

How to study the prevalence and mechanisms of racial differences in coronary vasomotor response

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The rapid progress of therapeutic modalities of cardiovascular diseases have led to the development of clinical practice guidelines on the basis of large scale clinical trials. However, an individual response of each patient may not match the mean effect of an intervention in these trials. Therefore, recommendations based on clinical trials performed in a given patient population may not be applicable to the other races. Here, we assessed epidemiological and pathophysiological differences in cardiovascular diseases across racial groups. The incidence of coronary artery disease is the lowest in Japan of all the industrialized nations. Our previous study that compared post-hospital course of acute myocardial infarction in Japanese and Caucasians in North America demonstrated that cardiac events were significantly less in Japanese even when the initial infarct size was similar. Ischemic heart disease constitutes the most common cause of heart failure in the United States but nonischemic cardiomyopathy occurs more frequently in Japan. On the other hand, vasospastic angina is by far more common in the Japanese population. The first comparative study we carried out in Japanese and Italian patients with acute myocardial infarction also showed that percentage of vasospasm in the infarct-related arteries is 3 times higher in Japanese. Thus, coronary spasm appears to be more important as well as the pathogenesis of myocardial infarction in Japan. This fact was reflected by the more frequent use of calcium antagonists in Japan during the acute phase of myocardial infarction. On the other hand, the use of inotropic agents has now been contraindicated for the treatment of patients with chronic heart failure, however it may not be the case in the Japanese population in whom mortality is relatively low. Cardiotonic therapy could be justified in Japanese as it allows optimal care in the context of relief of symptoms and an improved quality of life. Therefore, each racial group should obtain specific evidence aimed at developing its own guidelines for therapy rather than translating major guidelines developed for other populations.

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Among industrial nations the incidence of coronary artery disease is the lowest in Japan¹. Age-adjusted death rate due to ischemic heart disease in Japan has been estimated to be one sixth of that observed in the United States¹. We compared post-hospital outcome of acute myocardial infarction in 106 patients in Japan and 789 patients in North America during an average follow-up period of 26 months. Some risk factors were more frequent in Japanese patients who were older (61 vs 58 years, $p < 0.001$), with a higher percentage of males (88 vs 75%, $p < 0.008$) and of cigarette smokers (30 vs 14%, $p < 0.001$). After adjustment for clinical variables and medications Cox analysis showed a significantly greater risk of experiencing a primary endpoint (cardiac death, nonfatal myocardial infarction or unstable angina) in Northern Americans². According to the United Network for Organ Sharing data³, the most frequent cause of heart

transplantation is heart failure due to ischemic heart disease in the United States, while among 140 patients who applied for heart transplantation in Japan, ischemic heart disease constitutes 4% only⁴.

On the other hand, vasomotor angina is reported to be more common among Japanese. Table I⁵⁻¹¹ summarizes clinical characteristics of vasomotor angina in Japanese and Caucasians obtained by a pooled analysis of 7 large clinical trials¹². Vasomotor angina of Japanese patients differs significantly from that observed in Caucasians by lower incidence of prior myocardial infarction, lower association with obstructive coronary artery disease, less extensive coronary lesion, and less frequent impairment of left ventricular function. The survival rate at 3-year follow-up of patients with vasomotor angina is significantly better in Japanese patients (97 vs 89%, $p < 0.0001$). Fifty-two percent of Japanese

Table I. Differences in variant angina between Japanese and Caucasian patients.

Feature	Nakamura et al. ⁵	Yasue et al. ⁶	Shimokawa et al. ⁷	Severi et al. ⁸	Waters et al. ⁹	Mark et al. ¹⁰	Walling et al. ¹¹
Study country	Japan	Japan	Japan	Italy	Canada	USA	Canada
Sample size	349	245	158	138	169	62	217
Clinical characteristics							
Mean age (years)	54	54	57	53	51	52	51
Female (%)	12	13	14	7	31	26	24
Prior MI* (%)	8	6	6	33	18	18	–
Angiographic findings (%)							
0 vessel disease	66	40	80	8	39	38	42
1 vessel disease	27	44	16	36	36	35	39
Multivessel disease	7	16	4	56	25	27	19
LVEF	–	6	6	53	26	43	26
Spastic site (%)							
Anterior	46	51	47	69	57	35	52
Inferior	45	38	53	31	43	65	48
Anterior/inferior	9	11	–	–	–	–	–
3-year survival* (%)	98	97	96	91	87	84	92
3-year survival without MI* (%)	95	85	92	77	75	63	77
Death without CAD* (%)	57	50	50	9	8	17	24

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

patients with coronary fatalities have normal or near normal coronary arteries, compared with 16% only of Caucasian patients ($p = 0.0006$). Fatal ventricular arrhythmias are more common following reperfusion even if a preexisting obstructive lesion is less severe¹³. Therefore, Japanese patients are more prone to succumb with sudden cardiac death presumably due to arrhythmias rather than fatal myocardial infarction⁵.

Ethnic differences in the pathogenesis of coronary spasm

In the Western society focal coronary spasm has been attributed to an amplification of normal vasoconstriction at the site of plaques or to nonspecific smooth muscle cell hyperreactivity^{14,15}. In Japanese patients, coronary artery spasm typically occurs in angiographically normal coronary arteries and has been attributed to autonomic nervous imbalance¹⁶ or endothelial dysfunction¹⁷. Hyperreactivity of nonspastic coronary artery segments has often been observed in Japanese patients with vasomotor angina¹⁸. This is in contrast with the findings in Caucasian patients¹⁹ in whom no difference in coronary reactivity has been observed between nonspastic segments in patients with variant angina and in normal subjects. Analysis of heart rate variability has suggested an increase in parasympathetic activity in Japanese prior to an episode of coronary spasm²⁰. On the other hand, in Italian patients, a fall in high frequency activity was observed prior to spasm onset and a withdrawal of parasympathetic activity in these patients was suggested²¹. In Japanese patients with vasomotor angina, a localized deficiency of coro-

nary nitric oxide production has also been postulated to be responsible for coronary spasm^{17,21,22}.

Ethnic differences in vasomotor response in acute myocardial infarction

The pathophysiology of myocardial infarction could be different in Japanese and in Caucasian patients. In a French study inducible coronary spasm was observed in 21% of patients with acute myocardial infarction within 6 weeks of its onset²³ but in 9% only of control patients with obstructive coronary atherosclerosis but no infarction. In an Italian study the incidence of inducible spasm within 2 weeks of acute myocardial infarction was 11%²⁴. The incidence of coronary spasm in response to provocative agents in Japanese patients with a recent myocardial infarction is much higher; indeed it was observed in 69% of patients with recent myocardial infarction as compared with 21% of patients with stable angina without history of infarction²⁵. These findings suggest that coronary spasm might be more important in the pathogenesis of myocardial infarction in Japanese patients.

Despite the numerous reports in many countries, prospective studies comparing coronary vasomotor reactivity between different ethnic groups are limited. Thus, we carried out the first comparative study of coronary spasm in different ethnic groups in patients recruited by the same criteria, using the same provocative tests applied by the same team of investigators, and a centralized analysis of angiograms²⁶. Thirty-four patients with a first documented acute myocardial infarction were enrolled at the Catholic University of Rome

(Italy) and at Affiliate Hospitals of Kyoto University (Japan). On admission Italian patients received intravenous thrombolysis while Japanese patients underwent intracoronary thrombolysis. In patients with successful recanalization, the provocative test was performed within 7-10 days of admission by injecting incremental doses of acetylcholine in bolus first into the noninfarct-related artery (NIRA) and then into the infarct-related artery (IRA). At the completion of the study protocol, 250 µg of nitroglycerin were injected into both IRA and NIRA.

On admission, Japanese patients were significantly older, while Caucasian patients had a significantly higher body mass index, cholesterol and triglyceride levels. Other risk factors and clinical findings were not significantly different. Japanese patients had significantly higher peak creatine phosphokinase values but ejection fraction was not different between the two groups. Coronary spasm was more often focal than diffuse and occurred more frequently in proximal than in distal coronary segments in both populations. More importantly, coronary spasm was observed much more frequently in Japanese than in Caucasian patients (80 vs 37%). The incidence of spasm in the IRA was 3 times higher in Japanese than in Caucasian patients (66.7 vs 22.6%). Furthermore, the incidence of spasm in the NIRA and the incidence of multivessel spasm was 4 times higher in Japanese than in Caucasian patients (39.3 vs 11.1% and 64 vs 17%). Vasoconstrictor response defined as percent diameter reduction below baseline in nonspastic segments was slightly but significantly greater in Japanese than in Caucasian patients (-23 vs -20%) (Table II).

Ethnic differences in medical treatment of acute myocardial infarction

Medical treatment administered during the acute phase of myocardial infarction is considerably different

in Japan and in Western countries. Although the utilization of nitrates, acetylsalicylic acid and ACE-inhibitors is similar, calcium antagonists are used 3 times as much in Japan than in Western countries. Conversely, beta-blockers and heparin are more used in Western countries than in Japan. The greater utilization of calcium antagonists in Japan probably reflects the higher incidence of coronary spasm.

Another example of the racial difference in the therapeutic strategies is the use of inotropic agents in chronic treatment of heart failure. Depression of myocardial contractility plays an important role in the development of heart failure and intensive interest and passion have been generated by the search for orally effective inotropic agents over the past few decades. Several extensive clinical trials carried out in Western society have revealed that newly synthesized orally active inotropic agents that increase the concentration of intracellular cyclic AMP either by promoting its synthesis by beta-adrenergic receptor agonists or by inhibiting its degradation by phosphodiesterase inhibitors produce a dramatic short-term hemodynamic benefit in patients with advanced heart failure; yet, the long-term use of these agents is associated with mortality excess. Therefore, all of these agents are now regarded as unsuitable for chronic heart failure treatment. In contrast, in Japan mortality due to heart disease is substantially lower than that found in all other Western countries^{1,2}. In a clinical trial, 2 deaths only were observed among 276 symptomatic heart failure patients with average ejection fraction of 33%²⁷, and 4 deaths were observed among 173 patients with average ejection fraction of 30% during a follow-up period of 52 weeks in another study²⁸. In this setting inotropic agents have been shown to exert favorable effects on quality of life²⁷. Therefore, in Japan patients with heart failure have low mortality rate and may take advantages by treatment with oral inotropic agents which improve their quality of life.

Table II. Spastic response of coronary arteries in Caucasian and Japanese patients.

	Caucasian patients	Japanese patients	p
Incidence (% of patients)	37 (7/9)	80 (12/15)	0.02
Arteries with spasm (% of total no. arteries)			
Infarct-related arteries	22.6 (7/31)	66.7 (16/24)	
Noninfarct-related arteries	11.1 (7/63)	39.3 (22/56)	
Total	15 (14/94)	47 (38/80)	< 0.00001
Segments with spasm (% of total no. segments)			
Infarct-related arteries	12 (11/90)	38 (27/72)	< 0.0001
Noninfarct-related arteries	7 (13/189)	23 (36/160)	< 0.0001
Total	9 (24/279)	27 (63/232)	< 0.0001
Distribution of spasm			
Proximal segments	12 (3/24)	19 (12/63)	
Middle segments	29 (7/24)	30 (19/63)	
Distal segments	58 (14/24)	51 (32/61)	
Multivessel spasm (% of patients)	17 (3/18)	64 (9/14)	< 0.02

Conclusions

We have convincing evidence of ethnic heterogeneity in coronary vasomotor reactivity. Clinical and pathophysiological differences between Japanese and Caucasian patients are observed not only in coronary artery diseases but also in many aspects of heart failure. Our observations imply that data derived from studies in one population cannot be automatically extrapolated to the other. Accordingly, during every day patients' care, the individual response to a given medication is extremely important even when it does not match the mean effect of an intervention in a large trial as highlighted by more frequent use of calcium antagonists in acute coronary syndromes or treatment of chronic heart failure with oral inotropic agents in the Japanese population.

The initial sequencing and analysis of the human genome has already allowed the identification of more than 1.4 million single nucleotide polymorphisms²⁹. These genetic tools are expected to enable us to identify the genetic basis for differences in the diverse ethnic groups and facilitate individual tailoring of treatment for cardiovascular diseases.

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