Sinoatrial Arrest Caused by Ticagrelor after Angioplasty in a 62-Year-Old Woman with Acute Coronary Syndrome

The platelet aggregation inhibitor ticagrelor, a P2Y12 receptor antagonist, is widely used after angioplasty in patients with acute coronary syndrome. Clinical trial data have shown that it is well tolerated by most patients. We present the case of a 62-year-old woman whose ticagrelor-related asymptomatic and persistent sinus pauses after angioplasty resolved when ticagrelor was replaced with prasugrel.

Sinatrial arrest, or sinus pause, is defined as the transient absence of sinus P waves that may last for 2 seconds or longer. It can occur in the normal heart, especially during sleep, in well-conditioned athletes who have increased vagal tone, and in some elderly patients. Some other causes of sinus pause can be associated with intrinsic cardiac disorders such as sick sinus syndrome or inferior myocardial infarction, metabolic and environmental causes (for example, hypothermia or electrolyte abnormalities), medications such as β-blockers, and infection (for example, myocarditis).

After a patient undergoes primary angioplasty with stent implantation for myocardial infarction, a loading dose of P2Y12 receptor inhibitor such as clopidogrel, ticagrelor, or prasugrel should be administered as early as possible and continued in a maintenance dose for one year in the absence of bleeding. Pharmacologic options for these patients may vary depending on patient history (factors such as obesity, diabetes mellitus, and atrial fibrillation), and drug interactions may interfere with the metabolism of antiplatelet medication. Ticagrelor is a reversible P2Y12 receptor antagonist that does not require metabolic conversion to the active drug. Although one year of dual antiplatelet therapy (DAPT) is recommended after stent implantation, no strong evidence supports a preferred antiplatelet medication; the decision is often made according to the clinician’s personal preference. Ticagrelor has greater biologic efficacy than clopidogrel and is potentially clinically superior in the treatment of patients who have acute coronary syndrome (ACS). However, there are few studies of the rare side effects of ticagrelor. To our knowledge, our report is the first of a patient with ACS who had ticagrelor-induced asymptomatic sinus pauses after angioplasty that resolved when ticagrelor was replaced with prasugrel.

Case Report

In July 2017, a 62-year-old woman with a medical history of hypertension, osteoarthritis, and ongoing tobacco use was transferred to our hospital with severe chest pain. She had taken omeprazole and muscle relaxants without symptomatic improvement. In the emergency department, her initial electrocardiogram (ECG) and cardiac troponin I test results showed nothing unusual; however, a second troponin test revealed a level of 0.5 ng/mL. The pain persisted despite high doses of nitroglycerin and morphine, and the patient was transferred to our cardiology unit for higher-level care. The next morning, the patient’s severe substernal pressure-like discomfort continued. She had mild dyspnea and was slightly diaphoretic. Her troponin level had risen above 9 ng/mL, and an ECG showed only slight lateral ST-segment changes (Fig. 1). A transthoracic echocardiogram showed a normal left ventricular ejection fraction.

Because of the patient’s ongoing chest pain and non-ST-elevation myocardial infarction, she underwent urgent cardiac catheterization. Left-sided heart catheteriza-
tion revealed a normal-sized left ventricle with severe hypokinesis of the mid-to-apical anterior, apical, and inferoapical walls. Severe culprit stenosis was found in the proximal and mid segments of the left anterior descending coronary artery (LAD), with no stenosis in the distal left circumflex or right coronary artery. We deployed 2 overlapping drug-eluting stents in the LAD with good angiographic results. After angioplasty, the patient was started on DAPT (aspirin and ticagrelor) and continued to take lisinopril, atorvastatin, and metoprolol tartrate.

On postoperative day (POD) 2, the telemetry report showed multiple episodes of sinus pauses (Fig. 2), although the patient was asymptomatic. Her \( \beta \)-blocker was discontinued. On POD 3, substantial pauses persisted. We extensively reviewed the patient’s laboratory findings (Table I) and medications (Table II) but found no obvious cause of her bradycardia. On POD 4, the telemetry report again showed multiple episodes of sinus pauses. Evaluation of ECGs after sinus pauses on PODs 2, 3, and 4 showed sinus rhythm and no other changes when compared with the ECG at admission. During the sinus pauses, the patient was completely asymptomatic, and no hypo- or hypertension recordings were observed. Because of ticagrelor’s rare side effect of heart block (0.7% of cases), prasugrel was substituted. On POD 5, we observed a few episodes of sinus bradyca-

### Table I. The Patient’s Blood Biochemistry Values

| Variable                                      | Value (reference range) |
|-----------------------------------------------|-------------------------|
| **Hematology**                                |                         |
| White blood cell count (×10^9/L)              | 8.3 (4.5–11)            |
| Neutrophils (%)                               | 57.6 (50–75)            |
| Absolute neutrophils (cells/mm³)              | 4.8 (1.5–8)             |
| Lymphocytes (%)                               | 28.8 (17–42)            |
| Monocytes (%)                                 | 9.6 (4–11)              |
| Eosinophils (%)                               | 3.2 (0.4–6)             |
| Basophils (%)                                 | 0.8 (0–2)               |
| Red blood cell count (×10^12/L)               | 4.4 (3.8–5.2)           |
| Hemoglobin (g/dL)                             | 13.4 (12–15)            |
| Hematocrit (%)                                | 40.4 (38–49)            |
| MC volume (fL)                                | 91.8 (80–100)           |
| MC hemoglobin (pg/cell)                       | 30.5 (26.5–34)          |
| MC hemoglobin concentration (g/dL)            | 33.3 (32–36)            |
| Red blood cell distribution width (%)         | 13.5 (<17)              |
| Platelet count (×10^9/L)                      | 182 (150–450)           |
| Mean platelet volume (fL)                     | 10.2 (6.6–10.2)         |
| **Chemistry**                                 |                         |
| Sodium (mEq/L)                                | 139 (136–145)           |
| Potassium (mEq/L)                             | 4.2 (3.5–5.1)           |
| Chloride (mEq/L)                              | 109 (98–107)            |
| Carbon dioxide (mEq/L)                        | 21 (21–32)              |
| Anion gap (mEq/L)                             | 13.2 (3–15)             |
| Blood urea nitrogen (mg/dL)                   | 18 (7–18)               |
| Creatinine (mg/dL)                            | 0.64 (0.6–1.3)          |
| Glucose (mg/dL)                               | 182 (74–106)            |
| Calcium (mg/dL)                               | 8 (8.5–10.1)            |

MC = mean corpuscular

### Table II. Patient’s Medications

| Medication   | Dosage  | Initiation |
|--------------|---------|------------|
| Lisinopril   | 40 mg/d | 4 yr prior |
| Atorvastatin | 40 mg/d | 4 yr prior |
| Aspirin      | 81 mg/d | 10 yr prior|
| Metoprolol   | 12.5 mg, 2x/d | 3 yr prior |
| Ticagrelor   | 90 mg, 2x/d | After angioplasty |
dia, but telemetry monitoring showed no pauses. On PODs 6 and 7, no further bradycardia or pauses were noted. Metoprolol was restarted on POD 7 at a dose similar to that administered before sinus pauses were detected, and the telemetry report showed that the patient was doing well, without sinus pauses or bradycardia. On POD 10, the patient was discharged from the hospital with instructions to take aspirin, prasugrel, metoprolol, and other at-home medications. As of May 2019, no further sinus pauses were observed.

Discussion

Adenosine diphosphate (ADP) binds to purinergic receptors (P2Y1 and P2Y12) on platelets. The binding of either of these receptors to an antagonist results in blockade of ADP function, which leads to inhibited platelet aggregation. Ticagrelor is a P2Y12 receptor antagonist that reduces platelet aggregation and aids in preventing additional adverse cardiac events after ACS. According to the Platelet Inhibition and Patient Outcomes (PLATO) trial results, ticagrelor may cause bradycardia without clinical impact. The mechanism of ticagrelor-induced bradycardia is not well established, but it has been speculated that bradycardia could be triggered by an increase in the plasma concentration of adenosine, given that adenosine is released by endothelial cells and myocytes during hypoxia, oxidative stress, or ischemia. In ACS patients, ticagrelor was shown to increase adenosine plasma concentration more than did clopidogrel, although no differences were observed between ticagrelor and clopidogrel in terms of bradycardia episodes or related clinical results, including syncope or pacemaker insertion. In comparison with clopidogrel, ticagrelor provides faster and more efficacious P2Y12 inhibition without increasing bleeding, and it has significantly reduced cardiovascular mortality rates.

Our patient presented acutely with chest pain that was treated promptly with cardiac angioplasty, and her condition responded rapidly. Although the symptoms associated with myocardial ischemia resolved within days after treatment, sinus pause unexpectedly developed. The only obvious causes were her myocardial ischemia or the effect of a drug. The ischemia was unlikely as the cause: the right coronary artery was normal on angiography, the percutaneous coronary intervention after ACS was successful, and the clinical symptoms associated with the patient’s myocardial ischemia improved. On the other hand, the administered medications usually would not be associated with bradycardia, except for metoprolol. Metoprolol has a well-established role in bradycardia; however, our patient had been taking her current dose for several years without any pauses in her previous ECGs or telemetry reports. Because she was asymptomatic, we had time to identify other possible causes of her persistent sinus pauses without immediately placing a permanent pacemaker. Surprisingly, although metoprolol was discontinued, the patient’s sinus pauses persisted. Therefore, we focused on the possibility of a rare side effect of ticagrelor. As we hoped, our patient’s abnormal findings on telemetry resolved after she stopped taking ticagrelor. No recurrence was observed, indicating that ticagrelor had caused the abnormal sinus pauses.

This report reveals an unusual cause of sinus pauses, suggesting that awareness is needed when medications such as antiplatelet agents are administered after angioplasty, to avoid the unnecessary placement of a permanent pacemaker.

Acknowledgments

We thank Megan Marquez, MSc, and Hale Z. Toklu, PhD, for their assistance in proofreading the manuscript.

References

1. Hilgard J, Ezri MD, Denes P. Significance of ventricular pauses of three seconds or more detected on twenty-four hour Holter recordings. Am J Cardiol 1985;55(8):1005-8.
2. Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. Am J Cardiol 1977;39(3):390-5.
3. Spodick DH. Normal sinus heart rate: sinus tachycardia and sinus bradyarrhythmia redefined. Am Heart J 1992;124(4):1119-21.
4. Wung SF. Bradyarrhythmias: clinical presentation, diagnosis, and management. Crit Care Nurs Clin North Am 2016;28(3):297-308.
5. Semelka M, Gera J, Usman S. Sick sinus syndrome: a review. Am Fam Physician 2013;87(10):691-6.
6. Gussach E, Mont L. Diagnosis, pathophysiology, and management of exercise-induced arrhythmias. Nat Rev Cardiol 2017;14(2):88-101.
7. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published errata appear in Circulation 2014;130(25):e431-4]. Circulation 2014;130(25):e344-426.
8. Storey RF, Husted S, Harrington RA, Heptinstall SA, Wilcox RG, Peters G, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007;50(19):1852-6.
9. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Feld C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361(11):1045-57.
10. Turgeon RD, Fernandes KA, Juurlink D, Tu JV, Mamdani M. Ticagrelor and bradycardia: a nested case-control study. Pharmacoepidemiol Drug Saf 2015;24(12):1281-5.
11. Wijeyeratne YD, Heptinstall S, Antiplatelet therapy: ADP receptor antagonists. Br J Clin Pharmacol 2011;72(4):647-57.
12. Storey RF, Angiolillo DJ, Patil SB, Desai B, Ecob R, Husted S, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary
syndromes: the PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy. J Am Coll Cardiol 2010; 56(18):1456-62.

13. Scirica BM, Cannon CP, Emanuelsson H, Michelson EL, Harrington RA, Husted S, 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(19):1908-16.

14. Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromonot J, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. J Am Coll Cardiol 2014;63(9):872-7.