Cyclical sinus bradycardia and atrioventricular block induced by ticagrelor

Victor Waldmann, MD, MPH, Mikael Laredo, MD, Anil Nigam, MD, MSc, Paul Khairy, MD, PhD

From the Department of Cardiology, Montreal Heart Institute, Université de Montréal, Montreal, Canada.

Introduction

Ticagrelor, a direct-acting and reversible $P2Y_{12}$-adenosine diphosphate receptor antagonist, is recommended as a first-line antithrombotic agent in patients with acute coronary syndromes.[1] The superiority of ticagrelor over other $P2Y_{12}$ antagonists is thought to be mediated in part by pleiotropic properties associated with an increased concentration of adenosine, including cardioprotection, anticoagulant effects, and anti-inflammatory properties.[2] However, these pleiotropic properties can also be responsible for major adverse effects, including electrophysiological consequences. Herein, we describe the case of a patient with severe cyclical sinus bradycardia and atrioventricular (AV) block related to ticagrelor.

Case report

A 75-year-old woman presented with an acute coronary syndrome. She had known coronary artery disease with balloon angioplasty and stenting of the left anterior descending and circumflex arteries 7 years prior. Her past medical history was remarkable for hypertension, dyslipidemia, diabetes mellitus, and obesity. Her electrocardiogram during chest pain showed diffuse ST-segment depression. After she received a loading dose of 180 mg of ticagrelor along with 325 mg of aspirin, urgent coronary angiography revealed multivessel disease with chronic total occlusion of the right coronary artery and severe stenosis of the left main and circumflex arteries. Two new-generation drug-eluting stents were implanted, with excellent angiographic results. Her postprocedural left ventricle ejection fraction was 50%, with mild mitral regurgitation.

A few hours after the percutaneous coronary intervention, the patient developed Cheyne-Stokes respiration in the absence of overt heart failure, with marked sinus arrhythmia (Figure 1). Sinus tachycardia and severe sinus bradycardia < 30 beats/min were recorded during apneic and hyperpneic phases, respectively. As the pattern intensified, cyclical transient complete AV block occurred with up to 5-second pauses. Work-up including electrolytes, creatinine clearance, liver enzymes, and thyroid function was unrevealing.

Maintenance therapy with ticagrelor 90 mg orally twice daily was discontinued and clopidogrel introduced. Metoprolol was also suspended. A notable improvement was observed within 24 hours, with less pronounced sinus bradycardia and absence of AV block. The beta-blocker was reinstated and was well tolerated. The patient was discharged 2 days later following complete resolution of cyclical bradyarrhythmias. An electrophysiology study was not performed considering the presumed iatrogenic mechanism, prompt recovery, and normal electrocardiogram. At 1-month follow-up, the absence of a recurrent bradyarrhythmia was confirmed by 24-hour Holter monitoring.

Discussion

In the setting of an acute coronary syndrome, the differential diagnosis considered included ischemia of the conduction system and ischemia-provoked autonomic dysfunction. However, the time course, with onset of the bradyarrhythmia following ticagrelor loading and rapid recovery upon cessation of therapy, favored the diagnosis of an adverse pharmacologic effect. Bradycardia related to ticagrelor was first described in a phase IIb dose-ranging study, where a post hoc analysis of cardiac arrhythmias revealed an unexpected increased incidence of predominantly asymptomatic ventricular pauses.[3] These findings were corroborated by the prospective PLATO (Platelet Inhibition and Patient Outcomes) trial.[4] Among 2908 patients with 7-day electrocardiographic monitoring at the time of randomization and again at 1 month, ventricular pauses ≥ 3 seconds occurred more frequently in patients receiving ticagrelor compared to clopidogrel during the first week (5.8% vs 3.6%, relative risk 1.61, $P = .006$). Most pauses were asymptomatic, of sinoatrial origin, and nocturnal. However, no significant difference was observed in recorded bradyarrhythmias at 1 month and there were no apparent clinical bradycardic events during follow-up.[4]

KEYWORDS Adenosine; AV block; Coronary artery disease; Sinus node dysfunction; Ticagrelor
(Heart Rhythm Case Reports 2018;4:527–529)

Dr Khairy is supported by a research chair in electrophysiology and congenital heart disease. **Address reprint requests and correspondence:** Dr Paul Khairy, Montreal Heart Institute, 5000 Belanger St E, Montreal, QC, Canada, H1T 1C8. E-mail address: paul.khairy@umontreal.ca.

https://doi.org/10.1016/j.hrcr.2018.07.017

KEY TEACHING POINTS

- The antithrombotic agent ticagrelor is a $P2Y_{12}$-adenosine diphosphate receptor antagonist. It inhibits adenosine uptake by erythrocytes, thereby resulting in increased adenosine tissue concentrations.
- Sinus bradycardia and atrioventricular (AV) block are electrophysiological side effects that are reversible upon cessation of ticagrelor.
- Ticagrelor can also induce central sleep apnea with Cheyne-Stokes respiration, which may contribute to a cyclical pattern of sinus node dysfunction and AV block.

The effect of ticagrelor on sinoatrial and AV nodes is believed to be mediated by an increased tissue concentration of adenosine. Animal experiments and in vitro models demonstrated that ticagrelor interferes with adenosine metabolism, resulting in increased adenosine concentrations via inhibition of adenosine uptake by erythrocytes.[5] This is most likely due to inhibition of sodium-independent equilibrative nucleoside transporters.[5] Consistently, in the clinical realm, ticagrelor has been associated with increased coronary blood flow velocity in patients with acute coronary syndromes, providing a plausible mechanistic explanation for its off-target cardioprotective effects.[6,7] The adenosine-related hypothesis can also explain the predominance of ticagrelor-associated nocturnal pauses due to an increased local adenosine concentration that enhances vagal-mediated nocturnal bradycardia.

Few reports of clinically significant ticagrelor-related bradycardia requiring drug discontinuation have been published.[8] To the best of our knowledge, we report the first case of severe sinus respiratory arrhythmia combined with AV block after ticagrelor loading. Cheyne-Stokes respiration frequently occurs in patients with congestive heart failure[9] and has been associated with exaggerated respiratory heart rate variations.[10] While our patient had no evidence of heart failure, emerging reports suggest that ticagrelor may itself induce central sleep apnea and Cheyne-Stokes respiration.[11] The pathophysiological explanation remains unclear. Proposed mechanisms include antagonism of microglial $P2Y_{12}$ receptors and effects on pulmonary C fibers, either as a result of increased adenosine tissue levels or because of putative $P2Y_{12}$ receptors on pulmonary C fibers.[11]

Conclusion

This report demonstrates that, although rare, ticagrelor can induce significant bradyarrhythmias. Electrophysiologists should, therefore, be aware of this reversible cause of sinus node dysfunction and AV block in order to manage patients appropriately and avoid unnecessary pacemakers. As this case illustrates, it is possible that the combination of ticagrelor-induced Cheyne-Stokes respiration and bradyarrhythmias can provoke a more severe phenotype consisting of cyclical severe sinus bradycardia with concomitant AV block.

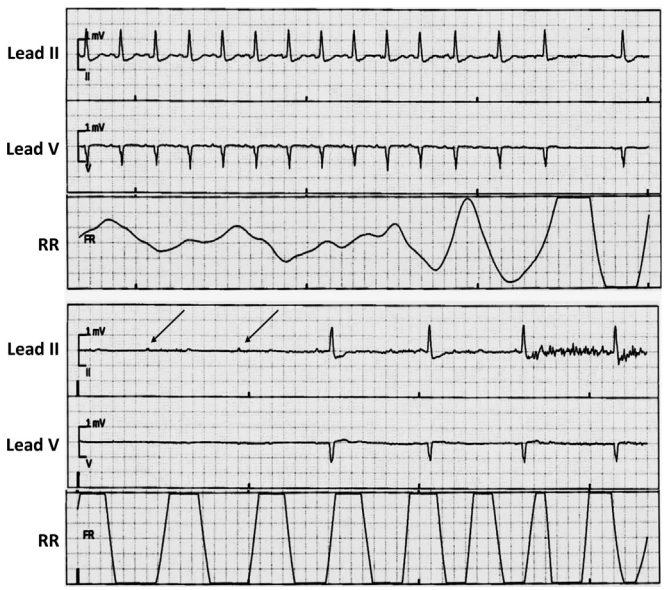

Figure 1 Cheyne-Stokes respiration with cyclical sinus bradycardia and atrioventricular (AV) block. Shown are electrocardiographic tracings from telemetry leads II and V along with the corresponding respiratory rate (RR). In the upper panel, sinus tachycardia is seen as the respiratory rate slows toward apnea. As respiration resumes and progresses toward hyperpnea, AV block follows in the lower panel, with nonconducted P waves indicated by the *arrows*.

References

1. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–1057.
2. Kubisa MJ, Jezewski MP, Gasecka A, Siller-Matula JM, Postula M. Ticagrelor - toward more efficient platelet inhibition and beyond. Ther Clin Risk Manag 2018; 14:129–140.
3. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007;50:1844–1851.
4. Scirica BM, Cannon CP, Emanuelsson H, et al. The incidence of bradyarrhythmias and clinical bradyarrhythmic events in patients with acute coronary syndromes treated with ticagrelor or clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial: results of the continuous electrocardiographic assessment substudy. J Am Coll Cardiol 2011;57:1908–1916.
5. van Giezen JJ, Sidaway J, Glaves P, Kirk I, Bjorkman JA. Ticagrelor inhibits adenosine uptake in vitro and enhances adenosine-mediated hyperemia responses in a canine model. J Cardiovasc Pharmacol Ther 2012;17:164–172.
6. Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, van Giezen JJ, Jonasson J, Nylander S, Gan LM. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. J Am Coll Cardiol 2013; 61:723–727.
7. Bonello L, Laine M, Kipson N, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. J Am Coll Cardiol 2014; 63:872–877.
8. De Maria E, Borghi A, Modonesi L, Cappelli S. Ticagrelor therapy and atrioventricular block: Do we need to worry? World J Clin Cases 2017;5:178–182.
9. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, Roselle GA. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998; 97:2154–2159.
10. Leung RS, Floras JS, Bradley TD. Respiratory modulation of the autonomic nervous system during Cheyne-Stokes respiration. Can J Physiol Pharmacol 2006; 84:61–66.
11. Revol B, Jullian-Desayes I, Tamisier R, Puel V, Mallaret M, Joyeux-Faure M, Pepin JL. Ticagrelor and central sleep apnea. J Am Coll Cardiol 2018; 71:2378–2379.