Impact of flecainide on left bundle branch capture criteria

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Introduction

Flecainide is a well-established class Ic antiarrhythmic medication commonly used to treat supraventricular and ventricular arrhythmias. Given its primary mechanism of action is inhibition of fast-inward sodium channels, flecainide prolongs depolarization within atrial and ventricular myocytes as well as slows conduction within the atrioventricular node and His-Purkinje system, with increased inhibition at faster heart rates.[1] Consequently, 12-lead electrocardiograms (ECGs) are necessary to monitor for significant QRS prolongation after initiation of flecainide, both at rest and with exercise. Although case reports have documented the risk of marked QRS prolongation[2,3] and left bundle branch (LBB) block[4,5] with flecainide, the effect of flecainide on electrophysiologic criteria during conduction system pacing has not been previously assessed. Herein, we present a patient who underwent pacemaker implantation with a conduction system pacing lead in the LBB area in whom LBB capture based on accepted criteria was noted only after discontinuation of flecainide.

Case report

An 82-year-old female patient with paroxysmal atrial flutter, atrial fibrillation, multifocal atrial tachycardia status post multiple ablations and cardioversions, heart failure with preserved ejection fraction, chronic kidney disease stage 3, hypertension, obstructive sleep apnea, and hypothyroidism was started on flecainide 50 mg twice daily for recurrence of her atrial arrhythmias. After initiation of flecainide, QRS duration (QRSd) increased from 98 ms to 116 ms, so she was maintained at the lowest dose of flecainide. A year later, she had symptomatic recurrence of atrial tachycardia; repeat ECG showed QRSd down to 102 ms, so her flecainide was increased to 100 mg twice daily, and QRSd further increased to 122 ms with an interventricular conduction delay. At the time, repeat stress echocardiography was negative for ischemia but noted mild left ventricular hypertrophy, with septal wall thickness of 1.1 cm.

She did well until 4 years later when she developed syncope, and Holter monitor demonstrated periods of sinus arrest with junctional rhythm as well as chronotropic incompetence. As such, she underwent implantation of a dual-chamber pacemaker; a 59 cm Ingevity+ lead (Boston Scientific Corporation, Marlborough, MA) was delivered via a SSPC2 sheath to achieve LBB area pacing. Intraprocedural recordings revealed a stim to R-wave peak time of 106 ms in lead aVL, which included a 46 ms latency period. Programmed electrical stimulation (PES) with extrastimuli (sensed S1 of 1116 ms, paced S2 of 692 ms and S3 of 664 ms) led to a change in morphology with a more pronounced latency period without a change in left ventricular activation time (LVAT; best

KEY TEACHING POINTS

- Flecainide is a class Ic antiarrhythmic that can increase the QRS duration and left ventricular activation times.
- Electrophysiologists need to be aware of potential masking of standard left bundle branch (LBB) capture criteria (stim to R-wave peak time in V_6 [V_6RWPT] $<$80 ms) when patients are on flecainide therapy.
- Either direct evidence of LBB capture (diagnostic morphology changes during threshold testing or programmed electrical stimulation) or comprehensive analysis of other LBB criteria (eg, V_6RWPT $<$90 ms in the setting of intrinsic conduction delay, V_6-V_1 interpeak interval $\geq$33 ms, LBB pacing score) should be sought to fully assess for LBB capture in patients taking flecainide.
- Temporary flecainide discontinuation should be considered prior to LBB pacemaker implantation to improve diagnostic performance of conventional LBB capture criteria.

KEYWORDS FlecainideAntiarrhythmic; Left bundle branch captureConduction system pacing, R-wave peak time
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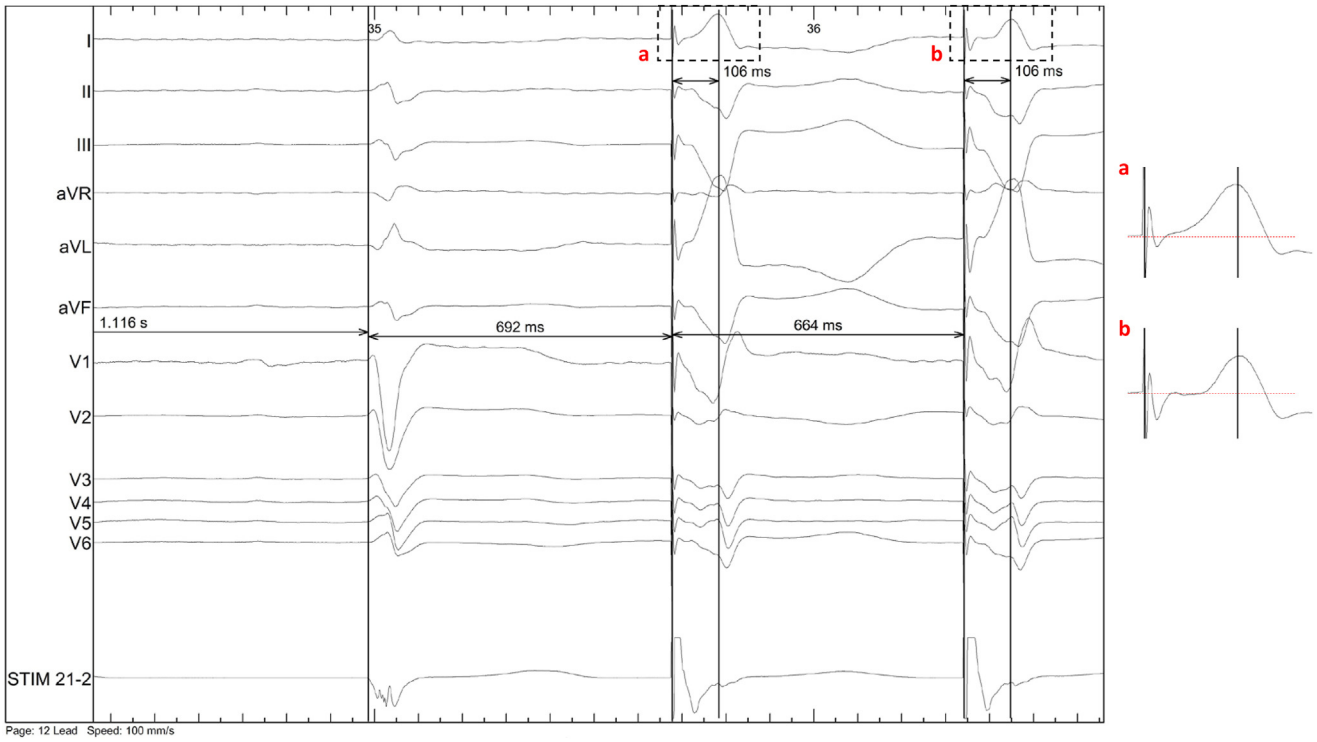

Figure 1 Intraoperative recordings of programmed electrical stimulation. Note the change in morphology with a pronounced latency period (panel **b** relative to panel **a**) following S1S2S3 extrastimulation without a change in R-wave peak time.

visualized in leads I and aVL; Figure 1) and with increase in magnitude of the R′ wave in V_1, consistent with transition from nonselective to selective LBB capture. Postoperative ECG analysis while on flecainide (Figure 2) revealed a stim to R-wave peak time in V_6 (V_6RWPT) of 108 ms, which included a 40 ms latency period. ECG showed evidence of R-wave notching in leads I/aVL and poor R-wave progression across precordial leads, with R<S in V_6.

Shortly after pacemaker implantation, the patient was hospitalized for a heart failure exacerbation requiring escalation of diuretics, and repeat echocardiogram showed progression to severe left ventricular hypertrophy with septal wall thickness of 1.9 cm. As such, flecainide was discontinued, and the patient was maintained on a rate-control strategy with diltiazem. A 12-lead paced ECG several months later (Figure 3) demonstrated significantly shorter V_6RWPT of 78 ms with a latency period of 32 ms. Notably, the R-wave notching in aVL seen previously had disappeared, and precordial leads showed appropriate R-wave progression (for right bundle branch block pattern). Table 1 summarizes the relevant paced intervals while on and off flecainide. While off flecainide, the patient had significant recurrence of atrial flutter, ultimately requiring atrioventricular node ablation and 100% ventricular pacing. The patient did well for several months but unfortunately developed progressive cognitive decline and subsequently died of noncardiac causes.

Discussion

This case highlights the impact of flecainide on the measurement of R-wave peak times during pacemaker implantation, specifically masking LBB capture by established threshold base criteria. Importantly, PES in our patient with extrastimuli led to a significant morphology change from loss of left septal capture owing to the longer refractory period of septal myocardium. While the high-output pacing artifact partially obscured the immediate postpacing interval, the morphological changes could be best seen in lead I (Figure 1). This indicated a shift from nonselective to selective LBB capture and provided direct evidence of conduction system pacing. Traditional LBB capture criteria have been previously defined as a V_6RWPT <75 ms[6] (with 100% specificity in the absence of pre-existing conduction delay), or V_6RWPT <83 ms[7] with an improved sensitivity of 84.7% while maintaining a high specificity of 96.3%. Importantly, these measurements use V_6RWPT as the total LVAT (sometimes termed "stim-LVAT"), which consists of the poststimulus latency period of left bundle and Purkinje activation and the subsequent ventricular depolarization. Prior electrophysiology studies have documented a 22%–26% increase in the H-V interval with flecainide,[8,9] which can explain the observed decrease in the latency period from 40 to 32 ms after flecainide discontinuation in our patient (Table 1). Furthermore, flecainide is known to increase QRSd owing to slowing of ventricular depolarization, which is consistent with our patient's decrease in QRSd from 146 ms to 102 ms (Table 1) off flecainide. Notably, the upward slurring and R-wave notching in leads I/aVL previously seen on flecainide were no longer noted, as was re-emergence of appropriate precordial R-wave progression, supporting the improvement in overall conduction off flecainide. Furthermore, V_6RWPT decreased from 108 to 78 ms after

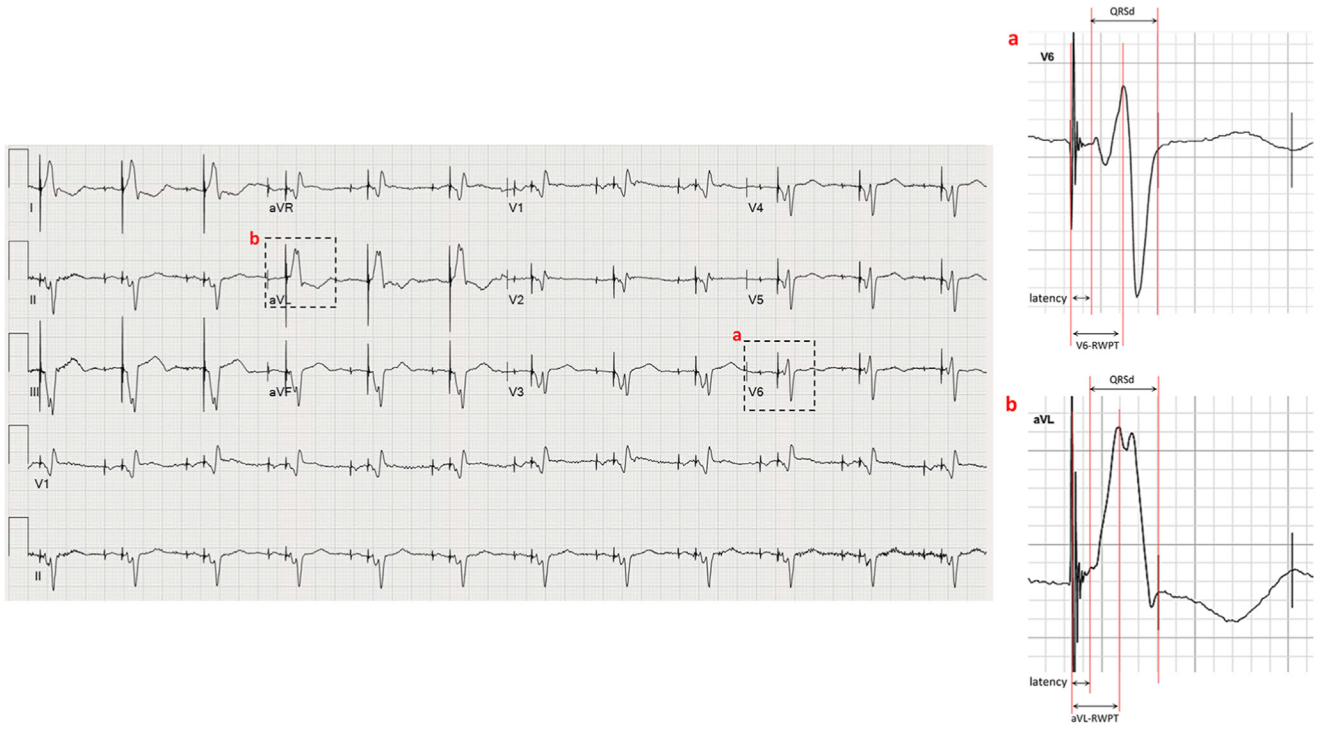

Figure 2 Paced 12-lead electrocardiogram of patient taking flecainide. Note the slurred upstroke and notching in leads I and aVL, lack of precordial R-wave progression, and long latency period and QRS duration (QRSd) in leads V_6 (**a**) and aVL (**b**). Part of the isoelectric period in aVL is obscured by the stimulus artifact.

discontinuation of flecainide, meeting the standard LBB capture criteria by LVAT only off flecainide despite no changes to her pacemaker leads or programmed parameters. Considering that our patient had an interventricular conduction delay prior to pacemaker implantation (QRSd of 122 ms), a modified total V_6RWPT of $<$101 ms proposed by Jastrzebski and colleagues[6] for LBB capture in the setting of pre-existing conduction disease can be applied, though our patient's initial LVAT

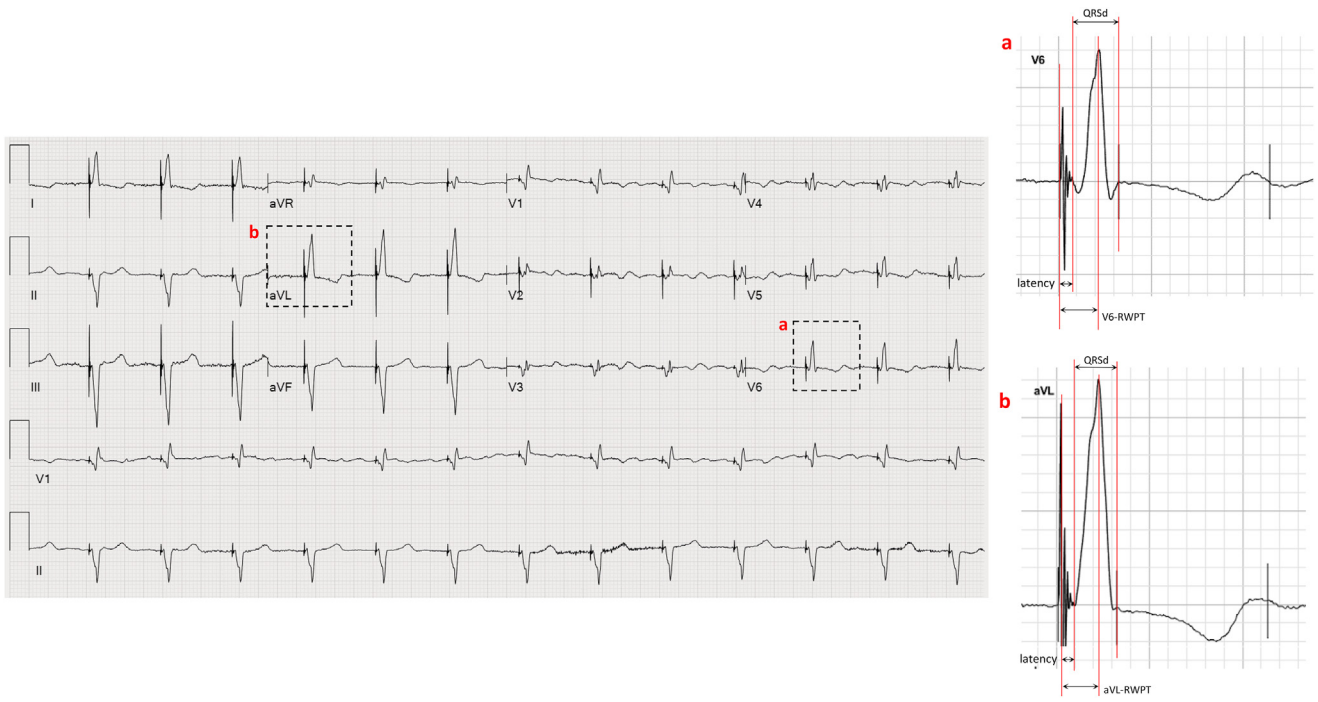

Figure 3 Paced 12-lead electrocardiogram of patient after discontinuation of flecainide therapy. Note the sharper upstroke in leads I/aVL, normal precordial R-wave progression, and shorter latency period and QRS duration (QRSd) in leads V_6 (**a**) and aVL (**b**).

Table 1 Improvement in paced ECG parameters used to assess for left bundle branch capture after discontinuation of flecainide therapy

Paced ECG parameter	ON flecainide	OFF flecainide	Δ with flecainide discontinuation
QRS duration	146 ms	102 ms	-44 ms
Latency period (V_6)	40 ms	32 ms	-8 ms
V_6RWPT	108 ms	78 ms	-30 ms
Latency period (aVL)	42 ms	30 ms	-12 ms
aVL-RWPT	106 ms	78 ms	-28 ms
V_6-V_1 interpeak interval	34 ms	26 ms	-8 ms
LBB pacing score	2	3	+1

aVL-RWPT = R-wave peak time in aVL; ECG = electrocardiogram; LBB = left bundle branch; RWPT = R-wave peak time; V_6RWPT = R-wave peak time in V_6.

of 108 ms would still not meet numerical criteria for LBB capture despite evidence of direct capture by PES.

Given the imperfect sensitivity of the V_6RWPT criteria for LBB capture, a novel criterion of the V_6-V_1 interpeak interval $\geq$33 ms was recently proposed[10] to account for increased latency periods, diseased His-Purkinje conduction systems, or substantial LV dilation. Interestingly, the patient met LBB capture criteria based on a V_6-V_1 interpeak interval of 34 ms while on flecainide, but this decreased to 26 ms off flecainide. Although this raises a possibility of having true LBB capture initially with only left ventricular septal capture subsequently, we believe that flecainide discontinuation likely allowed for earlier activation of the right ventricle, rather than loss of LBB capture (which is supported by the shorter LVAT off flecainide). This discrepancy highlights the heterogeneity of electrophysiologic measurements for assessment of LBB capture.

The European MELOS study[11] considered that LBB capture can be confirmed if at least 1 of several diagnostic criteria are met: diagnostic QRS morphology transition during threshold test or programmed stimulation, pacing stimulus to V_6RWPT <80 ms with narrow QRS (or <90 ms with wide QRS), LBB potential to V_6RWPT interval equal to stimulus to V_6RWPT interval within 10 ms, or V_6-V_1 interpeak interval $\geq$40 ms. Moreover, a recent addition to these proposed criteria includes assessment of LVAT in aVL, with total stim to aVL-RWPT <79 ms showing sensitivity of 71.2% and specificity of 88.4% for LBB capture, consistent with our patient's value of 78 ms only while off flecainide.[12] The authors further suggested an "LBB pacing score" by combining values from V_6-V_1 interpeak intervals and pacing stimulus to V_6RWPT and aVL-RWPT, with a score of $\geq$3 carrying a sensitivity of 89.2% and specificity of 100% for LBB capture. In our patient, despite evidence of direct LBB capture by PES at implant, the LBB pacing score similarly met this criterion for LBB capture ($\geq$3), again only off flecainide. As such, this report highlights the need to assess multiple criteria on and off flecainide therapy in order to appropriately establish a diagnosis of LBB capture, as well as perform PES whenever possible to assess for direct evidence of LBB capture.

Conclusion

Flecainide is a commonly used antiarrhythmic known for its class Ic properties resulting in slowed conduction throughout atrial and ventricular tissues. Electrophysiologists and other cardiologists should be aware of its ability to mask standard ECG criteria for LBB capture during pacemaker implantation. As such, clinicians are urged to apply multiple different LBB capture criteria including PES, and carefully reassess ECG parameters off flecainide therapy if applicable so as to make the correct diagnosis. Temporary discontinuation of flecainide should be considered prior to conduction system pacemaker implants.

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