Racial Differences in Patients with Coronary Vasomotion Disorders: Comparisons between Caucasian and Japanese Populations

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Racial differences regarding coronary vasomotion disorders between Caucasian and Japanese populations are controversial. In the past, coronary epicardial spasm was more often recognized in Japanese people than in Caucasian populations. In contrast, coronary microvascular dysfunction is typically observed in Caucasian patients. Japanese cardiologists perform spasm provocation testing actively in patients with unobstructive coronary artery disease, whereas Caucasian cardiologists except for those in some special institutions may skip coronary reactivity testing in the cardiac catheterization laboratory if they encounter patients with unobstructive coronary artery disease. In this review, we present the racial and ethnic disparities in the incidence and clinical characteristics between Caucasian and Japanese populations with coronary vasomotion disorders.

KEY WORDS: Caucasian, coronary microvascular dysfunction, epicardial spasm, ethnic disparity, Japanese, racial difference

I. Introduction

Approximately 20 years ago, Beltrame et al. reported racial heterogeneity in coronary artery vasomotor reactivity between Caucasian and Japanese patients¹. In variant angina, Japanese patients appear to have diffusely hyperreactive coronary arteries compared with Caucasian individuals who manifested with focal spasm rather than segmental spasm. Twenty years ago, spasm provocation testing studies in Japanese patients with a recent myocardial infarction revealed a higher incidence of provoked spasm than Caucasian patients².

Coronary vasomotion disorders include coronary epicardial spasm and coronary microvascular dysfunction (CMD). Furthermore, patients with chest pain in the absence of obstructive coronary artery disease (CAD) remain a challenging problem ³. The Women’s Ischemia Syndrome Evaluation (WISE) study showed that women with chest symptoms and signs suggestive of myocardial ischemia but without obstructive CAD are at an increased risk of cardiovascular events, and often have no improvement in chest pain and a reduction in quality of life because of readmission due to angina pectoris⁴⁻⁶. According to previous reports, patients with ischemia with nonobstructive CAD (INOCA) were frequently observed in Caucasian populations, whereas patients with coronary spastic angina (CSA) without obstructive CAD were markedly recognized in Japanese populations⁷⁻⁸. However, Japanese cardiologists have been performed spasm provocation tests for more than 30 years in the cardiac catheterization laboratory positively⁹⁻¹¹, whereas Caucasian cardiologists except for some cardiologists at special institutions, do not perform spasm provocation tests in the cardiac catheterization laboratory.

In this review, we investigated racial heterogeneity in patients with coronary vasomotion disorders including epicardial spasm and CMD diseases between Caucasian and Japanese patients. We also investigated ethnic differences regarding the diagnostic procedures between Caucasian and Japanese cardiologists.

II. Variant angina

In 1959, variant angina was first reported by Prizmetal et al. in the United States of America¹². However, Japanese physicians have made major contributions in this field of coronary epicardial spasm¹³⁻¹⁴. Compared with Caucasian variant angina, Japanese variant angina affect fewer female patients and exhibits less organic stenosis, less poor left ventricular function, less prior myocardial infarction, and good prognosis as shown in Table 1¹³⁻¹⁸. Under the optimal medications, Japanese variant angina had favorable clinical outcomes, whereas Caucasian variant angina did not have a benign prognosis in the clinic. The incidence of death without organic stenosis in Japanese variant angina is higher than that in Caucasian variant angina. We rarely experi-
ence variant angina possibly due to the widespread use of calcium channel blockers (CCBs) or percutaneous coronary interventions\(^1\). Furthermore, cardiologists worldwide do not perform noninvasive testing such as hyperventilation tests and cold stress tests when they diagnose patients with CSA\(^{20, 21}\).

III. Provoked spasm by pharmacological spasm provocation tests

As shown in Table 2, the incidence of epicardial spasm in Japanese populations is markedly higher than that in Caucasian populations (26.6% vs. 21.5%, p<0.001)\(^{22-26}\). The frequency of provoked spasm in Japanese patients with ischemic heart disease including rest angina, effort angina, and rest and effort angina, is significantly higher than that in Caucasian patients. Furthermore, the incidence of multiple spasms in Japanese populations is remarkably higher than that in Caucasian patients (34.4% vs. 24.5%, p<0.001). The frequency of provoked epicardial spasms in patients with nonischemic heart diseases is not different between Caucasian and Japanese populations. Of importance, Pristipino et al. reported that the ratio of inducible spasms in Japanese patients with recent myocardial infarction was three-fold higher than that in Caucasian patients\(^2\).

As shown in Table 3, we compared the inducible spasm frequency in patients with nonobstructive and ischemic heart disease between German Caucasian patients and Japanese populations irrespective of small sample size\(^{24, 27}\). Overall inducible spasm frequency is one and half-fold higher in Japanese patients than in German Caucasian patients (55.7% vs. 33.4%, p<0.001). Inducible spasm frequency in German Caucasian patients with effort angina, rest and effort angina, and myocardial infarction is similar to that in Japanese populations, whereas provoked spasm incidence regarding rest angina is approximately twofold higher.
in Japanese patients than in German Caucasian populations. Angiographical inducible spasm by pharmacological testing may be less than 2-fold higher in Japanese patients than in German Caucasian populations.

IV. CMD

According to previous report on Caucasian patients, up to half of patients undergoing coronary arteriography have no obstructive CAD with a relatively higher prevalence in women (65% in women versus 32% in men)\(^20\). Furthermore, of these patients, up to 60% may have CMD. Jespersen et al. reported the increased risks of major adverse cardiovascular events in patients with stable angina pectoris with no obstructive coronary artery disease. However, they did not investigate the proof of coronary epicardial spasm in symptomatic patients with normal coronary arteries and diffuse nonobstructive CAD. Furthermore, antihypertensive medications that may be included as coronary vasodilators were recognized in only 43.3% of these patients. In contrast, according to a previous Japanese report, approximately 60% of patients with INOCA were diagnosed with CSA by intracoronary acetylcholine testing. Only 13.5% of these Japanese patients have CMD. As shown in Table 4, females were observed in more than half of the patients\(^24, 25-32\). The incidence of microvascular angina is markedly higher in Caucasian patients than in Japanese populations (31.5% vs. 17.2%, \(p<0.001\)), whereas the frequency of CSA is remarkably higher in Japanese patients than in Caucasian patients. Sex differences were not observed in patients with CSA, whereas 90% of patients with CMD were female. There is a remarkable difference regarding the incidence of CMD between Caucasian and Japanese populations. However, Caucasian cardiologists except for some special institutions do not perform pharmacological spasm provocation tests to diagnose the presence of coronary spasm before measurement of physiologic functional coronary reactivity tests. There are many procedural changes regarding intracoronary ACh doses and injection time between the two races, as shown in Table 5. Furthermore, the definition of positive epicardial spasm is different among the five studies. The incidence of complications of bradycardia in Caucasian populations is frequently observed, whereas Japanese studies reported no complications of bradycardia under the insertion of pacemakers.

V. Definition of microvascular angina

The Coronary Vasomotion Disorders International Study Group (COVADIS) defined the diagnosis of microvascular angina as follows: 1) presence of symptoms suggestive of myocardial ischemia, 2) objective documentation of myocardial ischemia as assessed by the currently available technique, 3) absence of obstructive CAD (\(< 50\% \) coronary diameter reduction and/or fractional flow reserve (FFR) > 0.80), and 4) confirmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm\(^30\). However, epicardial spasm is not first excluded based on using coronary reactivity testing in their definition. Japanese cardiologists may first neglect the presence of coronary epicardial spasm before measuring the value of coronary flow reserve (CFR) and FFR.

VI. CMD in patients with myocardial infarction with nonobstructive coronary arteries (MINOCA)

The term MINOCA was first reported by Beltrame in 2012 in his editorial comment regarding the Stockholm Myocardial Infarction with Normal Coronaries study\(^30\). Their group reported myocardial infarction with angiographically normal coronary arteries (MINCA). However, he mentioned that it may be more appropriately termed MINOCA because many studies have included patients with nonobstructive lesions (\(< 50\% \) on angiography)\(^35\).

Microvascular spasms are often revealed in Caucasian MINOCA patients\(^36, 37\), whereas Japanese populations may have rare causes of microvascular dysfunction in patients with MINOCA. Japanese Circulation Society (JCS) guidelines regarding acute coronary syndrome did not mention Japanese MINOCA patients with CMD\(^39\). We have not experienced patients with MINOCA due to CMD. According to the report by Montone et al., among 80 Caucasian patients with MINOCA patients and undergoing invasive provocation tests, the provocative test was positive in \(37 (46.3\%) \) patients including \(24 (30.0\%) \) patients with epicardial spasms and \(13 (16.3\%) \) patients with microvascular spasms\(^39\). Of importance, patients with a positive test had a significantly

| Table 3 | Comparisons of provoked spasm frequency in patients with ischemic heart disease without obstructive coronary arteries by intracoronary acetylcholine tests |
|---------|-------------------------------------------------|
|          | Caucasian\(^24\) | Japanese\(^27\) | p value | Japanese/Caucasian |
| Rest angina | 33.4% (112/346) | 66% (68/103) | \(< 0.001\) | 1.98 |
| Effort angina | 32.4% (72/222) | 35.5% (11/31) | 0.7346 | 1.10 |
| Rest and effort angina | 34.5% (82/238) | 50% (17/34) | 0.0780 | 1.45 |
| Myocardial infarction | 41.5% (17/41) | 51% (26/51) | 0.3631 | 1.23 |
| Overall ischemic heart disease | 33.4% (283/847) | 55.7% (122/219) | \(< 0.001\) | 1.67 |

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higher occurrence of death from any cause, cardiac death, and readmission for acute coronary syndrome than those with a negative test. However, Japanese cardiologists rarely experience patients with MINOCA and CMD in the clinical situation. Further study is necessary to clarify the racial heterogeneity and clinical characteristics of MINOCA patients with CMD between Caucasian and Japanese populations.

### VII. Diagnosis of CSA and CMD

#### 1. Pharmacological spasm provocation test

1) Intracoronary acetylcholine testing without pacemakers in Caucasians

Caucasian cardiologists reported intracoronary ACh testing without a pacemaker for 3 minutes of injection. Based on the Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function (ENCORE) study, intracoronary injections of 2, 20, 100, and 200 µg ACh were administered into the left coronary artery (LCA), whereas intracoronary injections of 80 µg ACh were administered into the right coronary artery (RCA). Intracoronary ACh testing is employed as an evaluation of coronary endothelial function. The cardiologists employed the above test as the clinical coronary reactivity test for provoked coronary spasm. Their group performed intracoronary ACh testing mainly in the LCA. Of importance, they reported the results of ACh testing in the RCA in only one-third of their study subjects. Intracoronary ACh administration for 3 minutes resulted in vasospasm in 34.4% of subjects.

Table 5: Comparisons of coronary vasoreactivity testing and definition of epicardial spasm

|                  | Ong et al.24 | The CorMicA trial29 | Mohri et al.30 | Sun et al.31 | Ohba et al.32 |
|------------------|--------------|---------------------|---------------|--------------|--------------|
| Published year   | 2014         | 2018                | 1998          | 2002         | 2012         |
| Patients’ number | 847          | 151                 | 117           | 55           | 370          |
| Acetylcholine dose (µg) |   |                     |               |             |             |
| RCA              | 80           | 50                  | 5/15/50       | 50           |             |
| LCA              | 2/20/100/200 | 100                 | 10/30/100     | 10/30/100    | 20/50/100    |
| RCA done         | 291 (34.4%)  | 12 (7.9%)           | 336 (90.8%)   |              |
| LCA done         | 845 (99.8%)  | 139 (92.1%)         | 55 (100%)     |              |
| Not implemented  |              | 5 (3.3%)            | 370 (100%)    |              |
| Complications    | Non-sustained VT/short Paf/brady hypotension | bradycardia |              |              |
| Injection time (s) | 180 seconds bolus injection | over 30 seconds | over 30 seconds | over 30 seconds |
| Lactate production | no           | yes                 | yes           | yes          | yes          |
| Guide wire       | no           | yes                 | no            | no           | yes          |
| Positive epicardial spasm |      |                     |               |             |             |
| Angiographical stenosis | >75%        | >90%                | >75%          | >75%         | >90% stenosis |
| Usual chest pain | yes          | yes                 | yes           | yes          |             |
| Ischemic ECG changes | yes          | yes                 | yes           |             |             |
| With pacemaker   | no           | no                  | yes           | yes          | yes          |

RCA: right coronary artery, LCA: left coronary artery, VT: ventricular tachycardia, Paf: paroxysmal atrial fibrillation, ECG: electrocardiogram
minutes may cause transient brady cardia or cardiac arrest. The authors defined positive pathological tests as > 75% transient stenosis and ischemic electrocardiogram and usual chest symptoms. The European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines classified coronary reactivity testing as class IIa and class IIb.

2) Intracoronary ACh testing with pacemaker in Japanese

According to the JCS guidelines, temporary pacemaker insertion is necessary for performing intracoronary ACh tests for 20 seconds. After the insertion of a temporary pacemaker, ACh chloride was injected in incremental doses of 20, and 50 µg into the RCA and 20, 50, and 100 µg into the LCA over 20 seconds with at least a 3-minute interval between each injection. Positive provoked spasm is defined as ischemic findings and greater than 90% stenosis. Furthermore, we employed maximum ACh doses of 80 µg and 200 µg into the RCA and LCA, respectively, as necessary. JCS guidelines, as well as COVADIS group, confirmed this test as class I. No irreversible complications except one death were reported.

3) Intracoronary ergonovine test

JCS guidelines recommend the administration of ER 20–60 µg into both coronary arteries for 2–4 minutes. In our institution, ER in a 0.9% warm saline solution is injected at 10 µg/min for 4 minutes for a maximal dose of 40 µg into the RCA and 16 µg/min over 4 minutes for a total dose of 64 µg into the LCA, with at least a 5-minute interval between each injection. However, various procedures are performed worldwide, as shown in Table 6. Bolus injection or continuous administration of ER are employed in the cardiac catheterization laboratory. The worldwide standard procedure of intracoronary ER testing should be constructed in the future. The positive spasm definition for ER tests is ischemic findings and > 90% transient stenosis. JCS guidelines defined this ER testing as class I, whereas Caucasian guidelines defined it as class IIa and class IIb.

4) Intravenous ergonovine test

According to the JCS guidelines, the intravenous ER test is not recommended for safety procedures or nonselective methods. In the past, Buxton et al. reported 3 deaths during intravenous ER tests. Although the intravenous ER test may still be performed in some countries, the intracoronary ER test should be performed instead of the older nonselective procedure during coronary arteriography.

Ethnic difference of spasm provocation tests

Japanese cardiologists perform spasm provocation tests first before measuring physiological parameters, such as CFR, FFR, or index of microcirculatory resistance. The Japanese population had higher frequency of CSA than the Caucasian population. Furthermore, CMD may be less present in Japanese populations. Caucasian cardiologists may skip vasoactivity testing because they may think that spasm provocation testing is a dangerous and cumbersome technique. In some European institutions, ACh testing without pacemakers is mainly employed. However, it is difficult to perform ACh tests in the RCA without pacemaker because of bradycardia or cardiac arrest. If Caucasian cardiologists perform ACh spasm provocation testing with pacemakers similar to Japanese cardiologists, the incidence of CSA may be greater than initially observed. As shown in Fig. 1, Japanese cardiologists perform pharmacological spasm provocation tests (vasoactivity test) before measuring the value of coronary physiological function using some guidewires. However, Caucasian cardiologists measure the value of coronary physiological function using some guidewire before performing coronary reactivity tests. This is the most striking difference between Japanese and Caucasian procedures. Japanese cardiologists first neglect the presence of epicardial spasms when diagnosing patients with

| Year | Author                  | LCA dose (µg) | RCA dose (µg) | Total dose (µg) | Infusion time (s) | Interval (min) | Positive spasm |
|------|-------------------------|---------------|---------------|-----------------|------------------|----------------|----------------|
| 1987 | Hackett et al.          | 1/5/10/30     | 1/5/10/30     | 92              | >60              | 5              | >90%           |
| 1988 | Molari et al.           | 5/1/10/35     | 5/1/10/35     | 100             | 20-30            | 3              |                |
| 1989 | Fournier et al.         | 25/25         | 25/25         | 100             |                  |                | Total or >75%  |
| 1991 | Kashi et al.            | 20            | 20            | 40              |                  |                | >90%           |
| 1991 | Toyo-oka et al.         | 20/40/60      | 20/40/60      | 240             |                  |                | >90%           |
| 1992 | Suzuki et al.           | 1/5/10/30     | 1/5/10/30     | 92              | 3-5              | >90%           |
| 1993 | Fukai et al.            | 5/10/50       | 5/10/50       | 130             |                  | >75%           |
| 1997 | Kanazawa et al.         | 40            | 40            | 80              | >30              | 3              | >90%           |
| 1998 | Yamada et al.           | 25/50         | 25/50         | 150             |                  | Total or TIMI I|
| 2007 | Hung et al.             | 1/5/10/30     | 1/5/10/30     | 92              | 3                | >70%           |
| 2010 | Kim et al.              | 5/10/30       | 5/10/30       | 90              |                  | 3              | >70-90%        |

LCA: left coronary artery, RCA: right coronary artery, TIMI: thrombolysis in myocardial infarction flow grade
CMD, whereas Caucasian cardiologists neglect the proof of coronary epicardial spasms in the cardiac catheterization laboratory lastly.

In a Japanese study, intracoronary injection of ACh was administered for 20-30 seconds, whereas European cardiologists administered intracoronary ACh over 180 seconds. Intracoronary administration time is the critical for provoked positive spasm according to our previous report. Slow injection of ACh for 3 minutes may provoke microvascular spasm or microvascular dysfunction, whereas rapid injection of ACh for 20–30 seconds may induce epicardial spasm. This methodological difference may lead to ethnic disparities in the incidence of CMD and CSA between Caucasian and Japanese patients.

ACh administration time plays a key role in provoked spasm.

According to the JCS guidelines, intracoronary ACh injection for 20–30 seconds with a pacemaker is recommended, whereas Caucasian cardiologists administer intracoronary ACh for 3 minutes without a pacemaker. We compared the two procedures in the same patients. After relief or no spasm when intracoronary ACh was injected for 20 seconds, intracoronary ACh administration for 3 minutes was performed using the same dose of ACh into the 30 LCAs. As shown in Table 7, the incidence of provoked spasm, ischemic electrocardiogram changes and chest symptoms was greater after a 20-second ACh injection than after a 3-minute ACh injection. Furthermore, back-up support pacemaker rhythm was observed in patients with an ACh injection for 3 minutes. We observed no cases of CMD with a 3-minute injection of ACh into the LCA.

Back-up pacemaker support during a 20 second injection of ACh

We reported the incidence of back-up support pacemaker rhythm when we performed ACh testing based on the JCS guidelines. We set 40/min as back-up pacemaker support during ACh testing. Back-up support pacemaker rhythm was observed in approximately 39.6% of patients when 20/50/100 µg ACh was injected for 20 seconds.

Table 7  
Comparisons of provoked positive spasm, back-up support rhythm, ischemic ECG changes, and chest symptoms between the two procedures in all 30 patients into the left coronary artery

|                      | 3 minutes' injection of ACh | 20 seconds' injection of ACh | p value |
|----------------------|-----------------------------|------------------------------|---------|
| Back-up PM support rhythm | 7 (23.3%)                   | 19 (63.3%)                   | 0.0017  |
| Provoked spasm       | 10 (33.3%)                  | 22 (73.3%)                   | 0.0019  |
| LAD                  | 8 (26.7%)                   | 22 (73.3%)                   | 0.0007  |
| LCX                  | 3 (10.0%)                   | 8 (26.7%)                    | 0.1820  |
| Diffuse spasm        | 6 (20.0%)                   | 21 (70.0%)                   | 0.0003  |
| Focal spasm          | 5 (16.7%)                   | 9 (30.0%)                    | 0.3598  |
| Microvascular spasm  | 0                           | 0                            |         |
| Ischemic ECG changes | 7 (23.3%)                   | 15 (50.0%)                   | 0.0320  |
| ST elevation         | 2 (6.7%)                    | 6 (20.0%)                    | 0.2545  |
| ST depression        | 5 (16.7%)                   | 9 (30.0%)                    | 0.2221  |
| Chest symptoms (pain/oppression) | 13 (43.3%)     | 22 (73.3%)                   | 0.0184  |

ACh: acetylcholine, PM: pacemaker, LAD: left anterior descending artery, LCX: left circumflex artery, ECG: electrocardiogram
administered into the LCA, whereas 77.8% of patients had backup support pacemaker rhythm when 20/50 µg ACh was injected into the RCA. We may perform intracoronary ACh testing without a pacemaker in the LCA in more than half of the patients irrespective of performing ACh tests based on the JCS guidelines.**

**What is an initial test?**

The resting flow and CFR assessment may be inaccurate after a positive spasm test possibly due to coronary microvascular spasm. Caucasian cardiologist performed coronary physiological testing first and finally coronary spasm provocation testing. They performed coronary reactivity testing at least 10 minutes apart from the injection of small amount of glyceryl trinitrate (< 200 µg)\(^7\). However, spasm provocation tests should be performed without administration of coronary vasodilators at least 24-48 hours. Spasm provocation tests under the administration of nitroglycerine may lead to the pseudo-negative results. The effect of intracoronary administration of ACh into each coronary artery by doppler flow guidewire was within 10 minutes in our past study, as shown in Table 8\(^6\).**

**Table 8 The duration of effect after intracoronary injection of acetylcholine by doppler flow wire**

| RCA | Spasm positive | Spasm negative |
|-----|----------------|----------------|
| Acetylcholine dose (µg) | 20 | 50 | 80 |
| Total number of vessels | 22 | 20 | 16 |
| Mean recovery time (seconds) | 132 ± 59 | 187 ± 61 | 186 ± 70 |
| Range (seconds) | (60-240) | (100-290) | (60-270) |
| Acetylcholine dose (µg) | 20 | 50 | 100 |
| Total number of vessels | 22 | 22 | 18 |
| Mean recovery time (seconds) | 168 ± 108 | 279 ± 108 | 286 ± 156 |
| Range (seconds) | (70-284) | (150-517) | (75-612) |

RCA: right coronary artery, LCA: left coronary artery

3. Physiological functional parameters by guidewire

Caucasian cardiologists may prefer to measure coronary physiological functional values, such as CFR, FFR, and coronary resistance\(^11\). According to the ESC guidelines, guidewire-based CFR and/or microcirculatory resistance measurements are defined as class IIa\(^12\). These parameters should be considered in patients with persistent symptoms, but not for coronary arteries that are either angiographically normal or have moderate stenoses with preserved instantaneous wave-free ratio/FFR. In contrast, intracoronary ACh with ECG monitoring is classified as class IIb. This test may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved instantaneous wave-free ratio/FFR, to assess microvascular spasm. Caucasian cardiologists mainly focus on coronary physiological and functional dysfunction to diagnose proof of microvascular spasm except for epicardial spasm.

4. Noninvasive test

Cardiologists perform noninvasive tests, such as hyperventilation tests, cold stress tests, mental stress tests, and exercise tests, to document coronary spasms\(^13, 14\). However, cardiologists can easily detect coronary conditions by computed tomography coronary angiography\(^15\). Even in Japan, the majority of cardiologists do not perform noninvasive tests to diagnose the presence of coronary spasms. The decade of diagnosing the presence of coronary spasm by using noninvasive tests may pass by.

**VIII. Medication**

Renin-angiotensin converting enzyme inhibitors (ACEIs) or renin-angiotensin receptor blockers (ARBs), and beta-blockers are first administered in Caucasian patients with CMD\(^16\). If chest pain is not controlled under the above medications, a CCB is administered. In contrast, CCB or nitrate is mainly administered in
Japanese populations with CMD as well as ACEI/ARB\(^2\). Because epicardial spasm is sometimes observed in Japanese populations with CMD, CCB or nitrate may be first selected in the clinic. Amlodipine is mainly prescribed in Caucasian CSA patients, whereas dihydropyridine CCBs except other than amlodipine are prescribed in Japanese CSA and CMD patients. Furthermore, benzodiazepine CCBs are often administered to Japanese CSA patients. Sato et al. reported that nitrates, statins, ACEIs/ARBs, and beta-blocker prescriptions were markedly higher in Caucasian CSA patients than in Japanese CSA patients. However, the prescription of CCBs was higher in Japanese patients with CSA than in Caucasian patients with CSA\(^6\).

IX. Prognosis
Clinical outcomes in Caucasian patients with CMD were unfavorable, whereas those of Japanese patients with CMD were unknown. Acute myocardial infarction was frequently observed in Caucasian patients with MINOCA and CMD, whereas there have been no or fewer reports regarding the complications of acute coronary syndrome in Japanese patients with CMD\(^2\). The reasons for these differences between the two races are unknown. An ethnic or racial difference between Caucasian and Japanese populations may explain these differences. In contrast, the long-term prognosis remains better in Japanese CSA populations than in Caucasian CSA populations\(^5\).

X. Future
Caucasian and Japanese cardiologists should cooperate to investigate the racial differences regarding the incidence and clinical characteristics of patients with coronary vasomotion disorders. Caucasian cardiologists should perform spasm provocation testing routinely if they encounter patients with MINOCA and INOCA in the cardiac catheterization laboratory. In contrast, Japanese cardiologists should focus on investigating patients with microvascular dysfunction using physiological functional modalities in the cardiac catheterization laboratory as well as investigating the presence of coronary spasm. If a prospective randomized study is ongoing, ethnic differences between Caucasian and Japanese patients with CMD should be clarified.

XI. Ethnic difference
Caucasian cardiologists investigate proof of microvascular physiological function using a guidewire before diagnosing the presence of epicardial spasm, whereas Japanese cardiologists investigate proof of epicardial coronary spasm using a pharmacological spasm provocation test such as acetylcholine and ergonovine before diagnosing the presence of microvascular physiological dysfunction. A procedural disparity based on ethnicity may lead to racial differences regarding the frequency of inducible spasm and CMD between Caucasian and Japanese populations. If the same protocol using the same modality and same dose of ACh and adenosine is employed, real racial differences regarding the incidence and clinical characteristics of CSA and CMD may be revealed in the future.

XII. Study limitation
This review has several limitations. First is a selection bias of the previous papers. Second is the difference in spasm provocation testing and physiologic functional parameters. Third is the difference regarding the definition of CSA and CMD between Caucasian and Japanese populations. Fourth is that information regarding CSA and CMD between Caucasian and Japanese people from the same prospective trial is lacking.

XIII. Conclusions
Racial and ethnic differences about CSA and CMD are revealed between Caucasian and Japanese populations. CSA is often observed in Japanese patients, whereas CMD is remarkably higher in Caucasian patients. However, precise racial or ethnic disparities between Caucasian and Japanese individuals are controversial. A prospective randomized study regarding coronary vasomotion disorders between the two races is necessary in the future.

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Conflicts of interest
The authors declare that they have no conflicts of interest.

References
1) Beltrame JF, Sasayama S, Maseri A: Racial heterogeneity in coronary artery vasomotor reactivity: Differences between Japanese and Caucasian patients. J Am Coll Cardiol 1999; 33: 1442–1452
2) Pristipino C, Beltrame JF, Finocchiaro ML, et al: Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction. Circulation 2000; 101: 1102–1108
3) Michelsen MM, Mygind ND, Frestad D, et al: Women with stable angina pectoris and no obstructive coronary artery disease: closer to a diagnosis. Eur Cardiol 2017; 12: 14–19
4) Merz CN, Kelsey SF, Pepine CJ, et al: The women’s ischemia syndrome evaluation (WISE) study: Protocol design, methodology and feasibility report. J Am Coll Cardiol 1999; 33: 1453–1461
5) Pepine CJ, Anderson RD, Sharaf BL, et al: Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia: Results from the National Heart, Lung and Blood Institute WISE (Women’s Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010; 55: 2825–2832
6) AlBadri A, Merz CNB, Johnson BD, et al: Impact of abnormal coro-
51) Hackett D, Larkin S, Chierchia S, et al: Induction of coronary artery spasm by a direct local action of ergonovine. Circulation 1987; 75: 577–582.
52) Mohri M, Okamatsu S, Nakamura M: Biphasic response of coronary arterial diameter to intracoronary ergonovine. Clin Cardiol 1988; 11: 710–714.
53) Fournier JA, Cortacero JAP, Turá A, et al: Effects of intracoronary injection of ergonovine on angiographic normal coronary arteries: study of 108 consecutive patients. Clin Cardiol 1989; 12: 561–568.
54) Kaski JC, Tousoulis D, Gavriilides S, et al: Comparison of epicardial coronary artery tone and reactivity in Prinzmetal’s variant angina and chronic stable angina pectoris. J Am Coll Cardiol 1991; 17: 1058–1062.
55) Toyoda T, Saegawa T, Suzuki N, et al: Increased plasma level of endothelin-1 and coronary spasm induction in patients with vasospastic angina pectoris. Circulation 1991; 83: 476–483.
56) Suzuki Y, Tokunaga S, Ikekuchi S, et al: Induction of coronary artery spasm by intracoronary acetylcholine: comparison with intracoronary ergonovine. Am J Cardiol 1992; 74: 2260–2261.
57) Fukai T, Koyanagi S, Takeshita A: Role of coronary vasospasm in the pathogenesis of myocardial infarction: study in patients with no significant coronary stenosis. Am Heart J 1993; 126: 1305–1311.
58) Kanazawa K, Suzumoto M, Ishida T, et al: Disparity between serotonin- and acetylcholine-provoked coronary artery spasm. Clin Cardiol 1997; 20: 146–152.
59) Yamada T, Okamoto M, Sueda T, et al: Ergonovine-induced alteration in coronary flow velocity preceding onset of occlusive spasm in patients without significant coronary artery stenosis. Am J Cardiol 1998; 81: 150–159.
60) Hung MY, Hung MJ, Cheng CW, et al: Safety and predictors of a positive result of intracoronary ergonovine testing in patients with ischemic heart disease without hemodynamically significant coronary artery stenosis in Taiwan. Acta Cardiol Sin 2007; 23: 150–159.
61) Kim W, Cho JS, Hong YJ, et al: Coronary spastic angina (Coronary Spastic Angina)(JCS joint working group: Guidelines for diagnosis and treatment of coronary artery spasm in patients with acute coronary syndrome)study follow-up. J Am Coll Cardiol 2011; 57: 147–152.
62) Ong P, Athanasiadis A, Borgulya G, et al: 3-year follow-up of patients with coronary artery spasm as cause of acute coronary syndrome: the CASPAR (coronary artery spasm in patients with acute coronary syndrome)study follow-up. J Am Coll Cardiol 2011; 57: 147–152.
63) Montalescot G, Sechtem U, Achenbach S, et al: 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology [published correction appears in Eur Heart J 2014; 35: 2260–2261]. Eur Heart J 2013; 34: 2949–3003.
64) Anderson JL, Adams CD, Antman EM, et al: 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in Circulation. 2013; 127: e863–e864]. Circulation 2013; 127: e663–e828.
65) Suzuki S, Kaikita K, Yamamoto E, et al: Role of acetylcholine spasm provocation test as a pathological assessment in nonobstructive coronary artery stenosis. Am J Cardiol 2017; 119: 2349–2358.
66) Aziz A, Hansen HS, Sechtem U, et al: Sex-related differences in vasomotor function in patients with angina and non-obstructive coronary disease in the catheter laboratory. Heart 2019; 105: 1536–1542.
67) Saka T, Fujimoto K, SASAKI, et al: Necessity of back-up pace maker support during acetylcholine testing as a safe method. Coron Artery Dis 2020; 31: 197–198.
68) Ford TJ, Berry C: How to diagnose and manage angina without obstructive coronary artery disease: Lessons from the British Heart Foundation CorMicA Trial. Interv Cardiol 2019; 14: 76–82.
69) Sueda S, Kohno H, Fukuda H, et al: Induction of coronary artery spasm by intracoronary acetylcholine: comparison with intracoronary ergonovine. Am J Cardiol 1992; 74: 2260–2261.
70) Suzuki Y, Tokunaga S, Ikekuchi S, et al: Induction of coronary artery spasm by intracoronary acetylcholine: comparison with intracoronary ergonovine. Am J Cardiol 1992; 74: 2260–2261.
spasm by two pharmacological agents: comparison between intracoronary injection of acetylcholine and ergonovine. Coron Artery Dis 2003; 14: 451–457

71) Rahman H, Ryan M, Lamley M, et al: Coronary microvascular dysfunction is associated with myocardial ischemia and abnormal coronary perfusion during exercise. Circulation 2019; 140: 1805–1816

72) Merz CNB, Handberg EM, Shufelt CL, et al: A randomized placebo-controlled trial of late Na current inhibitor (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve. Eur Heart J 2016; 37: 1504–1513

73) Yasue H, Nagao M, Omote S, et al: Coronary arterial spasm and Prinzmetal’s variant form of angina induced by hyperventilation and Tris-buffer infusion. Circulation 1978; 58: 56–62

74) Sueda S, Saeki H, Otani T, et al: Investigation of the most effective provocation test for patients with coronary spastic angina: Usefulness of accelerated exercise following hyperventilation. Jpn Circ J 1999; 63: 85–90

75) Ito K, Ogawa T, Yoshimura M: Severe coronary spasm occasionally detected by coronary computed tomography. Eur Heart J 2009; 20: 2768

76) Merz CNB, Pepine CJ, Shimokawa H, et al: Treatment of coronary microvascular dysfunction. Cardiovasc Res 2020; 116: 856–870