Short-coupled Purkinje ectopy inducible by pharmacological and hyperventilation tests

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Introduction

Ventricular fibrillation associated with structurally normal hearts can have a variety of etiologies, including focal abnormalities, such as Wolff-Parkinson-White (WPW) syndrome, or premature ventricular complexes (PVCs) originating in the myocardium or Purkinje system.[1] Purkinje PVCs generally have short coupling intervals, but their identification can be difficult owing to their random and unpredictable occurrence, which unfortunately usually coincides with recurrences of ventricular fibrillation.[2,3] This malignant pathology lacks a diagnostic test, but recent studies have shown that pharmacological tests can have significant diagnostic value in a subset of these patients.[4,5] We report here the case of a patient with initial WPW syndrome, in whom Purkinje PVCs could be reproducibly induced using a sodium channel blocker but also with a simple physiological hyperventilation test, inducing acute hypocapnia-hypokalemia.

Case report

A 50-year-old man presented to the emergency department with repeated episodes of palpitations and history of syncope. The electrocardiogram (ECG) showed an episode of atrial fibrillation with ventricular pre-excitation. Echocardiography and blood tests revealed no acute abnormalities. Sinus rhythm was restored by electrical cardioversion.

After informed consent was obtained, an ablation procedure was performed the following day, removing the accessory pathway in the right posteroseptal area without complications. After the procedure, the patient was prescribed flecainide 100 mg twice daily, to prevent further episodes of atrial fibrillation. However, subsequent ECGs showed the appearance of frequent PVCs with a mean coupling interval of 310 ± 50 ms and a morphology compatible with a left Purkinje system origin (Figure 1A). Flecainide was therefore discontinued, resulting in the complete disappearance of PVCs after 24 hours.

A new electrophysiological study was carried out for the mapping and potential ablation of these short-coupled PVCs. We used 2 decapolar catheters (DECANAV®; Biosense Webster, Irvine, CA) in the right and left ventricles with the CARTO® system. We mapped the ventricular cavities using intracardiac echo and CARTO sound software and found no areas of abnormal electrogram voltage. Ajmaline was infused at a dose of 1 mg/kg over 10 minutes and produced frequent short-coupled PVCs (38/min; mean coupling interval 300 ± 40 ms) with multiple morphologies and repetitive runs (Figure 1B). PVC mapping showed an initial high-frequency, short-duration potential preceding a larger and slower ventricular electrogram, indicating their origin from the left conduction system (Figure 1C).

Catheter ablation was performed in the distal Purkinje area, as shown in Figure 1D using an irrigated ablation catheter (ThermoCool SmartTouch® SF; Biosense Webster; 45 W, 30 seconds for each point).[2] After the procedure, we discussed with the patient the benefits and risks of prophylactic antiarrhythmic medication (quinidine) or implantation of a subcutaneous implantable cardioverter-defibrillator. Based on the limited evidence regarding risk stratification in this setting, and the patient's history of syncope and polymorphic Purkinje PVCs, we decided to proceed with defibrillator

KEY TEACHING POINTS

- Dynamic tests are essential for unmasking potentially life-threatening arrhythmias.
- Purkinje ectopy is a significant cause of idiopathic ventricular fibrillation, but this diagnosis is likely underestimated, as its recognition may be prevented owing to random and unpredictable occurrence.
- We report a novel method of inducing short-coupled Purkinje ectopy using a simple physiological test of hyperventilation.

KEYWORDS Arrhythmias; Purkinje ectopy; Antiarrhythmic drugs; Hyperventilation test; Catheter ablation
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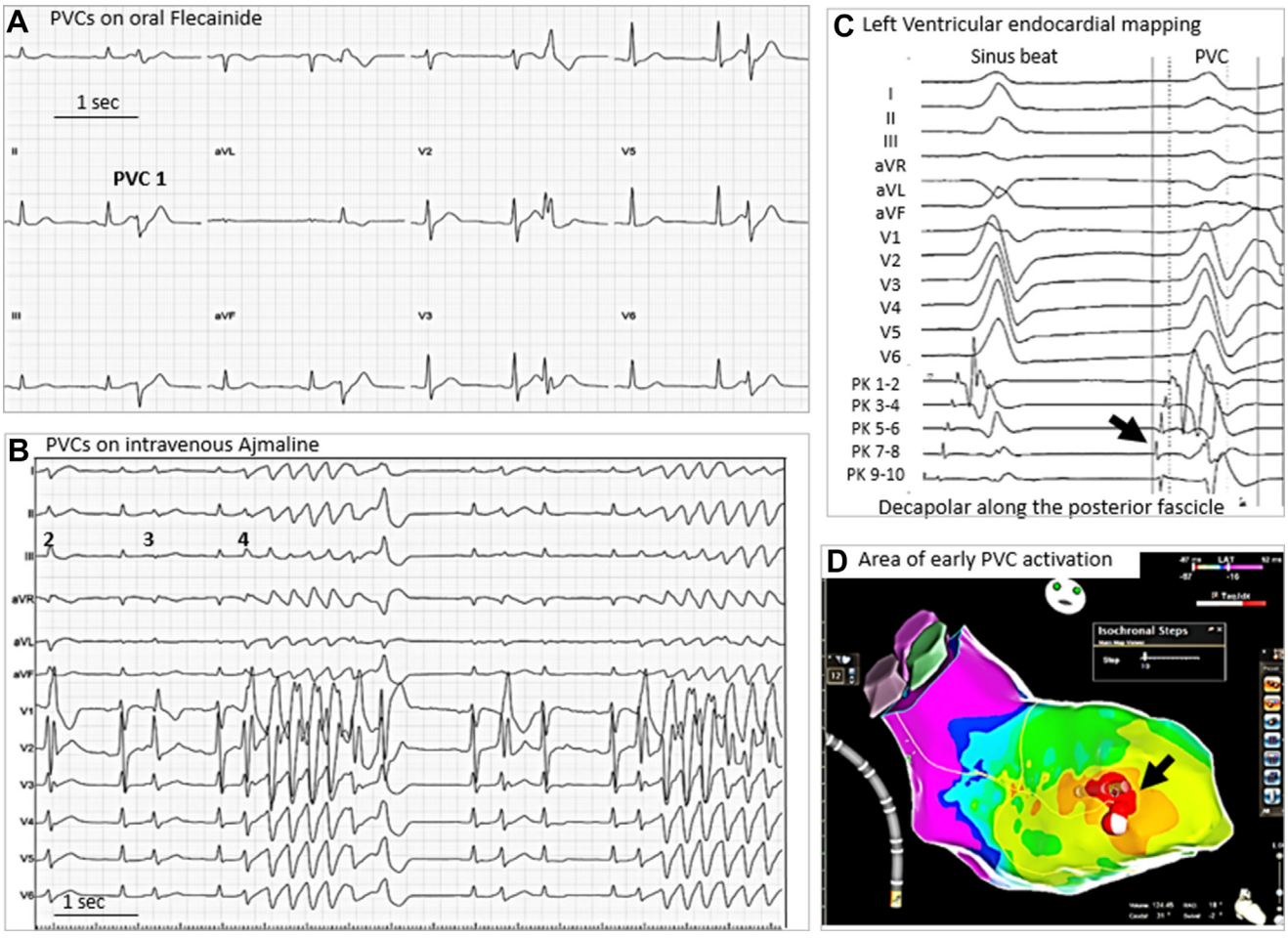

Figure 1 Twelve-lead electrocardiogram (ECG) morphology and Purkinje origin of premature ventricular contractions (PVCs) induced on sodium-channel blockers. **A:** ECG on oral flecainide 100 mg twice a day (after catheter ablation of the accessory pathway, not shown). **B:** ECG on ajmaline infusion testing (1 mg/kg). Note the multiple morphologies of PVCs (numbered 1–4) with a right bundle branch block pattern in V_1 lead. **C:** Endocardial recordings from a decapolar catheter showing fascicular activation (*arrow*) preceding myocardial activation. **D:** The area of early Purkinje activation is shown in the electroanatomical map (*arrow*).

implantation without antiarrhythmic medication. The patient also underwent magnetic resonance imaging and genetic testing, both of which yielded normal results.

At the 6-month follow-up visit, the patient reported no symptoms and defibrillator interrogation revealed no arrhythmic events; a 24-hour ECG Holter revealed no evidence of ventricular pre-excitation or PVCs. After obtaining informed consent, we performed clinical and pharmacological tests to evaluate the inducibility of Purkinje PVCs. Valsalva maneuvers were totally negative (no PVCs). Next, a hyperventilation test was performed according to a short-standardized protocol described previously[6]: in brief, after a 10-minute rest phase in the seated position, the patient hyperventilated at a rate of 30 breaths per minute for 1–2 minutes as long as he could tolerate.

The hyperventilation test induced a median of 4 PVCs per minute (min 2, max 5) with a mean coupling interval of 330 ± 30 ms from the left Purkinje system, with no repetitive phenomena. The hyperventilation test was repeated after a waiting period and again induced a median of 4 short-coupled Purkinje PVCs per minute (min 1, max 5) with mean coupling interval of 340 ± 30 ms. The impact of the hyperventilation test[6] was measured by hemogasometric analysis, which revealed hypocapnia (first test: pH 7.67 vs 7.42 at baseline; $PaCO_2$ 17 vs 43 mm Hg at baseline; second test: pH 7.65 vs 7.43; $PaCO_2$ 20 vs 38 mm Hg) and hypokalemia (first test: 3.1 vs 3.7 mmol/L at baseline; second test: 3.1 vs 3.5 mmol/L). Figure 2 shows the number and timing of Purkinje PVCs during the hyperventilation tests.

Finally, we performed 2 pharmacological tests. The isoprenaline test (50 µg/min for 3 minutes) achieved a maximum sinus rate of 128 beats per minute and did not induce PVCs.[7] In contrast, the ajmaline test induced frequent short-coupled PVCs (35 per minute) originating from the left Purkinje system, and episodes of nonsustained ventricular fibrillation. No Brugada pattern was elicited during tests. No further Purkinje ablation was attempted. The patient was discharged without antiarrhythmic drugs, and without arrhythmia recurrence for the following 5 months.

Discussion

Here, we report the case of a patient initially presenting with WPW syndrome in whom short-coupled PVCs originating from the Purkinje system could be reproducibly induced

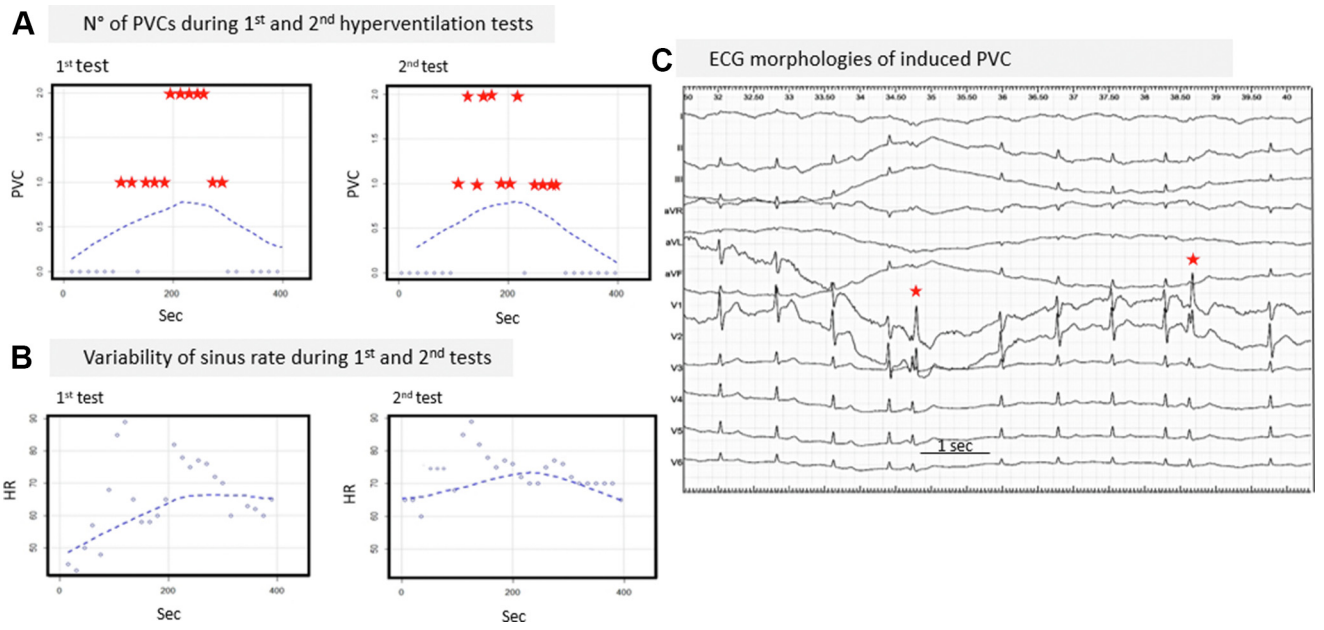

Figure 2 Purkinje ectopy during hyperventilation tests. **A:** Timing and number of premature ventricular contractions (PVCs) during the first and second hyperventilation test, producing a cumulative total of 17 PVCs and 16 PVCs, respectively. PVCs are represented by red stars; the line represents the event PVC over the time expressed in seconds. **B:** Simultaneous changes in heart rate (HR) during the tests. The line represents the HR change over the time expressed in seconds. **C:** Two examples of PVCs in 12-lead electrocardiogram; note that their coupling interval is longer than that observed in ajmaline tests (Figure 1B).

using a sodium channel blocker and a hyperventilation test inducing acute hypocapnia-hypokalemia.

The potential arrhythmogenicity of sodium channel blockers has recently been demonstrated in individual and group studies.[4,5] In a series of 52 patients with idiopathic ventricular fibrillation associated with short-coupled Purkinje PVCs, pharmacologically induced replication of PVCs was observed in 48% of patients, with ajmaline infusion being significantly more arrhythmogenic than the flecainide infusion test.[5] The proarrhythmic mechanism of sodium channel blockers on Purkinje excitability has not been evaluated in experimental studies, to our knowledge. However, a simulation study has suggested that loss of sodium current function provides more favorable conditions for spontaneous calcium release and delayed afterdepolarizations in Purkinje cells.[8] *SCN5A* gene variants have not been demonstrated in these patients, but rare polymorphisms affecting sodium channels may be hypothesized, in a similar way as predisposition to medication-induced QT prolongation is associated with *KCNH2* polymorphisms.

In addition to pharmacological inducibility, our patient showed an arrhythmogenic response to the hyperventilation test, associated with hypocapnia and hypokalemia. To our knowledge, this test has never been described in this context. The hyperventilation test has been used in a few previous studies to facilitate the induction of ventricular arrhythmias.[9] Hyperventilation reduces PCO_2 values in the blood (respiratory alkalosis), leading to a compensatory mechanism that reduces K+ concentration in the extracellular space (shift of H+ and K+ cations). The hyperventilation test thus produces reproducible hypocapnia and hypokalemia, which have been shown to facilitate the induction of ventricular fibrillation in acute ischemia, or to induce long QT and torsades de pointes under clofilium.[10,11] In healthy subjects, hyperventilation modifies repolarization and may prolong the QT interval, but is not arrhythmogenic.[6,12] In our patient the hyperventilation tests resulted in a combination of pH 7.6 and K+ 3.1 mmol/L, capable to induce isolated PVCs with the same morphology as that observed in ajmaline test, whereas the Valsalva maneuver and isoprenaline test did not induce PVCs. These results suggest a common arrhythmogenic mechanism favored by hypocapnia-hypokalemia and sodium channel inhibition. Purkinje fibers and myocardial fibers have distinct electrophysiological properties. In animal models, hypokalemia prolonged the action potential plateau in Purkinje fibers but shortened it in ventricular fibers.[13] Similarly, flecainide prolonged action potential duration in Purkinje fibers but shortened it in ventricular fibers.[14] However, the cellular determinants of the different responses observed here are not known, and functional studies are needed to identify the pathophysiological mechanisms.

Conclusion

The present study reports the use of a simple hyperventilation test to elicit acute hypocapnia-hypokalemia, which then induced short-coupled Purkinje PVCs. In this individual case report, a similar response was obtained pharmacologically with sodium channel blockers. Further studies are needed to assess the sensitivity and specificity of the hyperventilation test and its clinical utility in detecting vulnerable patients, as well as the optimal testing protocol.

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