Does a Brugada Pattern ECG Precipitated by Excessive-Dose Flecainide Provide a Diagnosis of a Brugada Syndrome Patient and/or Contraindicate Its Use?

A Case Study

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The patient is a 58-year-old white male cardiologist who first came to attention in 2004 at the age of 53 years, with a history of paroxysmal atrial fibrillation (PAF) dating to 1982. The episodes, which were often precipitated by recumbency and alcohol, occurred 2 to 3 times per year and lasted only minutes. His ECG (Figure 1) while in normal sinus rhythm was normal.

His PAF was not rapid and did not cause hemodynamic or ischemic symptoms. During 2003 to 2004, the PAF increased in frequency to several times per week and lasted longer, for which he began flecainide 50 mg bid with success for 6 months. Thereafter, however, they recurred with a progressive increase in frequency to several times per day, despite increasing the flecainide to 100 mg bid and then 150 mg bid and thereafter while trying sotalol up to 160 mg bid instead. A stress-echo was normal aside from a left atrial diameter of 4.5 cm (an increase from 10 years earlier). There was no family history of any dysrhythmia, syncope, seizure disorder, or sudden death and no other personal medical history of any relevance aside from simvacor-controlled hyperlipidemia (including no personal or family history of syncope or sudden death). His physical examination was entirely normal. All routine laboratory studies were normal, as was his 12-lead ECG and chest radiography. While taking flecainide, his PAF recurred as typical atrial flutter. The QRST pattern on his 12-lead ECG did not change during the flecainide or sotalol administration. Catheter ablation was recommended.

While considering ablation and proceeding to schedule it, the patient took a trip out of the country, during which, while on a cruise, a protracted episode recurred. At that time he was again taking flecainide 50 mg bid (on which his QRS and T waves had not changed). He decided to try a “pill-in-the-pocket”1 approach to terminate his AF and self-medicated with extra flecainide. However, he exceeded the typically used dose of 300 mg (or less if on a maintenance dose as well) to a total dose of 600 mg over a few hours (a dose for which no clinical trial has been reported). Sinus rhythm returned, at which time an ECG was done that showed a new ECG pattern suggestive of Brugada type 12–4 (Figure 2).

Subsequently, an ECG during flecainide 150 mg bid thereafter (prior to revisiting with me) suggested a Brugada type 3 pattern2 (Figure 3). I was first shown these ECGs at his next office visit.

Accordingly, flecainide was stopped and he proceeded to undergo electrophysiology study and catheter ablation. Ablation was successful in stopping his PAF, but flutter recurred, which was treated with a second ablation procedure. While in the electrophysiology laboratory, ventricular stimulation and a procainamide infusion test were both performed to further evaluate the recent flecainide-apparent Brugada pattern ECG. (Our laboratory does not have either intravenous flecainide or ajmeline available to us.) At baseline, the SCL (900 ms), AH (90 ms), HV (40 ms), and QT (348 ms) intervals were all normal. No ventricular tachyarrhythmia was inducible. Procainamide 1 g intravenously over 30 minutes, increased the AH (106 ms) and HV (58 ms) intervals but did not produce any change in his QRS morphology (totally normal).

Subsequent to these procedures, the patient had occasional runs of both PAF and an atrial flutter, which were treated with metoprolol alone and later combined with ranolazine (without any change in his QRST morphology), until he underwent a third ablation procedure without difficulty (at which time areas of conduction recurrence in previously demonstrated lines of block from the prior left atrial ablation were noted and reablated). Ranolazine (up to 1000 mg bid) was tried as part of our ongoing observations with this agent, as regards its utility in AF5 as well as the fact that it is not a potent blocker of the rapid sodium channel. No flutter or PAF recurred in the ensuing year of follow-up. During this follow-up period the patient has also had neither clinical nor ECG evidence of syncope or of a ventricular arrhythmia and no Brugada pattern on any ECG off drug therapy.
The patient declined to undergo genotyping, given his normal resting ECG, negative electrophysiology study, negative personal and family history, and uncertain interpretation if negative for currently known genes. Certainly a positive genetic test would have been quite useful in clarifying the interpretation of his ECG on flecainide and perhaps also the etiology of his PAF.

Discussion and Teaching Points

This case demonstrates several interesting findings and issues in a patient with both unexplained AF in the absence of overt structural heart disease plus an ECG strongly suggestive of a manifest type 1 Brugada pattern on a “supratherapeutic dose” of flecainide.1

Figure 1. ECG taken when the patient was not using flecainide.

(1) What Is the Possibility That This Patient’s Otherwise Unexplained PAF May Have Been a Brugada-Associated Phenomenon?

A relationship between AF and Brugada syndrome has been described previously.6,7 Alterations in the sodium current can be present nonhomogeneously in both atrial and ventricular tissue in patients with the Brugada syndrome. Notably, however, a Brugada pattern on the ECG does not itself equate with the Brugada syndrome, and AF in a patient with a Brugada pattern does not necessarily mean they are etiologically linked. Nonetheless, one must ask whether such an ECG pattern, when precipitated on therapy, should preclude the use of a class IC antiarrhythmic drug for the treatment of AF (in the absence of any other overt structural heart disease).

Figure 2. ECG taken when the patient took 600 mg of flecainide as “pill-in-the-pocket.”
We presume that safety concerns would dictate an affirmative answer.

(2) In This Patient, the Most Marked Brugada Pattern Only Became Manifest After a “Supratherapeutic” Dose of Flecainide (600 mg). Does Such a Finding Provide a Diagnosis?

When flecainide has been used clinically to bring out the Brugada pattern as a diagnostic test, it has either been done with intravenous flecainide (outside of the United States), or with doses typically used in AF therapeutics when given orally. However, to my knowledge, no single dose of 600 mg has been used to assess the induction of a Brugada pattern ECG. Similarly, I know of no single 600-mg dose studies of flecainide in normal subjects. So, how should the findings in our patient be interpreted, and does the finding in our patient preclude clinical administration of class I antiarrhythmic drugs when such an observation occurs?

In settings where the Brugada syndrome is clinically suspect and a pharmacological stress test is used diagnostically, false-negative results have been noted with both the class IC and IA antiarrhythmics (such that ajmeline is the preferred agent where it is available, eg, in Europe). Consequently, the observations in this patient raise the question as to whether when administered as a diagnostic test, higher flecainide doses than have been commonly...
used should be used, or, alternatively, whether the response in this patient could be a “false-positive” that might be seen in some normal individuals if exposed to this much flecainide. Were the latter to be the case, our observations could not be used to definitively indicate any relationship between the etiology of his AF and the Brugada pattern on the ECG during flecainide intake. Our case does not provide an answer to this question. Although a positive genotype finding in our patient might help answer this question, a negative one would not because many patients with the Brugada syndrome have not yet had their gene defect identified and test negative with the gene scans now available.

(3) Is Intravenous Procainamide Adequate as a Diagnostic Provoker of the Brugada Syndrome?
Intravenous procainamide has been used diagnostically as to induce the Brugada pattern in some patients with known or suspected disease. However, it failed to induce a Brugada pattern of any kind in our patient, even though a type 3 pattern was evident with 150 mg of flecainide bid. Hence, the patient, as his own control, suggests that a negative test on procainamide is not reassuring as to the absence of the syndrome—or at least the ability to predict the absence of a Brugada pattern on the ECG if a more potent sodium channel blocker were to be used.

(4) Is Ranolazine, a Blocker of the “Late” Sodium Current, a Concern in Patients With Known or Suspected Brugada Syndrome?
Although our patient’s QRST pattern did not change with sotalol (nor would we expect it to), it also did not change on ranolazine (Figure 4).

Ranolazine is a drug with multichannel blocking properties, including mild block of the “fast” sodium channel but significant inhibition of the slow sodium channel. If the absence of production of a Brugada pattern on the ECG is replicated in other patients given ranolazine, and ranolazine’s efficacy in treating AF is confirmed in ongoing studies, this might imply safety of ranolazine in attempting to treat AF in Brugada patients. Although this is a potentially important hypothesis, it remains to be tested. Given the negative response to procainamide in our patient, we cannot assess with certainly the significance of the absence of a change in ECG pattern in our patient with ranolazine.

(5) Is There a Role for “Pill-in-the-Pocket” Treatment of Intermittent AF?
We believe there is. The ideal role for “pill-in-the-pocket” therapy for AF is for episodes of AF that are not frequent, can be tolerated well for several hours up to a day or two, and are of recent onset (<7 days, preferably <1 to 2 days). The “pill-in-the-pocket” approach for such short, sporadic episodes of AF involves intermittent rather than daily self-administration of oral class IC antiarrhythmics when there is no evidence of structural heart disease. Dofetilide (in-hospital) or amiodarone may also be used, but they are logistically more difficult (dofetilide) or slower and less predictable (amiodarone). Very recently, the use of ranolazine, 2 g, has been reported to be similarly effective as “pill-in-the-pocket” and has the advantage of not being contraindicated by structural heart disease. However, given the findings in our case, it would appear prudent to suggest that higher doses than those reported in clinical trials should be avoided.

(6) Was This Patient Ultimately Treated in an Acceptable Manner Regarding Risk Prevention and ECG Presentation?
Because a Brugada pattern on an ECG does not equal the presence of the Brugada syndrome, and given the uncertainty of the significance of the Brugada type I ECG pattern with the exceptionally large dose of flecainide taken by the patient, combined with the negative results on electrophysiology testing (the predictive value of which remain unsettled in Brugada patients) and the negative personal and family history, it was elected not to initiate any prophylactic drug or implantable cardioverter-defibrillator therapy in this individual. To date, he has done well.

Disclosures
None.

References
EDITOR’S PERSPECTIVE

Traditionally, “teaching rounds” in General Cardiology and Internal Medicine occurs at the patient’s bedside, where an experienced clinician demonstrates an instructive, organized thought process and elicits important physical signs and phenomena. A process of developing either directly a diagnosis or generating a differential diagnosis that subsequently generates an appropriate plan for further tests and observation is then made.

Even in general clinical medicine, teaching rounds has shifted from the bedside to a workroom and computer workstation. In present-day cardiac electrophysiology training programs, the “bedside” has most often been at the side of a patient who is sedated and has had catheters inserted, with the diagnostic possibilities and maneuvers discussed being generated as electrograms, electroanatomic maps, and merged imaging sources.

The ECG remains probably the single most important diagnostic test, requiring careful interpretation and demonstrating to clinical trainees how such interpretation affects diagnostic possibilities and plans for both noninvasive and invasive care.

In this issue of Circulation: Arrhythmia and Electrophysiology, James A. Reiffel presents an instructive analysis of an unusual ECG finding. As with any truly instructive teaching endeavor, it is not the actual diagnosis or the “wow” factor that determines educational value, but, as demonstrated by Dr Reiffel, a logical and contextual analysis of the finding itself and its significance is what matters.

While at a general medical grand rounds, a final diagnosis of Hermansky-Pudlak syndrome with a bleeding diathesis and possible pulmonary infiltrates may pique curiosity, the trainee internist benefits from a discussion of how to handle pulmonary infiltrates or a bleeding diathesis in general.

- Was the patient’s unusual ECG pattern actually representative of Brugada syndrome? This brings in a discussion of the difficulties with making this diagnosis and teaching what we know about the genesis of this specific electrocardiographic pattern.

- The value of dynamic ECG: Although we all are familiar with the unique interpretive value of stress ECGs, pharmacological stress with agents such as flecainide probably has relevant information for how we should approach unique subsets of patients with atrial arrhythmia. Not knowing whether this is simply a normal finding (because the patient took an above normal dose), we can only look to further reports or study, but, matched with the difficulty with ablative management of atrial arrhythmia in this patient, perhaps risk stratification becomes a possibility. Although we have all become accustomed to expecting multiple procedures and recurrence in persistent and chronic forms of atrial fibrillation, multiple procedures for paroxysmal AF are less common in most centers.

Finally, Dr Reiffel’s teaching points discussion demonstrates for all of us involved in cardiovascular trainee education the importance of using a unique finding as a talking point to bring into focus important basic principles, physiology, and fundamentals of patient care.
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Circ Arrhythm Electrophysiol. 2011;4:e47-e51
doi: 10.1161/CIRCEP.111.962936

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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