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Ticagrelor Induced Cheyne-Stokes Respiration and Asystolic Ventricular Standstill: A Case Report

Ticagrelor is a potent, direct-acting, and reversible P2Y12-adenosine diphosphate receptor blocker. It has a rapid onset of action and an intense and consistent platelet reactivity inhibition that has been demonstrated to be superior to clopidogrel in decreasing major adverse events in acute coronary syndrome (ACS). Although ticagrelor is well tolerated in ACS patients, it has side effects, such as dyspnea and bradyarrhythmia, as reported in the Platelet Inhibition and Patient Outcomes (PLATO) study. Furthermore, it was reported that ticagrelor's bradyarrhythmic potential was transient and not clinically significant beyond the acute initiation phase. Nor was there a difference in rates of syncope or need for pacemaker insertion during 30 days of follow-up. Here we report a case of ticagrelor associated with Cheyne-Stokes respiration and asystolic ventricular standstill in a patient with ACS who required resuscitation and insertion of a temporary pacemaker.

Keywords Ticagrelor; bradyarrhythmia; Cheyne-Stokes respiration

For citations Bektas Murat, Selda Murat, Eylem Kivanc. Ticagrelor Induced Cheyne-Stokes Respiration and Asystolic Ventricular Standstill: A Case Report. Kardiologiia. 2024;64(2):80–84. [Russian: Бектас Мурат, Сельда Мурат, Эйлем Кыванч. Индуцированное тикагрелором дыхание Чейна–Стокса и асистолическая остановка желудочков: клинический случай. Кардиология. 2024;64(2):80–84].

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Introduction

Dual antiplatelet therapy with combination of aspirin and a P2Y12 platelet receptor inhibitor is a cornerstone of treatment in acute coronary syndrome (ACS) [1]. Ticagrelor is a potent, direct-acting, and reversible P2Y12-adenosine diphosphate receptor blocker. It has a rapid onset of action, and an intense and consistent inhibition of platelet reactivity that has been demonstrated to be superior to clopidogrel in decreasing major adverse events in ACS patients [2]. Although ticagrelor is well tolerated by ACS patients, it has been shown to have some side effects, such as dyspnea, gastrointestinal discomfort, and bradyarrhythmia, which were reported in the Platelet Inhibition and Patient Outcomes (PLATO) study. Although, it was reported that ticagrelor's bradyarrhythmic potential was transient and not clinically significant beyond the acute, initiation phase with no difference in rates of syncope or need for pacemaker insertion at 30 days follow-up [2, 3], but some case reports described severe ventricular arrests caused by ticagrelor that required temporary pacemakers [4].

Here we report a case of ticagrelor associated with Cheyne-Stokes respiration (CSR) and asystolic ventricular standstill in a patient with ACS who required resuscitation and insertion of temporary pacemaker.

Case presentation

A 67 yr old male with no history of coronary artery disease presented with a 3-hr history of typical angina pectoris. His only cardiac risk factor was smoking. No other significant medical background was revealed. The cardiovascular examination was normal. The electrocardiogram (ECG) on admission showed sinus rhythm, normal axis, and narrow QRS (96 ms); there was ST depression in V1–V6 leads (Figure 1). In the blood panels, high-sensitive cardiac troponin T was 530 ng/l (normal range is 0–34.2 ng/l) and CK-MB was 34 mg/ml (normal range is 0–5.2 mg/ml). Other blood panels, including renal and liver function, were normal. Echocardiography showed hypokinesia in the mid-inferior and mid-posterior left ventricular wall. Left ventricular injection fraction was 55% with mild mitral regurgitation. Due to the presence of typical angina, ischemic ST changes and echocardiographic evidence of ischemia and according to the ESC guidelines, the patient was diagnosed as having posterior myocardial infarction (MI) [1].

Femoral approach coronary angiography was performed. The patient had been given 300 mg of chewable aspirin in the emergency room, and 80 mg/kg unfractionated heparin was administered as an intravenous bolus before the procedure. The culprit vessels were shown to be the left circumflex artery and the right coronary artery, both with 100% stenosis in the mid-portion. These lesions were treated by deployment of a 2.25 × 25 mm drug eluting stent (Xience Pro, Abbott) in the left circumflex artery and a 2.75 × 33 mm drug eluting stent (Xience Pro, Abbott) in the right coronary artery (Figure 2). After this primary percutaneous coronary intervention, the patient was initially administered a loading dose of 180 mg ticagrelor, 40 mg atorvastatin 40 mg, and 2.5 mg ramipril.

Approximately 2 hr following the administration of ticagrelor, the patient suddenly complained of

ISSN 0022-9040. Кардиология. 2024;64(2). DOI: 10.18087/cardio.2024.2.n2123

severe dyspnea and anxiety. Clinical examination and respiratory monitoring by the intensive care unit (ICU) telemetry showed a crescendo-decrescendo respiratory pattern, particularly in the supine position, with hyperpnea and apnea along with oxygen desaturation that closely resembled CSR. During an episode of bradycardia (35–40 beats/min), presyncope was observed. These symptoms were followed by intensive sweating. The whole episode lasted about 1–2 min, and then it faded as quickly as it had begun. The patient was investigated for CSR etiology. There was no evidence of heart failure on physical examination, and echocardiography was repeated to evaluate for mechanical complications. Differential diagnosis excluded cardiac, pulmonary, and neurological etiology of dyspnea. Finally, it was suspected that these symptoms were the side effects of ticagrelor.

Slow intravenous infusion of theophylline (0,48 mg/ml at 40 ml/h), was started. By 2 hr after initiation of this infusion, the patient's dyspnea and bradycardia had ceased, and the patient felt better. Infusion of theophylline was continued for 5 hr and then stopped.

Figure 1. The patient's admission electrocardiogram

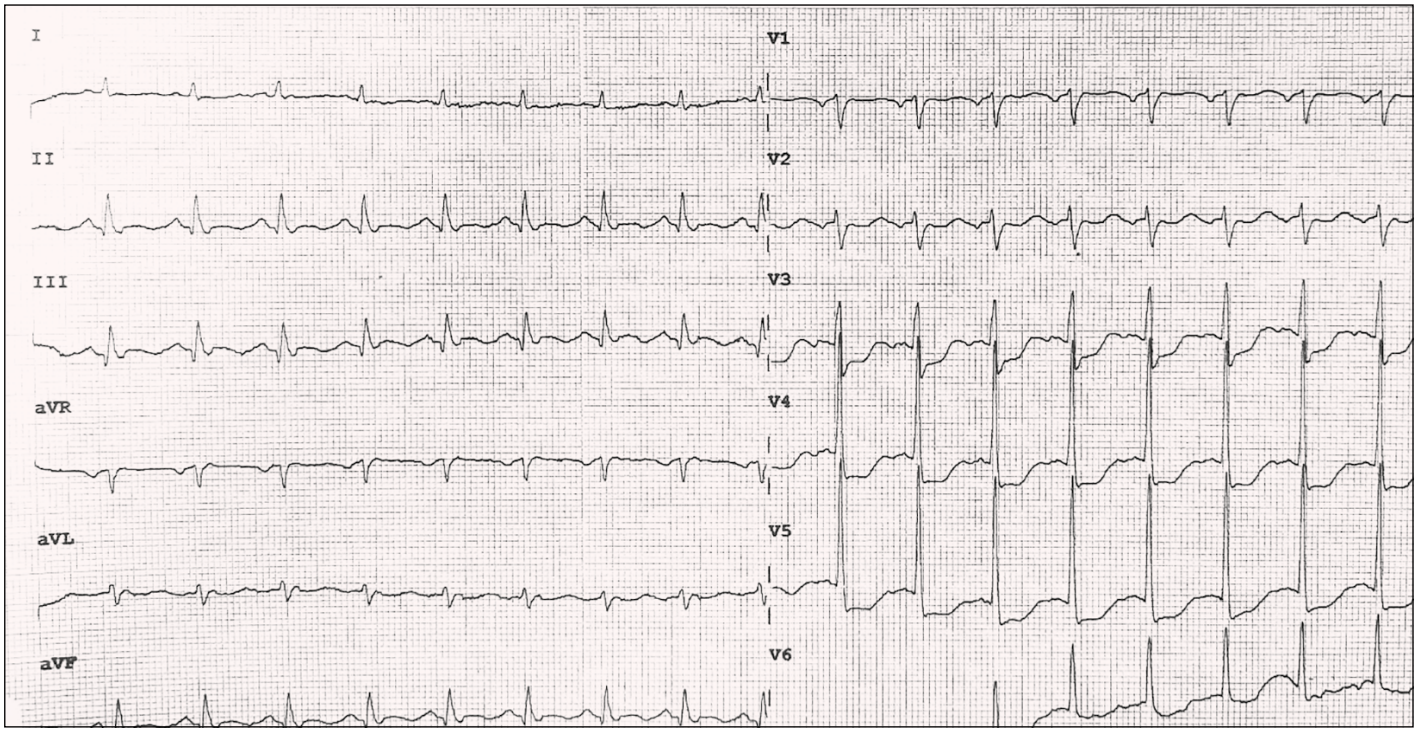


Figure 2. Pre- and post-stent angiograms of the left circumflex artery (panels a and b) and the right coronary artery (panels c and d)

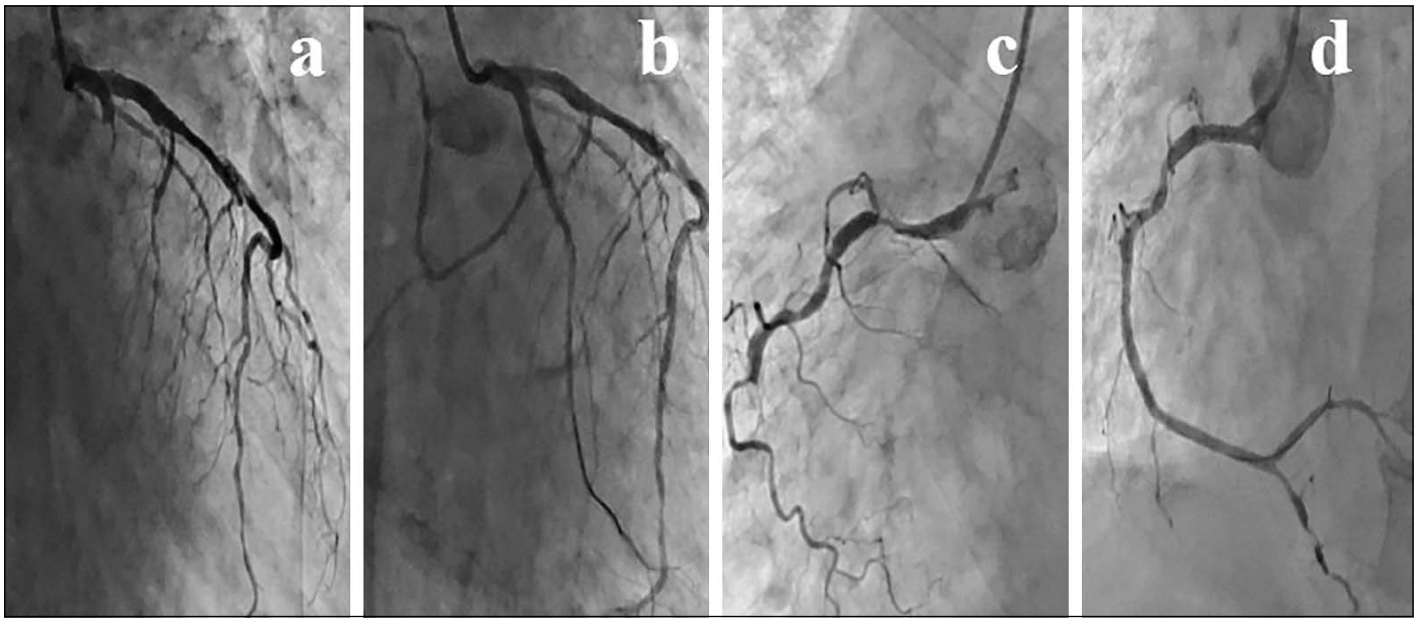


Figure 3. Telemetry strip showing the ventricular pauses examples which the longest pause duration is 15 seconds

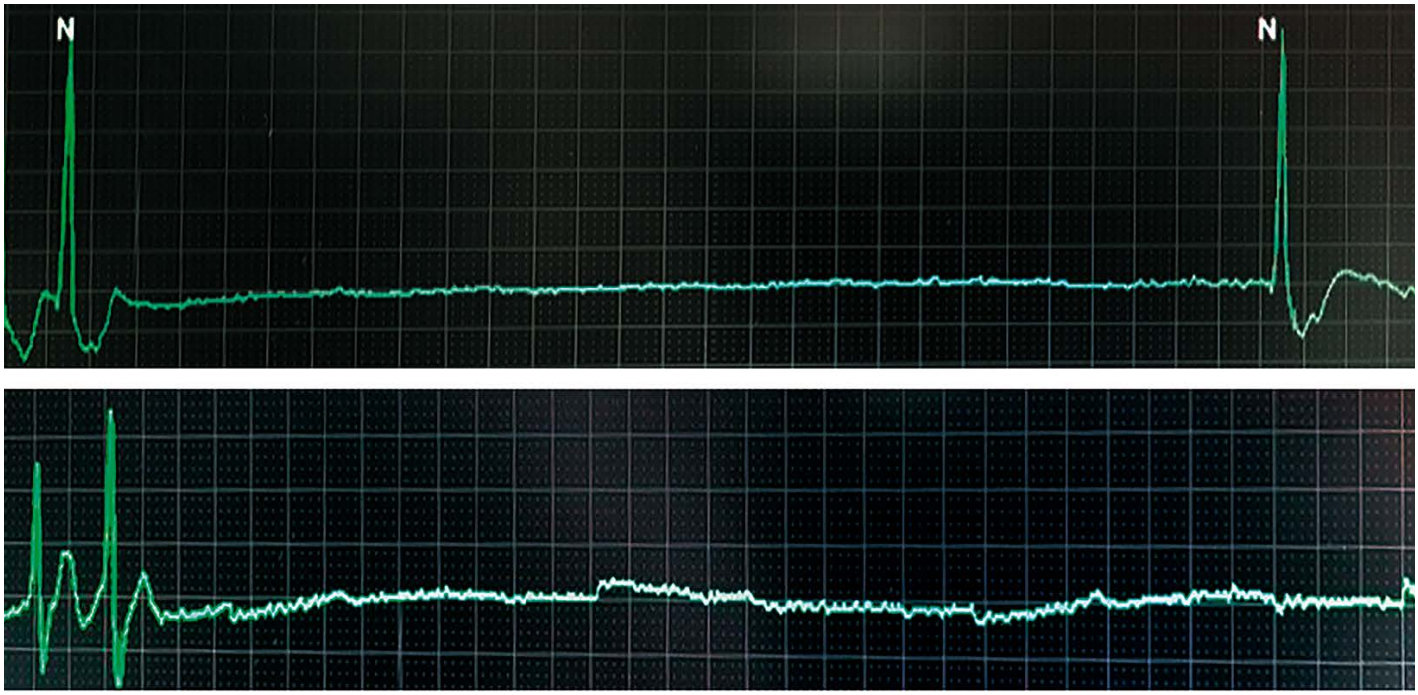
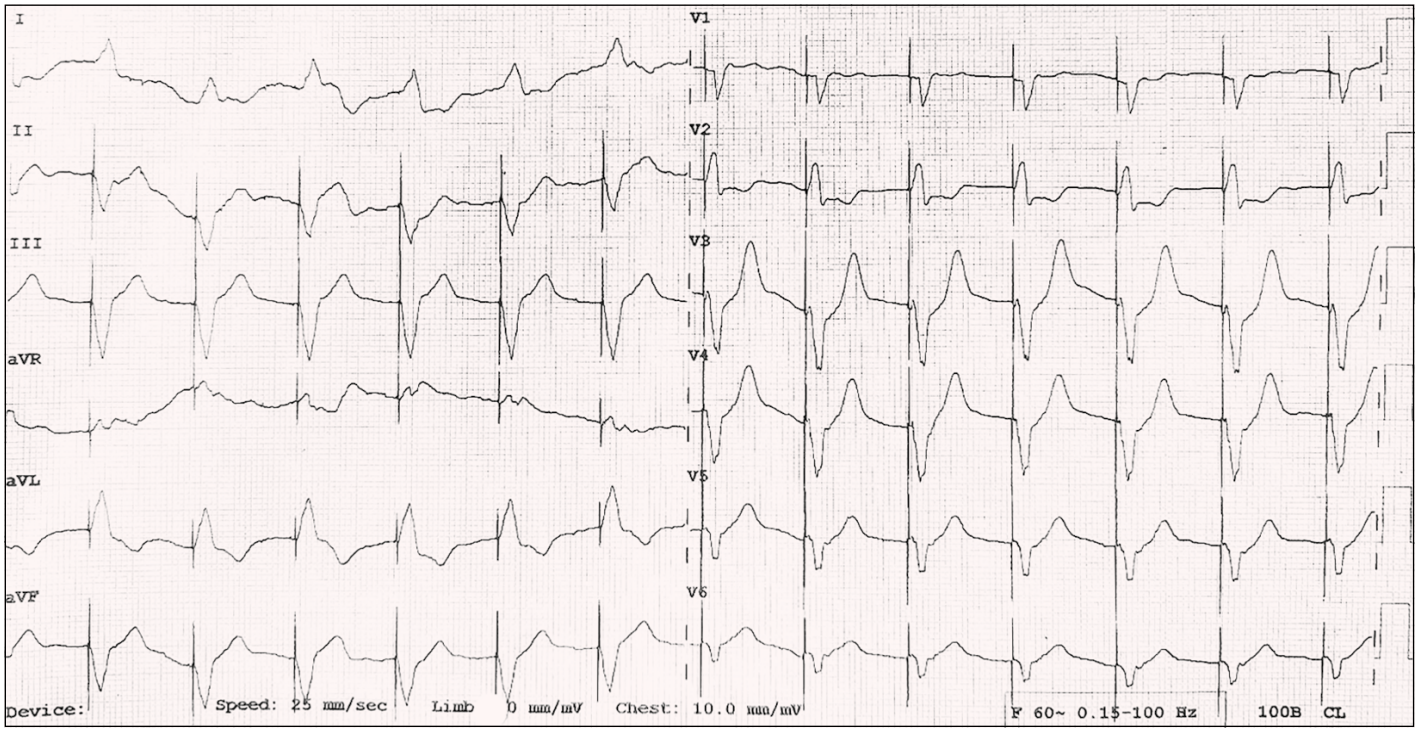


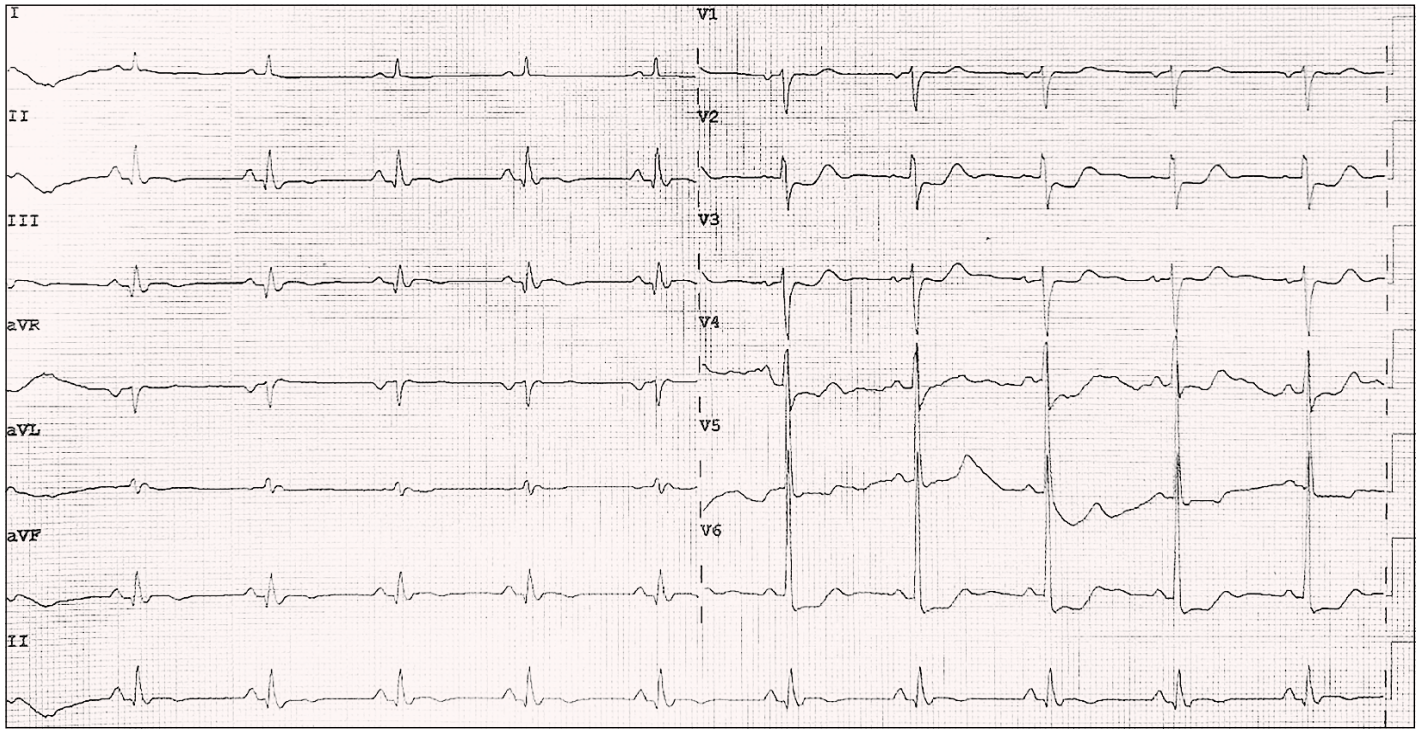
Figure 4. The patient's electrocardiogram after insertion of a temporary pacemaker



However, 8 hr later, the patient complained of severe weakness and dizziness. These symptoms quickly led to syncope with several ventricular pauses and the longest was 15 sec (Figure 3). Ventricular pauses continued intermittently with shorter periods. There were no responses to intravenous atropine and dobutamine infusions. Therefore, a temporary pacemaker was inserted and right ventricular pacing was initiated (Figure 4) with immediate hemodynamic and symptomatic improvement. Ticagrelor was switched to prasugrel, and patient was dependent on the temporary pacemaker for three days. On the 4th day, the patient's rhythm was normal (sinus rhythm with heart rate of 75 bpm), and on the 5th day, the temporary pacemaker was removed. On the 8th day, the patient was discharged in good clinical condition. The discharge ECG is shown in Figure 5. After 1 mo, the patient was seen in the outpatient clinic, and he was completely symptom free.

ISSN 0022-9040. Кардиология. 2024;64(2). DOI: 10.18087/cardio.2024.2.n2123

Figure 5. The patient's discharge electrocardiogram



Discussion

We present a case of CSR and severe, symptomatic, asystolic ventricular standstill in a patient loaded with ticagrelor post posterior MI. Ticagrelor is a potent oral anti-platelet agent that is recommended by the European Society of Cardiology Guidelines [1, 5]. Dyspnea and bradyarrhythmia are important, although rare, adverse side effects of ticagrelor. However, the mechanisms of ticagrelor-induced dyspnea and bradyarrhythmia are unknown.

Phase II and III studies have shown increased dyspnea, sinus arrest, high grade atrioventricular block, and ventricular escape rhythm with syncope in patients receiving large doses of ticagrelor [2]. In the PLATO study, it was reported that ticagrelor had a higher incidence of ventricular pauses ≥3 sec during the first week following the initiation of ticagrelor compared to those who received clopidogrel (5.8% vs. 3.6%; p = 0.01), but the 30-day incidence of ventricular pause was similar in these two groups (2.1% vs. 1.7%; p = 0.52) [3]. Sinus arrest and atrioventricular blocks due to ticagrelor were reported to be asymptomatic in the PLATO study and in its subgroup analyses [6], but some case reports described severe ventricular arrests caused by ticagrelor that required temporary pacemakers [4], as in our case. Although there are important differences between the case reported by Rosset S et al. and our case in terms of diagnosis and etiology. Our patient was elderly and diagnosed with acute coronary syndrome, while Rosset Set et al.'s patient was a case who was given ticagrelorol due to suspected unstable angina, both cases experinced the similar symptoms.

Although the mechanism of dyspnea is still unclear, two main mechanisms have been demonstrated, first connected with increased extracellular level of adenosine, second concerning P2Y12 receptors. According to the adenosine-hypothesis, the purine nucleoside stimulates vagal C fibres on bronchial wall through A1R and A2AR receptors and finally causes the sensation of dyspnoea. As adenosine induces bronchial smooth muscle cells contraction and increases the release of broncho-constrictive mediators from other cells expressing ARs, it is also possible, that ticagrelor – related dyspnoea may be the result of severe bronchospasm. Therefore, another hypothesis regarding dyspnea in ticagrelor treatment is possible appeared. This hypothesis does not rely on the action of adenosine on vagal C fibers but focuses on P2Y12 receptors. P2Y12 receptors are found not only on platelets but also on endothelial cells, smooth muscle cells, neuronal cells and microglia in the central nervous system [7]. One of the common causes of CSR is congestive heart failure, which has been associated with exaggerated respiratory associated alterations in heart rate. However, in this case, the patient had no evidence of heart failure or lung disease. In some previous case reports, it was reported that ticagrelor may induce central sleep apnea and CSR. Similarly, Conte et al. noted in a case report that CSR developed shortly after loading ticagrelor and that symptoms resolved after aminophylline infusion [8]. There have been also case reports showing that CSR developed long after ticagrelor treatment [9].

Several factors suggest that the Cheyne-Stokes respiration and asystolic ventricular standstill observed in the present

case were due to ticagrelor. The patient did not have any baseline ECG conduction abnormalities or personal/family history of syncope. There was no concurrent use of medications with negative dromotropic or chronotropic potential. The bradycardic symptom onset was 8 hr after oral ticagrelor loading, consistent with its anticipated peak plasma concentration. Lastly, there was no acute or late bradyarrhythmic recurrence after discontinuation of ticagrelor. In addition, it has been mentioned that AV block and other bradycardia are seen in the early hours of inferior MI and improved after revascularization [10]. Therefore, it is highly probable that the observed complications maybe related to ticagrelor, since there was no arrhythmia during the early hours of the MI. Also, despite early, complete revascularization, the complications occurred during the later days of the MI.

This was a rare and complicated case in which both the bradyarrhythmic effect of ticagrelor was serious enough to require a pacemaker, and the respiratory side effects occurred together. Thus, healthcare professionals should be alert for serious arrhythmias and serious respiratory problems after ticagrelor loading.

No conflict of interest is reported.

The article was received on 30/03/2022

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ISSN 0022-9040. Кардиология. 2024;64(2). DOI: 10.18087/cardio.2024.2.n2123