ORIGINAL ARTICLE

Assessment of coronary vasomotor responses to acetylcholine in German and Japanese patients with epicardial coronary spasm—more similarities than differences?

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Abstract

Coronary spasm is an established cause for angina pectoris. Ethnic differences have been suggested among Asian compared to Caucasian patients regarding prevalence, gender distribution, and angiographic patterns of coronary spasm. The aim of this study was to compare contemporary German and Japanese patients with coronary spasm. Between 2011 and 2015, 149 patients with resting angina and unobstructed coronary arteries with acetylcholine-induced epicardial spasm were enrolled in Stuttgart, Germany ($n = 69$) and Sendai, Japan ($n = 80$). All patients underwent intracoronary acetylcholine testing according to a standardized protocol. Comprehensive analysis included type of spasm (focal/diffuse), dose of acetylcholine leading to spasm, and frequency of multivessel spasm. Patients in this study were 61 ± 11 years old, predominantly female (54%), and had normal left ventricular ejection fraction ($73 \pm 9\%$). Diffuse spasm was the most prevalent type of spasm (85%) whereas focal spasm was found in the remaining 15% of patients. 31% of patients had multivessel spasm. Comparing the German with the Japanese patients, distribution of spasm type (focal/diffuse, $p = 0.19$) and frequency of multivessel spasm ($p = 0.22$) were comparable. Moreover, when Japanese patients were compared with German patients and diffuse spasm with focal spasm patients, respectively, no significant differences were observed regarding the acetylcholine dose required to induce spasm ($p = 0.078$ and $p = 0.46$, respectively). In conclusion, diffuse epicardial coronary spasm is the most frequent finding among German and Japanese patients with resting angina, unobstructed coronary arteries, and epicardial spasm on acetylcholine testing. Japanese and German patients share several similarities including comparable types of spasm and frequency of multivessel spasm.

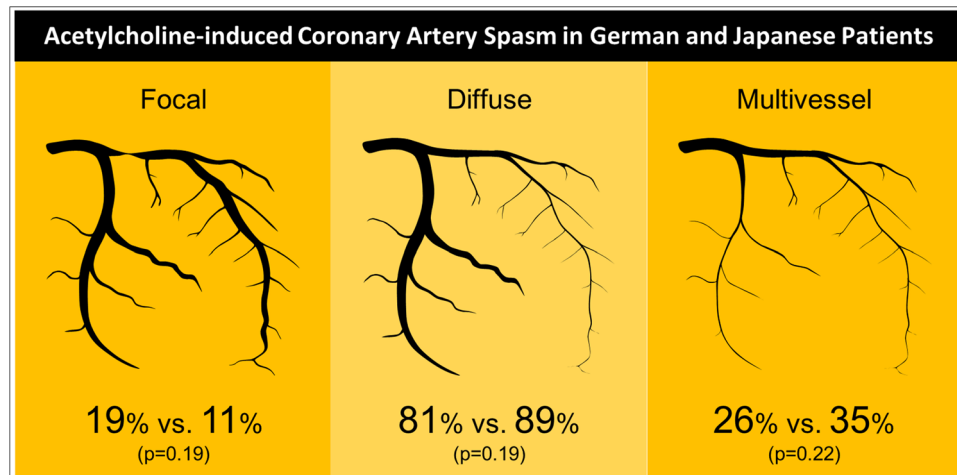Akira Suda, Andreas Seitz, Hiroaki Shimokawa and Peter Ong contributed equally to this study.

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Graphical abstract

Acetylcholine-induced Coronary Artery Spasm in German and Japanese Patients

Focal	Diffuse	Multivessel
19% vs. 11% (p=0.19)	81% vs. 89% (p=0.19)	26% vs. 35% (p=0.22)

Keywords Acetylcholine · Coronary spasm · Stable angina · Racial differences

Abbreviations

ACh	Acetylcholine
ECG	Electrocardiogram
JCS	Japanese Circulation Society
LCA	Left coronary artery
MINOCA	Myocardial infarction with non-obstructed coronary arteries
RCA	Right coronary artery

Introduction

Epicardial coronary artery spasm is a well-known and frequent clinical condition with characteristic features such as (resting) angina pectoris, ischemic ECG changes, and > 90% epicardial diameter reduction [1]. Over the past 40 years, coronary artery spasm research has made important progress [2]. From a pathophysiological point of view, it has been shown that vascular smooth muscle hyperreactivity with involvement of the Rho-kinase pathway plays a major role in the development of coronary spasm [3]. Clinically epicardial spasm can occur in patients with as well as those without epicardial atherosclerotic coronary artery disease and may also involve the coronary microcirculation [4]. Recently, much attention has been paid to the prevalence of coronary spasm in patients with chest pain and unobstructed coronary arteries [5] and more recently in those with myocardial infarction and unobstructed coronary arteries (MINOCA) [6, 7]. The diagnosis can be made by using intracoronary provocation testing with either acetylcholine (ACh) or ergonovine [8] and international standardized criteria for the diagnosis are now available [9]. However, spasm provocation tests are only broadly applied in daily clinical routine in Asia, especially in Japan, whereas they are underused in Western countries although they have been proven to be useful and safe [10]. Previously, it has been suggested that there are racial differences in coronary spasm between Asian and Caucasians patients, including the prevalence and angiographic pattern of spasm, suggesting that Japanese patients have more diffuse than focal spasm and a higher frequency of multivessel spasm [11, 12]. However, other studies have now shown that the prevalence of coronary spasm may be comparable between European and Asian patients [2, 13]. Moreover, current data from an international prospective coronary artery spasm registry have shown that European and Asian patients with coronary spasm—despite several differences—have most often diffuse spasm noted in both ethnicities [14]. Thus, in the present study, we compared a contemporary series of patients with resting angina, unobstructed coronary arteries, and proof of epicardial spasm on intracoronary acetylcholine testing from two centeres, i.e. Stuttgart (Germany) and Sendai (Japan). The aim was to assess clinical characteristics as well as detailed angiographic characteristics such as the frequency of focal and diffuse spasm as well as multivessel spasm between the two cohorts.

Methods

Patients

Between 2011 and 2015, a total number of 149 consecutive patients were enrolled in Stuttgart, Germany ($n = 69$)

and Sendai, Japan ($n = 80$). They fulfilled the following inclusion criteria: resting angina, unobstructed coronary arteries (< 50% epicardial diameter obstruction), epicardial coronary spasm on acetylcholine testing (see definition below). Patients with any of the following conditions were not included: cardiomyopathy, myocarditis, previous coronary bypass-operation, valvular heart disease, previous stent implantation, or a clinical presentation with acute coronary syndrome (including significant elevation of high-sensitive Troponin concentrations). The following clinical variables were recorded in all patients: age, sex, presence of hypertension, diabetes mellitus, hypercholesterolemia, current smoking, positive family history for cardiovascular disease (defined as myocardial infarction or stroke in a first degree relative < 60 years of age), and left ventricular ejection fraction as determined by transthoracic echocardiography.

Study protocol

The study protocol fully complied with the Declaration of Helsinki and all patients gave written informed consent before angiography. For the present retrospective data analysis, all data were handled anonymously. All patients underwent diagnostic coronary angiography followed by intracoronary provocation with acetylcholine (ACh-test) with proof of epicardial coronary spasm. In this study, patients at both institutions underwent intracoronary acetylcholine provocation testing according to the local institutional acetylcholine testing protocol [15, 16]. Differences between both institutional protocols include that the patients in Stuttgart were assessed with incremental doses of 2, 20, 100, and 200 μg of ACh and the patients in Sendai with incremental doses of 20, 50, and 100 μg. Moreover, a temporary pacemaker was placed for the test in Sendai according to the recommendations of the Japanese Circulation Society (JCS) [17], whereas the test was performed without pacemaker in Stuttgart. Acetylcholine was manually infused over 20 s into the left coronary artery (LCA) via the angiographic catheter. Patients were only included in this study when acetylcholine testing revealed an epicardial spasm in the LCA. A bolus of glyceryltrinitrate 0.2 mg was injected into the LCA to relieve angina and epicardial spasm and the vessels were again imaged. Cardiovascular medications (beta blockers, calcium channel blockers, and nitrates) were discontinued at least 24 h before coronary angiography. Heart rate, blood pressure, and the 12-lead-ECG were continuously monitored during ACh-testing. Ischemic ECG-changes were defined as transient ST-segment depression or elevation ≥ 0.1 mV in at least two contiguous leads [18].

ACh-test assessment and definitions

The ACh-test was considered 'positive' and indicative for epicardial coronary spasm in the presence of focal or diffuse epicardial coronary diameter reduction $\geq 90\%$ compared to the relaxed state following intracoronary nitroglycerine infusion in any epicardial coronary artery segment of the LCA, together with the reproduction of the patient's symptoms and ischemic ECG changes. Both the location and type of epicardial coronary spasm (i.e. focal vs. diffuse) were assessed. 'Focal' spasm was defined as a circumscribed transient vessel narrowing within the borders of one isolated coronary segment as defined by the American Heart Association [19]. 'Diffuse' spasm was diagnosed when the vessel narrowing was observed in ≥ 2 adjacent coronary segments. Due to the fact that at Stuttgart ACh testing of the right coronary artery (RCA) is only performed if the ACh-test of the LCA is uneventful, only ACh testing of the LCA was included in the present study. Subsequently, multivessel spasm was defined as ACh-induced spasm of the left anterior descending as well as the left circumflex artery. Serious adverse events during ACh-test were defined as severe arrhythmia (ventricular fibrillation/tachycardia or symptomatic bradycardia), cardiogenic or anaphylactic shock, acute myocardial infarction, respiratory failure, and death. No incidences of catheter-induced spasms were observed.

Statistical analysis

Statistical data analysis was carried out with SPSS 23.0 (IBM, USA). Results are expressed as mean ± standard deviation. The t test was used to compare continuous variables. For values without normal distribution, median and interquartile ranges are stated and the Mann–Whitney U test was used for analysis. The Fisher exact test was used for categorical variables. A two-tailed p value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

The 149 consecutive patients with epicardial coronary artery spasm enrolled in this study were on average 61 ± 11 years old and predominantly female (54%). There were significant differences in cardiovascular risk factors between the two ethnic groups; compared with the Japanese patients, German patients had a higher prevalence of hypertension (68% vs. 38%, $p = 0.011$), smoking (39% vs. 16%, $p = 0.002$), and a positive family history of cardiovascular disease (48% vs. 11%, $p < 0.001$) (Table 1). Left ventricular ejection fraction was comparable in both groups.

Table 1 Clinical characteristics of all patients in the study

	All patients	Stuttgart (Germany)	Sendai (Japan)	p value
n =	149	69 (46)	80 (54)	
Age (mean ± SD)	61 ± 11	61 ± 11	61 ± 11	0.98
Race (Caucasian/Asian)	69/80	69/0	0/80	**< 0.001**
Sex (male)	69 (46)	32 (46)	37 (46)	0.99
LVEF (mean ± SD)	73 ± 9	72 ± 10	73 ± 8	0.78
Cardiovascular risk factors				
Hypertension	85 (57)	47 (68)	38 (48)	**0.011**
Hypercholesterolemia	75 (50)	39 (57)	36 (45)	0.16
Diabetes mellitus	31 (14)	11 (16)	20 (25)	0.17
Current smoking	40 (27)	27 (39)	13 (16)	**0.002**
Positive family history of CVD	42 (28)	33 (48)	9 (11)	**< 0.001**

Data are absolute numbers (percentage) or mean ± SD

Significant p values are in bold (p < 0.05)

SD standard deviation, *LVEF* left ventricular ejection fraction, positive family history for *CVD* myocardial infarction or stroke in a first degree relative < 60 years of age

Angiographic findings during ACh testing

In the overall cohort of 149 patients, ACh testing revealed diffuse epicardial spasm in 85% of cases (Fig. 1 left). Focal spasm was noted in 15% of patients (Fig. 1 right; Table 2).

Multivessel spasm during ACh testing was observed in 31% of cases.

Comparing the two subpopulations of German and Japanese patients, respectively, no statistically significant difference was noted in the prevalence of the spasm characteristics; the rates of diffuse spasm (81% vs. 89%, p = 0.19), focal
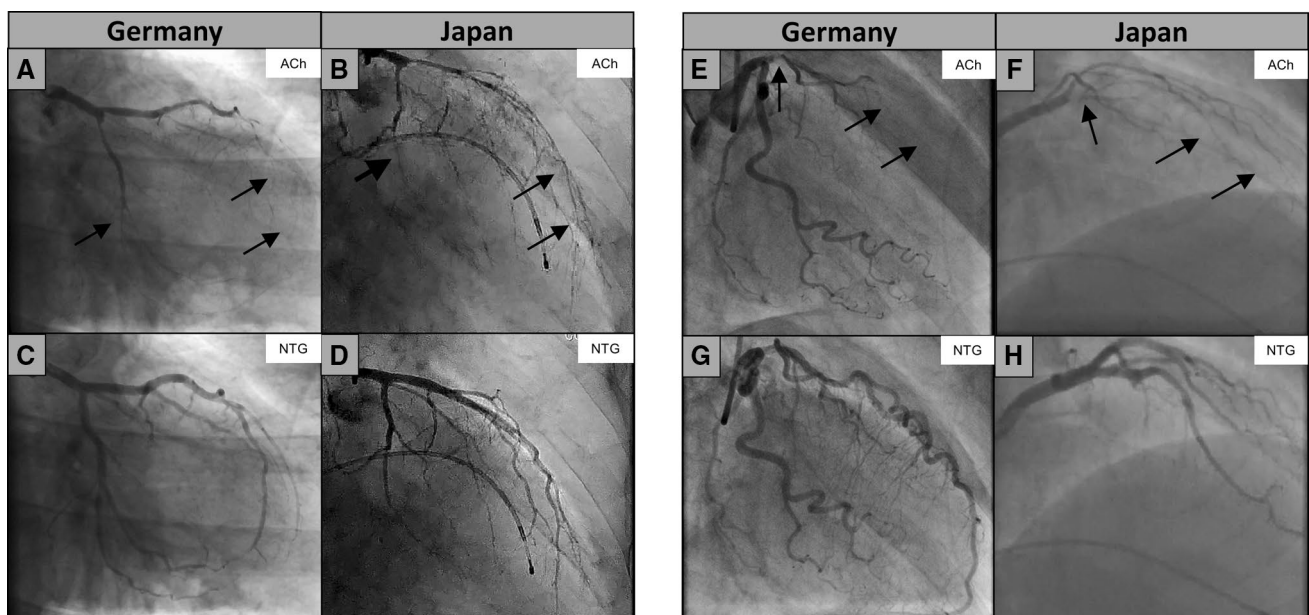

Fig. 1 Coronary angiograms of representative patients from Germany and Japan with similar diffuse (left) and focal (right) spasm. Left: The angiograms illustrate similar vasoconstricting response to intracoronary acetylcholine (**a** 20 µg ACh and **b** 50 µg ACh) to induce diffuse severe spasm of the left anterior descending artery and the left circumflex artery (arrows, **a** and **b**), which was accompanied by reproduction of the patient's usual angina and ischemic ECG changes. Coronary spasm was resolved by intracoronary nitroglycerine injection (NTG, 200 µg, **c** and **d**). Right: Illustration of similar subtotal focal spasm (arrows, **e** and **f**) of the proximal left anterior descending artery following acetylcholine injection (**e** 100 µg ACh and **f** 50 µg ACh) which was accompanied by reproduction of the patient's usual angina and ischemic ECG changes. Again, intracoronary nitroglycerine resolved the coronary spasm (NTG, 200 µg, **g** and **h**)

Table 2 Results of acetylcholine testing

	All patients	Stuttgart (Germany)	Sendai (Japan)	p value
n =	149	69 (46)	80 (54)	
Localisation of spasm				
Diffuse spasm	127 (85)	56 (81)	71 (89)	0.19
Focal spasm	22 (15)	13 (19)	9 (11)	0.19
Multivessel spasm	46 (31)	18 (26)	28 (35)	0.22
ACh dose leading to spasm				
20 µg	31 (21)	10 (14)	21 (26)	0.08
50 µg	22 (15)	–	22 (28)	
100 µg	62 (42)	25 (36)	37 (46)	0.21
200 µg	34 (23)	34 (49)	–	

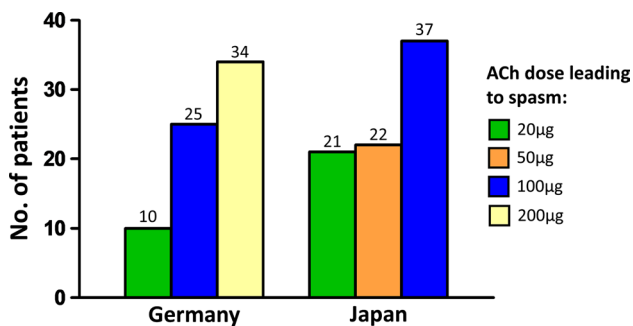Data are absolute numbers (percentage)

ACh acetylcholine

Fig. 2 Overview of the respective ACh doses required to induce coronary spasm among the German and Japanese patients. Incremental ACh dosages were used in both centers and frequency of spasm elicited at the 20-µg and 100-µg dose was comparable

spasm (19% vs. 11%, $p = 0.19$), and multivessel spasm (26% vs. 35%, $p = 0.22$) were comparable (Table 2).

No serious adverse events associated with the ACh test were observed in this study population.

ACh dose leading to spasm

We next sought to investigate whether there were any differences in the ACh dose that was necessary to induce epicardial spasm in the two patient groups (Fig. 2; Table 2). In the German patients, none of them developed epicardial spasm at the lowest ACh dose (2 µg). The next dose of 20 µg was applied in both the German and Japanese patients and induced epicardial spasm in 14% and 26% of the German and Japanese patients, respectively ($p = 0.078$). In the remaining patients, higher doses of ACh were required to induce the spasm. A dose of 50 µg of acetylcholine was only applied to the Japanese patients and led to coronary spasm in 28%

of cases. The next higher dose of 100 µg was again applied in both patient cohorts with 36% of the German and 46% of the Japanese patients showing epicardial spasm ($p = 0.21$). In the remaining German patients, a dose of 200 µg (i.e. the maximum dose of ACh given) was necessary to induce epicardial spasm in 49% of cases (Table 2).

Association between type of spasm and ACh doses

Next, we investigated the association of the ACh dose to induce spasm and the type of spasm. We did not observe any significant differences in ACh doses between focal and diffuse spasm ($p = 0.46$). This was the case for Japanese ($p = 0.50$) and German ($p = 0.45$) patients.

Impact of differences in ACh doses

Finally, we sought to assess a potential impact of the different dosages used for ACh testing in both centers. While a 20-µg as well as a 100-µg dose were part of both institutional protocols, the maximum ACh dose in Stuttgart was 200 µg; hence, patients with spasm provocation at the 200 µg dose were excluded from this subanalysis. Notably, patients with spasm provocation at the 50 µg dose, which was only performed in Sendai, were assumed to be positive at the 100-µg dose. This subanalysis revealed a similar rate of positive tests at 20 µg and 100 µg ACh at both centers, respectively (Fig. 3).

Discussion

This is the first study comparing Japanese and German patients with resting angina, unobstructed coronary arteries, and proof of acetylcholine-induced epicardial coronary spasm. The results show that despite differences in cardiovascular risk factor prevalence, Japanese and German patients with epicardial coronary spasm have comparable rates of diffuse vs. focal spasm (with diffuse spasm being the most prevalent finding). Moreover, the rate of multivessel spasm was also comparable between the two patient groups (Graphical abstract). The results are of importance as they suggest that angiographic characteristics of coronary spasm (rate of focal vs. diffuse spasm) in Japanese and German patients may not be as different as previously thought. This could have several implications for patient management, such as the recommendation to perform more coronary spasm testing in European/Caucasian patients with angina and unobstructed coronary arteries [20]. Previous studies have reported that Caucasian patients with coronary spasm have a higher frequency of fixed organic stenoses compared to Japanese patients [11]. However, a detailed comparison of patients with unobstructed coronary arteries and coronary

Fig. 3 Subanalysis correcting for different ACh doses used in German and Japanese patients during provocation testing. For this subanalysis, patients with spasm after injection of 200 µg ACh, which was only performed in German patients, were excluded and patients with spasm at 50 µg ACh (only performed in Japanese patients) and those with spasm at 100 µg were pooled. Thereby, similar rates of spasm at the lower (20 µg) and higher (50/100 µg) ACh doses were observed in German and Japanese, respectively
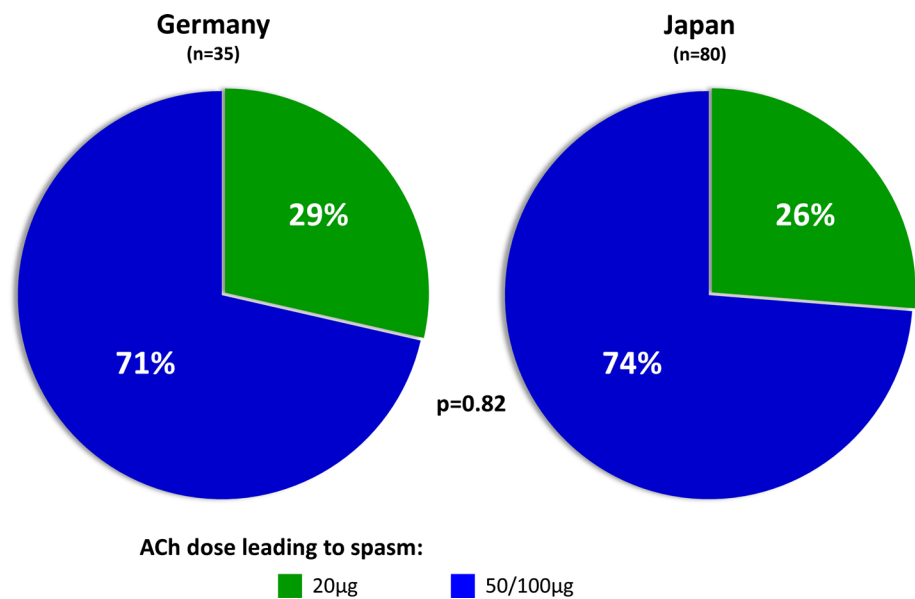
spasm—as in the present study—has not been performed so far.

Comparison of cardiovascular risk factors

In this study, as compared with the Japanese patients, the German patients had a significantly higher frequency of cardiovascular risk factors, such as hypertension, smoking, and a positive family history for cardiovascular disease. Such differences may well be explained by the previously reported differences in life style and body mass index between European and Japanese patients [21]. In addition, German patients with coronary spasm often have a positive family history for cardiovascular disease as reported previously [22]. Whether this points towards a relevant genetic background for the disease and whether this is in line with the previous Japanese study on genetic polymorphisms in coronary spasm [23] deserves further investigation.

Comparison with previous studies

To the best of our knowledge, there is no previous study explicitly comparing German and Japanese patients with resting angina, unobstructed coronary arteries, and proof of acetylcholine-induced epicardial spasm regarding the angiographic spasm characteristics. There are two important previous studies by Pristipino et al. [12] and Sato et al. [14] which reported racial differences regarding coronary artery spasm in Japanese and Caucasian patients. Pristipino et al. compared the coronary artery response to acetylcholine in 15 Japanese and 19 Italian patients in a period of 14 days after acute myocardial infarction [12]. It was shown that Japanese patients had a higher frequency of coronary spasm including

multivessel spasm compared with the Italian patients [12]. The large registry study by Sato et al. investigated the clinical characteristics and prognosis of Japanese and Caucasian patients with coronary spasm and observed a higher rate of multivessel spasm in Japanese patients (18% vs. 3%) [14]. In our present study, we focused on the assessment of angiographic characteristics and thereby did not observe any significant difference regarding the rates of diffuse/focal and multivessel spasm.

The difference in the rate of multivessel spasm may be explained by the differences in the study protocol and the way how the data were analyzed. It is well known that acetylcholine testing of the RCA is more regularly performed in Asian countries, where a backup pacemaker is inserted, compared to Caucasian patients. For example, in the German patients the RCA is only challenged with acetylcholine if LCA testing is uneventful. As a consequence, in the registry by Sato et al., the RCA was 3.5-times as often tested in the Japanese patients compared to the Caucasians [14]. Thus, it is no surprise that the rate of multivessel spasm was higher in the Japanese patients. To avoid this potential error in the present study, we decided to compare only patients in whom epicardial spasm was provoked in the LCA (and excluded those with spasm in the RCA) as the LCA is by default the first artery to be challenged with acetylcholine in both institutions (i.e. Sendai/Japan and Stuttgart/Germany). Due to this methodological difference, our analysis provides a more valid comparison than the previous ones suggesting similar frequency of multivessel spasm, although the true frequency of multivessel spasm in consecutive patients undergoing right and left coronary spasm testing still remains unknown. Another methodological difference compared to the previous study is that all spasm provocation

tests were performed using acetylcholine, whereas Sato et al. included also ergonovine testing [14]. The fact that ACh was used in the present study might explain the high rate of diffuse spasm as compared to ergonovine testing which often reveals more focal and proximal spasm. Indeed, ergonovine acts through serotonergic receptors, while ACh acts through muscarinic cholinergic receptors. Different vasoconstrictor stimuli may, therefore, cause different coronary vasomotor responses.

Study Limitations

To improve the comparability of the two study cohorts, we only included patients with coronary spasm in the LCA. Thus, the overall frequency of multivessel spasm as well as a potential different response in both coronary systems (e.g. diffuse RCA spasm and focal LAD spasm) may have been underestimated. Moreover, the differences between the two institutional protocols (i.e. different ACh doses, pacemaker back-up) may have had a potential impact on the results. However, a subanalysis accounting for the different maximum ACh doses by excluding patients with spasm at 200 μg ACh revealed no significant differences between both centers with regards to the rate of spasm at 20 μg and 100 μg, respectively. Finally, a temporary pacemaker was inserted in Japanese patients before ACh testing, while this was not the case in German patients. Since no serious adverse events were observed, we assume no relevant impact of the pacemaker on our analyses.

Conclusions

Diffuse epicardial coronary spasm is the most frequent finding among German and Japanese patients with rest angina, unobstructed coronary arteries, and epicardial spasm on acetylcholine testing. Japanese and German patients share several similarities including comparable types and frequency of multivessel spasm.

Author contribution All authors meet ICMJE recommendation criteria for authorship in this manuscript. AS, AS, HS, PO: study design, data analysis, manuscript preparation, final approval. YO, GP, KS, KH: data interpretation and manuscript preparation. AA, RB, JT, US: critical revision of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was conducted in accordance with the Helsinki Declaration. In both institutions (Sendai and Stuttgart) the ethical committees approved acetylcholine testing and scientific data acquisition.

Consent to participate For the present retrospective data analysis, all data were handled anonymously.

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