Case Reports

Sinoatrial Arrest Caused by Ticagrelor after Angioplasty

in a 62-Year-Old Woman with Acute Coronary Syndrome

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The platelet aggregation inhibitor ticagrelor, a $P2Y_{12}$ 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. ***(Tex Heart Inst J 2019;46(3):203-6)***

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Sinoatrial 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.[1,2] 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).[3-6]

After a patient undergoes primary angioplasty with stent implantation for myocardial infarction, a loading dose of $P2Y_{12}$ 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.[7] 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 $P2Y_{12}$ receptor antagonist that does not require metabolic conversion to the active drug.[8] 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).[9] However, there are few studies of the rare side effects of ticagrelor.[10] 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 β-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.[9] On POD 5, we observed a few episodes of sinus bradycar-

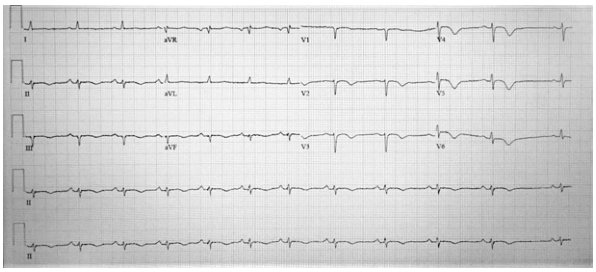

Fig. 1 *Electrocardiogram shows sinus rhythm with slight lateral ST-segment changes.*

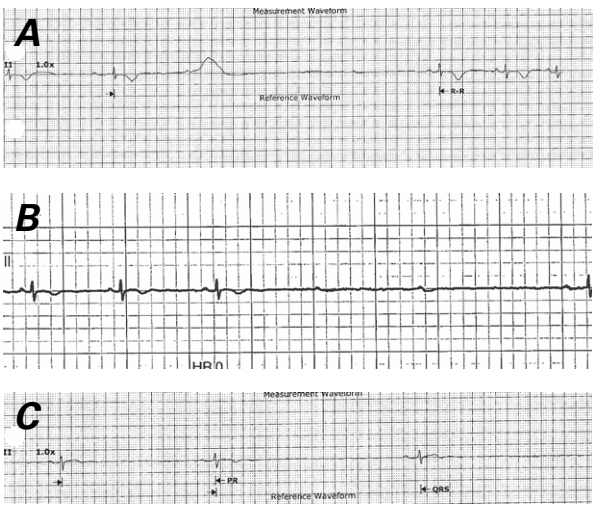

Fig. 2 *Telemetric tracings after coronary angioplasty show sinus pauses of **A**) 5.96 s (postoperative day 2), **B**) 5.72 s (day 3), and **C**) 3.57 s (day 4).*

TABLE I. The Patient's Blood Biochemistry Values

Variable	Value (reference range)
Hematology	
White blood cell count ($\times 10^9$/L)	8.3 (4.5–11)
Neutrophils (%)	57.6 (50–75)
Absolute neutrophils (cells/mm^3)	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 ($\times 10^{12}$/L)	4.4 (3.8–5.2)
Hemoglobin (g/dL)	13.4 (12–15)
Hematocrit (%)	40.4 (35–49)
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 ($\times 10^9$/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 ($P2Y_1$ and $P2Y_{12}$) on platelets. The binding of either of these receptors to an antagonist results in blockade of ADP function, which leads to inhibited platelet aggregation.[11] Ticagrelor is a $P2Y_{12}$ 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,[12,13] 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,[14] although no differences were observed between ticagrelor and clopidogrel in terms of bradycardia episodes or related clinical results, including syncope or pacemaker insertion.[9] In comparison with clopidogrel, ticagrelor provides faster and more efficacious $P2Y_{12}$ inhibition without increasing bleeding, and it has significantly reduced cardiovascular mortality rates.[12,14]

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.

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