx, and 4 (19.0%) of the 21 RCA. Thus, spasm occurred more frequently at the proximal than the distal segments in

the LAD, whereas it occurred more frequently at the distal than the proximal segments in the RCA (Figure 2). This is probably related to the fact that branch site is more numerous at the proximal segment in the LAD, whereas it is more numerous at the distal segment in the RCA<sup>15</sup> and confirms the close relation of the branch point to spasm. In the atherosclerosis group, the organic stenosis was identified in the 66 (32 LAD, 11 LCx, and 23 RCA) arteries as shown in Table 2. Of these, 52 (22 LAD, 8 LCx, and 22 RCA) arteries had 25% to 75% and 14 (10 LAD, 3 LCx, and 1 RCA) arteries had 75% to 90% luminal diameter narrowing. Thus, most (78.8%) patients had mild to moderate organic stenosis in the atherosclerosis group. Spasm was induced in 66 (32 LAD, 11 LCx, and 23 RCA) arteries. Of these, 6 (9.1%) were total occlusion, 9 (13.6%) were subtotal occlusion, 48 (77.2%) were segmental diffuse spasm, and 3 (4.5%) were entire artery diffuse spasm. Two shifted from entire artery diffuse spasm into total occlusion. Accordingly, the entire artery diffuse spasm occurred in 5 (7.6%) of the 66 spasms in the atherosclerosis group (Table 2). For the analysis of the localization of spasm at the branch or nonbranch points, 5 entire artery diffuse spasms were excluded and the remaining 61 (30 LAD, 11



**Figure 1.** Comparison of the involvement of coronary spasm between the branch and nonbranch points in the normal angiogram group. LAD, left anterior descending coronary artery; LCx; left circumflex artery; RCA, right coronary artery.



**Figure 2.** Comparison of the involvement of coronary spasm between the proximal and distal segments in the normal angiogram group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

LCx, and 20 RCA) were analyzed for comparison of localization between spasm and plaque in the atherosclerosis group. Spasm occurred at the branch site in 23 (76.7%) of the 30 LAD, 8 (72.7%) of the 11 LCx, and 12 (60.0%) of the 20 RCA. These results are in agreement with those in the normal angiogram group. On the other hand, plaque was localized at the branch point in only 7 (23.3%) of the 30 LAD, 1 (9.1%) of the 11 LCx, and 2 (10.0%) of the 20 RCA. Thus, there was a significant difference in the involvement of the branch point between spasm and plaque in each of the 3 arteries ( $P < 0.0001$  in LAD,  $P = 0.039$  in LCx, and  $P = 0.002$  in RCA, respectively) (Figure 3). Spasm involved the proximal segment in 17 (56.7%) of the 30 LAD, 2 (18.2%) of the 11 LCx, and 3 (15.0%) of the 20 RCA, whereas plaque was localized at the proximal segment in 28 (93.3%) of the 30 LAD, 9 (81.8%) of the 11 LCx, and 15 (75.0%) of the 20 RCA. Thus, there was a significant difference in the involvement of the proximal segment between spasm and plaque in each of the 3 arteries ( $P < 0.0001$  in LAD,  $P = 0.016$  in LCx, and  $P < 0.0001$  in RCA, respectively) (Figure 4). In accordance with these results, most spasms occurred at the nonplaque site in each of the 3 arteries ( $P = 0.018$  in LAD,  $P < 0.0001$  in LCx, and  $P = 0.041$  in RCA, respectively) (Figure 5). Spasm thus preferentially occurred at branch points and nonplaque sites, whereas the plaque preferentially occurred at nonbranch point

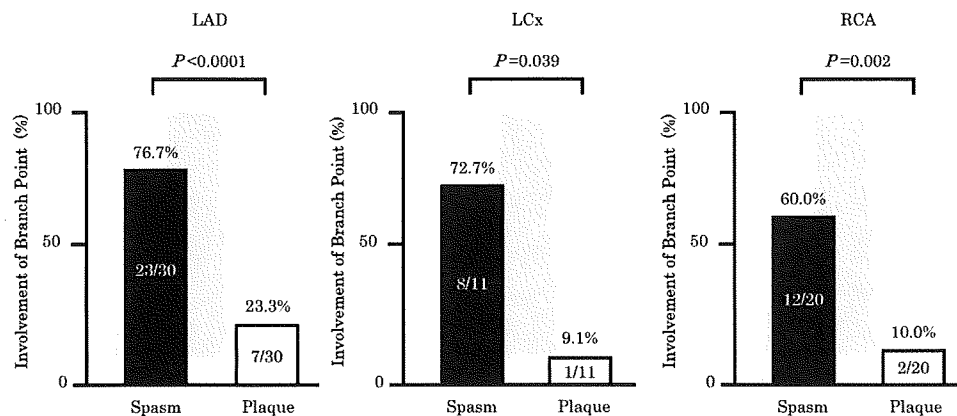
sites of the proximal segment in each of the 3 coronary arteries. Paired data using  $2 \times 2$  tables for Figures 1 to 5 are shown in Online Data supplements.

Nineteen (17.9%) of the 106 spasms in the normal angiogram group and 11 (16.7%) of the 66 in the atherosclerosis group were associated with ST-segment elevation and the 87 (82.1%) and 55 (83.3%) with ST-segment depression on the ECG, respectively, indicating that coronary spasm with ST-segment depression is more numerous than that with ST-segment elevation in both groups ( $P < 0.0001$ , respectively). Of the 11 spasms with ST-segment elevation, 8 (72.7%) involved the organic stenosis and 8 were total or subtotal occlusion in the atherosclerosis group.

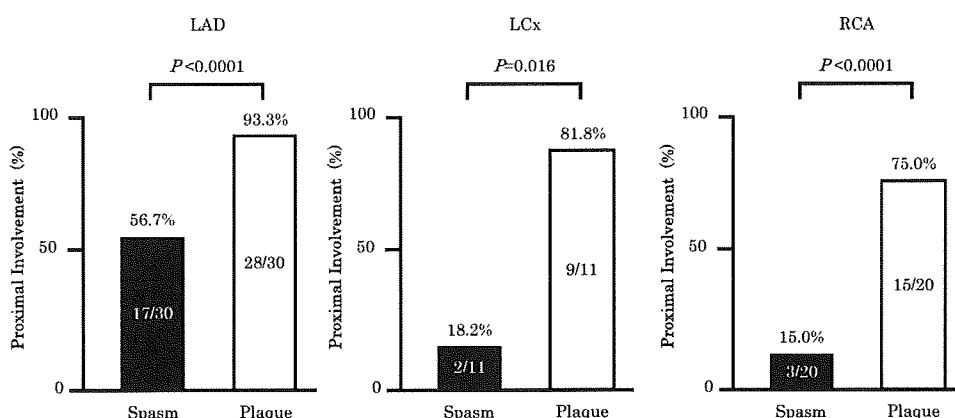
Figures 6 and 7 show the representative angiograms of spasm in the normal angiogram group and those of atherosclerosis group, respectively.

### Discussion

This study showed that most spasms were diffused and extensive, and the substantial number of these involved the entire arterial tree affecting the proximal and distal epicardial vessels and their intramural branches in the normal angiogram group. These findings are in agreement with the results of our previous angiographic study<sup>17</sup> and also with our intravascular ultrasound study, which revealed the existence



**Figure 3.** Comparison of the involvement of the branch point between spasm and plaque in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.



**Figure 4.** Comparison of the involvement of the proximal segment between spasm and plaque in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

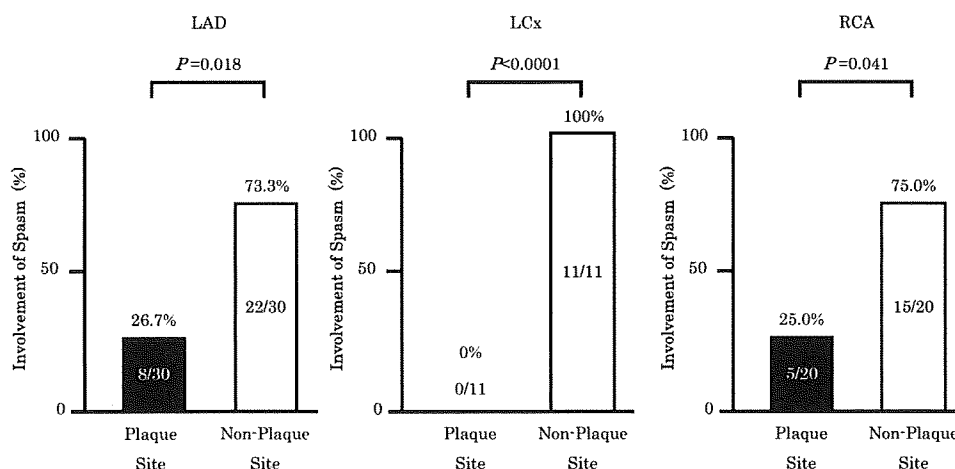
of diffuse intimal thickening in an entire coronary artery in patients with coronary spasm and normal angiograms.<sup>18</sup> Accordingly, the results strongly suggest that systemic factors play an important role in the pathogenesis of coronary spasm.<sup>18-21</sup> On the other hand, the atherosclerotic plaque lesion was focal and largely localized to the proximal segments in agreement with previous studies.<sup>7,8,22-24</sup> This suggests that local factors are more important in the pathogenesis of atherosclerosis as compared with those of coronary spasm.

We have shown that endothelial NO activity is deficient and endothelial function impaired in the spasm arteries.<sup>4</sup> NO not only modulates vasomotor tone, but also inhibits inflammation, production of reactive oxygen species, vascular smooth muscle proliferation, and platelet aggregation,<sup>5,6</sup> and reduced endothelial NO activity represents the early steps in the development of atherosclerosis.<sup>7-9</sup> The endothelium is exposed to shear stress and unidirectional laminar shear stress in straight parts of the arterial tree potently stimulates NO production, whereas disturbed flows at curvatures or branches have the opposite effect.<sup>5,9,10</sup>

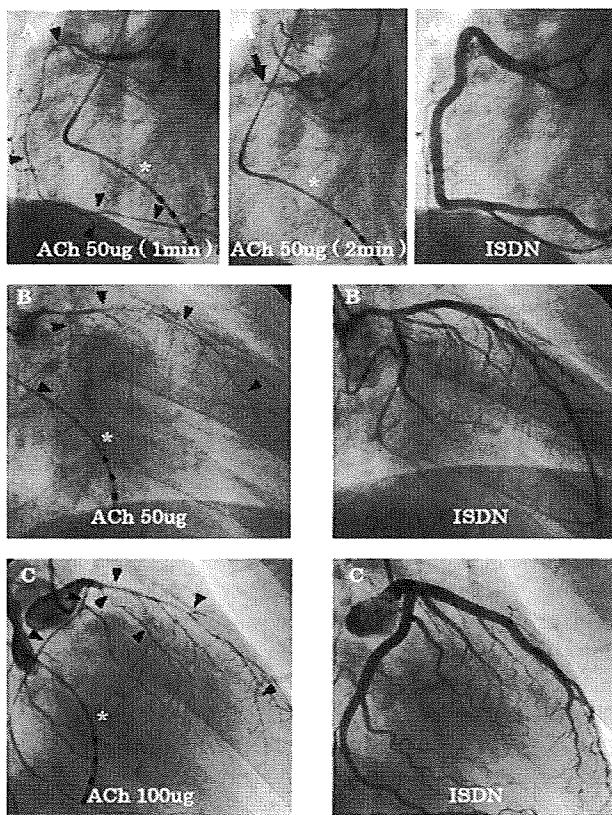
Studies of human coronary arteries provide evidence that regions prone to the development of atherosclerosis occur at sites of intimal thickening, which is mainly composed of

smooth muscle cells (SMCs), suggesting that SMCs in intimal thickening play a pathogenic role in the initiation and development of atherosclerosis.<sup>22-24</sup> Low shear stress occurs at the curvature or upstream of stenosis, whereas oscillatory shear stress occurs downstream of stenosis or branch points.<sup>9,10</sup> Recent studies revealed that low-shear stress lesions contained fewer SMCs and more lipids and were larger and more progressive and vulnerable,<sup>10,25,26</sup> whereas oscillatory-shear stress lesions contained more SMCs and fewer lipids and are more stable.<sup>25</sup>

This study further showed that spasm preferentially occurred at the branch point or downstream of the flow divider where shear stress is presumed to be oscillatory<sup>9,10</sup> both in the normal angiogram and atherosclerosis groups. This is in agreement with the result of Selwyn's group, which showed that branch point constricted more intensely than nonbranch sites in response to ACh infusion.<sup>27</sup> On the other hand, the atherosclerotic stenosis was localized predominantly at the nonbranch point of the curved proximal segment where shear stress is presumed to be low.<sup>9,10</sup> Thus, there was a difference in the predilection site between the spasm and atherosclerotic plaque and most spasms occurred at different sites from those of the plaque. These results thus suggest that atherosclerosis does not contribute to the occurrence of spasm or rather tends



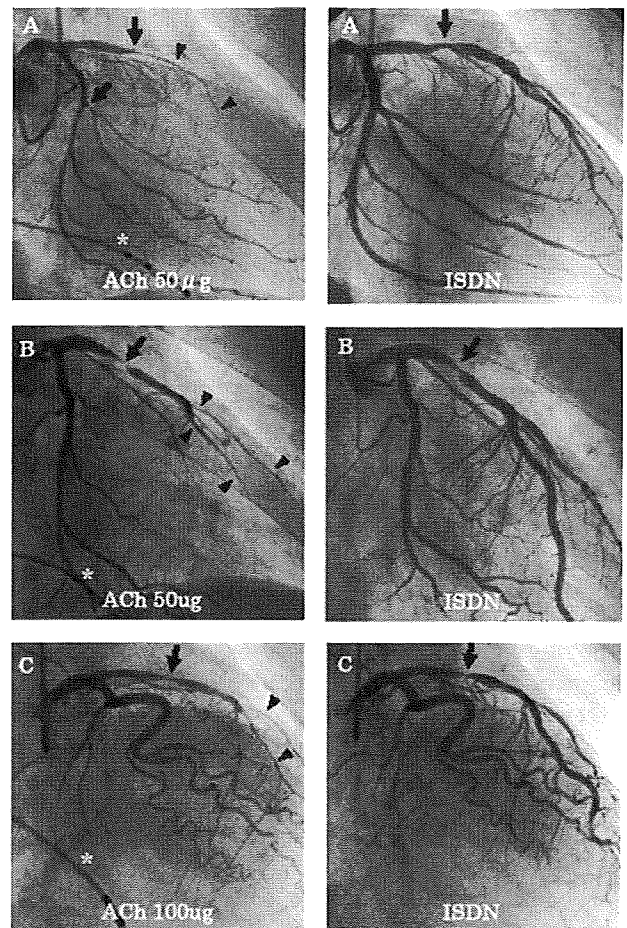
**Figure 5.** Comparison of the involvement of spasm between the plaque and nonplaque sites in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.



**Figure 6.** Coronary angiograms during spasm induced by ACh injection and after ISDN in the normal angiogram group. A, Severe diffuse spasm involving the entire RCA appeared after ACh (left) and converted into a total occlusion at the origin of the artery 2 minutes later (center, arrow). After ISDN, the artery was marked dilated and normal (right). B, Severe diffuse spasm involving the entire left coronary artery including intramural branches appeared after ACh (left, arrow heads) and disappeared after ISDN (right). C, Severe diffuse spasm involving the entire arterial tree of both the LAD and LCx appeared after ACh injection (left, arrow heads) and disappeared after ISDN (right). ACh indicates acetylcholine; ISDN, isosorbide dinitrate; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; \*, a pacing catheter.

to suppress it and are in agreement with those of Maseri's group.<sup>18-21</sup> However, MacAlpin<sup>29</sup> reported on the basis of the literature that most spasms were localized at the site of an organic lesion. The discrepancy between his results and ours may probably be explained by the difference of the study subjects. He reported on the patients with "variant angina," ie, angina associated with ST elevation on ECG. On the other hand, most spasms were associated with ST depression and mild to moderate organic stenosis in the atherosclerosis group of this study.

Coronary spasm has risk factors, such as smoking and aging,<sup>18-21</sup> and is associated with endothelial dysfunction,<sup>2,4</sup> inflammation,<sup>20,30</sup> and intimal thickening.<sup>18</sup> It thus shares the common risk and pathogenetic factors with atherosclerosis.<sup>7,8</sup> However, atherosclerosis is characterized by subendothelial retention of atherogenic lipoproteins,<sup>7,8,22-26</sup> develops early from infants,<sup>31</sup> and is usually associated with hyperlipidemia,<sup>7,8,32</sup> whereas coronary spasm does not occur in the young but in the old patients (mean age of 65.5±10.1 in this study), and hyperlipidemia is not a risk factor for coronary



**Figure 7.** Coronary angiograms during spasm induced by ACh injection and after ISDN in the atherosclerosis group. A, A subtotal occlusion spasm with diffuse vasoconstriction involving the curved proximal segment of the LAD and a focal spasm at the branch site of the LCx appeared after ACh (left, arrows and arrow heads) and disappeared after ISDN (right). A significant organic stenotic lesion was revealed at the curved proximal segment (right, arrow). Spasm was superimposed on the lesion (left, arrow). B, Subtotal occlusion at the proximal segment and diffuse spasm at its distal branch site of the LAD appeared after ACh (left, arrow and arrow heads) and disappeared after ISDN, revealing a severe organic stenosis at the nonbranch site of the curved proximal segment (right, arrow). Despite severe stenosis, total occlusion did not occur at this site during spasm. C, Diffuse spasm occurred at the distal branches, not at the site of severe organic stenosis at the curved proximal segment of the LAD after ACh (left, arrow heads and arrow). A severe organic stenosis lesion was revealed at the nonbranch site of the curved proximal segment after ISDN (right). ACh indicates acetylcholine; ISDN, isosorbide dinitrate; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; \*, a pacing catheter.

spasm.<sup>18-21</sup> Indeed, Morikawa et al have recently reported by using intravascular optical coherence tomography that the spasm arteries with normal angiogram had a diffuse intimal thickening and contained almost no lipid deposits, whereas the no-spasm arteries with normal angiogram had either intimal thickening containing lipid deposits or had no intimal thickening.<sup>33</sup>

Coronary spasm is caused by abnormal contraction of vascular SMCs and therefore contractile and not synthetic phenotype SMCs are likely to play a crucial role in the

pathogenesis of coronary spasm. We, therefore, propose that coronary spasm may be a manifestation of coronary arteriosclerosis distinctly different from coronary atherosclerosis, which is characterized by lipid accumulation and SMCs of synthetic phenotype.<sup>7,8,22–24,32</sup> Recent studies showed that oxidized lipids suppress SMCs marker genes<sup>34</sup> and that lipid lowering promotes accumulation of mature SMCs.<sup>35</sup> To be noted in this connection is the fact that the patients with coronary spasm with angiographically normal or almost normal coronary arteries are less prone to develop acute myocardial infarction as compared with those with other types of unstable angina.<sup>36,37</sup> Intriguingly, the incidence of coronary spasm, particularly variant angina, has decreased recently,<sup>38,39</sup> whereas that of hyperlipidemia has risen in Japan.<sup>40,41</sup>

This study further demonstrates that most coronary spasms were associated with ST-segment depression rather than ST segment elevation on ECG and thereby confirms the concept that variant angina is only one aspect of the spectrum of coronary spastic myocardial ischemia.<sup>42</sup>

### Study Limitations

In this study, we defined the site of spasm as that of total or subtotal obstruction or as that of the most severe and proximal constriction in the case of multifocal or segmental diffuse spasm and the site of atherosclerotic lesion as that of the most narrowed in each artery for the purpose of analysis. However, spasm is often, diffuse and or multifocal, or even migrates from site to site and thus the actual images of spasm may be more complex and dynamic than described in this study.<sup>2</sup> Atherosclerotic lesions also are often multifocal. In this study, however, most atherosclerotic lesions were mild and mostly monofocal, because we excluded the patients with multivessel or severe organic stenosis disease from the study. Thus, the results of this study may not necessarily be applicable to advanced atherosclerotic lesions with multiple plaques. Moreover, angiogram is not sensitive enough to detect atherosclerosis because it is highly likely that vascular remodeling may have occurred, and thus, the patients in the normal angiogram group in this study might not have been free from atherosclerosis.<sup>10</sup> In this study, we did not perform the intravascular ultrasound examination concurrently with angiography and thus could not present the data on shear stress and constituents of vessels walls. However, we have previously shown that the intimal thickening involved the entire arterial tree in the patients with coronary spasm and normal angiogram using intravascular ultrasound.<sup>18</sup>

### Conclusions

Diffuse spasm involving the entire arterial tree occurred in a substantial number of angiographically normal or almost normal coronary arteries in the patients with chest pain. Spasm preferentially occurred involving branch points, whereas atherosclerosis was predominantly focal and localized at the nonbranch points of the curved proximal segments. Most spasms occurred at the sites different from those of the atherosclerotic plaque. These results strongly suggest that coronary spasm may be a manifestation of a distinct type of

arteriosclerosis different from the lipid-laden coronary atherosclerosis.

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### Disclosures

None.

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### CLINICAL PERSPECTIVE

Coronary spasm plays an important role in the pathogenesis of ischemic heart disease. However, similarities and differences between coronary spasm and atherosclerosis are not known. This study examined the angiographic characteristics of coronary spasm in comparison with those of atherosclerotic plaque, first in the angiographically normal or almost normal coronary arteries and then in those with atherosclerotic plaque. The results showed that diffuse spasm involving the entire artery appeared in the substantial number of the angiographically normal arteries and that spasm preferentially occurred at branch points in both the angiographically normal arteries and those with plaque. On the other hand, plaque was predominantly localized at nonbranch point sites of the curved proximal segments. Most spasms did not occur at the sites of plaque. These results suggest that coronary spasm may be a manifestation of a distinct type of arteriosclerosis different from the lipid-laden coronary atherosclerosis. This study, thus, may provide a new insight into the pathogenesis not only of coronary spasm but also of atherosclerosis and may explain at least partially the decline of the number of coronary spasm with the increase of hyperlipidemia among Japanese in recent years.



## SUPPLEMENTAL MATERIAL

### **Coronary Spasm Preferentially Occurs at Branch Points**

-an angiographic comparison with atherosclerotic plaque -

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Figure 1  
LAD

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
3	8	8	6	14
15	9	24	23	47
total	11	32	29	63

P=0.042

Figure 1  
LCS

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
20	1	21	1	22
11	9	20	12	32
total	11	41	13	54

P=0.001

Figure 1  
RCA

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
9	4	13	4	17
17	6	23	12	35
total	10	36	16	52

P=0.067

Figure 1  
LAD

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
13	9	22	11	33
15	2	17	11	28
total	11	39	22	61

P=0.001

Figure 1  
LCS

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
7	3	10	2	12
7	1	8	9	17
total	4	18	11	29

P=0.013

Figure 1  
RCA

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
3	2	5	3	8
12	1	13	17	30
total	5	18	20	38

P=0.001

Figure 2  
LAD

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
9	18	27	21	48
22	9	31	21	52
total	27	58	42	100

P=0.010

Figure 2  
LCS

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
6	4	10	6	16
17	4	21	12	33
total	10	31	18	49

P=0.018

Figure 2  
RCA

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
6	17	23	12	35
4	9	13	6	19
total	26	36	18	54

P=0.087

Figure 3  
LAD

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
6	17	23	7	30
1	4	5	7	12
total	24	30	14	44

P=0.001

Figure 3  
LCS

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
6	6	12	1	13
1	2	3	1	4
total	13	15	2	17

P=0.020

Figure 3  
RCA

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
2	15	17	2	19
9	6	15	4	19
total	21	23	6	29

P=0.007

Figure 3  
LAD

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
2	22	24	6	30
6	9	15	6	21
total	28	30	12	40

P=0.0015

Figure 3  
LCS

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
6	11	17	9	26
2	4	6	9	15
total	15	26	18	44

P=0.001

Figure 3  
RCA

Program		No. of patients		total
Completed program	Not completed	Completed program	Not completed	
6	15	21	4	25
5	9	14	4	18
total	24	35	8	43

P=0.001

### **Figure legends**

Figure 1. Comparison of the involvement of coronary spasm between the branch and non-branch points in the normal angiogram group. Branch indicates the branch point; Non-branch, the non-branch point; LAD, left anterior descending coronary artery; LCx; left circumflex artery; RCA, right coronary artery.

Figure 2. Comparison of the involvement of coronary spasm between the proximal and distal segments in the normal angiogram group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Figure 3. Comparison of the involvement of the branch point between spasm and plaque in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Figure 4. Comparison of the involvement of the proximal segment between spasm and plaque in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Figure 5. Comparison of the involvement of spasm between the plaque and non-plaque sites in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx; left circumflex artery; RCA, right coronary artery.

# Significance of a Multiple Biomarkers Strategy Including Endothelial Dysfunction to Improve Risk Stratification for Cardiovascular Events in Patients at High Risk for Coronary Heart Disease

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<b>Objectives</b>	We investigated whether a multiple biomarkers strategy that includes plasma levels of endothelium-derived microparticles (EMP), reflecting endothelial dysfunction, can improve prediction of future cardiovascular events in patients at high risk for coronary heart disease (CHD).
<b>Background</b>	Detailed risk stratification using multiple biomarkers can provide clinical benefits in high-risk patients. Endothelial dysfunction has been described as a predictor of cardiovascular complications.
<b>Methods</b>	We measured 3 biomarkers in 488 consecutive patients with various CHD risks: B-type natriuretic peptide (BNP), high-sensitivity C-reactive protein (hsCRP), and EMP. We followed 387 stable patients at high risk for CHD and examined future cardiovascular events.
<b>Results</b>	During a mean follow-up of 36 months, 55 patients developed cardiovascular events. Multivariate Cox proportional hazards analysis adjusted for established risk factors identified age, BNP, hsCRP, and EMP as significant and independent predictors of future cardiovascular events (age: hazard ratio [HR]: 1.042, 95% confidence interval [CI]: 1.007 to 1.080, $p = 0.02$ ; BNP: HR: 1.242, 95% CI: 1.004 to 1.536, $p = 0.046$ ; hsCRP: HR: 1.468, 95% CI: 1.150 to 1.875, $p = 0.002$ ; EMP: HR: 1.345, 95% CI: 1.094 to 1.652, $p = 0.005$ ). The C statistics for cardiovascular events increased when each biomarker or combinations of biomarkers were added to the Framingham risk model (C statistics: Framingham risk model alone 0.636, Framingham risk + BNP 0.695, Framingham risk + hsCRP 0.696, Framingham risk + EMP 0.682, and Framingham risk + BNP + hsCRP + EMP 0.763).
<b>Conclusions</b>	The assessment of endothelial dysfunction by plasma levels of EMP can independently predict future cardiovascular events in patients at high risk for CHD. A multiple biomarkers strategy that includes endothelial dysfunction assessed by EMP can identify patients vulnerable to cardiovascular disease. (University Hospital Medical Information Network number: UMIN000000876) (J Am Coll Cardiol 2009;54:601-8) © 2009 by the American College of Cardiology Foundation

The present cardiovascular risk stratification with established coronary risk factors cannot fully predict the devel-

opment of cardiovascular events (1). Several biomarkers including B-type natriuretic peptide (BNP) and high-sensitivity C-reactive protein (hsCRP) have been reported to be useful for identifying the high-risk patients, independent of the established risk factors, and the multiple biomarkers strategy has been demonstrated to improve the risk stratification for cardiovascular events beyond the risk assessment based on established risk factors alone (2,3). Biomarkers reflecting different disease pathways may have the potential advantage of improving predictive power utility, and improvement of the assessment of cardiovascular risk with new biomarkers is desirable. It has been demonstrated that endothelial dysfunction is involved in the

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