A Drop Dead Healthy ECG

Ross MacKenzie, MD

The diagnostic and risk stratification implications of a borderline electrocardiogram, which could be a normal variant or a marker for sudden cardiac death, are explored.

In the context of life insurance risk selection, company medical directors are often presented with an electrocardiogram (ECG) that might be a normal variant but could also be related to a very serious form of heart disease with implications for premature mortality. Such is the challenge in this ECG case study. The ECG is from a life insurance applicant, but for privacy and confidentiality reasons, I have changed the clinical details into a hypothetical case scenario. At the time the case study was created, I was reading AJ Jacobs’ hilarious account of his humble quest for bodily perfection: Drop Dead Healthy, hence the article title.1

HYPOTHETICAL SCENARIO

A 32-year-old male, high-profile TV sports reporter is applying for life insurance. A former college athlete, his past health is unremarkable except for the ordinary diseases of childhood and arthroscopic surgery for a knee injury at age 21. He is asymptomatic with no past history of chest pain, syncope, heart murmur or underlying heart disease. Both parents and a younger brother are alive and well. There is no family history of premature sudden death or tachyarrhythmias. He is married with no children.

His physical examination (including BP 135/80) is reported as normal, and his lab work for age and amount is normal.

An electrocardiogram was obtained for age and amount (Figure 1). The computerized interpretation accompanying the ECG suggests that it is a borderline ECG due to the presence of minimal voltage criteria for left ventricular hypertrophy and a probable early repolarization pattern. A previous electrocardiogram 11 years ago was interpreted as normal. The case underwriter had been planning a preferred offer and brings the electrocardiogram to your colleague in the medical director’s office for an ECG interpretation opinion. How would you interpret the ECG?

ECG FINDINGS (TRACING #1)

The prevailing rhythm is sinus in origin with an average ventricular rate of 87 per
minute. The PR, QRS and QT intervals are normal. The mean QRS electrical axis in the frontal plane is normal (+13 degrees). The S wave in V2 plus the R wave in V5 is approximately 40 mm. The ST segment is minimally elevated in V1 with a flat contour, significantly elevated (>2 mm) in V2 with a concave upward (saddleback-type) contour and mildly elevated in V3 with a minimally concave upward contour (the ST segment is slightly below a line “drawn” from the J point to the apex of the T wave). No J point notching is seen.

ECG INTERPRETATION (TRACING #1)

Your colleague feels that the QRS voltage is within the normal range for the applicant’s age and does not feel there is enough evidence for a diagnosis of early repolarization. However, he is concerned about the saddleback ST elevation in V2 and the possibility of Brugada syndrome. You are asked for your opinion. What do you think?

ADDITIONAL INFORMATION

The application was postponed pending assessment by a cardiologist. A subsequent clinical examination, exercise stress test and echocardiogram performed by the cardiologist were normal.

In order to further evaluate his possibly abnormal electrocardiographic pattern, ECGs were recorded after placing the V1 and V2 electrodes at different intercostal positions from the second to the fifth intercostal space. This altered the configuration of the ST segments in leads V1 to V3, but no Brugada type 1 ECG pattern was seen.

This maneuver was performed because in some cases, the Brugada ECG pattern is only evident in the upper precordial V1–V2 leads recorded at the third or second intercostal space. This occurs because in some individuals, the abnormal electrical activity leading to the Brugada pattern arises from a limited zone located in the right ventricular outflow tract. In a study of 98 men who had a family member with a type I Brugada ECG, those with a type I Brugada ECG pattern only in high chest leads had a similar rate of cardiac events during >1 year of follow-up as those with type 1 Brugada ECG with standard positioning of chest leads.

The applicant then underwent a flecainide challenge test to assess whether flecainide, a sodium channel blocker, had any effect on his ECG (Figure 2). What do you think?
Among patients with the Brugada type 2 or type 3 ECG pattern, the Brugada type 1 ECG pattern can occasionally be unmasked by sodium channel blockers (eg, flecainide, procainamide, ajmaline, pilsicainide). For clinical purposes this knowledge is used as a diagnostic tool to evoke a type 1 ECG in patients suspected of Brugada syndrome who do not display a spontaneous type 1 ECG, for example in case of symptoms (syncope, aborted sudden cardiac death) or as part of family screening for Brugada syndrome. The reported sensitivity of pharmacologic challenge with these drugs has been variable, ranging from 100% to as low as 15%.

ECG FINDINGS (TRACING #2)

The prevailing rhythm is sinus in origin with an average ventricular rate of 88 per minute. The PR, QRS and QT intervals are normal. The mean QRS electrical axis in the frontal plane is normal. In V1–V3 there is a positive terminal r' wave (or an elevated J point). The QRS duration is longer in V2 than in the left precordial leads. In lead V2, there is initial J point elevation >2 mm, followed by a slowly descending ST segment with a coved pattern (concave or rectilinear with respect to the isoelectric baseline) followed by a negative slightly asymmetric T wave. Similar but less striking changes are present in V1 and V3.

ECG INTERPRETATION (TRACING #2)

When faced with a potential Brugada ECG pattern one has to distinguish between a number of possibilities including: (a) a true Brugada type 1, 2 or 3 pattern; (b) a typical Brugada type 1 pattern produced by certain drugs such as sodium channel blockers or other circumstances (eg, fever, etc) that unmask a true Brugada syndrome; (c) cases of Brugada ECG pattern especially type 1 induced by circumstances that disappear upon resolution of the underlying condition and that are not a true Brugada syndrome (referred to as phenocopies). These include acute ischemia, pericarditis, myocarditis, pulmonary embolism, metabolic disorders, electrolyte disturbances, administration of certain drugs; electrocution and a miscellaneous group and (d) cases of Brugada-like ECG patterns that are permanent and may be confused with a Brugada type 1 or 2 ECG pattern. These include right bundle branch block, asymmetric septal hypertrophy, arrhythmogenic right ventricular dysplasia/cardiomyopathy, athletic heart syndrome and pectus excavatum.

After administering flecainide, the ST segments in V1–V3 of our applicant’s ECG have changed from a possible Brugada type 2 pattern to a classical Brugada type 1 pattern. The positive terminal r' (or possibly
the J point) wave in V1–V3 differs from that seen with right bundle branch block. The positive terminal r' wave is usually peaked in right bundle branch block, whereas in the Brugada pattern it is rounded, wide and usually of low voltage as seen here. Also, in right bundle branch block, the ST segment is not elevated in the right precordial leads, the terminal wave (r' or R') is synchronous with a broad S wave observed in leads I and V6, and the QRS is wider (≥120 milliseconds). In type I Brugada pattern, usually no wide S wave is present in leads I and V6 because the terminal forces of the ventricular complex in V1 and V2 can be recorded only by electrodes placed in proximity to the site where the abnormal electrical activity occurs (the outflow tract of the right ventricle) and not from further away. Thus, the QRS in leads I and V6 is usually less than 120 milliseconds. This observation suggests that 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. At 40 milliseconds from this high take-off, the decrease in amplitude is less than 0.4 mm. This is much less than the decrease observed in right bundle branch block because the downslope is slower.2

In our applicant’s ECG, the most striking changes have occurred in lead V2. The utility of lead V3 and the necessity of having more than one lead positive in the diagnosis of Brugada syndrome have been called into question following a study of 186 patients with spontaneous or drug-induced type 1 Brugada ECGs. Among 376 ECGs, lead V3 provided no additional diagnostic information in any patient, and patients with ECGs with only one lead with a diagnostic pattern had similar outcomes to patients with 2 or 3 diagnostic leads. The authors of this report, including all three Brugada brothers, called for revision of the diagnostic criteria to exclude lead V3 and to include patients with one diagnostic lead (V1 or V2) in the diagnosis of Brugada syndrome.9,10

Does the presence of a type 1 Brugada ECG pattern make the diagnosis of Brugada syndrome? The answer is no. The diagnosis of Brugada syndrome requires the presence of at least one or more additional clinical factors suggestive of arrhythmias or familial occurrence, namely documented ventricular tachycardia or fibrillation, a family history of sudden cardiac death in relatives under the age of 45, the type 1 ST pattern ECGs in family members, electrophysiologic inducibility of ventricular tachyarrhythmias, unexplained syncope suggestive of a tachyarrhythmia or nocturnal agonal respiration. Thus, there is a difference between the presence of a Brugada ECG pattern (or sign) and Brugada syndrome.11

DISCUSSION

Brugada syndrome is an autosomal dominant condition associated with familial aggregation, specific electrocardiographic abnormalities in the right precordial leads and the risk of sudden cardiac death due to ventricular fibrillation. The signature sign of Brugada syndrome is its characteristic ECG. It has been the subject of two previous articles in the Journal of Insurance Medicine.12,13

The ECG abnormalities that suggest Brugada syndrome were first described in 1992 by Pedro Brugada and Josep Brugada, when it was first noted that patients with sudden death or aborted sudden death had ECGs with a right bundle branch block-like configuration and ST segment elevation in leads V1–V3.14 Two types of ST segment elevation were described in the right precordial leads: convex upward (“coved”) and concave upward (“saddleback-type”).

In 2002, a consensus conference endorsed by the Heart Rhythm Society and the European Heart Rhythm Association proposed ECG criteria for the diagnosis of Brugada syndrome. Three types of Brugada-electrocardiogram patterns were defined: the “diagnostic” (type 1) pattern characterized by a complete or incomplete right bundle branch block pattern with a coved morphology ST segment of at least
2 mm in the right precordial leads (V1–V3) followed by a negative T wave, and the “nondiagnostic” (type 2 and 3) patterns. Type 2 ST segment elevation has a saddleback appearance with a high takeoff ST segment elevation of >2 mm, a trough displaying >1 mm ST elevation followed by a positive or biphasic T wave. Type 3 has an ST segment morphology that is either saddleback or coved with ST segment elevation of <1 mm.11

A second consensus report, published in 2005, elaborated further on the diagnostic criteria and examined risk stratification schemes and device and pharmacologic approaches to therapy on the basis of the clinical and basic science data available at that time. This consensus conference established that conversion of a nondiagnostic ECG (type 2 or 3 Brugada pattern ECG) to a diagnostic ECG (type 1 Brugada pattern) with a sodium channel blocker test could be used as a diagnostic criterion for the Brugada syndrome.15

Although the recommendations arising out of the first two previous consensus documents describing the Brugada ECG patterns were extremely useful clinically, there were a few limitations. These limitations related to the differences between types 2 and 3 Brugada ECG patterns. As a result, a third consensus conference report has been published recently focusing again on the ECG criteria for the diagnosis of the Brugada ECG patterns.2

In the new ECG criteria, only two ECG patterns are considered: pattern 1 is identical to the classic type 1 (coved pattern) described above and a pattern 2 that joins types 2 and 3 as described above. This decision was based on the fact that there were only small morphological differences between the type 2 and 3 patterns and subsequent experience demonstrating that the difference in the two patterns did not impact on prognosis and risk stratification. Also experience with sodium channel blocker drug challenge conversion of a type 3 to a type 2 ECG pattern was found to be inconclusive.2

This new consensus document should serve as a useful reference for medical directors faced with an ECG that raises the possibility of Brugada syndrome. The document describes in detail the most important characteristics of the two patterns and also key points in the differential diagnosis with different conditions that lead to Brugada-like patterns in the right precordial leads such as right bundle branch block, early repolarization and right ventricular dysplasia/cardiomyopathy.

Brugada Phenocopy Concept

Some drugs and conditions can induce a Brugada Type 1 ECG pattern in the absence of true congenital Brugada syndrome, representing a discrete clinical entity with a different pathophysiology.2,16 Riera et al introduced the term “Brugada phenocopy” to describe this acquired Brugada-like ECG pattern.17 As discussed by Riera, the term phenocopy describes “an environmental condition that imitates one produced by a gene.” To distinguish between these entities and cases of unmasked true congenital Brugada syndrome it is important to understand the concept of Brugada phenocopies. Concealed or latent ECG manifestations are unmasked by certain agents and conditions in the presence of true Brugada syndrome. The defining feature of a Brugada phenocopy is the absence of true Brugada syndrome (based on an assessment of low clinical probability [symptoms, past medical history, family history], negative genetic test result for recognized Brugada syndrome mutations and/or a negative sodium channel blocker pharmacological challenge test result) despite the presence of characteristic Brugada Type 1 ECG findings.16

Transient Brugada ECG Patterns

Of importance to the life insurance risk selection process is the observation that the distinct Brugada Type 1 ECG pattern is dynamic and in some individuals the characteristic ECG changes can be concealed or
transient. This was illustrated in a series of 43 patients with Brugada syndrome, in whom serial ECGs were obtained over a median follow-up of 18 months. The following findings were noted:10,18

- Among 15 patients with a spontaneous type 1 ECG at presentation, 14 had at least one non-diagnostic (type 2, 3 or normal) ECG during follow-up.
- Among 28 patients whose initial ECG was non-diagnostic, 8 developed characteristic type 1 ECG abnormalities during follow-up. Thus, fluctuations in the ECG pattern appear to be common in Brugada syndrome.

Risk Stratification

Early reports on the Brugada syndrome, described young patients who experienced ventricular fibrillation as their first symptom (‘‘one strike and you are out’’), and as a result, it has been assumed that this is a highly lethal disease.19 Many cardiac diseases are associated with a potential risk for sudden cardiac death, but individuals with these conditions are not all at the same level of risk. Instead we can stratify these individuals into different risk groups for sudden death based on actual knowledge and up-to-date international guidelines.20

Recent research about the Brugada syndrome suggests that patients with this disease can also be classified into several risk categories. However, risk stratification in the Brugada syndrome poses significant challenges. The prevalence of the syndrome in the general population is low; yet high-risk individuals can manifest with sudden cardiac death at a young age. Many individuals will be asymptomatic on presentation, and their electrocardiographic changes may be nondiagnostic.20

Large-scale cohort studies on the clinical outcome of patients with Brugada syndrome have consistently demonstrated that symptomatic patients with documented ventricular tachyarrhythmias, cardiac arrest, and/or syncope (after the exclusion of noncardiac causes) have a significantly higher risk of sudden cardiac death than do asymptomatic patients.21

Numerous studies have also shown that patients who have spontaneous type 1 Brugada ECG do worse than patients who only have a type 1 pattern when challenged with a sodium-channel blocker. However, classifying patients as either type 1 or non-type 1 is tricky because as noted above, the Brugada ECG pattern is highly variable over time.21–29

In the last decade, it has become clear that most of the individuals with a Brugada ECG pattern have in fact a silent phenotype; they do not have and do not develop symptoms. Moreover, like our applicant, their type 1 ECG could only be uncovered through provocation with potent sodium channel blockers such as flecainide. We now recognize that the yearly arrhythmic event rate for individuals who are asymptomatic is somewhere between 0.4 and 1%, ie, potentially in the insurable range. Still, we do not know whether an annual event rate of 1% will accumulate to 20% after 20 years of follow-up.20

Indeed, Junttila et al documented the prevalence of Brugada ECG patterns in two Finnish populations consisting of 2479 healthy male Air Force applicants (age 18–30 years) and 542 healthy middle-aged subjects (age 40–60 years). Type 1 Brugada ECG pattern was not seen. Fifteen (0.61%) of subjects in the first population and 3 (0.55%) fulfilled the ECG criteria for type 2 or 3 Brugada ECG pattern. No mortality or life-threatening ventricular arrhythmias occurred in either study population during follow-up (19 and 11 years, respectively). They concluded that ‘‘the benign natural course of the patients with the Brugada sign’’ suggests that in asymptomatic subjects without a family history of sudden cardiac death, type 2 or 3 Brugada ECG pattern is a normal variant rather than a specific predictor of life-threatening ventricular arrhythmias.”30

Support for this more favorable natural history has come from the largest series of
Brugada syndrome patients reported thus far, the FINGER Brugada Syndrome registry, a multicenter study which included 1029 consecutive subjects from 4 European countries (France, Italy, Netherlands, and Germany) and showed that the cardiac event rate per year was 7.7% in patients with aborted sudden cardiac death, 1.9% in patients with syncpe, and 0.5% in asymptomatic patients (during a median follow-up of 31.9 months). The asymptomatic group included patients in whom the Brugada type 1 ECG manifested only after sodium channel blocker drug provocation. Inducibility of ventricular arrhythmias and family history of sudden cardiac death were not predictive of sudden cardiac death. Spontaneous type 1 ECG changes and the presence of symptoms were the only predictors of arrhythmic events in this population.

Based on the above considerations, we can return to our life insurance applicant. Our applicant is asymptomatic. There is no family history of premature sudden death or tachyarrhythmias. To date there is no evidence of a spontaneous Brugada type 1 ECG pattern; however, this pattern does appear with sodium channel blocker drug provocation. As suggested above, recent evidence from the literature from multiple sources indicates that such an individual has a cardiac event rate of 0.4–1% per year. The problem we have, in the context of risk selection for life insurance in such individuals, is that we can’t be sure on the basis of one ECG whether we have excluded the spontaneous occurrence of a type 1 Brugada ECG. In other words, the dynamic nature of ECG changes in Brugada syndrome makes it difficult to conclusively classify the type of Brugada ECG on the basis of a single recording.

The complexity of the Brugada syndrome was recently highlighted in a study from Raju et al that reported on a cohort of 202 patients given a diagnosis of Brugada syndrome following sudden arrhythmic death in a proband (first affected family member) from their individual families. It was revealing that the vast majority of probands were asymptomatic prior to their sudden death and that premortem ECGs (when available) were nondiagnostic. While the possibility remains that these probands had dynamic and transient diagnostic type 1 ECG changes that were simply not captured, it is also possible that there is much more to Brugada syndrome than we currently recognize.

Would invasive electrophysiological testing help? This approach was originally driven by data from Brugada showing that patients with inducible ventricular fibrillation have a 10-fold risk for developing spontaneous ventricular fibrillation. However, controversy started when neither Priori et al nor Eckart et al could reproduce such results. In 2006 and 2007, two subsequent independent meta-analyses showed that electrophysiologic testing was of little value for predicting spontaneous ventricular fibrillation. The most recent evidence in this debate comes from the Italian PRELUDE (Programmed Electrical stimulation Predictive value) study. In this large prospective study using a uniform stimulation protocol, they showed that inducibility of arrhythmias had no additive value in asymptomatic patients. Arrhythmia-free survival was nearly identical between those with and without induced sustained ventricular tachyarrhythmia.

Finally, what about genetic testing? Brugada syndrome has been linked to over 80 mutations in the SCN5A gene and demonstrates an autosomal dominant mode of transmission. Genetic testing is commercially available and can be useful in confirming the diagnosis. However, to date the genetic and clinical heterogeneity of Brugada syndrome has limited the test’s utility. The yield of genetic testing in overall patients with Brugada syndrome remains well below 50%. In addition, there is evidence that mutations in other genes can give rise to this disorder.

REFERENCES


