Brugada syndrome: Clinical presentation, diagnosis, and evaluation

AUTHOR: John V Wylie, MD, FACC
SECTION EDITOR: Samuel Asirvatham, MD
DEPUTY EDITOR: Susan B Yeon, MD, JD

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Literature review current through: **Jan 2024.**
This topic last updated: **Jun 19, 2023.**

INTRODUCTION

Brugada syndrome is a genetic disorder that can cause life-threatening ventricular tachyarrhythmias and thereby sudden cardiac arrest and sudden cardiac death. Patients have abnormal findings on the surface electrocardiogram (ECG) but do not usually have any apparent cardiac structural abnormalities.

The clinical manifestations, evaluation, and diagnosis of Brugada syndrome will be reviewed here.

The epidemiology, pathogenesis, management, and prognosis of Brugada syndrome, along with a discussion of the other causes of sudden cardiac arrest in apparently normal hearts, are discussed elsewhere.

- (See "Brugada syndrome: Epidemiology and pathogenesis".)
- (See "Brugada syndrome or pattern: Management and approach to screening of relatives".)
- (See "Approach to sudden cardiac arrest in the absence of apparent structural heart disease".)

BRUGADA PATTERN VERSUS SYNDROME

Two terms, distinguished by the presence or absence of symptoms, have been used to describe patients with the typical ECG findings of a pseudo-right bundle branch block and persistent ST-segment elevation in either or both leads V1 to V2 (waveform 1):

- **Brugada pattern** – Patients with typical ECG features who are asymptomatic and have no other clinical criteria are said to have the Brugada pattern (sometimes referred to as Brugada phenocopies).

Patients with ventricular premature beats or nonsustained ventricular tachycardia with no other types of ventricular arrhythmia (eg, sustained ventricular tachycardia) are generally considered to have Brugada pattern and not Brugada syndrome.

- **Brugada syndrome** – Patients with typical ECG features who have experienced sudden cardiac death or a sustained ventricular tachyarrhythmia, or who have one or more of the other associated clinical criteria, are said to have Brugada syndrome.

Persons with either Brugada pattern or Brugada syndrome can have identical findings on the surface ECG. (See '12-lead ECG' below.)

CLINICAL PRESENTATION

Demographic information — Brugada syndrome is generally diagnosed between 22 and 65 years of age; it is rarely diagnosed in children. (See "Brugada syndrome: Epidemiology and pathogenesis", section on 'Age at diagnosis'.)

Brugada syndrome is more common in males than females. (See "Brugada syndrome: Epidemiology and pathogenesis", section on 'Male predominance'.)

Common scenarios

- **ECG pattern without obvious symptoms** – Some patients with the Brugada pattern ECG do not present with symptoms. In these patients, Brugada syndrome can be identified as follows:
  - When an ECG is performed for another reason (eg, preoperative evaluation, annual physical examination, etc).

- Part of the screening of first-degree relatives of a Brugada proband (ie, the first person in a family who brings the concern of a genetic disorder to the attention of healthcare professionals). In first-degree relatives, careful history taking reveals high-risk symptoms or intermediate-risk factors that guide further testing for risk stratification and confirm the diagnosis.

- **ECG and symptoms** – Patients with Brugada syndrome typically present with ECG findings characteristic of the Brugada ECG pattern (waveform 1) and a clinical presentation that suggests ventricular arrhythmia. (See 'Symptoms' below.)

- **Transient ECG pattern** – In some people, the Brugada pattern ECG may come and go, depending on whether provoking factors are present; such factors include fever, autonomic dysfunction, and exposure to specific prescription and illicit drugs. These are discussed in detail separately. (See "Brugada syndrome: Epidemiology and pathogenesis", section on 'Pathogenesis'.)

In one series of 43 patients with Brugada pattern ECGs in whom 310 ECGs were obtained over a median follow-up of 18 months, the following findings were noted [1]:

- Among 15 patients with a spontaneous Brugada type 1 ECG at presentation, 14 had at least one nondiagnostic (ie, not type 1) ECG during follow-up.

- Among 28 patients whose initial ECG was nondiagnostic, eight developed characteristic Brugada type 1 ECG abnormalities during follow-up.

In a cohort of 251 patients with Brugada pattern ECG (including 30 percent with spontaneous Brugada type 1 ECG and 70 percent with drug-induced Brugada type 1 ECG) who underwent 12-lead ambulatory monitoring for 24 hours, the Brugada type 1 ECG pattern was frequently intermittent or absent during the 24-hour monitoring period [2]. (See 'Drug challenge for type 2 or equivocal ECG' below.)

Symptoms — Most clinical manifestations of the Brugada syndrome are related to life-threatening ventricular arrhythmias [3,4]. Specific symptoms are summarized as follows:

Sudden cardiac arrest and/or death — Sudden cardiac arrest resulting from ventricular tachyarrhythmia is one of the most significant clinical manifestations of Brugada syndrome.

Clinical features in Brugada — Arrhythmic events and sudden cardiac arrest have the following features:

- They are more common at night than in the day.

- They occur more commonly during sleep than while awake [5,6].
- Ventricular fibrillation and polymorphic ventricular tachycardia are more common than monomorphic ventricular tachycardia [7].
- Episodes are not usually secondary to exercise [8].
- Premature ventricular beats can initiate ventricular fibrillation [9]. Stored electrograms from implantable cardioverter-defibrillators have shown that frequent spontaneous premature ventricular beats, which are identical in morphology to those that initiate ventricular fibrillation, are often seen before the onset of the arrhythmia [9]. (See 'Conditions causing ventricular arrythmia and no structural heart disease' below.)

Sudden unexpected noctural death syndrome — Sudden cardiac arrest is more common at night in patients with Brugada syndrome, and sleep-disordered breathing appears to be more commonly seen in patients with Brugada syndrome [10]. A pattern of **nocturnal agonal respiration** with gasping breaths during sleep has been reported and may represent aborted cardiac arrhythmias. This is generally considered an ominous symptom that should be considered the equivalent of arrhythmogenic syncope or malignant ventricular arrhythmias when evaluating the patient using diagnostic criteria.

Sudden unexpected nocturnal death syndrome (SUNDS; also called sudden unexpected death syndrome or SUDS) has been described in young, apparently healthy males from different Asian countries; this syndrome has several names depending on geography, including the following [11-13]:

- Lai tai (death during sleep) in Thailand
- Bangungut (to rise and moan in sleep followed by death) in the Philippines
- Bokkuri (unexpected sudden cardiac death at night) in Japan

SUNDS and Brugada syndrome are phenotypically, genetically, and functionally the same disorder [14,15]. Thus, the management of these patients should be the same as that for classic Brugada syndrome. (See "Brugada syndrome or pattern: Management and approach to screening of relatives", section on 'High-risk patients'.)

A low serum potassium level may contribute to sudden cardiac arrest in these patients [14]. It has been suggested that a high carbohydrate meal may precipitate sudden cardiac arrest, perhaps by increasing the secretion of insulin, which drives extracellular potassium into cells.

A relationship between SUNDS and Brugada syndrome was initially suggested by the observation that a majority of patients with SUNDS have the ECG manifestations of Brugada

syndrome [13]. This association was confirmed by observations that patients with SUNDS have mutations in the same cardiac sodium channel gene (*SCN5A*) that is abnormal in Brugada syndrome [15]. (See "Brugada syndrome: Epidemiology and pathogenesis".)

Syncope — Syncope resulting from ventricular tachyarrhythmias is a clinically significant clinical manifestation of Brugada syndrome; however, not all episodes of syncope are due to ventricular arrhythmia. One study of patients with Brugada syndrome suggested that 30 percent of syncopal episodes may be due to nonarrhythmic causes (eg, neurocardiogenic) [16].

Palpitations — Palpitations related to ventricular tachyarrhythmia are not common in patients with Brugada syndrome and when present may be due to atrial fibrillation. Atrial fibrillation is associated with Brugada syndrome and may be the first presentation of the disease [17,18]. The relationship between atrial arrhythmias and Brugada syndrome results from sodium channel abnormalities that involve both the atria and the ventricles.

The incidence of atrial fibrillation is 10 to 20 percent in patients with Brugada syndrome. Among 611 patients with Brugada pattern ECG, the diagnosis of atrial fibrillation preceded the diagnosis of Brugada pattern ECG in 5.7 percent [19].

Patients with Brugada syndrome are also at increased risk of other atrial arrhythmias [17,18,20,21]. The presence of atrial fibrillation has been associated with increased disease severity and a higher risk of ventricular fibrillation. This is discussed in detail separately. (See "Brugada syndrome or pattern: Management and approach to screening of relatives", section on 'Intermediate-risk factors'.)

Provoking factors

- **Fever** – Fever can be a trigger for both induction of Brugada pattern ECG abnormalities and cardiac arrest among persons known to have Brugada pattern ECG or Brugada syndrome. Animal models have helped elucidate how hyperthermia causes changes in sodium current function; a reduction in sodium current results in changes to the action potential predisposing to ventricular fibrillation [22].

- **Brugada pattern is more common in patients with fever** – In a study of 402 febrile emergency department patients and 909 controls, type I Brugada pattern ECG changes were 20 times more common in febrile patients (2 versus 0.1 percent) [23]. Reassuringly, none of these patients had cardiac events over 30 months of follow-up.

- **Sudden cardiac arrest in febrile patients with Brugada syndrome** – In a single-center retrospective review of 111 patients with confirmed Brugada syndrome, 22 patients had

cardiac arrest, of whom four (18 percent) had a preceding fever [24]. In a subset of 24 of the 111 patients with ECGs recorded during fever and normothermia, ECGs taken during fever had prolonged QRS and QT intervals and worsening ST elevation (waveform 2).

In the Survey on Arrhythmic Events in Brugada Syndrome (SABRUS), an international multicenter registry of 678 patients with a documented arrhythmic event, 6 percent had an arrhythmic event during febrile illness [25]. The pediatric population displayed the highest rate of fever-related arrhythmic event (age <16 years), with a disproportionally higher event rate in the very young (age 0 to 5 years, 65 percent).

- **Medications** – The characteristic Brugada pattern ECG abnormalities may be exposed by a sodium channel blocker, such as flecainide, ajmaline, or procainamide (table 1) [5,14,26-28]. The known properties of some of these agents allow them to be utilized as part of a drug challenge to confirm the diagnosis. (See 'Drug challenge for type 2 or equivocal ECG' below.)

Other common medications that can unmask or modulate the Brugada ECG pattern are beta blockers and tricyclic or tetracyclic antidepressants. Lithium and local anesthetics can also provoke Brugada (table 1) [14,29,30]. A reference website has been established that identifies drugs that can provoke adverse events in patients with Brugada syndrome [31].

The clinical significance of drug-provoked ECG changes in the absence of symptoms or family history of Brugada syndrome or pattern is undetermined.

- **Toxins** – Alcohol and cocaine can unmask Brugada syndrome [32,33].

- **Metabolic disturbances** – Patients with metabolic disturbances (eg, severe hyperkalemia) may present with Brugada pattern ECG, which is reversible following correction of the underlying metabolic disturbance [34]. (See "Brugada syndrome: Epidemiology and pathogenesis", section on 'Cocaine abuse' and "Brugada syndrome: Epidemiology and pathogenesis", section on 'Psychotropic drugs'.)

DIAGNOSTIC EVALUATION

When a patient is suspected to have Brugada syndrome, additional evaluation may be required to confirm the diagnosis (algorithm 1). In general, all additional diagnostic testing should be performed following consultation with an electrophysiologist or a general cardiologist with specific training and expertise in the diagnosis and management of Brugada syndrome [35].

We perform initial steps in all patients with suspected Brugada syndrome, regardless of our index of suspicion. After these initial steps, our subsequent approach to the evaluation and risk stratification of patients with Brugada pattern ECG finding (waveform 1) depends on whether there is an intermediate or low suspicion that the patient has Brugada syndrome. (See "Brugada syndrome or pattern: Management and approach to screening of relatives", section on 'Risk factors for arrhythmia or sudden cardiac arrest'.)

We do not perform genetic testing as part of our diagnostic work-up. However, there may be a role for genetic testing in screening of first-degree relatives of a person diagnosed with Brugada syndrome. This is discussed separately. (See "Brugada syndrome or pattern: Management and approach to screening of relatives", section on 'Screening relatives'.)

Initial steps to diagnose Brugada syndrome — In all patients in whom Brugada syndrome is suspected, we undertake a medical history, 12-lead ECG, and evaluate for any underlying structural heart disease. Both Brugada pattern ECG findings and clinical features consistent with ventricular arrhythmia are required to make the diagnosis [36,37].

We evaluate for structural heart disease to rule out causes that could underlie the ventricular arrythmia other than Brugada syndrome. If this evaluation **does not** reveal structural heart disease or myocardial ischemia, and the patient has clinical risk factors and spontaneous type 1 Brugada pattern ECG changes, Brugada syndrome is diagnosed and patients should be treated accordingly.

The appearance of typical ECG changes alone without other clinical manifestations or intermediate risk factors is considered to represent the Brugada ECG pattern but not the Brugada syndrome.

Medical history — The first step in the evaluation of patients with suspected Brugada syndrome is to take a medical history with a central goal of identifying clinical risk factors that would support the diagnosis of Brugada syndrome along with the ECG findings. (See 'Clinical presentation' above.)

12-lead ECG — Our initial diagnostic test is a 12-lead ECG. (See "ECG tutorial: Basic principles of ECG analysis" and "ECG tutorial: Electrical components of the ECG".)

If the initial ECG is equivocal, we move the right precordial leads up to the second or third intercostal space, as this modification may increase the sensitivity of detecting these abnormalities [14,38].

Two distinct patterns of ST elevation have been recognized in patients with Brugada syndrome (figure 1 and table 2) [14,39,40]:

- In the type 1 Brugada ECG pattern, the elevated ST segment (≥2 mm) descends with an upward convexity to an inverted T wave (figure 1). This is referred to as the "coved type" Brugada pattern.

- In the type 2 Brugada ECG pattern (combined from the original designation of types 2 and 3 patterns), the ST segment has a "saddle back" ST-T wave configuration, in which the elevated ST segment descends toward the baseline, then rises again to an upright or biphasic T wave (figure 1).

Other ECG findings characteristic of Brugada syndrome include:

- **"J" wave** – There is a high takeoff of the ST segment in the right precordium (ie, a "J" wave rather than a true right bundle branch block) due to abnormal repolarization in the right ventricular outflow tract [41]. Thus, the widened S wave in left lateral leads that is characteristic of right bundle branch block (waveform 3) is absent in most patients with Brugada pattern ECGs. [42,43]. (See "Brugada syndrome: Epidemiology and pathogenesis", section on 'Pathogenesis'.)

- **QT interval prolongation** – This may be seen in the right precordial leads [44]. The degree of prolongation is usually modest, but some patients have genetic abnormalities that cause both Brugada pattern ECG and long QT syndrome [45-47]. (See "Brugada syndrome: Epidemiology and pathogenesis", section on 'Related disorders with SCN mutations'.)

- **Increased S wave voltage and duration** – The finding of an S wave in lead 1 that is ≥0.1 millivolts and ≥40 milliseconds in duration (thought to represent delayed right ventricular outflow tract conduction) may be a strong predictor of sudden death. In a cohort of 347 asymptomatic patients with spontaneous type 1 Brugada pattern ECGs, 9 percent developed ventricular fibrillation or sudden cardiac death over a mean follow-up of four years [48]. The presence of an S wave in lead 1 (hazard ratio 39.1) was associated with sudden death, with a negative predictive value of nearly 99 percent. This finding has not been confirmed in subsequent studies.

Persons with Brugada pattern findings on a surface ECG have some form of a pseudo-right bundle branch block and persistent ST-segment elevation in leads V1 to V2 (waveform 1) [49].

Testing for underlying heart disease — All patients with suspected Brugada syndrome require additional testing to exclude underlying structural heart disease, and many may require

testing to exclude myocardial ischemia. It is important to recognize that patients with Brugada syndrome do not typically have structural heart disease. Therefore, standard cardiac testing, including cardiac imaging (with echocardiography and/or cardiac magnetic resonance imaging) and cardiac stress testing, often reveal no abnormalities or if abnormalities are present, this suggests an alternative diagnosis. (See 'Differential diagnosis' below.)

Testing for underlying heart disease will typically include one or more the following:

- Echocardiogram to evaluate for myocardial diseases and ischemic heart disease. (See "Echocardiographic recognition of cardiomyopathies".)

- Cardiac stress testing to evaluate suspicion for obstructive coronary artery disease if there is intermediate or high risk of coronary artery disease. (See "Stress testing for the diagnosis of obstructive coronary heart disease".)

- Cardiac magnetic resonance imaging. Some centers may perform cardiac magnetic resonance imaging in lieu of echocardiography (or as a follow-up if the echocardiogram is of suboptimal technical quality). (See "Clinical utility of cardiovascular magnetic resonance imaging".)

  Among patients in whom a signal-averaged ECG suggests arrhythmic substrate, we obtain cardiac magnetic resonance imaging to rule out widespread scar and other cardiac structural abnormalities that may make a diagnosis of Brugada syndrome less likely.

  Patients with Brugada syndrome may have morphological changes in the right ventricular outflow tract related to Brugada syndrome, including dilation and fibrosis, although these are not specific enough to aid in the diagnosis [50]. In 69 patients who underwent cardiac magnetic resonance imaging, those with spontaneous type 1 Brugada pattern ECGs had 2 centimeter larger right ventricular outflow tract dimensions (as well as mildly lower left and right ventricular ejection fractions) compared with patients with drug-induced type 1 Brugada pattern ECGs and controls.

Drug challenge for type 2 or equivocal ECG — If the initial evaluation of a patient does not reveal structural heart disease or myocardial ischemia, and the patient has spontaneous type 2 Brugada pattern or other equivocal ECG changes, we perform a drug challenge using a sodium channel blocker in an attempt to elicit the type 1 Brugada ECG pattern.

Among some patients with the type 2 Brugada ECG pattern, the type 1 Brugada ECG pattern can be unmasked by sodium channel blockers (eg, flecainide, procainamide, ajmaline, pilsicainide) (waveform 4 and waveform 5) [14,26-28]. The importance of unmasking the

type 1 Brugada ECG pattern relates to its relevance for risk stratification in asymptomatic patients and for confirming the diagnosis of Brugada syndrome in symptomatic patients [51].

While drug challenge can be helpful when positive, the reported sensitivity of pharmacologic challenge with these drugs has been variable, ranging from as low as 15 percent to as high as 100 percent [27,52]. The duration of monitoring following the administration of the challenge agent is likely related to the sensitivity of the test.

Indications — We **do** perform a drug challenge in the following patients:

- For **asymptomatic** patients if the resting ECG shows the type 2 Brugada pattern and there is a family history of sudden cardiac death at less than 45 years of age and/or a family history of type 1 Brugada pattern ECG changes.
- For **symptomatic** patients whose resting ECG shows the type 2 Brugada pattern, our experts feel that drug challenge is not always necessary. Patients who are high risk will undergo treatment of Brugada syndrome regardless of the results of drug testing. However, drug testing may be used in these patients to establish a diagnosis, which may guide future management and prompt risk stratification of family members. (See "Brugada syndrome or pattern: Management and approach to screening of relatives", section on 'High-risk patients'.)

In a study of 245 patients with Brugada syndrome who underwent sodium channel blocker challenge with pilsicainide (181 patients with spontaneous type 1 ECG, 64 patients with non-type 1 ECG), induced ventricular arrhythmias and ST-segment augmentation were associated with an increased risk of the development of ventricular tachycardia/ventricular fibrillation events during a mean follow-up of 113 months [53].

We **do not** perform a drug challenge in patients with the following:

- Spontaneous type 1 Brugada pattern ECG findings, **with or without symptoms**.
- For **asymptomatic** patients whose resting ECG shows the type 2 Brugada pattern and who have no known family history of sudden cardiac death, we do not recommend a drug challenge.

Procedure — A drug challenge should only be performed by clinicians experienced in the administration of sodium-channel-blocking drugs and interpretation of ECGs. During the drug challenge, continuous ECG monitoring is required. The typical duration of monitoring is 30 minutes following intravenous drug administration and up to four hours or longer if oral flecainide is used for the drug challenge.

One of several sodium-channel-blocking drugs can be used for the drug challenge [54]. Testing should be performed in a closely monitored setting on telemetry with a code cart readily accessible, as drug challenge may precipitate ventricular arrhythmias in some patients. Recommended doses for the different drugs include [14]:

- Flecainide – 2 mg/kg over 10 minutes intravenously or 400 mg orally
- Procainamide – 10 mg/kg over 10 minutes intravenously
- Ajmaline – 1 mg/kg over 5 minutes intravenously
- Pilsicainide – 1 mg/kg over 10 minutes intravenously

The choice of one agent versus another is typically site specific and based upon availability, as no head-to-head comparisons have been performed. One nonrandomized study of 425 patients referred for drug challenge showed that patients challenged with ajmaline were more likely to develop a type I Brugada ECG pattern than those challenged with procainamide (26 versus 4 percent) [55].

We terminate the drug challenge for the following reasons:

- Development of a diagnostic type 1 Brugada ECG pattern
- ≥2 mm increase in ST-segment elevation in patients with a type 2 Brugada ECG pattern
- Development of ventricular premature beats or other arrhythmias
- Widening of the QRS ≥30 percent above baseline

Ventricular arrythmias — Sustained ventricular arrhythmias following drug challenge have been reported in 1 to 2 percent of drug challenges and with all of the drugs used for the challenge [27,56-60].

- **With ajmaline challenge** – In a systematic review of 16 studies of ajmaline challenge (totalling 3515 tests), 33 patients (0.9 percent) developed ventricular tachycardia or ventricular fibrillation [59]. In a large cohort of 503 patients with unmasking of a Brugada pattern ECG following ajmaline administration, 2 percent developed sustained ventricular arrhythmias requiring defibrillation [58].

- **Family members of probands with Brugada syndrome** – Among 672 such patients who were asymptomatic and underwent screening with drug challenge, ventricular tachycardia or fibrillation developed in 10 patients (1.5 percent) [60].

Risk stratification for those with uncertain diagnosis — In patients with intermediate risk factors for Brugada syndrome, we undertake risk stratification to establish a diagnosis and to decide therapy (table 3).

Signal-averaged ECG (SAECG) — In patients with suspected Brugada syndrome in whom there is a negative drug challenge or in whom the diagnosis is still uncertain (eg, type 1 ECG with intermediate or other equivocal risk factors), we obtain an SAECG for risk stratification. The SAECG may be helpful in identifying patients with Brugada pattern ECG and an increased risk of future arrhythmic events [61].

A normal SAECG makes the diagnosis of Brugada syndrome highly unlikely. The SAECG is useful for detecting subtle abnormalities in the surface ECG that are not visible to the naked eye. One example of such an abnormality is the "ventricular late potential," a low-amplitude signal near the end of the QRS complex that can be used to stratify risk for ventricular tachyarrhythmias in patients with cardiomyopathies of various etiologies.

In a study of 43 patients with Brugada syndrome, the presence of late potentials on SAECG were associated with later arrhythmic events [61]. Patients with late potentials had a greater incidence of arrhythmic events over 34 month of follow-up compared with those without late potentials (72.4 versus 14.3 percent) [62]. (See "Signal-averaged electrocardiogram: Overview of technical aspects and clinical applications".)

Electrophysiology testing — In certain cases, electrophysiology testing may be offered to patients for further risk stratification in the presence of equivocal symptoms or moderate or possible risk factors; in these cases, an electrophysiologic study may be part of the decision-making process when determining further management. This is discussed in detail separately. (See "Brugada syndrome or pattern: Management and approach to screening of relatives", section on 'Intermediate-risk patients'.)

Patients with a Brugada ECG pattern and certain high-risk clinical features (ie, a history of sudden cardiac arrest, sustained ventricular tachyarrhythmias, or unexplained syncope) have an indication for implantable cardioverter-defibrillator implantation, so invasive electrophysiology testing is unlikely to impact management [5,41,63-66].

For the majority of asymptomatic patients with Brugada pattern ECG findings, invasive electrophysiology testing is not necessary [61,67]. Indeed, the role of electrophysiology testing in asymptomatic patients remains an area of investigation, and prior studies have been equivocal.

- In a 2017 systematic review performed as part of the 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines, which included six studies of 1138 asymptomatic patients with Brugada ECG findings who had undergone invasive electrophysiology testing with programmed ventricular stimulation, 34.3 percent were found to have inducible ventricular tachycardia

during electrophysiology testing [67]. During follow-up, those who had inducible ventricular tachycardia had a higher rate of arrhythmic events (sustained ventricular tachycardia, sudden cardiac death, or appropriate defibrillator therapy) compared with those with no inducible ventricular tachycardia (3.3 versus 1.6 percent; odds ratio 2.3; 95% CI 0.6-8.7); however, this was not statistically significant.

- In a 2016 metaanalysis of eight nonrandomized studies of 883 asymptomatic patients with a spontaneous type 1 Brugada pattern ECGs who were followed for 33.8 months, patients had a low incidence of subsequent cardiac arrest or ventricular arrythmia (annual incidence per 100 persons = 1). Those with inducible ventricular arrhythmias on electrophysiology testing had a similar rate compared with patients without inducible arrythmias (hazard ratio 1.70- 95% CI 0.73-3.35) [68]. The overall low event rate is reassuring and suggests asymptomatic patients with Brugada ECG findings have a low risk of future arrhythmic events.

There is some evidence that electrophysiology testing combined with myocardial substrate electroanatomic mapping may be a way to more accurately predict inducible arrhythmias [69]; however, this has not been well studied.

Insertable cardiac monitor — For patients who have nonspecific symptoms for Brugada syndrome (eg, neurocardiogenic syncope, palpitations, or presyncope), the risk of life-threatening arrythmia may be uncertain; in such patients, an insertable cardiac monitor (ICM) may help elucidate a diagnosis. A registry study of 50 patients with Brugada syndrome treated with ICM demonstrated a 22 percent diagnostic yield [70]. The majority of these events were bradyarrhythmias, and only one patient had a concerning ventricular arrhythmia (nonsustained polymorphic ventricular tachycardia) [70]. (See "Ambulatory ECG monitoring", section on 'Insertable cardiac monitor'.)

Genetic testing — Genetic testing for a mutation in the *SCN5A* gene or other causative genetic variant should be performed in asymptomatic patients with a Brugada pattern ECG only when a definitive mutation has been identified within the family proband. The genetic and clinical heterogeneity of Brugada syndrome limit the utility of genetic testing, as the absence of a mutation in *SCN5A* or other pathogenic variant does not exclude Brugada syndrome, and the presence of such a variant does not confirm the diagnosis of Brugada syndrome. (See "Brugada syndrome or pattern: Management and approach to screening of relatives", section on 'Screening relatives'.)

ALTERNATIVE APPROACHES AND OTHER GUIDELINE GROUPS

Because of the clinical variability in presentation and the different ECG manifestations that can be seen in Brugada syndrome, diagnostic criteria have been proposed by professional societies from both Europe and North America [3,14,39]. In 2013, three major professional societies, the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society (APHRS), jointly issued an expert consensus statement on inherited arrhythmia syndromes, which included updated diagnostic criteria for Brugada syndrome [3]. We broadly agree with this statement that suggests that Brugada syndrome should be "definitively diagnosed" with symptoms, and the presence of type I Brugada pattern ECG changes in at least one right precordial lead (specifically V1 or V2), either spontaneously or following drug challenge with a sodium channel blocker, using standard or superior ECG lead placement. (See 'Drug challenge for type 2 or equivocal ECG' above.)

For a patient with type I Brugada pattern ECG findings who is otherwise asymptomatic, clinical findings that would support the diagnosis of Brugada syndrome include the following:

- Presence of first-degree atrioventricular block and left axis deviation on the ECG
- Atrial fibrillation (see 'Palpitations' above)
- Late potentials seen on signal-averaged ECG (SAECG) (see "Signal-averaged electrocardiogram: Overview of technical aspects and clinical applications")
- Fragmented QRS complex
- ST-T wave alternans with spontaneous ventricular premature beats in a left bundle branch block pattern on prolonged ECG recording
- Ventricular refractory period <200 milliseconds and HV (His bundle to ventricular myocardium) interval >60 milliseconds during invasive electrophysiology study
- Absence of structural heart disease, including myocardial ischemia

We agree with the 2013 HRS/EHRA/APHRS consensus statement, which updated the 2005 criteria, but the original criteria continue to be frequently cited in clinical practice and more specifically define criteria to diagnose Brugada syndrome [14]. This includes the appearance of type 1 ST-segment elevation (coved type) in more than one right precordial lead (V1 to V2) in the presence or absence of a sodium channel blocker, **plus** at least one of the following:

- Documented ventricular fibrillation
- Polymorphic ventricular tachycardia
- Family history of sudden cardiac death at less than 45 years of age
- Family history of type 1 Brugada pattern ECG changes
- Inducible ventricular tachycardia during electrophysiology study
- Unexplained syncope suggestive of a tachyarrhythmia

- Nocturnal agonal respiration

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Brugada syndrome includes conditions that have similar ECG findings with Brugada syndrome and/or conditions that have clinical features consistent with ventricular arrhythmia.

Conditions with ECG similar to Brugada pattern — The differential diagnosis for Brugada pattern ECG changes includes other conditions that result in apparent conduction and ST-segment abnormalities in leads V1 to V2 on the ECG.

Arrhythmogenic right ventricular dysplasia — The Brugada pattern on ECG can be seen as an early subclinical manifestation of arrhythmogenic right ventricular cardiomyopathy (ARVC) [64]. ARVC is a genetic disorder, usually autosomal dominant, that primarily involves the right ventricle, as the right ventricular myocardium is typically replaced by fat, with scattered residual myocardial cells and fibrous tissue. (See "Arrhythmogenic right ventricular cardiomyopathy: Pathogenesis and genetics".)

A study of 96 victims of sudden cardiac death who were ≤35 years and had a baseline ECG available suggested an association between ARVC and the Brugada pattern on ECG [8]. Right precordial ST-segment elevation with or without right bundle branch block was present in 13 percent of patients; at autopsy, all but one had ARVC. However, this study was from southern Italy, where ARVC has a high prevalence and is an important cause of sudden cardiac death. Furthermore, mutations in *SCN5A* have not been described in ARVC but are a recognized cause of Brugada syndrome. (See "Brugada syndrome: Epidemiology and pathogenesis", section on 'SCN5A'.)

Patients with ARVC often have abnormalities in the right ventricle that can be seen on echocardiography or cardiac magnetic resonance imaging. In contrast, the vast majority of patients with Brugada syndrome do not have apparent structural heart disease on routine imaging studies [14]. (See "Arrhythmogenic right ventricular cardiomyopathy: Diagnostic evaluation and diagnosis", section on 'Diagnostic evaluation'.)

Other causes of ST changes in V1 to V2 — These include:

- Right bundle branch block (see "Right bundle branch block", section on 'ECG findings and diagnosis')
- Early repolarization (see "Early repolarization", section on 'ECG findings')

- Acute pericarditis (see "Acute pericarditis: Clinical presentation and diagnosis", section on 'Electrocardiogram')
- Acute myocardial ischemia or infarction (see "Electrocardiogram in the diagnosis of myocardial ischemia and infarction")
- Left ventricular hypertrophy (see "Left ventricular hypertrophy: Clinical findings and ECG diagnosis")
- Pectus excavatum (see "Pectus excavatum: Etiology and evaluation", section on 'Cardiac function')
- Hypothermia (see "ECG tutorial: Miscellaneous diagnoses", section on 'Hypothermia')
- Blunt chest trauma (eg, driver in an motor vehicle accident)

Conditions causing ventricular arrythmia and no structural heart disease — The differential diagnosis of Brugada syndrome includes a broad range of conditions in which there are clinical manifestations of ventricular tachyarrhythmias (ie, sudden cardiac death, syncope) and no apparent cardiac structural abnormalities.

Congenital long QT syndrome (LQTS) — Patients with a documented or suspected ventricular arrhythmia associated with prolongation of the QT interval are more likely to have LQTS than Brugada syndrome. Congenital LQTS should be suspected if the patient has no acquired cause of a long QT such as medications of electrolyte imbalance. (See "Congenital long QT syndrome: Epidemiology and clinical manifestations".)

Acquired LQTS with polymorphic ventricular tachycardia — This diagnosis should be considered if the patient has a QTc prolongation or has been exposed to medications or other triggers, such as electrolyte imbalance, that may prolong the QT interval. Similarly, patients with ventricular tachycardia or sudden cardiac death whose QT interval is markedly shortened are more likely to have short QT syndrome. (See "Acquired long QT syndrome: Definitions, pathophysiology, and causes".)

Short QT syndrome — Patients with a documented or suspected ventricular arrhythmia associated with a short QT interval (usually <360 milliseconds with a range of 220 to 360 milliseconds) are more likely to have a short QT interval rather than Brugada syndrome. (See "Short QT syndrome".)

Catecholaminergic polymorphic ventricular tachycardia — Patients who experience ventricular tachycardia or sudden cardiac death in the setting of exertion are more likely to have catecholaminergic polymorphic ventricular tachycardia than Brugada syndrome, in which symptomatic tachyarrhythmias are more likely to occur at rest. (See "Catecholaminergic polymorphic ventricular tachycardia".)

Commotio cordis — Patients with ventricular tachycardia or sudden cardiac death immediately following blunt chest trauma are more likely to have experienced commotio cordis than Brugada syndrome. Commonly, the blunt trauma is experienced during a sporting event by a projectile object (eg, baseball or hockey puck) traveling at a velocity greater than 20 miles per hour. Often, the patient collapses within two to three seconds of impact. (See "Commotio cordis".)

Idiopathic ventricular tachycardia or fibrillation — If patients undergo a thorough evaluation for Brugada syndrome and are not found to have spontaneous or drug-induced ECG findings consistent with Brugada syndrome or any other cause of ventricular arrythmia in the absence of structural heart disease, it is possible that idiopathic ventricular tachycardia or ventricular fibrillation are present. It is important to note that both of these are diagnoses of exclusion. (See "Ventricular tachycardia in the absence of apparent structural heart disease" and "Approach to sudden cardiac arrest in the absence of apparent structural heart disease", section on 'Idiopathic VF'.)

PEDIATRIC PATIENTS

Brugada syndrome is rarely diagnosed in children. In the largest international multicenter registry (SABRUS) of patients with Brugada syndrome with a documented first arrhythmic event, only 0.8 percent of patients were <16 years. [71].

- **Demographic features** – In a report from the SABRUS cohort, which included 57 patients age ≤20 years, pediatric patients (age ≤12 years) were more likely than adolescents (age 13 to 20 years) to be female (42 versus 13 percent) [72].

- **Clinical diagnosis and natural history** – The majority of children diagnosed with Brugada syndrome are identified based on family screening, whereas a smaller subset presented with a clinical event consistent with ventricular arrhythmia. This was illustrated in a cohort of 30 children with Brugada syndrome (mean age eight years) diagnosed at 13 referral centers in Europe [73]. In this study, 17 of 30 were diagnosed based on family screening, 10 had prior unexplained syncope, and one presented with aborted sudden cardiac death.

  The following are more common among pediatric compared with adolescent patients [72]:

  - Spontaneous type I Brugada ECG pattern (81 versus 52 percent),
  - Fever associated with their arrhythmic event (54 versus 7 percent).
  - Recurrent events earlier

- **Drug challenge** – Repeat ajmaline challenge following the development of puberty (in patients with a negative result prior to puberty) has been shown to unmask the Brugada ECG pattern in asymptomatic relatives of Brugada syndrome patients [74]. (See 'Drug challenge for type 2 or equivocal ECG' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Inherited arrhythmia syndromes".)

SUMMARY AND RECOMMENDATIONS

- **Background** – Brugada syndrome is a genetic disorder that can cause life-threatening ventricular tachyarrhythmias and thereby sudden cardiac arrest and sudden cardiac death; patients have abnormal findings on the surface electrocardiogram (ECG) but do not usually have any apparent cardiac structural abnormalities. (See 'Introduction' above.)

- **Clinical manifestations** – Brugada syndrome is generally diagnosed between 22 and 65 years of age; it is rarely diagnosed in children. Most clinical manifestations of Brugada syndrome are related to life-threatening ventricular arrhythmias, most often ventricular fibrillation or polymorphic ventricular tachycardia. Patients may also present with syncope, palpitations, atrial fibrillation, nocturnal agonal respiration, or sudden unexpected nocturnal death. (See 'Clinical presentation' above.)

- **Diagnostic evaluation**

  - **Initial steps** – In all patients, we take a medical history, perform 12-lead ECG, and rule out any structural causes of heart disease. (See 'Initial steps to diagnose Brugada syndrome' above and 'Diagnostic evaluation' above.)

  - **Drug challenge if ECG is type 2 or equivocal** – If the initial evaluation for a patient does not reveal structural heart disease or myocardial ischemia, and the patient has spontaneous type 2 Brugada pattern or other equivocal ECG changes, we perform a drug challenge using a sodium channel blocker in an attempt to elicit the type 1 Brugada ECG pattern. (See 'Drug challenge for type 2 or equivocal ECG' above.)

- **Further risk stratification in those with a negative drug challenge** – In patients with intermediate risk factors for Brugada syndrome, we undertake risk stratification in order to establish a diagnosis and decide therapy. (See 'Risk stratification for those with uncertain diagnosis' above.)

  - We suggest first evaluating with a signal-averaged ECG (SAECG) rather than other tests. If this test is negative, the likelihood of Brugada syndrome is much lower. (See 'Signal-averaged ECG (SAECG)' above.)

  - If the SAECG is positive, we further evaluate with electrophysiologic testing for further risk stratification. (See 'Electrophysiology testing' above.)

  - In some patients, we may use an insertable cardiac monitor (ICM) if there is suspicion of ventricular arrythmia that would indicate a diagnosis of Brugada syndrome, but this has not been yet confirmed. (See 'Insertable cardiac monitor' above.)

  - Genetic testing for a mutation in the *SCN5A* gene or other causative genetic variant should be performed in asymptomatic patients with a Brugada pattern ECG only when a definitive mutation has been identified within the family proband. (See 'Genetic testing' above.)

- **Differential diagnosis** – The differential diagnosis of Brugada syndrome includes conditions that have similar ECG findings with Brugada syndrome and/or conditions that have clinical features consistent with ventricular arrhythmia. (See 'Differential diagnosis' above.)

- **Pediatric patients** – The majority of children diagnosed with Brugada syndrome are identified based on family screening, whereas a smaller subset presented with a clinical event consistent with ventricular arrhythmia. Pediatric patients are more likely to have a spontaneous type I Brugada ECG pattern and fever associated with their arrhythmic events. (See 'Pediatric patients' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Ann Garlitski, MD, who contributed to earlier versions of this topic review.

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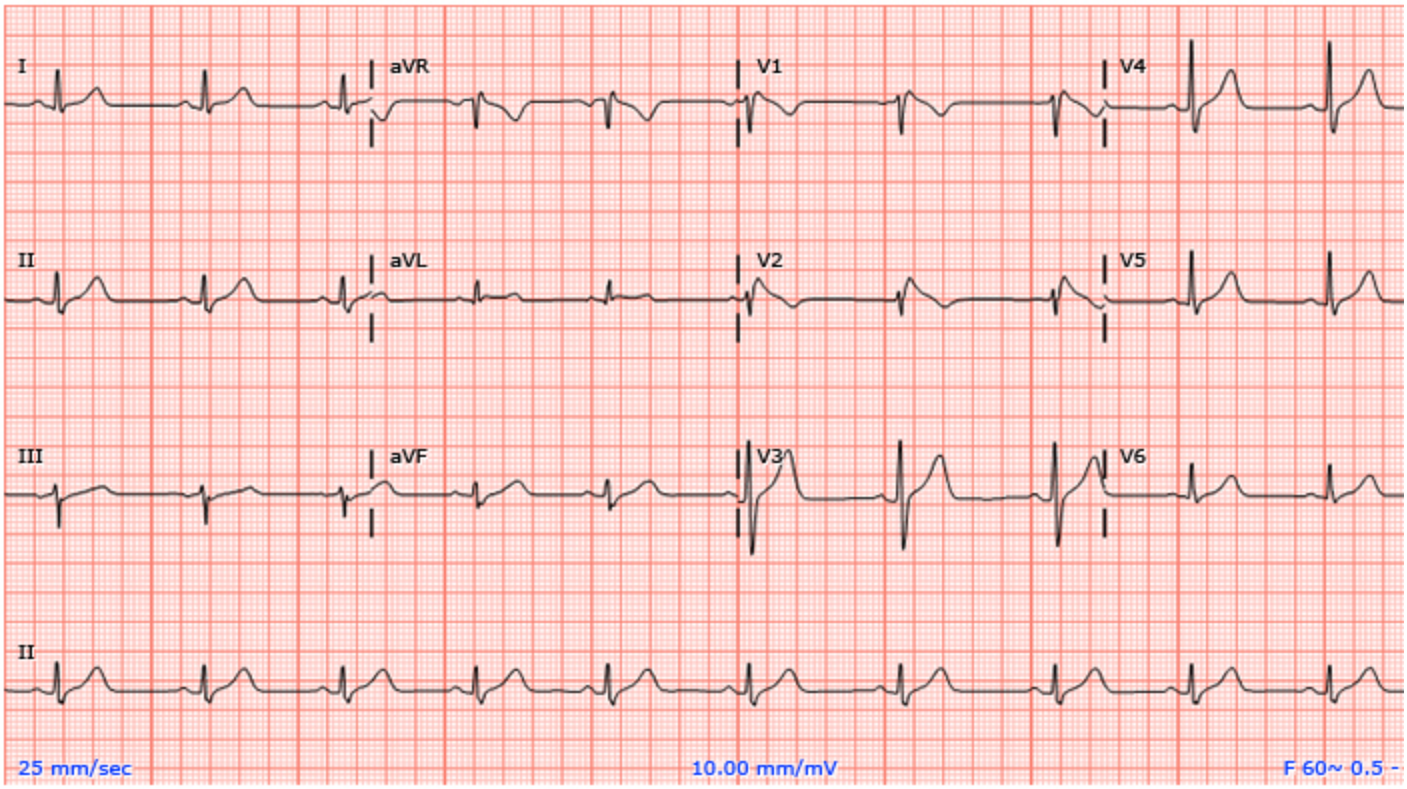
Topic 106759 Version 33.0

GRAPHICS

12-lead electrocardiogram Brugada pattern



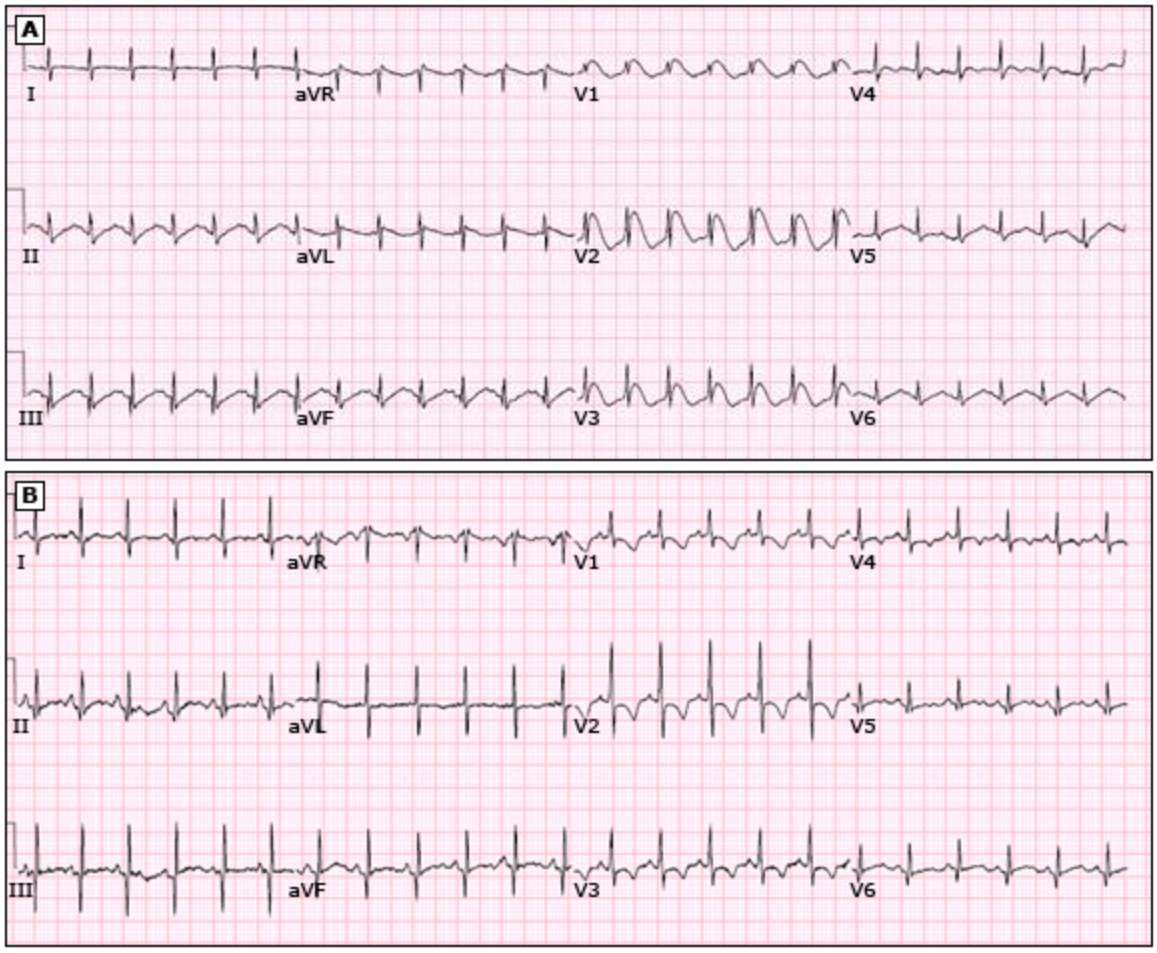
Patient with Brugada pattern ECG. Note the presence of pseudo-right bundle branch block and persistent ST segment elevation in leads V1 to V2.

ECG: electrocardiogram

Courtesy of Ann C Garlitski, MD, FACC, FHRS.

Graphic 122897 Version 1.0

Sinus tachycardia with ST segment changes due to fever in an 11-month-old child with Brugada syndrome



(A) Electrocardiography demonstrating sinus tachycardia and ST segment changes triggered by fever in an 11-month-old child with Brugada syndrome.

(B) Electrocardiography reverts to normal with the resolution of fever in the same patient.

Graphic 100119 Version 3.0

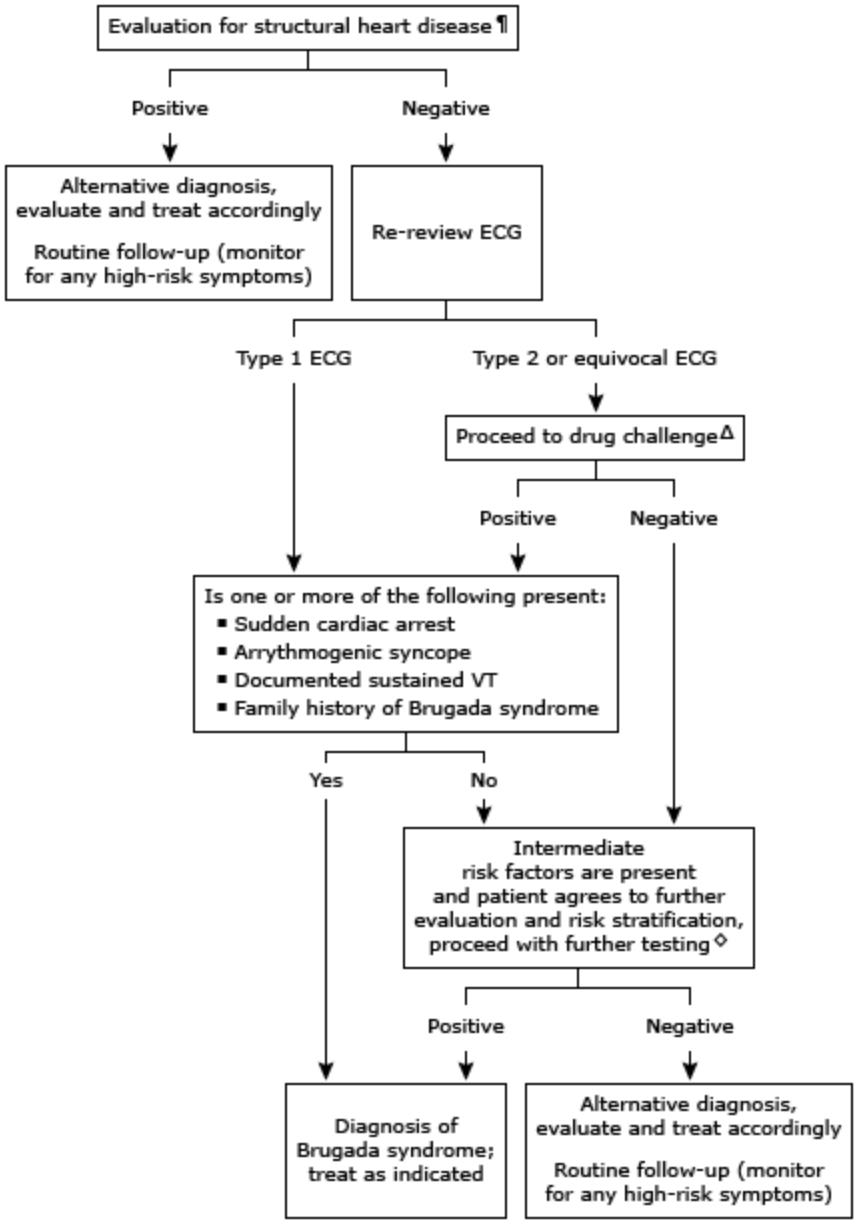
Drugs that can induce Brugada-like patterns on the surface electrocardiogram (ECG)

Antiarrhythmic or antianginal drugs
Cardiac sodium channel blockers (some have been used for drug challenge in patients with Brugada type 2 or 3 ECG pattern)
Class IC drugs (flecainide, pilsicainide, propafenone)
Class IA drugs (ajmaline, procainamide, disopyramide, cibenzoline)
Lithium
Calcium channel blockers
Beta blockers
Nitrates
Nicorandil (a potassium channel opener)
Psychotropic drugs
Tricyclic antidepressants
Amitriptyline
Nortriptyline
Desipramine
Clomipramine
Tetracyclic antidepressants
Maprotiline
Phenothiazines
Perphenazine
Cyamemazine
Selective serotonin reuptake inhibitors
Fluoxetine
Other
Dimenhydrinate
Cocaine intoxication
Alcohol intoxication

Adapted from: Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005; 111:659.

Graphic 73611 Version 5.0

Diagnostic approach to patients with intermediate or high suspicion for Brugada syndrome*



ECG: electrocardiogram; VT: ventricular tachycardia.

* Brugada syndrome is suspected based on the combination of symptoms and typical Brugada pattern ECG changes (either type 1 or 2). Refer to related UpToDate content for further information.

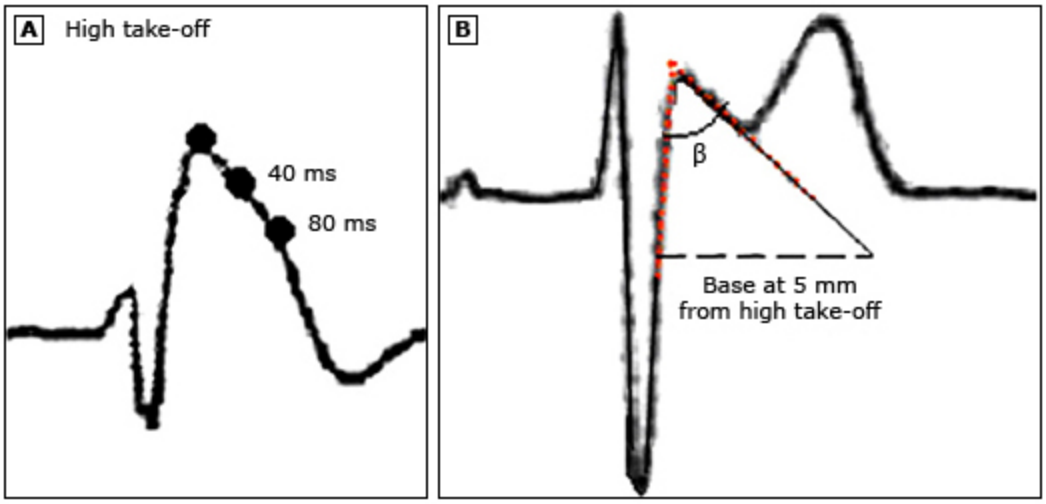
¶ This is usually done with stress testing, echocardiography, and sometimes with cardiac magnetic resonance imaging. The presence of structural heart disease makes Brugada syndrome less likely and points to the structural heart disease as the probable diagnosis.

Δ A drug challenge typically involves giving a sodium channel-blocking medicine in an attempt to elicit the type 1 Brugada ECG pattern. Refer to related UpToDate content for further information.

◇ Tests such as electrophysiologic studies and signal-averaged ECG can be used for further risk stratification and evaluation. Refer to related UpToDate content for further information.

Graphic 141729 Version 1.0

ECG patterns of Brugada syndrome in leads V1-V2



(A) This typical **coved pattern** present in V1-V2 shows the following:

1. At the end of QRS, an ascending and quick slope with a high take-off ≥2 mm followed by concave or rectilinear downsloping ST. There are few cases of coved pattern with a high take-off between 1 and 2 mm.
2. There is no clear r' wave.
3. The high take-off often does not correspond with the J point.
4. At 40 milliseconds of high take-off, the decrease in amplitude of ST is ≤4 mm. In RBBB and athletes, it is much higher.
5. ST at high take-off N ST at 40 milliseconds N ST at 80 milliseconds.
6. ST is followed by negative and symmetric T wave.
7. The duration of QRS is longer than in RBBB, and there is a mismatch between V1 and V6.

(B) This typical **saddle-back pattern** present in V1-V2 shows the following:

1. High take-off of r' (that often does not coincide with J point) ≥2 mm.
2. Descending arm of r' coincides with beginning of ST (often is not well seen).
3. Minimum ST ascent ≥0.5 mm.
4. ST is followed by positive T wave in V2 (T peak N ST minimum N 0) and of variable morphology in V1.
5. The characteristics of triangle formed by r' allow to define different criteria useful for diagnosis.
   - β angle.
   - Duration of the base of the triangle of r' at 5 mm from the high take-off greater than 3.5 mm.
6. The duration of QRS is longer in BrP type 2 than in other cases with r' in V1, and there is a mismatch between V1 and V6.

RBBB: right bundle branch block.

Graphic 91152 Version 2.0

Patterns of ST abnormalities in leads V1 to V3 in Brugada syndrome*

Feature	Type 1	Type 2
J wave amplitude	≥2 mm	≥2 mm
T wave	Negative	Positive or biphasic
ST-T configuration	Coved type	Saddle back
ST segment (terminal portion)	Gradually descending	Elevated ≥1 mm

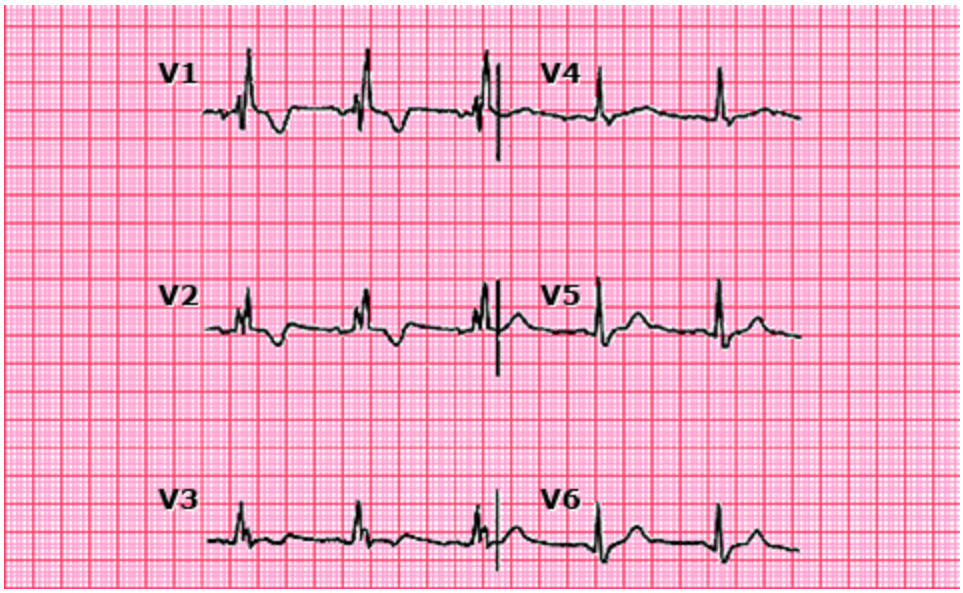
ECG: electrocardiographic.

* In contemporary studies of Brugada syndrome, the focus has generally been on ECG findings in leads V1 and V2 only.

Modified with permission from: Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome. Eur Heart J 2002; 23:1648. Copyright © 2002 Elsevier Science.

Graphic 71258 Version 7.0

Electrocardiogram (ECG) showing common right bundle branch block (RBBB)

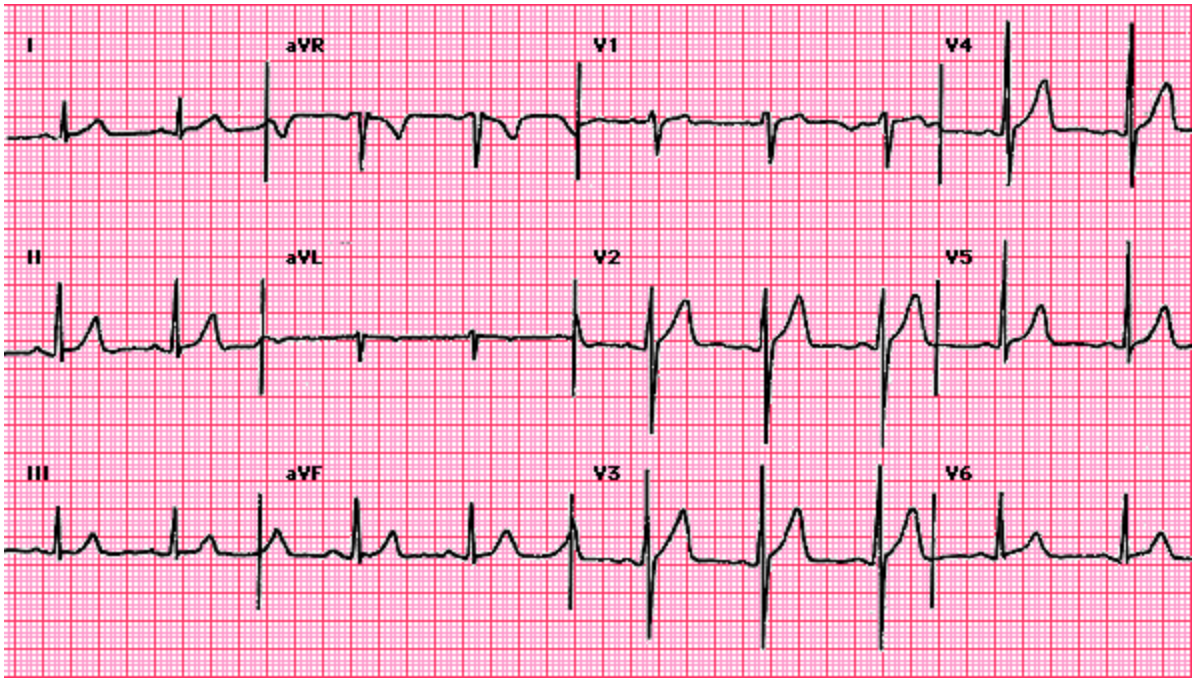


Electrocardiogram showing characteristic changes in the precordial leads in complete RBBB. The asynchronous activation of the 2 ventricles increases the QRS duration (0.13 seconds). The terminal forces are rightward and anterior due to the delayed activation of the right ventricle, resulting in an rsR' pattern in the anterior-posterior lead V1 and a wide negative S wave in the left-right lead V6 (and, not shown, in lead I).

Courtesy of Ary Goldberger, MD.

Graphic 64393 Version 8.0

Normal ECG

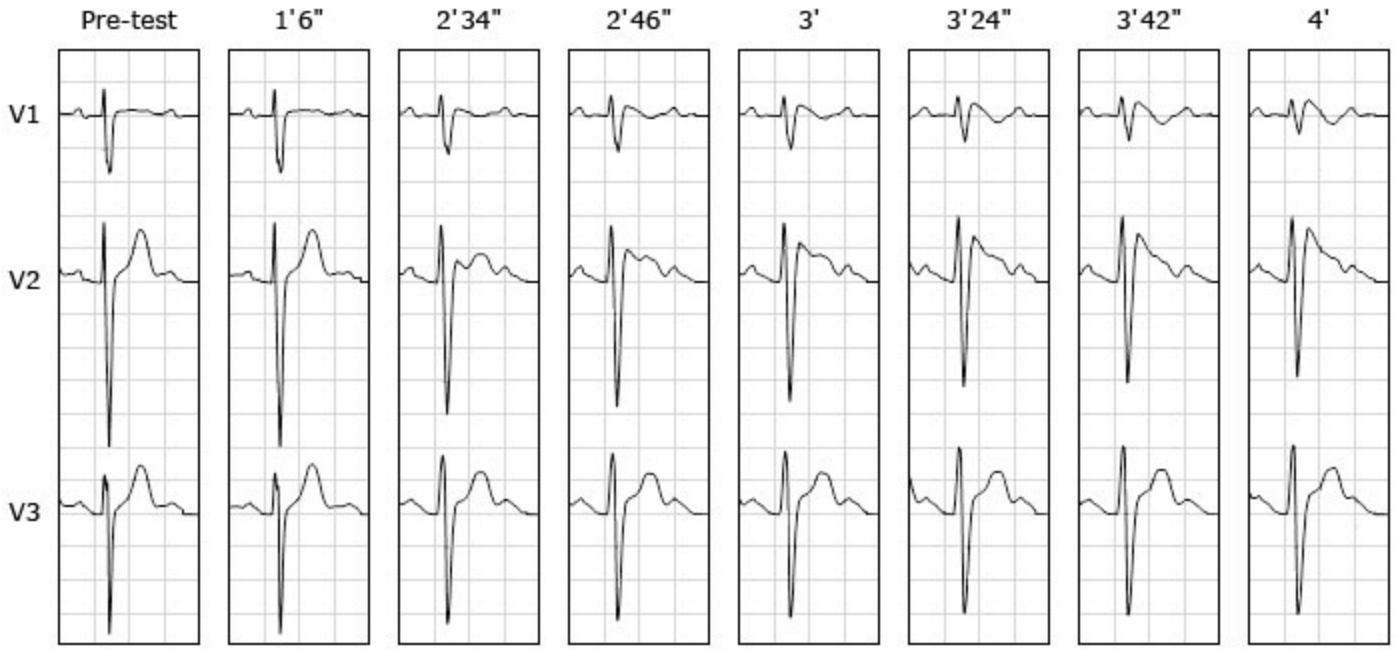


Normal electrocardiogram showing normal sinus rhythm at a rate of 75 beats/minute, a PR interval of 0.14 seconds, a QRS interval of 0.10 seconds, and a QRS axis of approximately 75°.

Courtesy of Ary Goldberger, MD.

Graphic 76183 Version 4.0

ECG Brugada ajmaline challenge

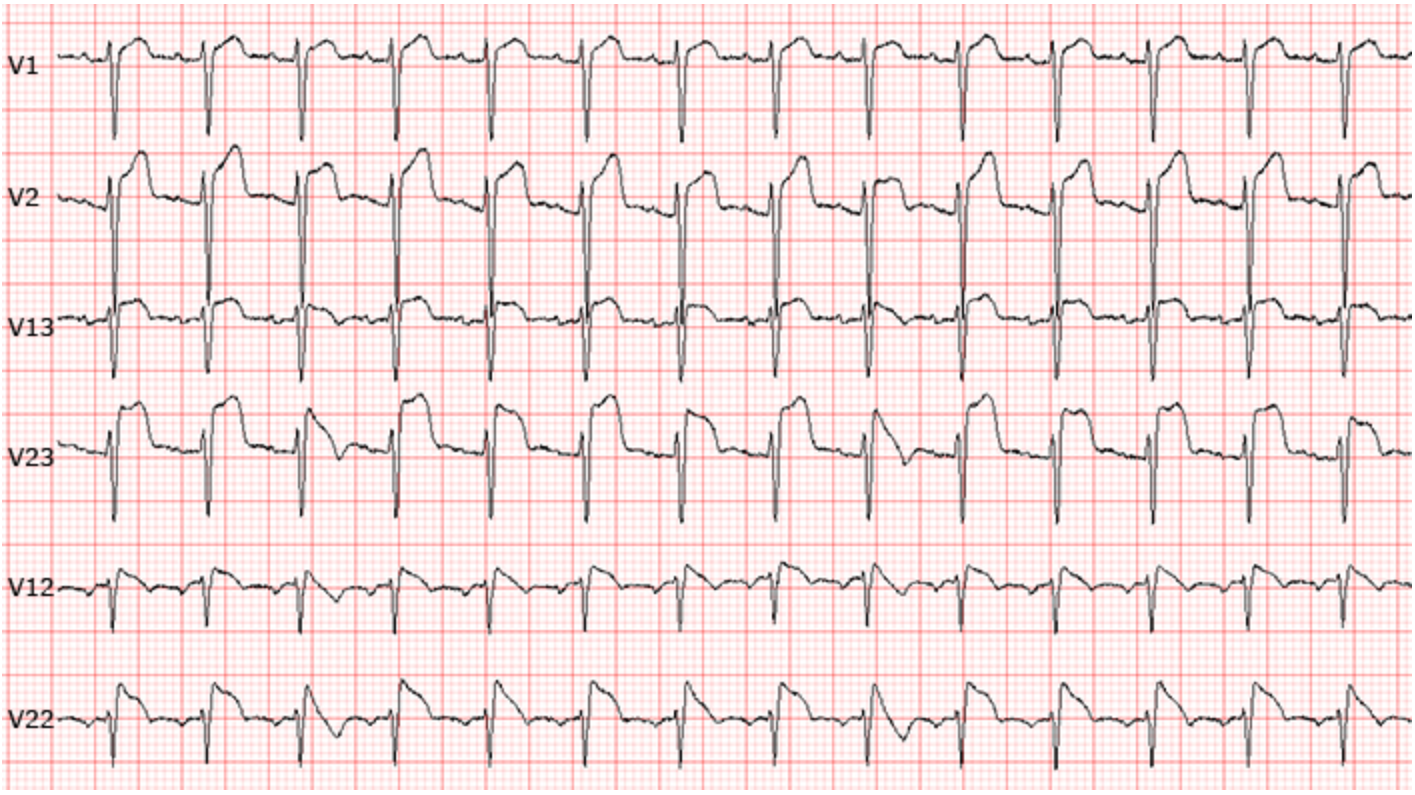


The panels display leads V1 to V3 (25 mm/ssecond, 1 cm/mV) acquired at baseline ("pre-test") and up to the 4th minute during intravenous administration of the sodium-channel blocker ajmaline in a 15-year-old female patient with suspected Brugada syndrome and a nondiagnostic baseline ECG. A type 1 Brugada pattern ECG is unmasked, which is important for prognosis and risk stratification purposes.

ECG: electrocardiogram.

Graphic 116958 Version 2.0

Irregular beat-to-beat variations in the shape and amplitude of the ST-T wave during a positive diagnostic ajmaline test



The figure demonstrates visible irregular beat-to-beat variations in the shape and amplitude of the ST-T wave during a positive diagnostic ajmaline test in a 58-year-old female patient with no previous history of arrhythmic events. Only leads V1 and V2 recorded from their standard positions, from the 3rd intercostal space (leads V13 and V23, respectively), and 2nd intercostal space (V12 and V22) are presented (12.5 mm/second, 1 cm/mV). Note the irregular pattern of ST-T wave variability.

Graphic 116875 Version 1.0

High- and intermediate-risk factors for arrhythmia or sudden cardiac arrest in patients with Brugada syndrome or pattern

High-risk symptoms	Intermediate-risk factors
▪ Sudden cardiac arrest ▪ Syncope ▪ Sustained ventricular tachycardia	▪ Syncope that may be nonarrhythmic in origin* ▪ Family history of sudden cardiac arrest and/or Brugada syndrome ▪ Spontaneous type 1 ECG pattern ▪ Atrial fibrillation

* This symptom is the most concerning of the intermediate-risk factors.

Graphic 141594 Version 1.0