Prevalence of the type 1 Brugada electrocardiogram in Caucasian patients with suspected coronary spasm

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Aims
Sporadic cases have reported the coexistence of coronary spasm and Brugada syndrome. However, the prevalence of the Brugada phenotype in coronary spasm is unknown, particularly in non-Japanese populations. In this study, we sought to examine the prevalence of the type 1 Brugada electrocardiogram (ECG) in a large European patient population undergoing intracoronary acetylcholine provocation testing for suspected coronary spasm.

Methods and results
We retrospectively evaluated ECG data for the presence of type 1, 2, and 3 Brugada ECGs from 955 consecutive German patients without obstructive coronary artery disease undergoing intracoronary acetylcholine (ACH) provocation (ACH-test). Eight hundred and twenty-seven patients (age 63 ± 12 years; 42% male) with complete ECG data were eligible for further analysis. The ACH-test revealed coronary spasm in 325 patients (39.3%). A Brugada ECG of any type was found in six patients (0.7%) at baseline and eight patients (0.9%) at any time. There was no difference in the prevalence of coronary spasm in patients with (37.5%) and without (39.3%) Brugada-type ECGs. The type 1 Brugada ECG was not seen at baseline, but two type 1 Brugada ECGs were observed during ACH-administration into the right coronary artery (RCA; 0.2%), one with simultaneous RCA spasm and one without. Ajmaline provocation testing reproduced the type-1 Brugada ECG in the patient without coronary spasm but she had no other features of the Brugada syndrome.

Conclusions
This study reports a low prevalence of the type 1 Brugada ECG in the largest known European collection of intracoronary ACH provocation. In these patients, we found no evidence for the coexistence of Brugada syndrome and coronary spasm. This is in contrast to available Japanese data.

Keywords
Brugada syndrome • Coronary spasm • Acetylcholine • Ajmaline • Prevalence

Introduction
Coronary artery spasm and Brugada syndrome (BrS) are associated with an increased risk of ventricular arrhythmias and sudden cardiac death.¹² Sporadic case studies in Japanese patients have reported the coexistence of coronary artery spasm and Brugada syndrome identifying patients at a high risk of cardiac events.³⁴ It is currently unknown as to whether this is a common occurrence among Caucasian patients, as racial differences have been described between Asian and Caucasian patients suffering from both conditions.⁵,⁶ Recent studies have reported a higher frequency of coronary spasm and unobstructed coronary arteries in European patients than previously described.⁷,⁸ The prevalence of the type 1 Brugada electrocardiogram (EGG) pattern, however, appears to be higher in South East Asian populations.⁹–¹² The coexistence of coronary artery spasm and Brugada syndrome is of potential clinical relevance, particularly as management strategies differ and treatment of coronary artery spasm with calcium channel blocker therapy may exacerbate the Brugada phenotype. We therefore sought to determine the...
prevalence and significance of a Brugada-type ECG pattern at baseline and during provocation testing in 955 German (Caucasian) patients undergoing intracoronary acetylcholine (ACH) provocation for suspected coronary artery spasm.

**Methods**

**Patient characteristics**

Nine hundred and fifty-five consecutive German (Caucasian) patients with unobstructed coronary arteries (no stenosis >50%) who underwent intracoronary ACH provocation for the detection of coronary artery spasm between 2007 and 2009 were included in the study. Of these, 827 (87%) had a complete set of ECG data (12-lead ECGs at baseline, during each step of provocation testing and following glyceryl trinitrate) and were, therefore, eligible for further analysis. Their demographic, angiographic, and electrocardiographic data were analysed retrospectively and the initial patient presentation was recorded. All patients gave written informed consent before angiography and the study complied with the Declaration of Helsinki.

**Coronary angiography and administration of acetylcholine**

Intracoronary ACH provocation was performed immediately following diagnostic coronary angiography as a routine standardized procedure at the Robert-Bosch-Krankenhaus in patients with suspected coronary artery disease who were found to have normal coronary arteries or no stenosis >50%.

Relevant cardiovascular medications (beta blockers, calcium channel blockers, and nitrates) were discontinued at least 24 h before coronary angiography. During the ACH-test heart rate, blood pressure, and the 12-lead-ECG were continuously monitored (Siemens AXS Axiom Artis Sensis). Incremental doses of 2, 20, 100, and 200 μg of ACH were infused over a period of 3 min into the left coronary artery (LCA) via the angiographic catheter. In patients who remained asymptomatic and showed no diagnostic ST-segment changes during LCA ACH infusion, 80 μg of ACH were injected into the right coronary artery (RCA). A bolus of glyceryl trinitrate 0.2 mg (Perlinganit, Schwarz Pharma, Monheim, and Germany) was injected into the LCA or RCA to relieve angina and/or coronary artery spasm. Nitrates were also infused routinely at the end of the ACH-test into the RCA and LCA.

**Analysis of intracoronary acetylcholine provocation**

All ACH-test results were quantitatively analysed using computerized quantitative coronary angiography (QCA-CMS, version 6.0, Medis-Software, Leiden, The Netherlands). The ACH-test was considered ‘positive’ for coronary spasm when it resulted in epicardial coronary diameter reduction ≥75% compared with the diameter following glyceryl trinitrate administration together with a reproduction of the patient’s symptoms.

**Electrocardiogram analysis**

12-lead ECGs were recorded at baseline, during each step of the ACH-test and after glyceryl trinitrate injection. These were analysed by two cardiologists (R.B. and P.O.). All ECGs with suspected Brugada-type changes were independently reviewed by a third cardiologist (E.B.).

Our primary aim was to detect ECG changes that fulfilled criteria for the type 1 ECG. The type 1 ECG is characterized by coved ST segment elevation ≥2 mm (0.2 mV) followed by a negative T wave in >1 right precordial lead (V1–V3). Type 2 ST-elevation has a saddleback appearance of ≥2 mm with a trough of ≥1 mm followed by a positive or biphasic T wave. Type 3 has either a coved or saddleback appearance with ST-elevation <1 mm. Brugada syndrome is diagnosed when a type 1 ECG is found in conjunction with other clinical features.

**Ajmaline provocation testing**

An ajmaline challenge was performed in patients who developed a type 1 Brugada ECG pattern during the ACH-test. Ajmaline provocation was also performed in patients who presented with cardiopulmonary arrest without evidence of other cardiac disease. A dose of 1 mg/kg was administered intravenously over 5 min with continuous acquisition of a 15-lead ECG using a PC-based digital ECG recorder (Cardiosoft, GE Medical, Milwaukee, WI, USA, 500 Hz, 5 μV amplitude resolution). Leads V1 and V2 from the third and second intercostal (i.c.) space were acquired simultaneously with all standard leads except for lead V3. This lead configuration is routinely used at St George’s University of London during diagnostic ajmaline testing in patients with suspected Brugada syndrome. It is based on previous reports showing that recording leads V1 and V2 from higher chest positions (second and third instead of third i.c. space alone) increases the sensitivity for detection of type 1 Brugada ECG pattern whereas lead V3 is of limited diagnostic value. All ECGs were subsequently converted to XML text files for analysis using a custom-developed programme. The ajmaline test was considered positive if a type 1 Brugada ECG pattern as described above was detected in two or more right precordial leads.

**Statistical analysis**

Statistical data analysis was carried out with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± standard deviation. Comparison between groups was carried out via paired t-test or chi square test where appropriate. A two-tailed P value <0.05 was considered significant.

**Results**

**Patients**

Out of 955 patients, 827 with complete ECG data were included. There were no significant differences in age, sex, and clinical presentation between patients who were included and those who were not included in the study (data not shown). Seven hundred and forty-three patients (89.8%) presented with angina. A further 41 (5%) had non-ST-segment-elevation myocardial infarction (NSTEMI) and 5 (0.6%) ST-segment-elevation myocardial infarction (STEMI). Thirteen patients (1.6%) presented with syncope and one (0.1%) experienced cardiac arrest. The remaining 24 patients (2.9%) had other initial reasons for admission including atrial arrhythmia and cardiac failure (Table 1).

**Induction of coronary artery spasm and electrocardiogram data**

The ACH-test revealed coronary spasm in 325 patients (39.3%). They were more often male than those without coronary spasm (P = 0.011). There was no significant difference between age and clinical presentation in the two groups (Table 1). In addition, there were no significant differences in clinical presentation of patients who underwent RCA and LCA compared with LCA coronary injection only (data not shown).
The type 1 Brugada ECG was not seen at baseline but was observed in two patients during ACH-provocation in the RCA (Table 2). In one patient this was associated with coronary spasm, but not the other (Table 3). The prevalence of the type 1 ECG in all patients who underwent ACH-testing was, therefore, 0.2%, and 0.7% among those in whom both RCA and LCA were catheterized. The prevalence of the type 1 ECG in patients with a positive ACH-test was 0.3%.

A type 2 Brugada ECG was observed in three patients at baseline (0.3%) but only in two during provocation (0.2%), as one patient’s type 2 ECG pattern normalized during ACH provocation. A type 3 Brugada ECG was observed in three patients (0.3%) both at baseline and during provocation (Table 2). Detailed characteristics of patients with Brugada-type electrocardiograms are displayed in Table 3.

A comparison of the prevalence of coronary spasm in patients with any Brugada-type ECG (3 out of 8 patients, 37.5%) and those without Brugada-type ECG (322 out of 819 patients, 39.3%) revealed no statistical difference ($P = 1.0$).

### Patients with type 1 Brugada electrocardiogram during provocation

Patient 1 (Figure 1) was a 59-year-old male who presented with acute coronary syndrome. There was no history of syncope or family history of sudden death. Diagnostic coronary angiography revealed no culprit lesion and during ACH-testing the patient had triple-vessel spasm with a reproduction of his symptoms. During RCA injection the type 1 Brugada ECG was seen at a dose of 80 µg of ACH. A subsequent complete dose ajmaline test did not precipitate the type 1 Brugada ECG pattern. Treatment with diltiazem was initiated. The patient was alive and pain free after 27 months of follow-up.

Patient 2 (Figure 2) was an 81-year-old female who presented with acute chest pain and rate controlled atrial fibrillation without ischaemic ECG changes. There was no history of syncope or family history of sudden death. There was no significant coronary stenosis at angiography. The type 1 Brugada ECG was observed during RCA injection of 80 µg ACH without symptoms or evidence of spasm. The ajmaline test, given to full dose, induced a less dramatic but unequivocal type 1 Brugada ECG pattern in leads V2, V1–3 and V2–3 (V1 and V2 elevated to the third i.c. space) (Figure 3). Treatment for atrial fibrillation was continued. The patient had no blood relatives alive for further evaluation. She was considered at low risk of sudden death and, therefore, did not undergo electrophysiological studies and was given advice on preventative strategies including drugs to avoid. She was alive after 17 months of follow-up.

### Patients presenting with syncope or cardiopulmonary arrest

Assessment of the 13 patients presenting with syncope (4 male, mean age 58 years), revealed an underlying diagnosis of coronary spasm in 4 patients (31%), myocarditis in 1 patient (8%), and atrioventricular nodal re-entry tachycardia in 1 patient (8%). In the remaining seven patients, orthostatic and vasovagal causes for
Table 3 Characteristics of patients with Brugada-type electrocardiograms

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Age</th>
<th>RV-characteristics echocardiography</th>
<th>Potassium (n = 3.4–5.0) (mmol/L)</th>
<th>Sodium (n = 135–148) (mmol/L)</th>
<th>Creatinine (n = 0.5–1.4) (mg/dL)</th>
<th>Baseline medication</th>
<th>Presentation</th>
<th>ACH-test</th>
<th>Arterial spasm</th>
<th>Reproduction of symptoms</th>
<th>ECG baseline</th>
<th>ECG provocation</th>
<th>Arterial injection causing ECG change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>59</td>
<td>Normal RV-size and RV-function</td>
<td>4.1</td>
<td>137</td>
<td>10</td>
<td>Aspirin, isosorbide dinitrate, simvastatin, ramipril, amiodarone, verapamil</td>
<td>STEMI Positive</td>
<td>All vessels</td>
<td>Yes</td>
<td>Normal</td>
<td>Type 1 Brugada</td>
<td>RCA</td>
<td>RCA</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>81</td>
<td>Normal RV-size and RV-function</td>
<td>4.7</td>
<td>141</td>
<td>0.7</td>
<td>Metoprolol, digoxin, ramipril, aspirin, warfarin, simvastatin</td>
<td>Angina Negative</td>
<td>None</td>
<td>n/a</td>
<td>Normal</td>
<td>Type 1 Brugada</td>
<td>RCA</td>
<td>No change</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>76</td>
<td>Normal RV-size and RV-function</td>
<td>3.3</td>
<td>138</td>
<td>0.5</td>
<td>Metoprolol, aspirin, captopril, fluvastatin</td>
<td>Angina Negative</td>
<td>None</td>
<td>n/a</td>
<td>Type 2 Brugada</td>
<td>Type 2 Brugada</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>68</td>
<td>Normal RV-size and RV-function</td>
<td>4.3</td>
<td>138</td>
<td>0.6</td>
<td>Nebivolol, aspirin, clopidogrel, metformin, simvastatin, amiodarone, insulin</td>
<td>Angina Negative</td>
<td>None</td>
<td>n/a</td>
<td>Type 2 Brugada</td>
<td>Normal</td>
<td>LCA</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>84</td>
<td>Normal RV-size and RV-function</td>
<td>4.1</td>
<td>141</td>
<td>0.6</td>
<td>Aspirin, enalapril, meropenem</td>
<td>NSTEMI Negative</td>
<td>None</td>
<td>n/a</td>
<td>Type 3 Brugada</td>
<td>Type 3 Brugada</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>67</td>
<td>Normal RV-size and RV-function</td>
<td>4.6</td>
<td>141</td>
<td>1.2</td>
<td>Aspirin, bisoprol, ramipril, procainamide</td>
<td>Angina Positive</td>
<td>LAD = LCX Yes</td>
<td>No change</td>
<td>Type 2 Brugada</td>
<td>Type 2 Brugada</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>70</td>
<td>RV-size RV-function mildly reduced</td>
<td>4.6</td>
<td>141</td>
<td>1.3</td>
<td>Aspirin, enalapril, simvastatin, metoprolol, insulin</td>
<td>Angina Negative</td>
<td>None</td>
<td>n/a</td>
<td>Type 3 Brugada</td>
<td>Type 3 Brugada</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>54</td>
<td>Normal RV-size and RV-function</td>
<td>4.1</td>
<td>141</td>
<td>0.6</td>
<td>Bisoprol</td>
<td>Angina Positive</td>
<td>LAD Yes</td>
<td>Yes</td>
<td>Type 1 Brugada</td>
<td>Type 1 Brugada</td>
<td>RCA</td>
<td>No change</td>
</tr>
</tbody>
</table>

RV, right ventricle; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; pRBBB, partial right bundle branch block; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; n/a, not applicable; M, male; F, female.

**Discussion**

This is the first report on the prevalence of Brugada-type ECG in patients undergoing ACH provocation for suspected coronary artery spasm. The cohort of patients comprises the largest European experience with cardiac symptoms and unobstructed coronary arteries at diagnosis. It indicates a low prevalence of the type 1 Brugada ECG in this group during ACH testing (0.2%). Only one patient (0.1%) demonstrated a reproducible pattern with a Brugada ECG during challenge and did not fulfill criteria for coronary spasm.

The reported prevalence of the type 1, 2, and 3 Brugada ECGs in different nationalities ranges from 0.1 to 6%. In Japan, the prevalence of the type 1 Brugada ECG is very low (0.002%). However, it is not clear whether this is due to the low prevalence of Brugada ECGs in different populations or to the high sensitivity of the ACH provocation test in these populations. Similarly, we found no evidence of the type 2 Brugada ECG in our study.

The prevalence of Brugada ECGs in patients undergoing ACH provocation has been reported to be higher in Japanese patients with coronary artery disease (CAD) than in Caucasian patients. This difference may be due to differences in the prevalence of genetic polymorphisms associated with Brugada ECG, such as rs1801282 (MTHFR) and rs2228570 (CYP2C19).

In conclusion, we found no evidence of a Brugada ECG pattern in our cohort of patients undergoing ACH provocation. However, we cannot rule out the possibility that Brugada ECGs may be present in a subset of patients with cardiac symptoms and unobstructed coronary arteries at diagnosis. Further studies are needed to determine the prevalence of Brugada ECGs in different populations and to better understand the role of Brugada ECGs in the development of cardiac arrhythmias.
unobstructed coronary arteries. Our frequency of 39% is similar to that reported in previous Japanese cohorts. Overall, although different inclusion criteria and definitions for coronary spasm might account for some differences between the studies, there seems to be growing evidence for a higher prevalence of coronary spasm in Caucasian patients than previously reported.

Figure 1 Electrocardiographic and angiographic findings of patient 1 showing the 12-lead electrocardiogram at baseline (A) and during acetylcholine provocation in the right coronary artery (B) with typical type 1 Brugada electrocardiogram changes in the precordial leads. During right coronary artery provocation the patient exhibited severe coronary artery spasm (C) with reproduction of symptoms which both resolved after intracoronary glyceroltrinitrate administration (D).

Figure 2 Electrocardiographic and angiographic findings of patient 2 showing the 12-lead electrocardiogram at baseline (A) and during acetylcholine provocation in the right coronary artery (B) with typical type 1 Brugada electrocardiogram changes in the precordial leads. There was no epicardial vasoconstriction or reproduction of symptoms during the test, (C) during acetylcholine and (D) after glyceroltrinitrate.
The coexistence of BrS and coronary spasm has been previously reported in Japanese patients. Noda et al. demonstrated coronary artery spasm in 3 out of 27 (11%) patients diagnosed with BrS. There have also been a few case reports describing the occurrence of a type 1 Brugada ECG during provocation testing for coronary spasm. Interestingly, Sasaki et al. observed a type 1 Brugada ECG during ACH injection into the RCA with simultaneous RCA spasm in one patient, in line with our findings in patient 1 (Figure 1). Nishizaki et al. reported occurrence of a type 1 Brugada ECG during RCA injection of ACH without coronary spasm, similar to our patient 2 (Figure 2). The fact that we found no evidence for the coexistence of the type 1 Brugada ECG pattern and coronary spasm suggests a difference between the European and Japanese experience. However, at present, data associating the two conditions are limited to case reports and a case series and the prevalence of a type 1 Brugada ECG in patients with coronary spasm has not yet been reported in a large Japanese series.

**Mechanisms**

Acetylcholine induced a type 1 Brugada ECG pattern in two patients. In both patients the ECG changes occurred during provocation testing in the RCA. This is compatible with experimental findings from a canine ventricular wedge preparation where ACH-induced typical Brugada ECG changes after RCA injection.

Ajmaline reduces the inward sodium current via direct block of voltage-gated sodium channels. Sodium channel blockade has been shown to cause transmural dispersion of repolarization in the same canine model leading to a type 1 Brugada ECG. Right ventricular ST-elevation due to myocardial ischaemia (mimicking the type 1 Brugada ECG) has also been shown to be mediated by dispersion of repolarization.

An alternative theory for the mechanism underlying ST-elevation in the type 1 Brugada ECG, however, suggests that conduction delay facilitates re-entry and subsequent arrhythmia. Recent but limited evidence in humans supports this theory by demonstrating subtle structural disease in Brugada syndrome. Ajmaline, ACH and ischaemia can also delay myocardial conduction and this may precipitate ST-elevation although muscarinic receptor-associated currents may not be present in human ventricular tissue.

Myocardial ischaemia with concomitant epicardial spasm, possibly involving the conus branch, is the most likely cause of the observed type 1 Brugada ECG in patient 1 given his positive ACH-test but negative ajmaline test. Unlike patient 1, patient 2 appears to have an electrophysiological predisposition towards a type 1 Brugada ECG with both ACH and ajmaline, and without apparent ischaemia. Despite the absence of other diagnostic markers for Brugada syndrome in this case, we feel that further investigation of patients presenting with an ACH-induced type 1 ECG pattern is advisable, following exclusion of ischaemia.

**Study limitations**

Only 827 of 955 patients had a complete set of ECG data and were, therefore, eligible for further analysis. However, statistical comparisons between patients with and without complete ECG data revealed no significant differences reducing the likelihood of significant selection bias. Acetylcholine provocation testing in both coronary arteries was not performed when the RCA was hypoplastic or when glyceroltrinitrate had been administered to resolve angina and/or spasm in the LCA. The number of type 1 Brugada ECGs might have been higher if RCA provocation had been performed in all patients. In addition, during ACH-testing, the 12-lead ECG was performed with standard lead positions. High right ventricular lead position may have further increased sensitivity for the type 1 Brugada ECG. Ajmaline provocation in the whole cohort may have identified further cases of a drug-induced type 1 ECG pattern in patients without ACH-provoked ECG changes including those with prior syncpe, but this was not clinically indicated. Absence of the Brugada pattern during ACH-test does not exclude Brugada syndrome.
Conclusions

This study reports a low prevalence of the type 1 Brugada ECG in the largest known collection of patients undergoing intracoronary ACH provocation testing. We found no evidence for the coexistence of Brugada syndrome in patients with coronary spasm. A study of ACH provocation in Caucasian patients with Brugada syndrome would be necessary to clarify any relationship suggested by Japanese data. In Caucasians, the presence of a type 1 Brugada ECG pattern during ACH-testing, particularly if it is independent of spasm, should prompt further evaluation of the patient for evidence of the Brugada syndrome.

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