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MINI-FOCUS ISSUE: ELECTROPHYSIOLOGY

INTERMEDIATE

CASE REPORT: CLINICAL CASE

Nifekalant

A New Option for Pre-Excited Atrial Fibrillation With a High-Risk Accessory Pathway

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ABSTRACT

Atrial fibrillation along with accessory pathway–induced ventricular pre-excitation may be life-threatening due to the high risk of developing severe hypotension, ventricular fibrillation, and sudden death. We demonstrate nifekalant as an effective agent in the pharmacological cardioversion of atrial fibrillation with high-risk accessory pathways. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:235–9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 54-year-old male patient presented to the emergency department, complaining of palpitation of 3 h duration. He reported intermittent shortness of breath at night during the past 2 weeks, which usually lasted for about 1 min and was alleviated without any treatment. He stated that he had no syncope and chest pain.

The patient presented with the following vital signs: blood pressure was 125/70 mm Hg, and pulse rate was about 237 beats/min. His skin was dry and warm. Heart rate was 260 beats/min with relatively irregular rhythm. No cardiac murmur or extra heart sound was heard. There was no jugular venous distension and no basal crackles in the lungs. The rest of the physical examination was unremarkable.

LEARNING OBJECTIVES

- To be able to make an immediate diagnosis of AF with ventricular pre-excitation.
- To broaden the clinical implications of nifekalant to these patients and understand the underlying electrophysiological mechanisms.

PAST MEDICAL HISTORY

He had a history of obsolete pulmonary tuberculosis, and denied the use of cigarettes or alcohol. Family history was noncontributory.

INVESTIGATIONS

The 12-lead echocardiogram demonstrated a polymorphic wide QRS complex tachycardia without distinct P waves (Figure 1A). The ventricular response was between 235 and 260 beats/min (shortest R-R interval 200 ms, average R-R interval 237 ms), likely not conducting through the AV node. Notably, there was a beat-to-beat variation in QRS width, QRS amplitude, and R-R interval. These findings indicated atrial fibrillation (AF) associated with ventricular pre-excitation. Moreover, the accessory pathway (AP) was a high-risk pathway as its effective refractory period (ERP) was much <270 ms. The cardiac structure and

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Informed consent was obtained for this case.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AP = accessory pathway

ERP = effective refractory period

VF = ventricular fibrillation

systolic function were within normal range, according to the transthoracic echocardiography. There was no abnormality in laboratory results (serum potassium level: 4.3 mmol/l, reference range 3.5 to 5.1 mmol/l).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis was polymorphic ventricular tachycardia.

MANAGEMENT

The heart rate was up to 260 beats/min, suggesting a high risk of developing hemodynamic instability and spontaneous ventricular fibrillation (VF). Immediate cardioversion was required. Because he was at that point hemodynamically stable, we decided to perform pharmacological cardioversion but not synchronized direct current cardioversion. Nifekalant (0.3 mg/kg) was administered intravenously, which immediately slowed down the heart rate (shortest R-R interval 296 ms, average R-R interval 451 ms) (**Figure 1B**). Ten minutes after the injection, the heart rhythm successfully converted to sinus activity, with a wide QRS complex, short PR interval, and delta wave (**Figure 1C**). This confirmed our previous diagnosis that this patient had pre-excited AF with a high-risk AP. He was then carefully monitored in the cardiac intensive care unit for 1 more day, and there were no complications. An electrophysiological study was performed to locate the AP, which was eliminated by radiofrequency catheter ablation (**Figures 1D** and **2**).

DISCUSSION

The initial diagnosis for a wide QRS complex tachycardia is essential for the selection of a proper clinical intervention. In this case, there were some lines of evidence supporting the diagnosis of pre-excited AF: irregular R-R interval, broad and varying QRS complexes, and rapid ventricular response. The differential diagnosis included polymorphic ventricular tachycardia, such as torsade de pointes, which usually comes with an undulating baseline with alternating QRS polarity. Generally speaking, it is quite difficult to distinguish these arrhythmias based on an electrocardiogram. Age and medical history may be helpful. Young patients without any medical history are more likely to have pre-excited AF (1).

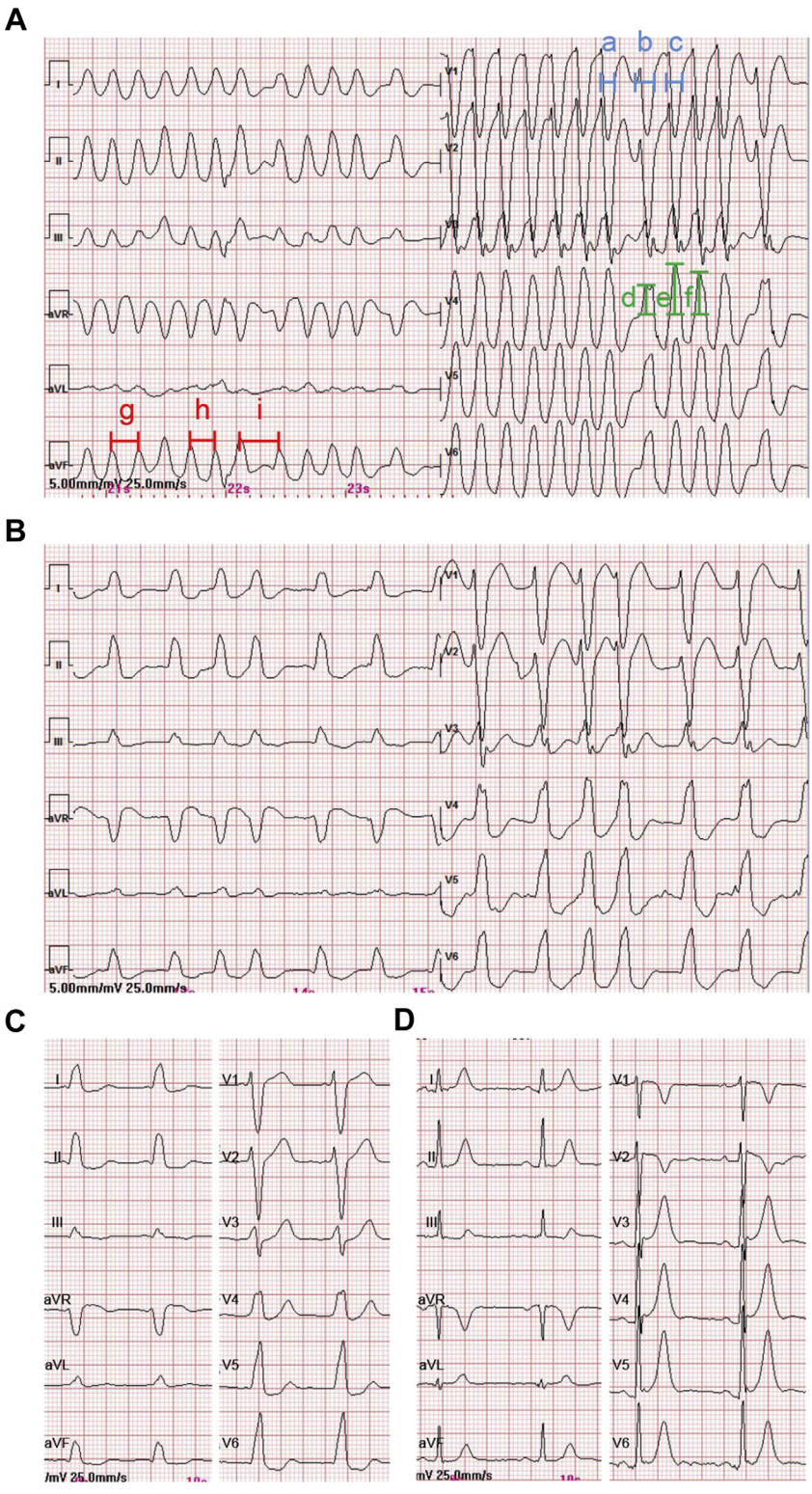
About one-third of patients with ventricular pre-excitation develop AF (2). The development of AF in the setting of ventricular pre-excitation may be life-threatening because fast ventricular response due to anterograde conduction of AF through APs may result in severe hypotension, VF, and cardiac arrest. Immediate intervention is required in most cases.

Treatment of pre-excited AF includes electrical or pharmacological cardioversion. For those patients who are hemodynamically compromised, electrical cardioversion is highly recommended to restore sinus rhythm. If the patient is hemodynamically stable and tolerates the symptoms, pharmacological treatment may be considered. According to the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline for the management of patients with AF, intravenous injection of procainamide or ibutilide is recommended to restore sinus rhythm or slow the ventricular rate by reducing the rate of conduction over the APs (3). However, there is a risk of hypotension when the heart rate is too fast. Amiodarone was previously recommended and widely used in these patients (4). However, an increasing number of case reports challenged its safety due to the risk of hypotension and VF (1,5,6). On the basis of these findings, the most recent guideline suggests that intravenous amiodarone is potentially harmful for patients with pre-excited AF (3).

Nifekalant, developed in Japan, is a pure Class III antiarrhythmic drug (**Table 1**) that is highly selective for blocking the cardiac delayed rectifier potassium current without affecting the inward sodium and calcium currents or β-adrenergic activity (7). It is usually used for ventricular arrhythmia and has the potential to convert current-onset atrial arrhythmia to sinus rhythm by increasing the ERP of ventricular and atrial myocytes (8). Compared with amiodarone, nifekalant has a more rapid time to onset with a shorter half-life, suggesting that it is an optimal drug for immediate cardioversion without affecting the subsequent electrophysiological study.

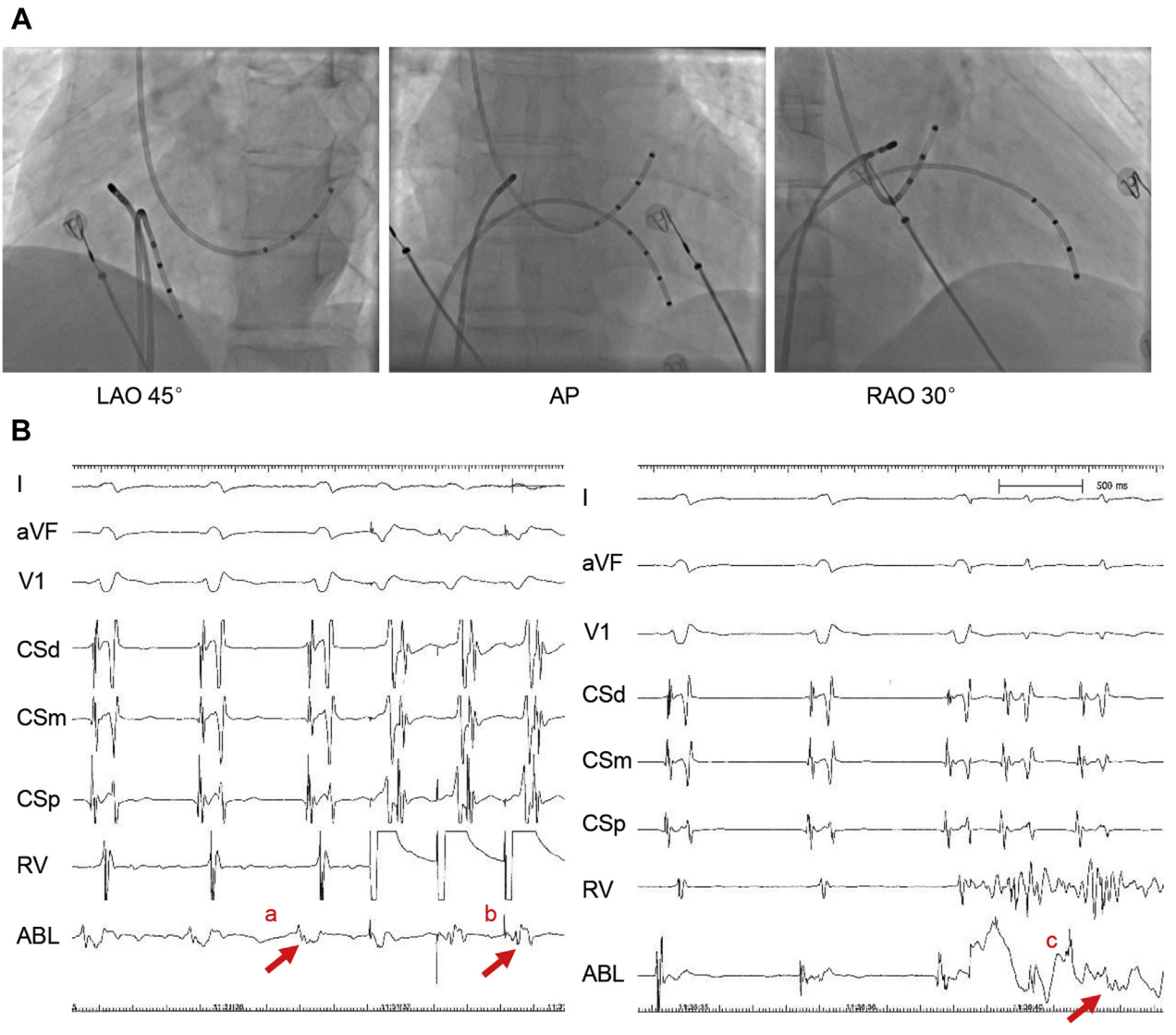
In this case, we explored the use of nifekalant in the treatment of pre-excited AF. Our clinical observation showed immediate effect of nifekalant in decreasing the ventricular response, likely due to the increase in ERP of APs without affecting the AV nodal conduction. Nifekalant also successfully restored the sinus rhythm 10 min after injection. This may result from the prolongation of the monophasic action potential duration and ERP of the atria. In addition, the elimination half-life of nifekalant is 1.53 to 2.07 h in healthy subjects (9). Thus, administration of nifekalant does not affect the subsequent electrophysiological investigation and

FIGURE 1 **Electrocardiogram of the Patient Before, Immediately After, and 10 Min After the Administration of Nifekalant**



Electrocardiogram (ECG) **(A)** before, **(B)** immediately after, and **(C)** 10 min after administration. **(D)** ECG after catheter ablation of the AP. QRS width: 0.14 ms **(a)**, 0.17 ms **(b)**, and 0.12 ms **(c)**. R-wave amplitude: 0.60 mV **(d)**, 1.02 mV **(e)**, and 0.85 mV **(f)**. R-R interval: 0.23 ms **(g)**, 0.20 ms **(h)**, and 0.33 ms **(i)**.

FIGURE 2 Fluoroscopy of Target Site and Electrophysiological Study and Radiofrequency Catheter Ablation



(A) Fluoroscopy of target site. **(B)** Electrophysiological study and radiofrequency catheter ablation. **(a)** ABL recorded atrioventricular fusion during the sinus rhythm as well as **(b)** ventricular and atrial wave fusion during RV pacing. **(c)** ABL recorded normal atrioventricular interval after ablation. ABL = ablation catheter; AP = anteroposterior; CS = coronary sinus; LAO = left anterior oblique; RAO = right anterior oblique; RV = right ventricle.

TABLE 1 A Brief Introduction to Nifekalant

CAS name	6-[[2-[(2-Hydroxyethyl)[3-(4-nitrophenyl)propyl]amino]ethyl]amino]-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione
Molecular formula	$C_{19}H_{27}N_5O_5$
Molecular weight	405.45
Percent composition	C 56.28%, H 6.71%, N 17.27%, O 19.73%
Mechanism of action	Pure potassium ion channel blocker
Side effect	QT prolongation; induction of torsade de pointes
Indications	Ventricular tachycardia; ventricular fibrillation
Contraindications	QT prolongation; administration along with amiodarone; pregnant women

radiofrequency catheter ablation. Thus, our findings suggest nifekalant as a promising agent in the pharmacological cardioversion of pre-excited AF even with high-risk APs.

FOLLOW-UP

The patient was discharged and had no evidence of pre-excitation on electrocardiograms or recurrent symptoms on a 1-year follow-up.

CONCLUSIONS

This clinical case demonstrates nifekalant as a promising agent in the pharmacological cardioversion of pre-excited AF even with high-risk APs.

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