ESC European Society of Cardiology

European Heart Journal - Case Reports (2020) **4**, 1–5
doi:10.1093/ehjcr/ytaa202

CASE REPORT
Arrhythmias/electrophysiology

Case report: Synergetic effect of ischaemia and increased vagal tone inducing ventricular fibrillation in a patient with Brugada syndrome

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Received 26 June 2019; first decision 15 August 2019; accepted 11 June 2020; online publish-ahead-of-print 30 July 2020

Background Brugada syndrome (BS) is a hereditary channelopathy associated with syncope, malignant ventricular arrhythmia, and sudden cardiac death. Right ventricular ischaemia and BS have similar underlying substrates precipitating ventricular tachycardia or fibrillation (VF).

Case summary A 72-year-old woman with BS and a stenosis on the proximal right coronary artery received several subsequent implantable cardioverter-defibrillator shocks due to VF during an episode of extreme nausea with vomiting.

Discussion This case report emphasizes on the synergetic effect of mild ischaemia and increased vagal tone on the substrate responsible for BS to create pathophysiological changes precipitating VF.

Keywords Brugada syndrome • Ischaemia • Myocardial infarction • Vagal tone • Ventricular arrhythmia • Shock • Case report

Learning points

- Multiple factors are known to contribute to ventricular tachycardia/ventricular fibrillation initiation in Brugada syndrome, and there may be a synergetic effect when several precipitating factors occur at the same time.
- Increased vagal tone plays an important role and has often been underestimated.

Introduction

Brugada syndrome (BS) was first described in 1992 and is characterized by an accentuated J wave or ST-segment elevation in the right precordial leads (V1–V3), often followed by a negative T wave. It is associated with life-threatening ventricular arrhythmias, syncope, and sudden cardiac death (SCD).[1] The typical electrocardiogram (ECG) pattern as well as the clinical presentation may be variable over time and can be modulated by temperature or hormonal changes, exercise, ischaemia, increased vagal tone, and medications that interact with the cardiac sodium channel or the autonomic nervous system.[2–6]

The *SCN5A gene* is the major gene responsible for BS, and it encodes the pore-forming α-subunit of the cardiac Nav1.5 voltage-gated sodium channel. The amount of sodium channel current (I_{Na}) reduction and thus the risk to develop ventricular arrhythmia depends on the type of mutation.[7]

This is the first case illustrating the impact of simultaneously occurring ischaemia and increased vagal tone in a patient with BS carrying a severe mutation.

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Handling Editor: Ross Hunter
Peer-reviewers: Habib Khan
Compliance Editor: Stefan Simovic
Supplementary Material Editor: Ross Thomson

Timeline

At age 57	Three brutal syncopes
At age 61	Routine electrocardiogram (ECG): type 2 ECG (saddle back pattern)
	Flecainide provocation test: type 1 ECG (coved type pattern)
	Implantable cardioverter-defibrillator (ICD) implanted
	Genetic testing: G1743E mutation in SCN5A gene
At age 72	Nausea, vomiting, chest pain
	6 appropriate ICD shocks (ventricular fibrillation)
	Baseline type 1 ECG
	Increased troponin and CKMB
	Coronary angiography: critical stenosis in proximal right coronary artery -> stenting.

Case presentation

A 61-year-old Caucasian woman with a history of dyslipidaemia, hypertension, smoking, and three syncopes had a routine electrocardiogram (ECG) taken previous to a scheduled operation. This ECG showed a typical type 2 Brugada syndrome (BS) pattern, with a saddleback shaped ST-T configuration and ST-segment elevation ≥ 1 mm in V2–V3 (*Figure 1A,B*). During a subsequent flecainide provocation test (*Figure 1C,D*), a typical coved type 1 configuration in V1–V2 was induced, diagnostic for BS. Her father and grandfather had syncopes after the age of 50 and 70. No other significant family history had been reported. A single chamber implantable cardioverter-defibrillator (ICD) was implanted to prevent SCD. Genetic testing confirmed the diagnosis of BS, showing a G1743E mutation in exon 28B of the SCN5A gene on chromosome 3P21-24.

At the age of 72, she developed extreme nausea and vomiting during household activities, accompanied by radiating chest pain to the left arm. She went to bed and subsequently experienced six defibrillator shocks within 10 min time. It was not until the next morning that she went to the hospital. At that moment, she was asymptomatic and physical examination was completely normal. ICD interrogation showed these six shocks to be appropriate therapy for ventricular fibrillation (VF) during a baseline bradycardia with ventricular extrasystoles (*Figure 2*). All shocks were successful, however with reoccurrence of VF following the first five shocks. Routine chest X-ray and transthoracic echocardiography were normal. The resting ECG showed a baseline type 1 BS pattern in the in V1–V2, a saddleback shaped type 2 BS pattern in V3 and no signs of ischaemia (*Figure 1E,F*). As troponin and creatine kinase-MB isoenzyme levels were increased [0.48 μg/L (0–0.02 μg/L) and 35.7 μg/L (0–4.6 μg/L), respectively], the chest pain in this patient with a high cardiovascular risk profile was considered suspicious for unstable angina or non-ST elevation myocardial infarction and therefore coronary angiography was performed. This revealed a triple vessel disease with one critical stenosis at the proximal-mid right coronary artery (RCA) for which direct stenting (Xience V 2.5 mm × 15 mm) was performed with excellent result (*Figure 3*). Cardiac enzymes further decreased. No complications occurred during follow-up. Subsequent ECGs showed no signs of any scar. She remained syncope and arrhythmia free during follow-up. Unfortunately, she died from cancer a few years later.

Discussion

Ischaemia of the right ventricle and currents

Several reports have been published concerning BS and concomitant acute myocardial infarction (AMI) or ischaemia.[2,8] It is shown that right ventricular (RV) ischaemia and BS have similar underlying substrates precipitating ventricular tachycardia/ventricular fibrillation (VT/VF).[2,9] Transient outward current (I_{to}) plays an essential role and causes a notched appearance of the action potential (AP). This I_{to}-mediated notch is most prominent in RV epicardial tissues, which forms the basis for the RV nature of BS,[10,11] and is responsible for a transmural (TM) voltage gradient during ventricular activation that has been shown to underlie the J-wave and J-point elevation on the ECG.[12] During ventricular repolarization, a heterogeneous loss of the epicardial RV AP dome may result in both TM and epicardial dispersion of repolarization. This creates a vulnerable window which serves as the substrate for phase 2 re-entry (P2R), responsible for closely coupled ventricular extrasystoles initiating VT/VF.[3,11] Because I_{to} is much more prominent in the RV[12] and because a large epicardial I_{to} is necessary for an all-or-none repolarization in order to have loss of the epicardial AP dome, the incidence of primary VF is higher with an AMI or ischaemia involving or having a border with the RV.[3,13] Right ventricular ischaemia or AMI due to critical lesions in the proximal RCA, particularly with right ventricular outflow tract involvement, have been reported to result in ST-segment elevation, similar to that in BS (Brugada phenocopy).[2] This effect is secondary to a reduction in I_{Ca} and activation of $I_{K\text{-}ATP}$ during ischaemia. As in this case, patients with BS may therefore be more prone to ischaemia-related SCD.[9]

Genetics

SCN5A mutations may provide a genetic predisposition for ischaemia-related acquired VF.[14] G1743E, which confirmed the diagnosis of BS in this case, is a causal missense SCN5A mutation, located between segments 5 and 6 of domain 4. Biophysical analysis associated mutant G1743E channels with a markedly reduced $I_{Na,}$[4] so the presence of this mutation can be expected to also exacerbate arrhythmogenesis in the setting of AMI.[9]

Autonomic imbalance

Brugada syndrome is characterized by an autonomic imbalance, due to a decreased adrenergic tone, resulting in a predominant parasympathetic tone.[5] Acetylcholine is known to facilitate loss of AP dome by suppressing I_{Ca} and/or increasing potassium currents,[5,9,11] predominantly located in the epicardium. When vagal tone further increases, these epicardial ion currents are modulated even more, resulting in a more pronounced TM and epicardial dispersion,

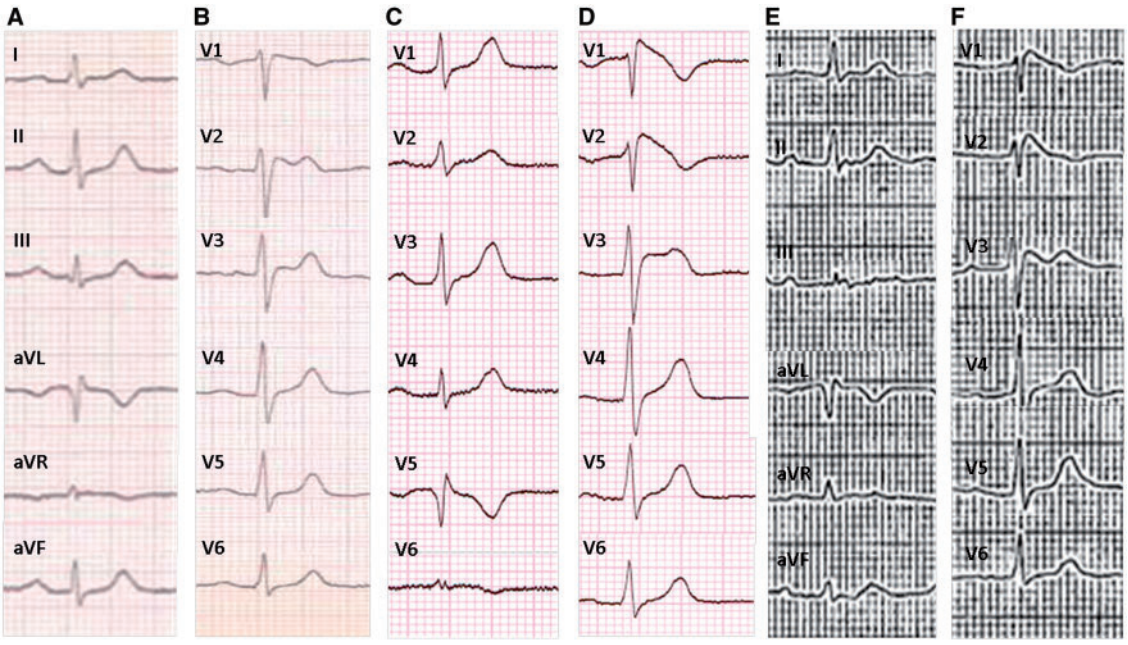

Figure 1 Subsequent electrocardiogram's. Preoperative electrocardiogram (*A,B*) at the age of 61 showing an right bundle branch block-like pattern in the right precordial leads with only a slight J-point elevation and negative T wave in V1, but a saddleback shaped ST-T configuration with segment elevation ≥ 1 mm in V2–V3, being a typical type 2 Brugada syndrome pattern. Flecainide provocation (*C,D*): the electrocardiogram pattern in the precordial leads recorded at baseline (*C*) was normal and 5 min after 50 mg flecainide injection (*D*) it changed into a typical type 1 coved ST-segment elevation ≥2 mm with a gradually descending terminal portion followed by a negative T wave in V1–V2, diagnostic of Brugada syndrome. In V3, we observe an additional typical saddleback shaped ST-elevation. Electrocardiogram on administration the morning after chest pain and six appropriate implantable cardioverter-defibrillator shocks (*E,F*) also showing a typical baseline type 1 Brugada syndrome pattern in two right precordial leads (V1–V2) and a saddleback shaped pattern in V3. There were no negative T waves, nor typical ischaemia-related ST-segment changes. Right precordial electrocardiogram tracings in Brugada syndrome may be concealed and dynamic as shown in *A–C–F*, in part due to changes in vasovagal tone.

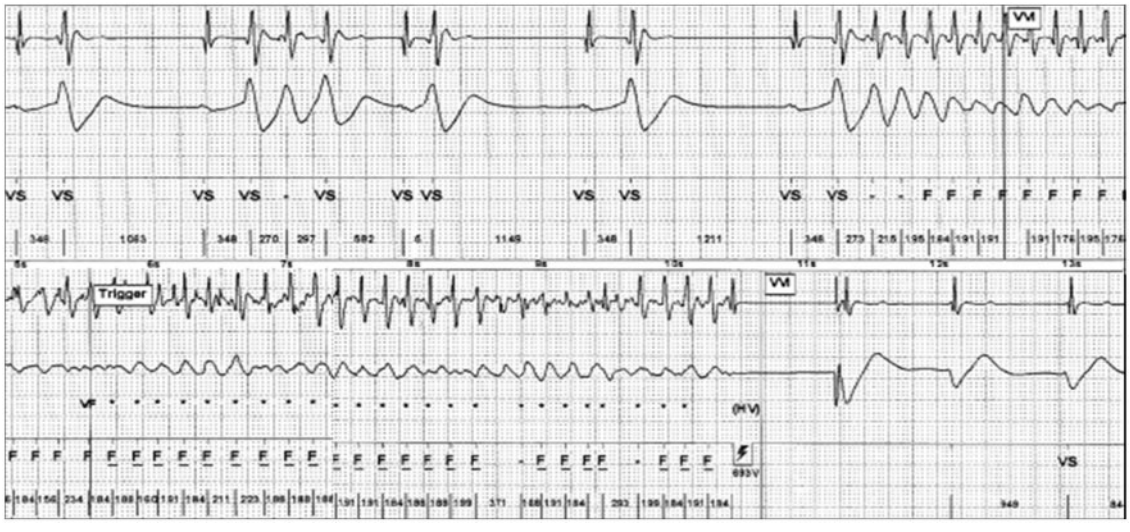

Figure 2 Implantable cardioverter-defibrillator record (Atlas^{TM}+ VR V-193, single chamber implantable cardioverter-defibrillator, St Jude Medical): first of six ventricular fibrillation episodes recorded: note short-coupled ventricular extrasystoles, preceding ventricular fibrillation and the implantable cardioverter-defibrillator shock terminating the arrhythmia.

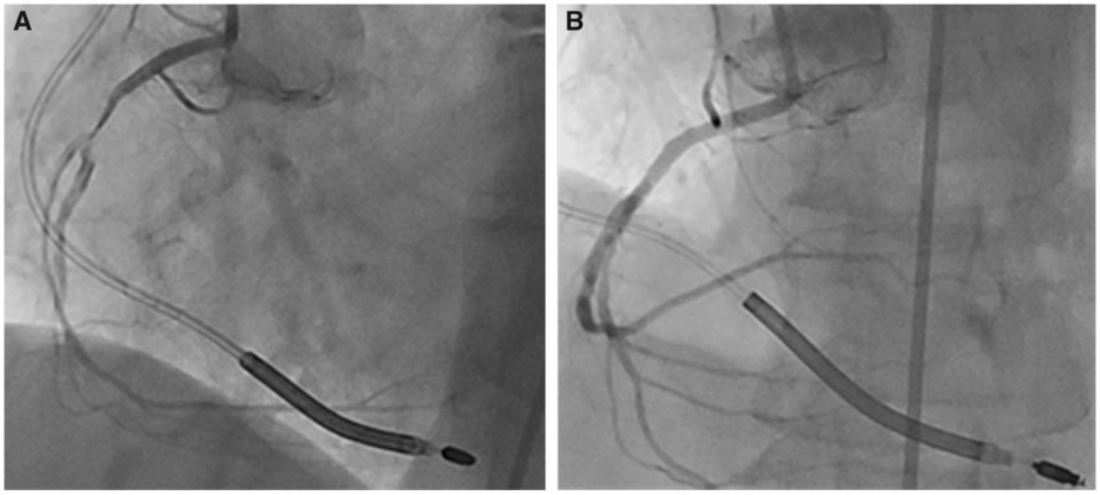

Figure 3 Coronarography: 'culprit' lesion on proximal-mid right coronary artery, before (*A*) and after (*B*) stenting (Xience V 2.5 mm × 15 mm).

consistent with aggravation of ST-segment elevation and higher propensity for P2R. This partly explains why VT/VF in BS most often occurs at rest, during sleep, following vagal stimuli, or use of antiarrhythmic or vagotonic agents.[5] Changes in parasympathetic tone also contribute to the dynamic aspect of the typical right precordial ECG as shown in *Figure 1A–C–F*. Acute myocardial infarction and subsequent chest pain are mostly associated with increased sympathetic tone. However, RV or inferior AMI/ischaemia may also be associated with increased vagal tone[6] as seen in our case (bradycardia, nausea, vomiting), which would therefore be another additional factor increasing the risk for VF in this patient.

Conclusion

We present a unique case of BS in association with a critical proximal RCA lesion, illustrating that mild RV ischaemia and additional vagal influences act synergistically with the substrate responsible for BS to create ST segment elevation and precipitate re-entry and VF.

Lead author biography

Sophie CH Van Malderen was born in Dendermonde, Belgium on 8th May 1980. She started Medical school at the Free University of Brussels in 1998 and graduated cum laude in 2005. In 2011, she became a cardiologist. Afterwards, she started a fellowship in clinical Electrophysiology at the Thorax Center in Rotterdam (Erasmus MC) until 2014. She completed her PhD entitled 'Altered right ventricular electromechanical conduction in Brugada Syndrome' in 2018. She currently works as a cardiologist-electrophysiologist at the AZ Monica hospital in Deurne and the University Hospital in Antwerp, Belgium. She is a member of the Belgium Heart Rhythm Association.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: Consent was acquired from the ethical committee of the Erasmus MC hospital in Rotterdam because the patient had died from cancer. This has been discussed and agreed with the journal editors.

Conflict of interest: none declared.

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