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REVIEW ARTICLE

Racial Heterogeneity in Coronary Artery Vasomotor Reactivity: Differences Between Japanese and Caucasian Patients

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Japanese investigators have provided a substantial contribution in the understanding of coronary vasomotor reactivity. On occasions, their findings have been at variance with those undertaken on caucasian patients, raising speculation that vasomotor differences between races may exist. In a comparative review of the published literature, we evaluated the vasoreactive differences among Japanese and caucasian patients with variant angina or myocardial infarction. In variant angina, Japanese patients appear to have diffusely hyperreactive coronary arteries compared with caucasian people, manifested by their segmental rather than focal spasm, hyperreactive nonspastic vessels and multivessel spasm. These differences may reflect the increased basal tone among Japanese variant angina patients and may relate to controversial differences in endothelial nitric oxide production or autonomic nervous system activity. Provocative vasomotor studies of Japanese patients with a recent myocardial infarction report a higher incidence of inducible spasm than caucasian studies, an observation recently supported by a controlled study. Furthermore, the hyperreactivity was diffuse, occurring in both non–infarct- and infarct-related vessels. These observations support the existence of racial coronary vasomotor reactivity differences but require confirmation in further prospectively conducted studies. (J Am Coll Cardiol 1999;33:1442–52) © 1999 by the American College of Cardiology

Japanese investigators have made significant contributions in cardiovascular research, particularly in the field of coronary vasomotor reactivity. On occasions discrepancies have arisen between the findings of such investigators and those of their Western colleagues. Some researchers (1–4) have speculated that the discrepancies are due to ethnic differences in coronary vasomotor reactivity; however, except for a study that we have conducted in patients with recent myocardial infarction (5), prospective studies comparing coronary vasomotor reactivity between different ethnic groups are limited. The aim of this review is to examine the evidence for possible differences in coronary vasomotor reactivity between Japanese and caucasian patients by reviewing comparable published studies from the Medline database (1966–1998) which differ in the racial group assessed. Where appropriate, the findings of both caucasian and Japanese studies were pooled and comparisons between these racial groups made using chi-squared analysis.

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IMPORTANT FACTORS IN CORONARY VASOMOTOR REACTIVITY

Before embarking upon comparisons between vasomotor studies, it is important to distinguish between coronary "spasm" and "vasoconstriction" (6). These two entities differ with regard to the extent of luminal reduction, induction of myocardial ischemia, associated predisposing risk factors and possibly the pathophysiologic mechanisms.

For the purposes of this review, coronary "spasm" is defined as a total or subtotal (≥90%) reduction of luminal diameter which would invoke myocardial ischemia. Other researchers have used less conservative reductions in coronary luminal diameter such as 75% and even 50%, which would not be expected to reduce resting blood flow (7). Although in such patients a stronger constrictor stimulus might have resulted in occlusion, we adopted a stricter definition to maximize the specificity of the diagnosis.

At the other end of the vasomotor spectrum, provocative testing with vasoconstrictor agents may produce a mild reduction in luminal diameter (i.e., <30%), which will be referred to as "vasoconstriction" in this review. This vasomotor response would not invoke myocardial ischemia per se and may or may not be pathologic depending upon the vasoconstrictor agent and dosage utilized. For example, a 10% constrictor response to high dose ergonovine would be considered an appropriate response, whereas a similar re-

sponse to low dose acetylcholine or serotonin may be regarded as abnormal.

Between these two extremes are patients with intermediate/severe vasoconstriction, where luminal reduction is less than subocclusive and therefore may result in ischemia only in the presence of additional factors such as increased oxygen demand and associated distal vessel constriction.

Clinical risk factors predisposing to coronary "spasm" and "vasoconstriction" also differ. Cigarette smoking is the only predisposing factor associated with coronary spasm (8–11), whereas age ≥30 years (3), male gender (12), hypertension (13–15), hypercholesterolemia (12), family history of coronary disease and atherosclerosis (16) have all been associated with an exaggerated constrictor response to intracoronary acetylcholine. Whether Japanese ethnicity is also a predisposing factor to coronary spasm or vasoconstriction requires further evaluation (3).

Different clinical syndromes may also respond differently to vasoactive agents. For example, ergonovine (17) and acetylcholine (18) produce coronary spasm in patients with variant angina but only a mild constrictor response in chronic stable angina patients. In the following sections, Japanese- and caucasian-based studies of patients with variant angina or recent myocardial infarction will be compared to determine if there are racial differences in coronary vasomotor reactivity in these clinical syndromes.

VARIANT ANGINA: Is there a "Japanese variant"?

Variant angina is the conventional clinical manifestation of large vessel coronary spasm, and Japanese researchers have made major contributions in the understanding of this disorder. A review of the Medline database over the past 30 years has identified over 600 original studies of variant angina, with 30% of these being performed on Japanaese variant angina patients. The apparent ease with which the Japanese researchers have accumulated these patients (compared with the studies by caucasian researchers) has prompted the belief that this disorder is more prevalent in Japan (19,20). However, there are no systematic studies comparing the incidence of variant angina between countries.

In evaluating racial differences in variant angina, the definition of this syndrome must be clarified. Variant angina is clinically characterized by recurrent episodes of rest pain associated with reversible ST elevation and preserved exercise tolerance (21). Angiography during an ischemic episode typically demonstrates a subtotal/total occlusive spasm of a major epicardial coronary artery. In their original report, Prinzmetal et al. (22) postulated an increase of "tonus" at the site of a subcritical stenosis, but over a decade later a "variant of the variant" with angiographically normal coronary arteries was reported (23).

Vasospastic angina is a disorder of large vessel vasomotor reactivity which has particularly featured in Japanese research articles. The definition of vasospastic angina focuses more upon the angiographic demonstration of coronary spasm in patients with rest pain irrespective of the electrocardiogram showing ST elevation or depression (24,25).

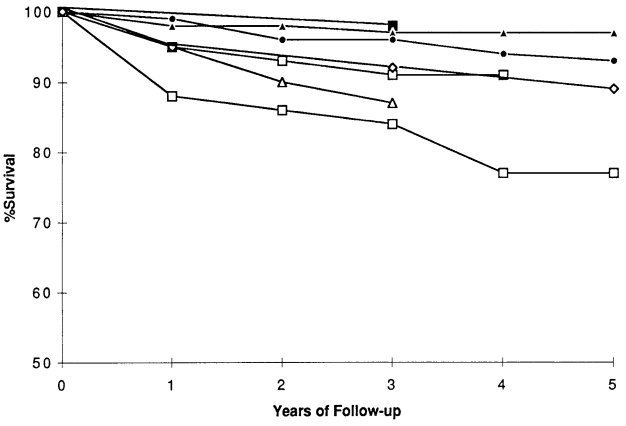

Figure 1. Survival in variant angina patients. Major prognostic studies in variant angina patients showing up to 5-year survival figures for Japanese-based studies (26–28) **(filled shapes)** as compared with caucasian studies (29–32) **(open shapes)**. **Filled squares** = Nakamura et al. (26); **filled triangles** = Yasue et al. (27); **filled circles** = Shimokawa et al. (28); **open squares** = Severi et al. (29); **open triangles** = Waters et al. (30); **open squares** = Mark et al. (31); **open diamonds** = Walling et al. (32).

For the purpose of this review, patients will only be considered as "variant angina" if they fulfill the following criteria: 1) rest pain, 2) spontaneous or induced reversible ST elevation and 3) no evidence of myocardial infarction on serial cardiac enzymes. "Vasospastic angina" will be used for patients with 1) rest pain, 2) reversible ST elevation or depression and 3) spontaneous or induced coronary spasm on angiography. This distinction between "variant" and "vasospastic" angina is rather artificial, but is used in this review largely to categorize the characteristics of the populations being compared with regard to the reported studies. Overall, it may well be that the two groups should be combined and designated "vasomotor angina."

Comparison of vasomotor angina studies undertaken on Japanese or caucasian patients reveal both clinical and pathophysiologic differences between these groups and are outlined below.

Clinical differences. Table 1, and Figures 1 and 2, summarize the results of seven large clinical studies (26–32) which have endeavored to determine the prognosis of variant angina; however, they also serve to provide information on clinical characteristics of such patients. Table 1 shows a similar mean age and male preponderance among the variant angina patients, although the condition appears to be slightly more common in caucasian than Japanese women (i.e., 22% vs. 13% respectively, $p < 0.0001$).

Pooled analysis of the data from Table 1 reveals significant differences between Japanese and caucasian variant angina patients with respect to: 1) prior myocardial infarct (7% vs. 24% respectively, $p < 0.0001$), 2) the presence of obstructive coronary artery disease (41% vs. 66%, $p <$

Table 1. Major Variant Angina Prognostic Studies

Feature	Nakamura et al. (26)	Yasue et al. (27)	Shimokawa et al. (28)	Severi et al. (29)	Waters et al. (30)	Mark et al. (31)	Walling et al. (32)
Study country	Japan	Japan	Japan	Italy	Canada	United States	Canada
Sample size (n)	349	245	158	138	169	62	217
Clinical characteristics							
Age (yr)							
Mean	54	54	57	53	51	52	51
Range	28–83	34–70	31–76	24–75	24–71	28–70	24–71
Female*	12%	13%	14%	7%	31%	26%	24%
Prior MI*	8%	6%	6%	33%	18%	18%	
Angiographic features							
Angiograms performed (n)	349	245	116	107	162	62	208
CAD							
Nil significant	66%	40%	80%	8%	39%	38%	42%
Single vessel	27%	44%	16%	36%	36%	35%	39%
Multivessel	7%	16%	4%	56%	25%	27%	19%
Abnormal LV function		6%	6%	53%	26%	43%	26%
Spastic ischemic site							
Anterior	46%	51%	47%	69%	57%	35%	52%
Inferior/lateral	45%	38%	53%	31%	43%	65%	48%
Anterior and inferior	9%	11%					
Prognosis							
Follow-up (mo)							
Mean	41	80	55	~36	15	~12	65
Range	24–60	36–184	1–207	24–96	1–68	6–122	2–123
Survival at 3 years*	98%	97%	96%	91%	87%	84%	92%
MI-free survival at 3 years*	95%	85%	92%	77%	75%	63%	77%
Deaths without CAD*	57%	50%	50%	9%	8%	17%	24%

*Significant difference between Japanese and Caucasian studies in assessed parameter ($p < 0.001$).
CAD = coronary artery disease; LV = left ventricular; MI = myocardial infarction.

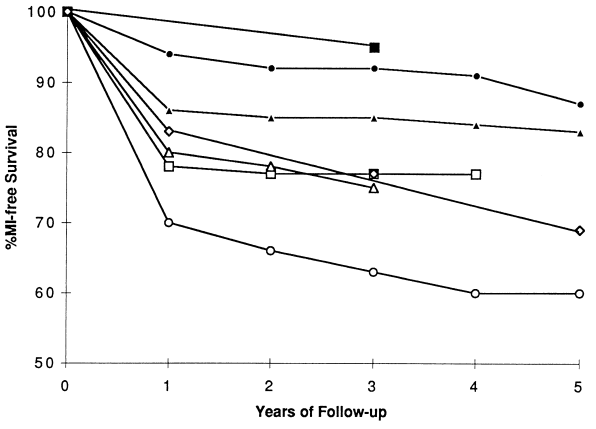

Figure 2. Survival without myocardial infarction in patients with variant angina. Five-year survival without myocardial infarction in Japanese (26–28) **(filled shapes)** and caucasian (29–32) **(open shapes)** variant angina patients. Symbols as in Figure 1.

0.0001), 3) survival at three-year follow-up (97% vs. 89%, $p < 0.0001$), and 4) myocardial infarct-free survival at three-year follow-up (91% vs. 75%, $p < 0.0001$).

Analysis of Table 1 confirms that caucasian variant angina patients not only have a higher incidence of atherosclerotic disease than Japanese, but also have more extensive disease (i.e., multivessel disease in Japanese = 24% vs. caucasian = 44%, $p < 0.0001$), which has also been reported in the respective general populations (28,33). Multivariate analysis of predictors of infarction in variant angina patients has shown that the extent of atherosclerosis is an important determinant (27); thus the more extensive atherosclerotic disease in caucasian variant angina patients accounts for the higher incidence of myocardial infarction observed in this group (Table 1) (26–30).

Caucasian variant angina patients have a worse overall survival than their Japanese counterparts (Table 1, Fig. 1 and 2), which may relate to their more extensive atherosclerotic coronary disease, higher incidence of myocardial infarction and more frequent left ventricular dysfunction (Table 1). Yet, 52% of the Japanese patients with cardiac fatalities have normal or near-normal coronary arteries compared with only 16% of the caucasian patients (chi-square = 11.8, $p = 0.0006$). Hence, the Japanese patients more often succumb with sudden cardiac death (presumably arrhythmic) rather than fatal myocardial infarction (26,34).

The overrepresentation of normal or nonobstructive coronary disease in the Japanese variant angina cardiac fatalities may be due to several factors. Animal experiments have demonstrated that ventricular fibrillation after reperfusion of an occluded coronary artery is more common if the affected vessel is "normal" than if it had a preexisting obstructive lesion (35). Hence occlusive spasm of a normal coronary artery may be more likely to produce sudden death than if it occurred in a significantly obstructed vessel. Alternatively, the autonomic nervous system response to ischemia may differ.

Multivessel spasm (i.e., spasm involving more than one epicardial vessel) has also been shown to be an important predictor of cardiac mortality in patients with variant angina (36). Although early reports of multivessel spasm were in caucasian (37), this disorder appears to be much more common among Japanese (i.e., Table 1; up to 11% of Japanese patients have both anterior and inferior ST elevation, whereas none of the caucasian patients are affected) and may account for some of the cardiac fatalities in patients with normal coronary angiograms. Review of the literature shows that multivessel spasm is well described in Japanese patients, with reports characterizing the clinical features (38,39) of the phenomenon and over 20 studies reporting on its incidence. In contrast, description of the disorder in caucasian variant angina patients has largely been limited to case reports (37,40,41) suggesting that the phenomenon is uncommon in this population. Some of the Japanese studies have suggested that as many as 76% of their variant angina patients (42) have multivessel spasm. This variability in the reported incidence of multivessel spasm (i.e., 9% to 76% in Japanese variant angina patients) reflects differences in the definitions of coronary spasm.

Pathophysiologic differences. The exact subcellular mechanism(s) responsible for spasm remain to be elucidated, although interesting data have been obtained from a pig model (43). Furthermore, why patients with variant or vasospastic angina are predisposed to coronary artery spasm is unclear. Studies examining the pathophysiology of coronary vasospastic disorders have occasionally found conflicting results, and some of these paradoxes may be due to differences between Japanese and caucasian patients as outlined below.

Focal versus segmental spasm. Studies in Europe and North America have noted that coronary artery spasm in variant angina was usually focal and localized to a coronary plaque. This observation stimulated diverse theories, such as focal coronary spasm initiating atherosclerotic lesion development (44) and the geometric theory of coronary spasm, which proposed that spasm is an amplification of normal vasoconstriction at atheromatous plaques (45). Such theories have since been discredited (46,47) but illustrate the thought processes based upon clinical observation of caucasian variant angina patients. Currently, Western researchers propose that coronary spasm involves postreceptoral smooth muscle hyperreactivity of a coronary segment because it can be caused by several pharmacologic stimuli acting on different receptors (6,48).

In contrast, studies of Japanese patients with variant angina have generally observed segmental or diffuse coronary artery spasm, typically involving normal coronary artery segments. Accordingly, Japanese researchers have explored mechanisms involving generalized coronary hyperreactivity,

Table 2. Vasoconstrictor Responses of Nonspastic Segments

Study	Provocative Agent	Control Group		Variant/Vasospastic Angina	
		n	% Vasoconstriction	n	% Vasoconstriction
Caucasian patients					
Freedman et al. (46)	Ergot	21	17 ± 12	11	20 ± 14
Hackett et al. (55)*	Ergot	9	16 ± 6	6	20 ± 14
Kaski et al. (56)*	Ergot	9	10 ± 6	13	15 ± 11
Japanese patients					
Hoshio et al. (51)	Ergot	35	8 ± 6	30	24 ± 11†
Kuga et al. (52)*‡	Ergot	24	27 ± 10	20	38 ± 14§‖
Okumura et al. (53)	ACh	20	12 ± 12	36	28 ± 17§
Kugiyama et al. (50)‡	ACh	25	12 ± 12	20	50 ± 39¶
		12	10 ± 10	9	46 ± 31¶

*Study patients enrolled conform to variant angina definition. †$p < 0.01$ vs. control group. ‡Angiographically normal coronary arteries. §$p < 0.05$ vs. control group. ‖Nonspastic segments include segments adjacent to spastic site and from nonspastic arteries. ¶$p < 0.001$ vs. control group.
ACh = acetycholine. Vasoconstriction data presented as mean ± SD.

such as autonomic nervous system imbalances (49) and endothelial dysfunction (50).

Hyperreactive nonspastic coronary artery segments. Several studies (50–53) of Japanese patients with vasomotor angina have demonstrated that not only the spastic segments are hyperreactive to provocative agents but also remote nonspastic segments. Table 2 summarizes the response to vasoconstrictor agents in nonspastic coronary artery segments from caucasian and Japanese patients with either atypical chest pain and no inducible spasm (control patients) or vasomotor angina. All the Japanese studies demonstrate an increased constrictor response in vasomotor angina patients as compared with control subjects, an observation confirmed in an in vitro study (54). This diffuse coronary hyperreactivity in the Japanese patients is consistent with the above-mentioned diffuse segmental spasm and the high frequency of multivessel spasm. However, it contrasts with studies performed in caucasian people (46,55,56), where there were no differences in coronary reactivity between control subjects and variant angina patients (Table 2). This finding can be explained by a greater prevalence of multiple hyperreactive sites in Japanese patients.

Increased basal tone. The response to nitrates has been utilized as an index of basal tone (57), where a greater dilator response suggests a higher resting tone. Table 3 demonstrates that the nitrate response is similar between caucasian (55,56,58) and Japanese (50–53,59) control patients (i.e., atypical chest pain and no inducible spasm). Also, the caucasian patients with variant angina have a vasodilator response in nonspastic and spastic segments similar to that of control subjects. However, Japanese patients with variant angina show a marked dilator response at both spastic and nonspastic sites. This has been consistently shown in all but one (59) of six studies and suggests that Japanese patients with vasomotor angina have a higher basal tone in both spastic and nonspastic segments (50–53).

Table 3. Basal Tone at Nonspastic and Spastic Segments

Author	Nitrate	Control Group		Vasomotor Angina		
		n	% Vasodilation	n	% Vasodilation (Nonspastic)	% Vasodilation (Spastic)
Caucasian patients						
Hill et al. (58)*	NTG	34	16	17	15	
Hackett et al. (55)*	ISDN	9	13 ± 12	6	16 ± 16	4 ± 18
Kaski et al. (56)*	ISDN	9	13 ± 6	13	11 ± 11	
Japanese patients						
Hoshio et al. (51)	NTG/ISDN	35	16 ± 6	30	42 ± 11†	64 ± 27‡§
Kuga et al. (52)*‖	NTG	24	15 ± 6	20	20 ± 14†¶	31 ± 18†#
Okumura et al. (53)	NTG	20	21 ± 11	36	40 ± 22‡	
Kugiyama et al. (50)‖	NTG	25	21 ± 16	20		43 ± 18†
		12	22 ± 17	9		40 ± 20†
Egashira et al. (59)*‖	ISDN	8	16 ± 8	8	17 ± 7¶	27 ± 11#

*Studies enrolled patients fulfilling criteria for variant angina; in other studies, patients fulfilled vasospastic angina criteria. †$p < 0.01$ vs. control group. ‡$p < 0.05$ vs. control group. ‖Angiographically normal coronary arteries. §$p < 0.05$ vs. nonspastic segment. ¶Nonspastic segments include segments adjacent to spastic site and from nonspastic arteries. #$p < 0.01$ vs. nonspastic segment.
ISDN = isosorbide dinitrate; NTG = nitroglycerin. Vasodilation data presented as mean ± SD.

Furthermore, the tone is higher in spastic as compared with nonspastic segments, thus suggesting that basal tone may be related to hyperreactivity in Japanese patients (51,52).

The role of endothelial nitric oxide in Japanese vasospastic angina patients. There are two schools of thought in Japan concerning the role of endothelium-derived nitric oxide in vasospastic angina patients. Unfortunately, there are no comparable studies in caucasian patients to date.

One group of investigators has proposed that a localized deficiency of coronary nitric oxide production is responsible for coronary spasm in vasospastic angina patients. This is supported by the following findings in vasospastic angina patients relative to control subjects: 1) an exaggerated vasodilator response to nitrates but not diltiazem (50), 2) impaired flow-dependent (nitric oxide mediated) epicardial coronary artery dilation (60), 3) a reduced constrictor response to intracoronary N^G-monomethyl-L-arginine (an inhibitor of nitric oxide synthase) (50) and 4) an increased prevalence of a point mutation in the endothelial cell constitutive nitric oxide synthase gene (61). Accordingly, the deficient endothelial nitric oxide production may predispose to a higher basal tone and coronary spasm with acetylcholine provocation testing because of unopposed constrictor effects.

Paradoxically, other Japanese investigators have reported that endothelial nitric oxide production is intact in vasospastic angina patients (62). These researchers have demonstrated the following in vasospastic angina patients: 1) intact endothelium-dependent vasodilation by low dose acetylcholine (62), substance P (62,63) and bradykinin (64); and 2) an increased constrictor response to N^G-monomethyl-L-arginine at spastic sites compared with nonspastic sites (59). The explanation for these disparate findings as regards vascular reactivity requires further evaluation but appears to relate to methodological differences between the studies (65,66). The status of caucasian vasospastic angina patients with regard to endothelial nitric oxide production requires investigation. Acetylcholine does not appear a suitable agent because it does not allow the separation of the role of endothelial dysfunction from that of smooth muscle hyperreactivity.

The role of parasympathetic activity in coronary spasm. Although the stimuli responsible for triggering coronary spasm in patients with variant angina remain unknown, the autonomic nervous system has been implicated from studies utilizing heart rate variability. Yoshio et al. (67) assessed heart rate variability 30 min before an episode of spontaneous ST elevation in seven Japanese variant angina patients with nonobstructive coronary artery disease. They observed an increase in high frequency activity 10 min before the onset of an episode of ST elevation, suggesting an increase in parasympathetic activity before an episode of coronary spasm. Low frequency (sympathetic) activity also increased 5 min before the onset of spasm.

Lanza et al. (68) also assessed heart rate variability 30 min before an episode of spontaneous ST elevation in 23 Italian variant angina patients with nonobstructive or single vessel (56% of patients) coronary artery disease. Unlike the Japanese study they observed a fall in high frequency activity 5 min before spasm onset and concluded that there was a withdrawal of parasympathetic activity in their patients. Furthermore, subgroup analysis demonstrated that this occurred independent of the presence of significant coronary artery disease.

Although these differences may, in part, be due to methodological variations between the studies, they may also reflect racial differences in the pathogenesis of coronary spasm between Italian and Japanese variant patients and warrant further investigation. Also, the diurnal variability of coronary spasm, which may be influenced by the autonomic nervous system, should be investigated because previous studies have suggested differences between Japanese and caucasian variant angina patients (69). These earlier studies did not account for differences in coronary stenoses, which have since been shown to influence coronary spasm circadian variation (70).

Racial vasomotor heterogeneity in vasomotor angina: a synthesis of the data. In summary, reviewing the literature would suggest that Japanese and caucasian patients with vasomotor angina have clinical and pathophysiologic differences. These differences essentially relate to two fundamental features, namely 1) a reduced prevalence of "fixed" coronary artery stenoses and 2) diffuse coronary hyperreactivity in the Japanese patients. The reduced extent of coronary stenoses may result in a lower incidence of myocardial infarction and better prognosis; the diffuse vasomotor reactivity could relate to the increased basal tone, the increased incidence of multivessel spasm and greater representation of normal/nonobstructive coronary arteries in the cardiac fatalities. The role of the autonomic nervous system, endothelial nitric oxide synthesis and specific smooth muscle hyperresponsiveness to constrictor stimuli, in this apparent racial heterogeneity in variant angina, requires further evaluation.

ACUTE MYOCARDIAL INFARCTION: Do Japanese patients differ?

Since the landmark "Seven Countries Study" (71), it has been appreciated that the Japanese have a substantially lower coronary artery disease mortality compared with most caucasian populations (e.g., in the U.S., men aged 25 to 74 years the coronary mortality is 156/100,000 population as compared with 27/100,000 among age-matched Japanese men [72]). This difference is primarily due to environmental factors, as shown by coronary artery disease mortality studies in men of Japanese ancestry which demonstrate an increasing mortality gradient from Japan to Hawaii to California, despite a common genetic origin (73,74). Furthermore, cholesterol levels have been implicated (71,75) because they follow the same gradient (76).

Table 4. Inducible Coronary Spasm in Postmyocardial Infarct Patients

Study	Provocative Agent	Myocardial Infarct Patients			Control Patients	
		n	Days Post-MI	Spasm	n	Spasm
Recent myocardial infarct						
Caucasian patients						
Bertrand et al. (79)	Methylergonovine	131	< 42	21%	353	9%
Mongiardo et al. (80)	Serotonin	24	6–12	11%		
Pristipino et al. (5)	Acetylcholine	19	7–10	37%		
Japanese patients						
Okumura et al. (81)	Acetylcholine	16	25–725	69%	16	21%
Pristipino et al. (5)	Acetylcholine	15	7–10	80%		
Remote myocardial infarct						
Caucasian patients						
Bertrand et al. (82)	Methylergonovine	64	> 6 weeks	6%	248	1%
Japanese patients						
Nosaka et al. (83)	Ergonovine	398		23%	648	1%

MI = myocardial infarction.

Clinical differences. Although the prevalence of myocardial infarction is lower in Japanese, the Japanese patient with a myocardial infarct appears to differ clinically from his or her caucasian counterpart. Both Saito et al. (77) and Nakamura et al. (78) reported differences in the posthospital course of Japanese and caucasian patients with acute myocardial infarction. Compared with caucasian patients, Japanese patients with a similar initial infarct size had a more favorable posthospital course with fewer coronary events. This difference was independent of coronary risk factors or medications utilized (78) and remains unexplained.

Pathophysiologic differences. These clinical differences raise the possibility of different pathophysiologic mechanisms in Japanese and caucasian patients with myocardial infarction. Coronary vasomotor studies examining the inducibility of coronary spasm in patients with a recent myocardial infarction support the existence of pathophysiologic racial differences.

Inducible coronary spasm in patients with myocardial infarction. Bertrand et al. (79) performed provocative testing within six weeks of acute myocardial infarction and found that 21% of French infarct patients developed coronary spasm in response to intravenous methylergonovine. This was significantly more frequent than the 9% observed in control patients with coronary atherosclerosis but without infarction. Similarly Mongiardo et al. (80), utilizing intracoronary serotonin in Italian myocardial infarct patients 7 to 10 days postinfarction, observed an 11% incidence of inducible spasm.

In contrast, Okumura et al. (81) found a very high incidence of coronary spasm, with 69% of their Japanese myocardial infarct patients showing a spastic response to provocative agents as compared with 21% of stable angina patients without previous infarction (Table 4). This suggests that Japanese patients with a recent myocardial infarct have greater coronary vasoreactivity than their caucasian counterparts and so may imply that spasm is a more important factor in the pathogenesis of infarction in the Japanese patients. This racial difference in coronary vasomotor reactivity is also observed when patients undergo provocative testing remote from the time of infarction (82,83) (e.g., >6 weeks), as shown in Table 4. These observations are particularly impressive when it is considered that the largest caucasian study (79) utilized a broad definition of spasm (i.e., ≥75% reduction in lumen diameter in normal arteries) and therefore would have inflated frequencies compared with the other tabulated studies.

This marked difference in inducible spasm may be due to other potential confounding factors which may affect vasomotor responses including, 1) smoking (8–11), 2) associated atherosclerosis (27), 3) the provocative agents utilized (84,85), 4) the timing of testing after infarction between the studies (79), and 5) inadvertent enrollment of patients with variant angina. Thus the tentative conclusion at this stage would be that the incidence of postmyocardial infarct spasm is greater in Japanese than caucasian patients, and that in both cases the incidence reduces with the efflux of time postinfarct. No study to date has examined all of these factors prospectively.

In the first prospective comparative study of coronary spasm across racial groups, we compared the incidence of inducible spasm in Japanese and Italian patients 7 to 10 days after myocardial infarction. This study observed a marked difference in vasomotor reactivity between these two groups, with 80% of the Japanese and 37% of the caucasian patients showing inducible coronary artery spasm (5), despite a similar frequency of cigarette smoking between groups. The similarity of these findings to those previously published (Table 4) add further credence to the data and confirm that there is a difference between races in patients with a recent myocardial infarct. Furthermore, the hyperreactivity among the Japanese was

observed in both the infarct-related and noninfarct-related arteries (5).

Multivessel spasm in myocardial infarction. As observed in vasomotor angina, our study (5) found a higher incidence of acetylcholine-induced multivessel spasm in Japanese infarct patients as compared with caucasian patients (64% vs. 17%, $p < 0.00001$, respectively). Thus, in a study population with similar clinical characteristics, the Japanese again show coronary hyperreactivity compared with their caucasian counterparts.

Coronary occlusion in myocardial infarction. Definitive data in caucasian patients on the temporal relationship between acute myocardial infarction and occlusion of the relevant coronary artery have been provided by DeWood et al. (86). This group demonstrated that 87% of patients with transmural infarction had total coronary occlusion when angiography was performed within 6 h of chest pain onset. The incidence of total occlusion decreased with the duration postinfarct so that by 24 h only 65% of patients had totally occluded vessels (86).

In contrast to the above findings, Akiyama et al. (87) observed total occlusions in only 59% of the 296 Japanese patients undergoing angiography within 6 h of infarction. Furthermore, 21% of the patients showed Thrombolysis in Myocardial Infarction grade 3 (TIMI-3) flow and thus were believed to have "spontaneously reperfused." These patients were also shown to have an increased resting coronary tone (reflected by a greater response to intracoronary nitrate) as compared with matched segments proximal to a total occlusion, therefore suggesting that coronary spasm may be an important contributor to infarction in the reperfusion patients.

Although this study is particularly relevant to the current review, comparable data on "spontaneous reperfusion" in caucasian patients are not available. Also, the data concerning total occlusions are not directly comparable with DeWood's study, as Akiyama et al. included patients with non–Q-wave infarction; a condition less frequently associated with total occlusion (88). However, a number of studies have examined the frequency of total occlusion within 6 h of infarct onset (and before reperfusion therapy) in caucasian (86,89–97) and Japanese (98–100) patients presenting with ST elevation (Table 5). Pooled analysis of these data suggests that persistent total occlusion in the first 6 h of infarct onset is more common in caucasian patients (pooled data, 82% vs. 65%, respectively, $p < 0.0001$), a finding that would be consistent with Akiyama's data, again raising the possibility that Japanese people and caucasian people differ in their pathogenetic components of myocardial infarction.

Myocardial infarction in patients with insignificant coronary artery disease. Patients with acute myocardial infarction who have normal or near-normal coronary arteries on angiography form an interesting subset whose pathogenesis of infarction remains unclear. A number of small caucasian-based studies (79,101–105) have undertaken provocative ergot testing in these patients and reported an incidence of inducible spasm between 0 and 31%. In contrast, Fukai et al. (106) reported a 75% incidence of inducible spasm among Japanese patients with myocardial infarction and angiographically normal/near-normal coronary arteries. Thus, similar to patients with myocardial infarction associated with atherosclerotic coronary artery disease, the Japanese have shown a higher frequency of inducible spasm.

Table 5. Total Coronary Occlusion in Acute Myocardial Infarct Patients

Study	n	Total Occlusion
Caucasian patients		
DeWood et al. (86)	208	87%
Ganz et al. (89)*	20	90%
Timmis et al. (90)†	72	90%
Anderson et al. (91)‡	24	83%
Leiboff et al. (92)‡	55	78%
Simoons et al. (93)‡	152	82%
Valentine et al. (94)	98	87%
von Essen et al. (95)	461	79%
Messmer et al. (96)	469	79%
Steg et al. (97)	325	82%
Japanese patients		
Nakagawa et al. (98)	45	71%
Yasue et al. (99)§	84	62%
Dote et al. (100)	336	63%

*Patients presented within 3 h. †Patients presented within 5 h. ‡Patients presented within 4 h. §Mean time to angiography from pain onset = 4 ± 1.9 h.

CONCLUSIONS

This review has examined clinical and pathophysiologic differences between Japanese and caucasian patients in two coronary ischemic syndromes and provided evidence for racial heterogeneity in coronary vasomotor reactivity. In particular, Japanese patients with variant angina or myocardial infarction have hyperreactive vessels compared with caucasian patients. Furthermore this hyperreactivity is diffuse, as nonspastic/noninfarct arteries also exhibited enhanced vasomotor reactivity, and there is a high incidence of multivessel spasm.

The implications of these observations effect both clinical and research practice. In particular, data derived from coronary vasomotor studies in one population can no longer be automatically extrapolated to another. Furthermore, the observations justify the tendency of Japanese physicians to frequently undertake provocative tests for coronary spasm in patients with unexplained chest pain and to routinely use calcium antagonists in preference to beta-adrenoceptor antagonists in acute coronary syndromes (5,78).

The mechanism responsible for the diffuse hyperreactivity among Japanese variant angina/myocardial infarct patients remains to be elucidated, but both genetic and environmental factors are likely to play a role. Genetic factors predisposing to coronary spasm have recently been implicated in Japanese patients (61,107,108), with particular interest fo-

cusing upon an amino acid substitution of the endothelial nitric oxide synthetase gene (thereby resulting in deficient nitric oxide production). Although no comparable data on caucasian patients are available, the missense gene mutation is more frequent in Japanese patients with either vasospastic angina (61) or myocardial infarction (108), as compared with control subjects. However, the frequency of the gene in these coronary syndromes is low (approximately 21% in each group), suggesting that other factors also contribute. Future studies of Japanese patients living in caucasian societies may further aid our understanding of environmental factors contributing to the phenomenon.

Study Limitations. The findings of this review should be interpreted with caution, because most of the data are derived from published reports, thus introducing publication bias. Furthermore, comparisons between the independent studies may be limited because of undisclosed confounding factors. For example, cigarette smoking is the only known risk factor predisposing to coronary spasm, yet many studies do not report the frequency of smokers in their study group.

These limitations indicate the need for more prospective comparative studies evaluating racial differences in vasomotor activity. The only such study to date examining differences between Japanese and caucasian patients has supported the findings in published reports, and we hope other studies will support the observations made in this review. Certainly, assessing racial heterogeneity in coronary vasomotor reactivity may have further important implications regarding both pathophysiology and also therapeutics of coronary disease.

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