Oral theophylline for treatment of painful left bundle branch block

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Introduction

Painful left bundle branch block (LBBB) is characterized by chest pain with transient LBBB, in the absence of underlying ischemia. The true prevalence is likely underestimated owing to poor recognition and diagnosis of such an entity. To date, successful treatment has relied on permanent pacing, while pharmacological therapy focusing on sinus node suppression with beta-blockers or ivabradine have had suboptimal success rates. Herein we report a case of a 71-year-old man with painful LBBB successfully treated with oral theophylline.

Case report

A 71-year-old man with hyperlipidemia presented with chest pain on minimal exertion occurring several times every day, greatly limiting his daily activities. Symptoms always coincided with his heart rates above 80 beats per minute (bpm) on his Apple Watch. He denied any associated nausea, vomiting, diaphoresis, dyspnea, palpitations, presyncope, or syncopal episodes. Resting electrocardiogram revealed sinus bradycardia at a rate of 54 bpm. Echo showed normal left ventricular function and no ischemia on stress test. Coronary angiography revealed no significant stenosis. Ranolazine therapy for presumed microvascular ischemia was ineffective. Electrophysiology study (EPS) with minimal sedation showed reproducibility of symptoms with onset of LBBB at a cycle length of 550 ms (~109 bpm) with prompt resolution of symptoms with narrowing of QRS at lower pacing rates. Chest pain was reproduced not only with atrial pacing, but also with right ventricular (RV) apical pacing and with left ventricular lateral wall pacing through a coronary sinus catheter. He was started on propranolol 120 mg per day with no relief of symptoms. A repeat electrophysiology study was performed to test the integrity of his conduction system without sedation and consider pacing options. Atrial pacing at 550 ms reproducibly resulted in LBBB and onset of pain (Figure 1A). Transient right bundle branch block was intentionally caused by catheter manipulation to assess whether the left bundle was functional or not (Figure 1B). Atrial pacing at or below 530 ms resulted in 2:1 atrioventricular (AV) conduction without evidence of Wenckebach and without any chest pain (Figures 2A). The block occurred above the His bundle (Figure 2B). Following recovery of the right bundle branch block, isoproterenol infusion up to

KEY TEACHING POINTS

- Pathophysiology of painful left bundle branch block (LBBB) is yet to be understood; current hypotheses state ventricular dyssynchrony and/or increased cardiac sensitivity contribute to symptom development.
- Diagnosis of painful LBBB must include ruling out ischemic etiology, with subtle hints on electrocardiogram including inferior QRS axis and S/T ratio <1.8 suggestive of diagnosis.
- Treatment of painful LBBB has mainly been by permanent pacing or pharmacological sinus node suppression.
- Management with theophylline may be considered if other medical management strategies have failed or invasive management with pacemaker is not desired.

KEYWORDS Chest pain; Angina; Painful LBBB; Rate-related LBBB; Theophylline

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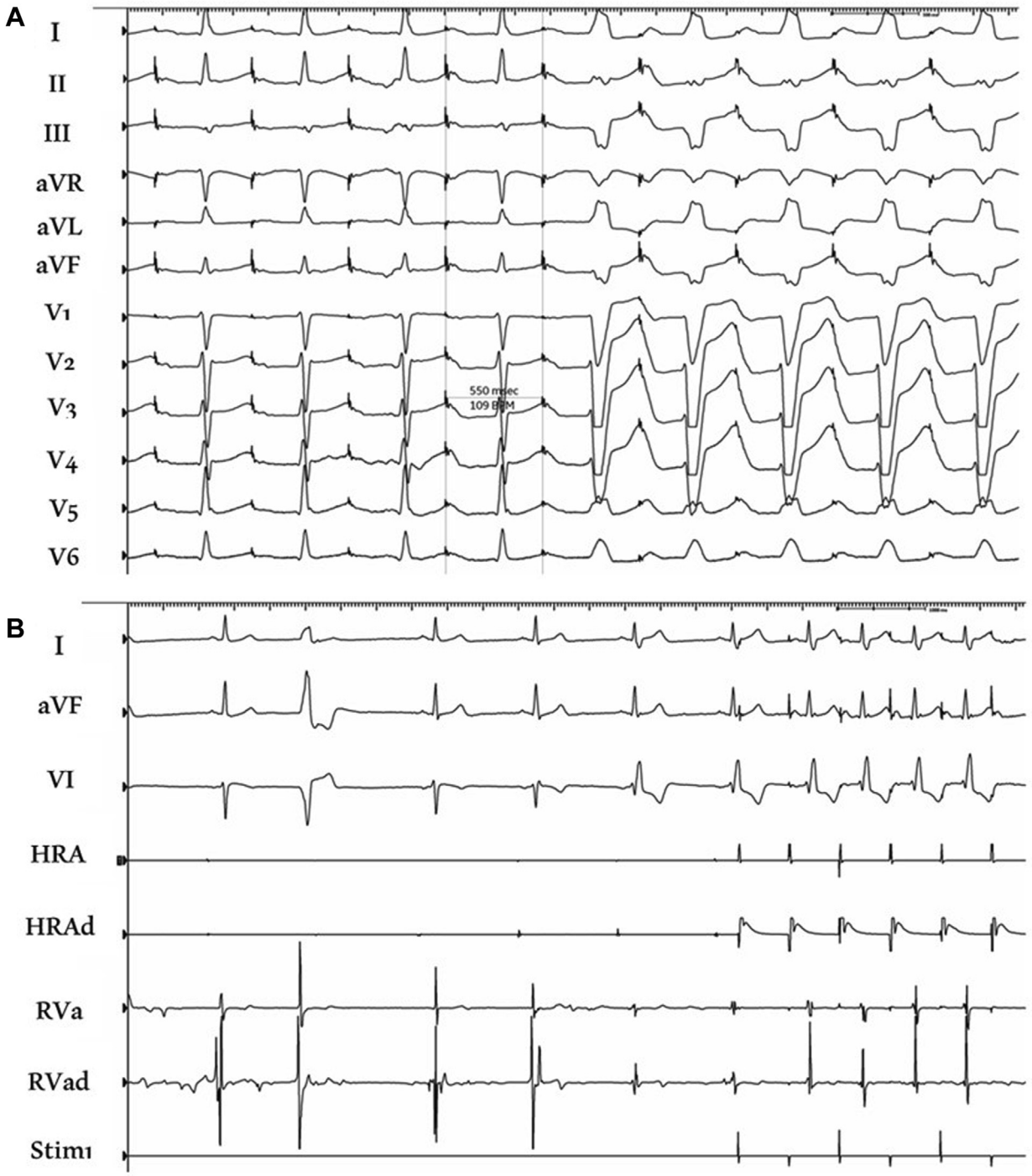

Figure 1 **A:** A 12-lead surface electrocardiogram showing atrial pacing at a cycle length of 550 ms causing rate-related left bundle branch block. **B:** Surface and intracardiac electrograms showing induction of right bundle branch block and initiation of atrial pacing. The second QRS is a PVC generated by catheter-induced trauma at the level of the right bundle branch.

20 mcg/kg/min was administered to augment AV conduction. Rate-related LBBB occurred at 470 ms (127 bpm) with no chest pain until the appearance of LBBB (Figure 3). Based on improvement of AV node conduction and narrow QRS at higher heart rates, he was started on oral theophylline 100 mg twice daily with remarkable improvement in symptoms and no chest pain during routine activities at 1-month and 3-month follow-ups.

Discussion

Painful LBBB is an underrecognized and underreported entity characterized by sudden-onset chest pain associated with intermittent LBBB, without evidence of underlying ischemia. Although this entity was first described in 1946, the exact pathogenesis is yet to be fully understood.[1]

Myocardial ischemia, leading to both a rate-related LBBB and chest pain, was initially thought to be the culprit.

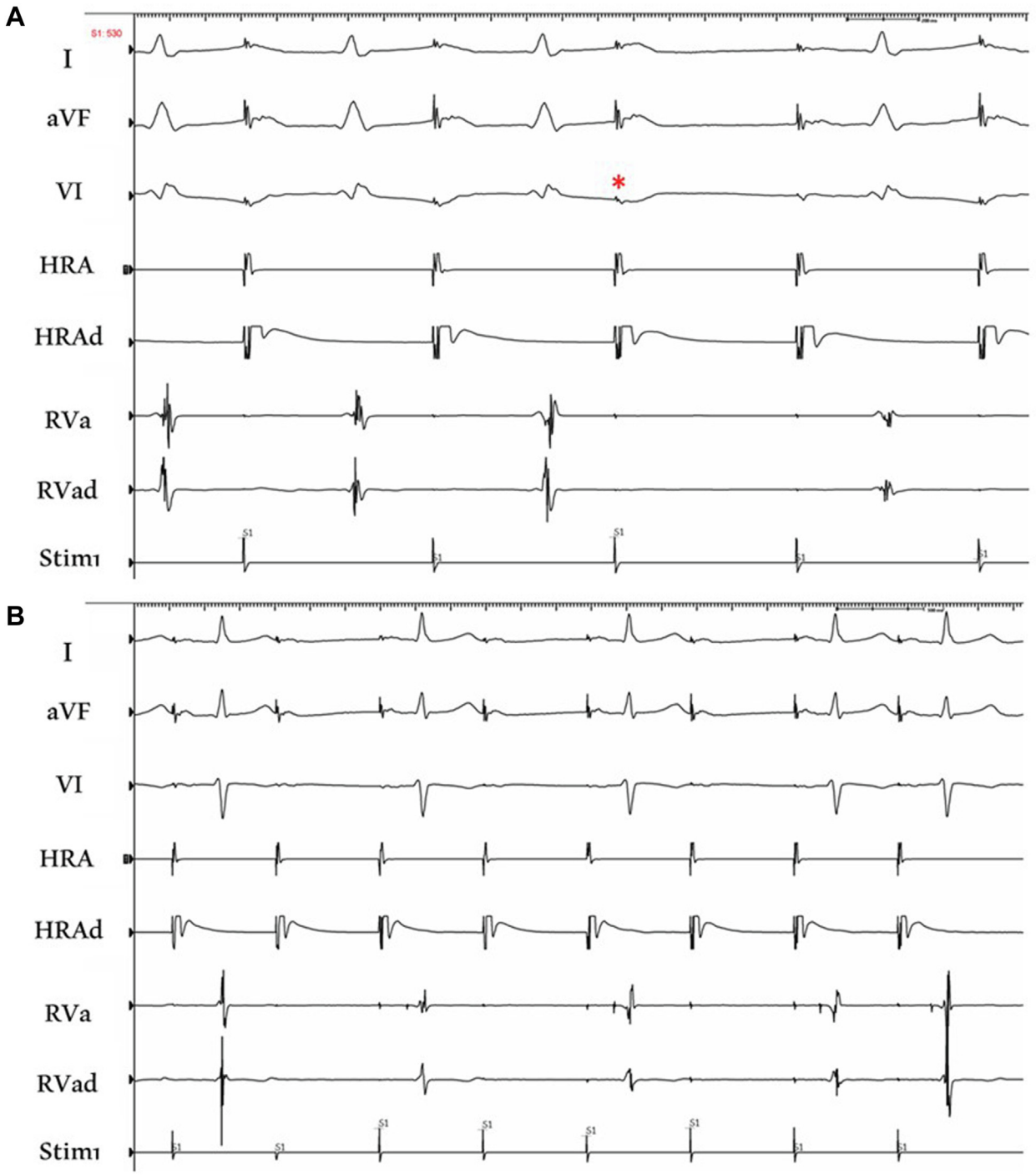

Figure 2 **A:** Intracardiac electrogram showing incremental atrial pacing during transient right bundle branch block at cycle length 530 ms causing 2:1 atrioventricular (AV) block. *Initiation of 2:1 AV block. **B:** Surface and intracardiac electrograms showing atrial pacing leading to 2:1 AV nodal block. The right ventricle quadripolar catheter is positioned at the level of the His.

However, all current published cases, including our patient above, had coronary angiograms, nuclear imaging, or coronary sinus lactate samples with no evidence of obstructive coronary artery disease or ischemia. Virtanen and colleagues[2] were the first to hypothesize that myocardial dyssynchrony, specifically abnormal systolic septal motion, is the cause of chest pain in such conditions, similar to that observed in some patients with biventricular (BiV) pacing. An alternate theory is that heightened cardiac sensitivity owing to interoceptive neural network disorders contributes to this phenomenon.[3]

The definitive diagnosis of painful LBBB presents a challenge on its own. It is typically characterized by sudden onset and offset of symptoms that strongly correlate to presence and, subsequently, resolution of LBBB. Some additional indicators suggestive of a diagnosis of painful LBBB include

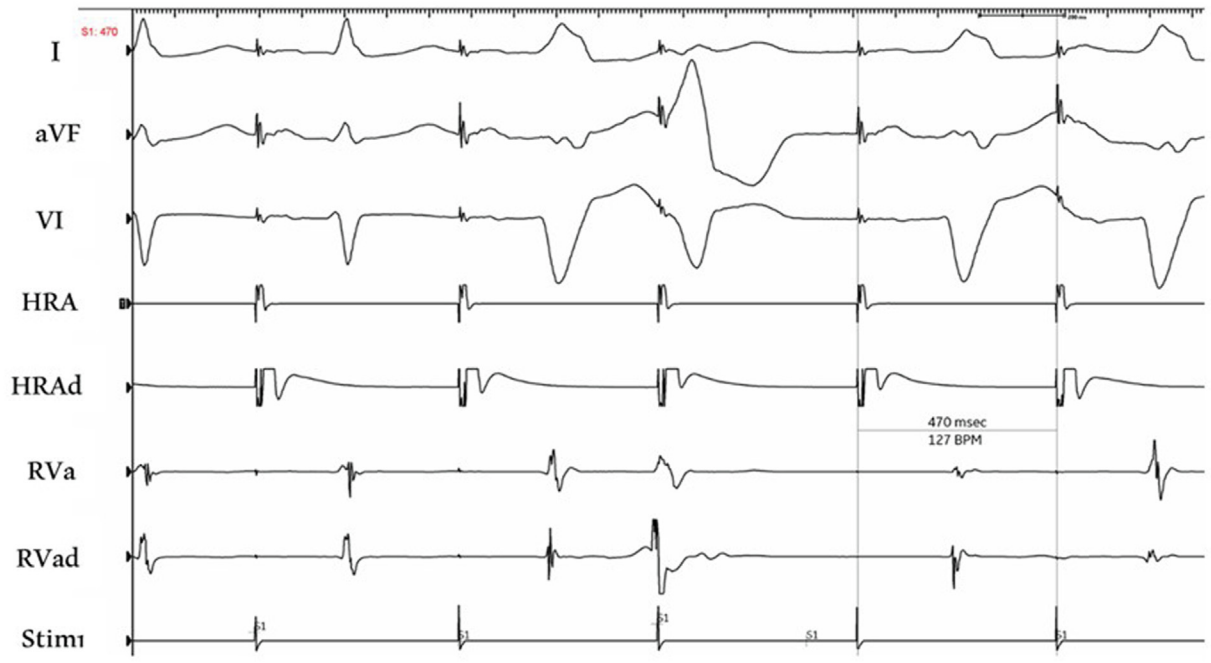

Figure 3 Intracardiac electrogram showing initiation of left bundle branch block (third QRS) at an atrial pacing cycle length of 470 ms while on isoproterenol. A premature ventricular contraction is also noted (fourth QRS).

inferior QRS axis (predominantly positive deflections in inferior leads), compared to normal and left axis expected with classic LBBB. This could imply that painful LBBB occurs with a distinguished ventricular excitation pattern. Other subtle indicators of painful LBBB include low precordial S/T ratio <1.8 (deepest S wave to largest T wave).[4] Another method to confirm diagnosis is to induce symptoms while monitoring for correlation with LBBB, which was done during the EPS in our patient. However, this process can be difficult, as it includes major adjustments to sedation to allow the patient to be awake and alert, yet still comfortable, during the procedure in order to have successful communication.

To date, the mainstay of treatment of painful LBBB consists of either sinus node suppression or pacing, both of which have their own limitations. The approach of sinus node suppression using pharmacological agents, including beta-blockers or ivabradine, focuses on attenuating heart rate response with activity, hence preventing aberrant conduction from occurring and subsequently preventing symptom onset. However, data suggest that this approach is not often successful, although this could be owing to publication bias. In our case, the patient was not able to tolerate high doses of beta-blockers and was not experiencing relief with lower doses. Additionally, this approach is suboptimal in patients like ours whose primary goal is to stay physically active, requiring the ability to mount adequate heart rate response to exertion. An alternate approach is using device-based therapies for pacing with different modalities such as BiV pacing and His pacing, both of which would improve ventricular synchrony and lead to a narrow QRS complex.[5,6] Most recently, RV pacing was also found to be therapeutic in patients described by Shvilkin and colleagues[4] and Sroubek and colleagues.[7] The success of RV pacing in treating painful LBBB is truly perplexing, as it in itself leads to a wide QRS complex with a left bundle morphology. This may suggest that the pathophysiology of painful LBBB is more so owing to increased cardiac sensitivity as opposed to ventricular dyssynchrony. Unfortunately, the attempt to BiV pace our patient was unsuccessful at providing symptomatic relief, exhausting the second main modality of treatment of painful LBBB.

Newer treatment modalities include left bundle branch area pacing, with capture of the left bundle via transventricular septal approach.[8] This method of pacing provides a more physiologic pattern of conduction with higher level of synchrony than His pacing. However, this would have been an additional invasive procedure for the patient, which the patient was keen on limiting.

During his second EPS, an attempt was made to force conduction down the left bundle branch by transiently blocking the right bundle branch while atrial pacing. Although that led to resolution of the LBBB and provided symptomatic relief, it also led to 2:1 conduction at rates greater than 117 bpm without evidence of Wenckebach. Intracardiac electrograms suggested the level of block to be above or at the His bundle (either AV nodal or infranodal), more evident in fibers destined for the left bundle. Therefore, isoproterenol was administered in the electrophysiology lab to improve conduction in both the AV nodal and infranodal systems. Isoproterenol is both a beta-1 and beta-2 adrenergic receptor agonist, which has historically been used for treatment of symptomatic bradycardia and various degrees of heart block not requiring permanent pacing. By stimulating beta-1 receptors, an increase in intracellular calcium occurs in cardiac pacemaker cells, leading to an increase in the slope of phase 4

of the action potential, thus allowing cells to reach threshold earlier and increasing heart rate. In addition to shortening action potential duration, B1 adrenergic stimulation increases the maximum diastolic potential of Purkinje fibers, increasing availability of sodium channels for initiation of an action potential.[9,10] This mechanism may lead to an increase in the left bundle block cycle length. Hence, isoproterenol use results in both positive chronotropy (increase in heart rate) and positive dromotropy (increase in conduction velocity). Administration of isoproterenol in our patient resulted in improved chronotropy and dromotropy, allowing for atrial pacing up to 127 bpm without evidence of LBBB and without reproduced chest pain.

Theophylline, a methylxanthine with adenosine receptor antagonistic action directly antagonizing A1A receptors in both the sinoatrial node and AV node, has a similar chronotropic and dromotropic effect to isoproterenol and is available in both intravenous and oral forms.[11] Although literature is sparse, theophylline has reportedly been suggested for treatment of symptomatic bradycardia in the elderly who declined or could not tolerate pacemaker implantation, bradycardia owing to spinal cord injuries, and, most recently, COVID-19-induced bradycardia.[12] No clear guidelines are available regarding the dosing of theophylline for such an indication; however, current literature suggests that a dose between 200 mg and 700 mg daily is sufficient. In a prospective study including 17 patients with symptomatic bradycardia and sick sinus syndrome, the total daily dose of theophylline administered was 700 mg/day with improvement in resting heart rate from 46 $\pm$ 7 bpm to 62 $\pm$ 18 bpm in 5 days; however, these patients were noted to have increased number of premature supraventricular and ventricular beats that did not achieve statistical significance.[13] In another prospective study, 11 patients with similar indication were treated with lower total doses of 200–400 mg/day with improvement in resting heart rate from 55 $\pm$ 11 bpm to 62 $\pm$ 9 bpm in 24 hours.[14] In the 2018 American College of Cardiology / American Heart Association / Heart Rhythm Society guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay, it is a class IIa recommendation to use theophylline to increase heart rate in post–heart transplant patients.[15] The initial recommended dose is 300 mg intravenously followed by 5–10 mg/kg/day titrated to effect, with the typical dose being 450 $\pm$ 100 mg/day and a therapeutic serum concentration 10–20 mcg/mL; however, no exact recommendation regarding titration method was made. Before initiation of theophylline, detailed review of the patient's medical regimen should be completed owing to high rates of interaction with commonly used medications. Antibiotics such as ciprofloxacin and erythromycin, some class Ib and Ic antiarrhythmics including mexiletine and propafenone, and some calcium channel blockers such as verapamil cause increase in serum concentration of theophylline by decreasing overall clearance; while others, including antiepileptic drugs such as carbamazepine, phenytoin, and phenobarbital, increase theophylline clearance, thus decreasing serum concentration by up to 40%. Common side effects include gastrointestinal symptoms of nausea, vomiting, and diarrhea, as well as headaches, restlessness, and insomnia, while more serious side effects, which are less commonly encountered, include hypotension and arrhythmias, given potential proarrhythmic effect.

Therefore, a review of our patient's medical regimen was completed and a total of 200 mg/day of theophylline was administered in divided doses (100 mg orally, twice daily), with great response. There was no requirement for additional titration and no observed side effects during follow-up. According to our knowledge, this is the first case in literature to report successful management of painful LBBB with theophylline.

Conclusion

The mainstay of treatment of painful LBBB over the years has been permanent pacing, while medical therapy for sinus node suppression was associated with lower success rates. We report the first case of successful treatment of painful LBBB with oral theophylline.

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