Intermittent failure to capture: What is the mechanism?

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Introduction

Failure to capture can result from several causes, including battery depletion, circuit failure, lead dislodgement or maturation, elevated capture thresholds due to progressive cardiac disease, metabolic abnormalities and or drugs. We present a unique case of intermittent failure to capture and describe the mechanism.

Case report

An 82-year-old Caucasian female patient, who had a history of hypertension, dual-chamber pacer implantation for paroxysmal atrial fibrillation, and sick sinus syndrome 3 years ago, was transferred from an outside hospital for evaluation and management of a wide complex tachycardia at 115 beats per minute (bpm). Her home medications included candesartan-hydrochlorothiazide (32/12.5 mg daily), flecainide (100 mg twice daily), metoprolol tartrate (25 mg twice daily), and amiodarone (200 mg daily). She was started on doxycycline for left foot infection 4 days prior to the admission, which resulted in nausea and multiple episodes of vomiting. She was hemodynamically stable. Initial laboratory test results were pertinent to acute kidney injury, with serum bicarbonate level of 12 mmol/L (normal range 17–29 mmol/L), blood urea nitrogen level of 63 mg/dL (normal range 8–23 mg/dL), and serum creatinine concentration of 2.5 mg/dL (normal 0.5–1.0 mg/dL). Her presenting electrocardiogram (ECG) showed a wide complex rhythm with intermittent loss of ventricular capture (Figure 1A). What is the mechanism of this intermittent failure to capture?

The initial ECG (Figure 1A) showed a very wide complex tachycardia (QRS duration of 240 ms) at 115 bpm with group beating due to intermittent failure to capture. An examination of the lead V1 results demonstrated P waves preceding every QRS complex, which was consistent with P synchronous ventricular pacing. This finding was also demonstrated on the intracardiac electrogram from the pacing device (Figure 1B). Differential diagnoses included sinus tachycardia or atrial tachycardia with ventricular tracking. Interestingly, the width of the QRS complex gradually increased such that the last QRS complex before the pause was much wider than the first QRS after the pause. This phenomenon of rate-dependent or use-dependent widening of QRS complexes is classically seen with flecainide (class IC antiarrhythmic agent). The intermittent failure to capture during ventricular pacing is the result of the pacing stimulus occurring during the refractory period of the previous beat, with a very delayed depolarization (Figures 1A and 1B). This phenomenon is referred to as *functional noncapture*. These ECG findings in our patient in the setting of acute kidney injury from intravascular volume depletion (multiple episodes of vomiting, use of diuretic) and concurrent use of amiodarone strongly raised the suspicion for flecainide toxicity. Flecainide and amiodarone therapies were discontinued. The pacing device was reprogrammed from DDD mode to DDI mode at 70 bpm to avoid tracking and to decrease the ventricular rate. The patient was aggressively hydrated with intravenous fluids. Anion gap metabolic acidosis, in the setting of a very wide QRS, was acutely treated with 100 milliequivalents of intravenous sodium bicarbonate. Flecainide levels obtained at the time of admission were elevated, at 1400 ng/mL (normal 200–1000 ng/mL). After 48 hours of conservative management, her acidosis and acute kidney injury resolved. The nonpaced ECG before and after treatment demonstrated remarkable narrowing of QRS complexes (Figures 2A and 2B).

Discussion

Flecainide (class IC antiarrhythmic agent) is a potent sodium channel blocker, which thereby decreases the slope of the phase 0 depolarization (V_{max}) and slows down the conduction velocity in cardiac tissue.[1] It has negative inotropic effects and therefore should be avoided in patients with depressed ejection fraction.[1] Furthermore, the use of flecainide is contraindicated in patients with myocardial infarction, because of excessive mortality risk as demonstrated in the Cardiac Arrhythmia Suppression Trial (CAST).[2] Flecainide can also increase pacing and defibrillation

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KEY TEACHING POINTS

- Flecainide is a drug with a narrow therapeutic index. A thorough understanding of the pharmacokinetics and pharmacodynamics is essential to prevent fatal overdose.
- The characteristic rate-dependent or use-dependent effect property of flecainide is due to its high affinity for open-state or inactivated sodium channels and very slow unbinding kinetics.
- Widening of the QRS at rapid rates predisposes patients to ventricular arrhythmias and can potentially result in a loss of ventricular capture in patients with pacemakers.

thresholds. Currently, flecainide is indicated, in patients without structural heart disease, for the prevention of paroxysmal supraventricular tachycardias (atrioventricular nodal reentry, atrioventricular reentry), paroxysmal atrial fibrillation/flutter, and sustained life-threatening ventricular tachycardia. Flecainide is also emerging as a novel strategy in preventing ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia, by inhibiting the cardiac ryanodine receptors and thus preventing diastolic calcium overload.[1] On oral administration, flecainide is extensively absorbed, with bioavailability reaching 90%–95%. It undergoes negligible hepatic first-pass metabolism and is poorly bound to the plasma proteins. The elimination half-life is 12–27 hours. It undergoes extensive hepatic biotransformation via cytochrome P450 (CYP) 2D6 into two major metabolites. Flecainide and its metabolites are excreted primarily (85%) in urine.[3] Hence, the dose should be adjusted in patients with renal or hepatic impairment. Furthermore, drugs that inhibit CYP2D6 and decrease hepatic metabolism can increase the plasma concentrations of flecainide by 2-fold or more.[3] One such example is amiodarone, which our patient was taking along with flecainide. In the present case, amiodarone was prescribed by an outside physician, and its prescription was probably an oversight. In one study, the mean percent increase in the dose-adjusted plasma flecainide levels after initiation of amiodarone was 60%.[4] The authors hypothesized that more than one mechanism of interaction may be operative including decreased rate of enzymatic biotransformation from altered hepatic function, a decrease in renal elimination, and/or a change in drug distribution.[4]

The electrocardiographic changes associated with flecainide ingestion include PR prolongation and widening of the QRS interval, even at physiologic heart rates. Flecainide has high affinity for open-state and inactivated sodium channels and exhibits very slow unbinding kinetics from these channels. At faster heart rates, as the sodium channels spend more time in an open or inactivated state, there is greater binding of flecainide to these channels. The shortened diastolic time for recovery from the block at rapid heart rates coupled with the slow dissociation properties of flecainide from these channels further enhances sodium channel blockade and the slowing of the conduction. This phenomenon explains the characteristic property of flecainide referred to as "rate-dependent" or "use-dependent" effect that occurs at rapid heart rates, resulting in profound QRS widening that predisposes to ventricular proarrhythmia.[2] Additionally, rate-dependent widening of the QRS can lead to functional noncapture, as was observed in our case, that may have grave consequences in a pacemaker-dependent patient. Exercise treadmill testing can be performed to assess the use-dependent QRS widening in patients who are treated with flecainide. The risk factors for ventricular proarrhythmia in patients taking flecainide include wide QRS (>120 milliseconds), depressed ejection fraction, coronary artery disease, high heart rates, high dose of Flecainide, hypokalemia, severe renal failure (creatinine clearance ≤ 35 mL/min/1.73 m^2), and excessive QRS widening ($>150\%$ from baseline).[1]

Flecainide is considered to be a narrow therapeutic-index drug, with steep dose-response relationships for the efficacy, toxicity or both in the usual dosing interval.[5] The cardiovascular adverse effects begin to rise at a plasma level of approximately 750 ng/mL and reach 50% at 1500 ng/mL.[5] Drug overdose with flecainide is frequently fatal with reported mortality rates as high as 10%.[6] Toxicity presents electrocardiographically as widening of the PR and QRS intervals, and clinically as hypotension, bradycardia, atrioventricular conduction block, premature ventricular ectopy, ventricular tachycardia, and/or ventricular fibrillation. The treatment is support with aggressive fluid resuscitation. Flecainide should be promptly discontinued, and any electrolyte derangements should be corrected. There is no specific antidote for flecainide overdose. Hypertonic sodium bicarbonate has been shown to be effective in patients with wide QRS, hypotension, and ventricular ectopy. Hypertonic sodium bicarbonate competes with binding of flecainide to the sodium channels, thereby reversing the effect of flecainide on cardiac excitability and conduction.[3] Intravenous lipid emulsion as a novel adjunctive therapy has also been shown to be effective in reversing the adverse cardiac effects associated with flecainide overdose. Intravenous lipid emulsion is hypothesized to function as a "lipid sink," thus recruiting and sequestering the lipophilic medications (eg, flecainide) from the receptor sites.[7]

Conclusions

Flecainide is a narrow therapeutic-index drug, and drug overdose can be fatal. The characteristic rate-dependent or use-dependent effect property of flecainide is due to high affinity for open-state or inactivated sodium channels and very slow unbinding kinetics from these channels. Widening of the QRS at rapid rates predisposes patients to ventricular arrhythmias and can potentially result in a loss of ventricular

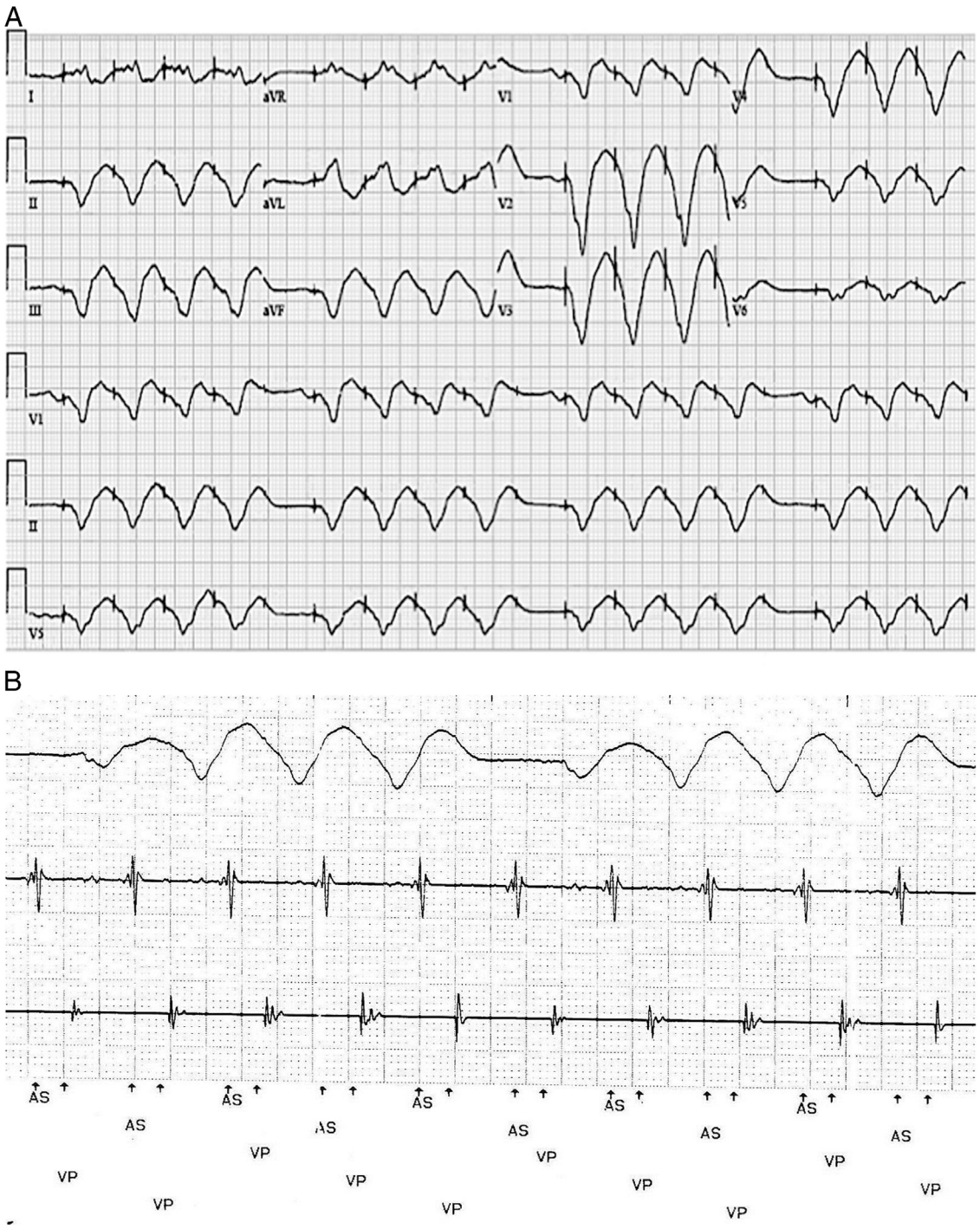

Figure 1 **A**: Baseline paced electrocardiogram. Electrocardiogram shows atrial sensed ventricular paced rhythm with a very wide complex tachycardia (QRS duration of 240 milliseconds) at 115 beats per minute with group beating due to intermittent failure to capture. Note, the width of the QRS complex gradually increases such that the last QRS complex before the pause is much wider than the first QRS after the pause**. B**: Intracardiac electrogram. Atrial sensed ventricular paced rhythm with intermittent failure to capture.

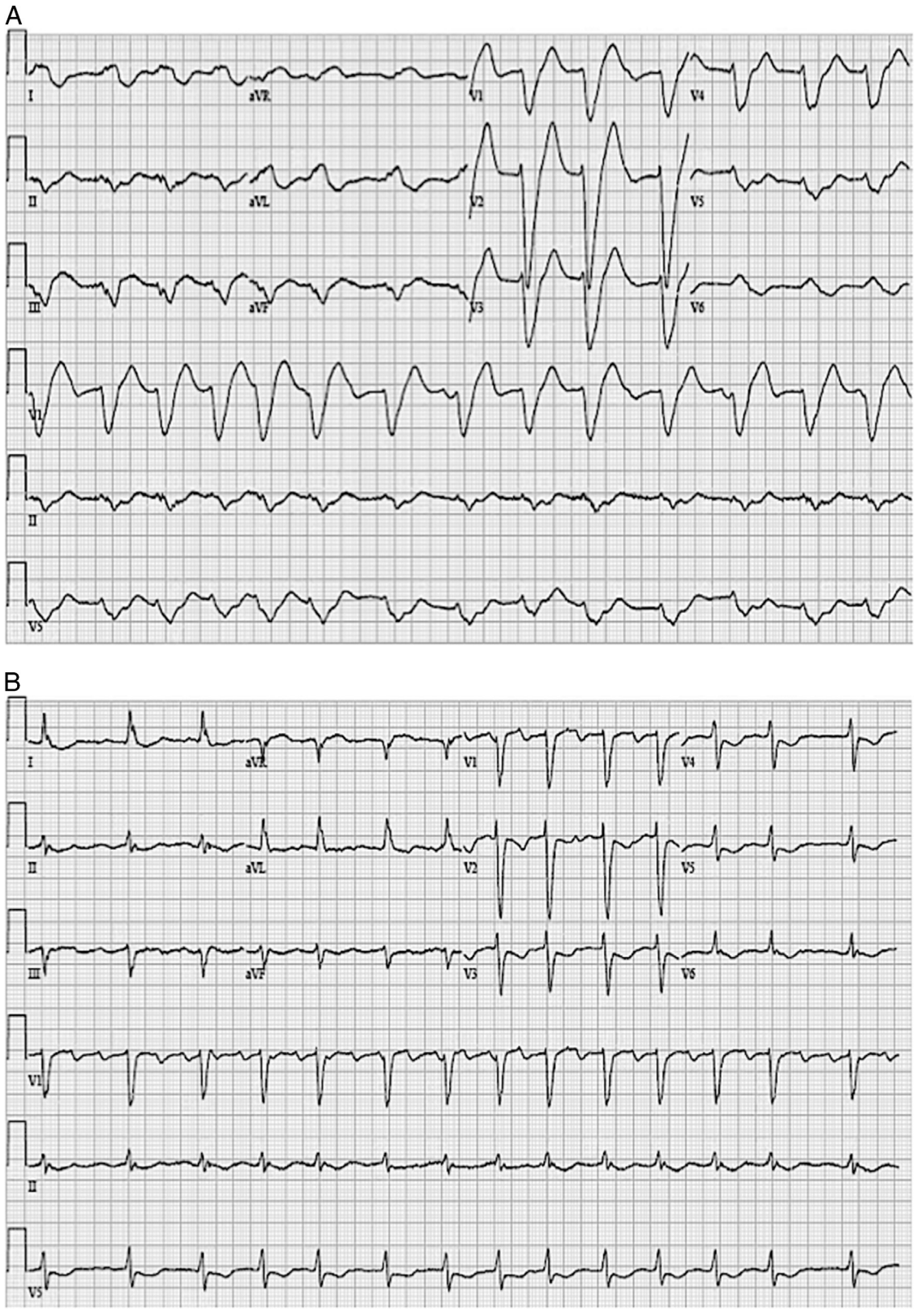

Figure 2 **A**: Baseline nonpaced electrocardiogram shows atrial fibrillation with a wide complex QRS measuring 200 milliseconds. **B**: Nonpaced electrocardiogram recorded after 48 hours. The electrocardiogram shows atrial fibrillation with QRS measuring 136 milliseconds.

capture in patients with pacemakers. Physicians prescribing or managing patients on flecainide should have thorough understanding of the pharmacology of flecainide so as to avoid drug-drug interactions. Patients on flecainide, especially elderly patients and in those with renal or hepatic insufficiency, should be carefully monitored for adverse drug effects.

References

1. Aliot E, Capucci A, Crijns HJ, Goette A, Tamargo J. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. Europace 2011;13(2):161–173.
2. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321(6):406–412.
3. Tamargo J, Capucci A, Mabo P. Safety of flecainide. Drug Saf 2012;35(4):273–289.
4. Shea P, Lal R, Kim SS, Schechtman K, Ruffy R. Flecainide and amiodarone interaction. J Am Coll Cardiol 1986;7(5):1127–1130.
5. Tamargo J, Le Heuzey J-Y, Mabo P. Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. Eur J Clin Pharmacol 2015;71(5):549–567.
6. Köppel C, Oberdisse U, Heinemeyer G. Clinical course and outcome in class IC antiarrhythmic overdose. J Toxicol Clin Toxicol 1990;28(4):433–444.
7. Ellsworth H, Stellpflug SJ, Cole JB, Dolan JA, Harris CR. A life-threatening flecainide overdose treated with intravenous fat emulsion. Pacing Clin Electrophysiol 2013;36(3):e87–e89.