


Ticagrelor-Related Severe Dyspnoea: Mechanisms, Characteristic Features, Differential Diagnosis and Treatment

Clinical Medicine Insights: Case Reports
Volume 13: 1–7
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DOI: 10.1177/1179547620956634



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ABSTRACT: With a growing number of patients on ticagrelor therapy after stent implantation, we observe many cases of side effects of the drug, mostly dyspnoea and bradycardia. In our article we present 2 patients, in which the symptoms were particularly severe. Then we describe possible mechanisms of these complications, explain how to carry out differential diagnosis, discuss when to switch ticagrelor to other antiplatelet drug and finally we present the way to deal with the symptoms.

KEYWORDS: Ticagrelor, dyspnoea, bradycardia, acute coronary syndrome

RECEIVED: July 13, 2020. **ACCEPTED:** August 13, 2020.

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

In this article, we present 2 cases of patients with ticagrelor-related dyspnoea and bradycardia. We show how to conduct differential diagnostics, how to treat the patients and finally we discuss the 2 main hypotheses concerning these side effects.^{1,2}

Case Report 1

Patient 59 years old male, former smoker, with arterial hypertension and history of previous ST-elevation myocardial infarction (STEMI) treated with right coronary artery angioplasty (2008) was admitted to hospital due to another STEMI. He has received a 180 mg loading dose of ticagrelor and was transferred directly to Cath lab, where coronary angioplasty of left anterior descending artery was performed and drug eluting stent (DES) was implanted. Two hours later he presented strong dyspnoea and anxiety. His pattern of breathing resembled Cheyne–Stokes respiration. During the episode bradycardia of 35 to 40/min with presyncope was observed. The symptoms were followed by intensive sweating. The whole episode lasted about 1 to 2 minutes and then it faded as quickly as it came. Numerous attacks repeated every few minutes. The patient was afraid of further attacks.

Due to recent acute coronary syndrome (ACS) sinus node disorders and heart failure exacerbation were suspected, but the patient had no pulmonary congestion (nor auscultatory features of bronchial obstruction), no orthopnoea. He lie down without any symptoms between the attacks, which every time ceased away without any action or sequelae. In echocardiography the ejection fraction of left ventricle (EF) was significantly

reduced EF = 30%, there were no haemodynamically significant valvular defects nor mechanical complication of myocardial infarction.

Differential diagnosis excluded cardiac etiology of dyspnoea and finally side effect of ticagrelor was suspected. According to the literature theophylline 200 mg in slow intravenous infusion was administered and after short time from the beginning of the infusion the shortness of breath and the episodes of bradycardia disappeared. But 2 hours after the infusion was terminated, the attacks returned, however they were less intensive and without bradycardia. Infusions of theophylline 200 mg iv twice daily were administered for 3 days. The patient was immediately switched to clopidogrel with a loading dose of 300 mg (prasugrel should be the first choice but was not available in our country at that time). Further hospitalisation went without any complications and on day 5 the patient was discharged home.

Case Report 2

Patient 62 years old male, smoker, so far untreated for any reasons was admitted to hospital due to non ST elevation myocardial infarction. He received a loading dose of ticagrelor and was transferred to Cath lab. Significant stenosis of right coronary artery was found and coronary angioplasty with DES implantation was performed. Two hours after administration of ticagrelor patient presented strong anxiety, then heavy dyspnoea and generalised sweating. There were auscultatory features of heavy bronchial obstruction and significant drop of blood oxygen saturation. The patient was ordered inhalation of beta-mimetics,



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cholinolytics and corticosteroids, then corticosteroids intravenously. This treatment improved patients status only partially and for a short time. The attacks were recurrent and numerous, each time starting with strong anxiety and panic. Only when theophylline 200 mg in slow intravenous infusion was applied, dyspnoea episodes ceased to appear and the patient felt much better. It was then realised, that the use of ticagrelor can be the reason of bronchial obstruction. When ticagrelor was stopped and the patient was switched to clopidogrel (prasugrel should be the first choice but was not available in our country at that time), the attacks subsided. Spirometry made before discharging from hospital revealed no bronchial obstruction and the patient remained without pulmonary therapy.

Ticagrelor – Mechanisms of Action

Ticagrelor, a cyclopentyltriazolopyrimidine class drug, causes anti-platelet effects after oral administration. It binds reversibly to P2Y₁₂ receptor and prevents adenosine diphosphate (ADP) mediated platelet activation and aggregation. Its binding site on the P2Y₁₂ receptor is different from that of ADP, thus ticagrelor does not prevent ADP from binding to the receptor.³⁻⁵ P2Y₁₂ receptor inhibits adenylyl cyclase activity through activation of an inhibitory G protein. As a result the level of cAMP decreases. It leads to dense granule secretion, activation of fibrinogen receptor and thrombus formation. P2Y₁₂ receptor also participates in recruitment of other platelets, their adhesion to collagen and von Willebrand Factor and activation by other agonists. P2Y₁₂ receptor opposes the anti-platelet effects of platelet inhibitors such as prostacyclin.⁵⁻⁷

In contrast to other drugs (clopidogrel and prasugrel) ticagrelor does not require metabolic activation.⁸ However, an active metabolite AR-C124910XX, also exhibits effect on platelets. According to the researches, ticagrelor and its metabolite reach their maximum plasma concentration in median time of 1.3 to 2 hours and 1.5 to 3 hours, respectively. Ticagrelor's half-life is about 7.7 to 13.1 hours so it is administered twice a day.^{9,10} The dose of ticagrelor does not require adjustment on the basis of gender, age and renal or hepatic diseases,^{8,11,12} whereas clopidogrel has its restrictions, mainly genetic variations in the enzymes responsible for its metabolism.¹³ The results of the PLATO study, which compared ticagrelor to clopidogrel, showed that ticagrelor significantly reduced the rate of cardiovascular deaths, myocardial infarction (MI) or stroke.¹⁴

Why Does Ticagrelor Induce Dyspnoea and Bradycardia?

Research into the mechanisms of dyspnoea in patients on ticagrelor therapy has been ongoing for years. Finally, 2 main mechanisms have been demonstrated, first connected with increased extracellular level of adenosine, second concerning P2Y₁₂ receptors.^{1,2}

Adenosine is a purine nucleoside which is present in every cell. It is likely to cooperate with A1, A2A, A2B and A3

receptors (A1R, A2AR, A2BR and A3R). A1R and A3R are coupled with inhibitory G protein and the other 2 – A2AR and A2BR are coupled with stimulatory G protein. During stress, hypoxia, allergic stimulation and exercise formation of adenosine and its extracellular concentration significantly increases. Biological effects of adenosine include modulation of inflammatory response, inhibition of platelets aggregation, stimulation of airway afferent sensory nerve endings and inducing bronchial smooth muscle cells contraction. Adenosine plays a crucial role in pathogenesis of bronchospasm and inflammation in asthma. It also mediates coronary artery vasodilatation, limits ischaemia/reperfusion injury and has chronotropic effects.^{6,15-19}

Extracellular adenosine has a half-life of a few seconds as it is rapidly taken up by cells through sodium-dependent and sodium-independent receptors. Then it is quickly metabolised to inosine or adenine nucleotides.^{8,15,16} It has been proven that ticagrelor blocks the sodium-independent equilibrative nucleoside transporters (ENT 1/2) and adenosine uptake to cells. As the result ticagrelor increases half-life of extracellular adenosine and its tissue concentration.^{7,8,20} There are some evidence that circulating adenosine may also increase.^{21,22} According to the so-called adenosine-hypothesis, this purine nucleoside stimulates vagal C fibres on bronchial wall through A1R and A2AR and finally causes the sensation of dyspnoea.^{21,23-25} 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^{17-19,26,27} (Figure 1).

Although adenosine-hypothesis seems plausible, there are many inaccuracies.^{1,2} Dipyridamole inhibits adenosine reuptake stronger than ticagrelor and does not cause dyspnoea.^{7,28} There are studies, where plasma adenosine does not differ in patients with or without ticagrelor-related dyspnoea after loading and maintenance doses.²⁹ Similarly there are no differences in circulating adenosine in patients taking ticagrelor as compared to patients on clopidogrel or prasugrel therapy.²⁹⁻³¹ Thus, another hypothesis concerning dyspnoea on ticagrelor therapy emerged. This hypothesis does not rely on adenosine's influence on vagal C-fibres but focuses on P2Y₁₂ receptors.^{1,28} P2Y₁₂ receptors are present not only on platelets, but also on endothelial cells, smooth muscle cells, neuron cells and microglia in the central nervous system.^{28,32} Activation of P2Y₁₂ receptors decreases neuronal signalling by inhibiting the activation of adenylyl cyclase and therefore decreasing the levels of cAMP. When P2Y₁₂ receptors are blocked, it leads to increased signalling, which finally may concern vagal C-fibres or glial cells. The glial cells have potential to stimulate the central chemoreflex system and to elicit Cheyne–Stokes respiration^{28,32} (Figure 2).

It has been proven that the sensation of dyspnoea occurs during the administration of other anti-platelet drugs, such as clopidogrel. According to the ONSET/OFFSET study

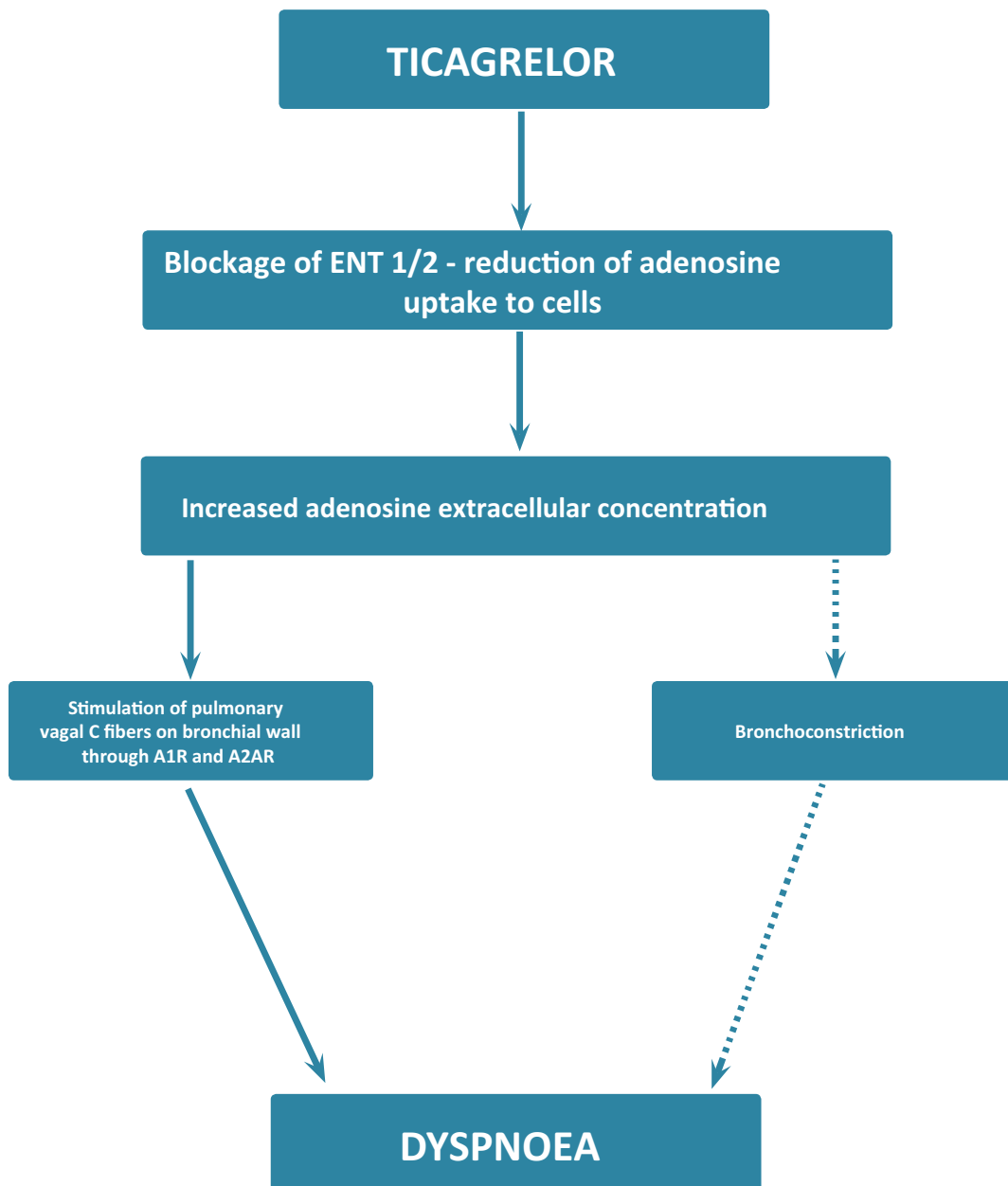


Figure 1. Mechanism of ticagrelor-related dyspnoea – adenosine hypothesis.

dyspnoea was reported by 38.6%, 9.3% and 8.3% of patients in the ticagrelor, clopidogrel and placebo groups ($P < .001$).³³ Platelets do not have nuclei and can not produce new P2Y₁₂ receptors, therefore even 1 daily administration of clopidogrel is sufficient to permanently inhibit platelets. On the contrary neurons and glial cells, which have nuclei, are able to produce new receptors. When irreversible drug, such as clopidogrel, binds to the P2Y₁₂ receptors, these are replaced by the newly produced ones, thus neurons and glial cells are not inhibited through most of the day. But ticagrelor as a reversible inhibitor is administered twice a day. This leads to a constant high concentration of the drug, which ensures platelets inhibition, but also binds to newly produced receptors in neurons or glial cells, which remain permanently blocked.^{28,34} Increased plasma levels of ticagrelor in patients with dyspnoea as compared to the

patients without dyspnoea, both during the loading and maintenance dose, support P2Y₁₂ hypothesis.²⁹ Also the reversible nature of sensory neuron P2Y₁₂ inhibition could play a role, since other reversible agents, like cangrelor also increase dyspnoea occurrence.²⁸

Summarising, there are pros and cons for both mechanisms concerning ticagrelor-related dyspnoea and in our opinion none of them may be completely ruled out. The increase in endogenous adenosine is unlikely to be the only cause, although it might contribute to the sensation of dyspnoea in some predisposed patients.

The bradycardic events occurring in patients undergoing ticagrelor treatment can be explained by adenosine hypothesis.^{35,36} At the level of sinus and atrio-ventricular (AV) nodes, adenosine activates potassium channels, increasing the potassium outward

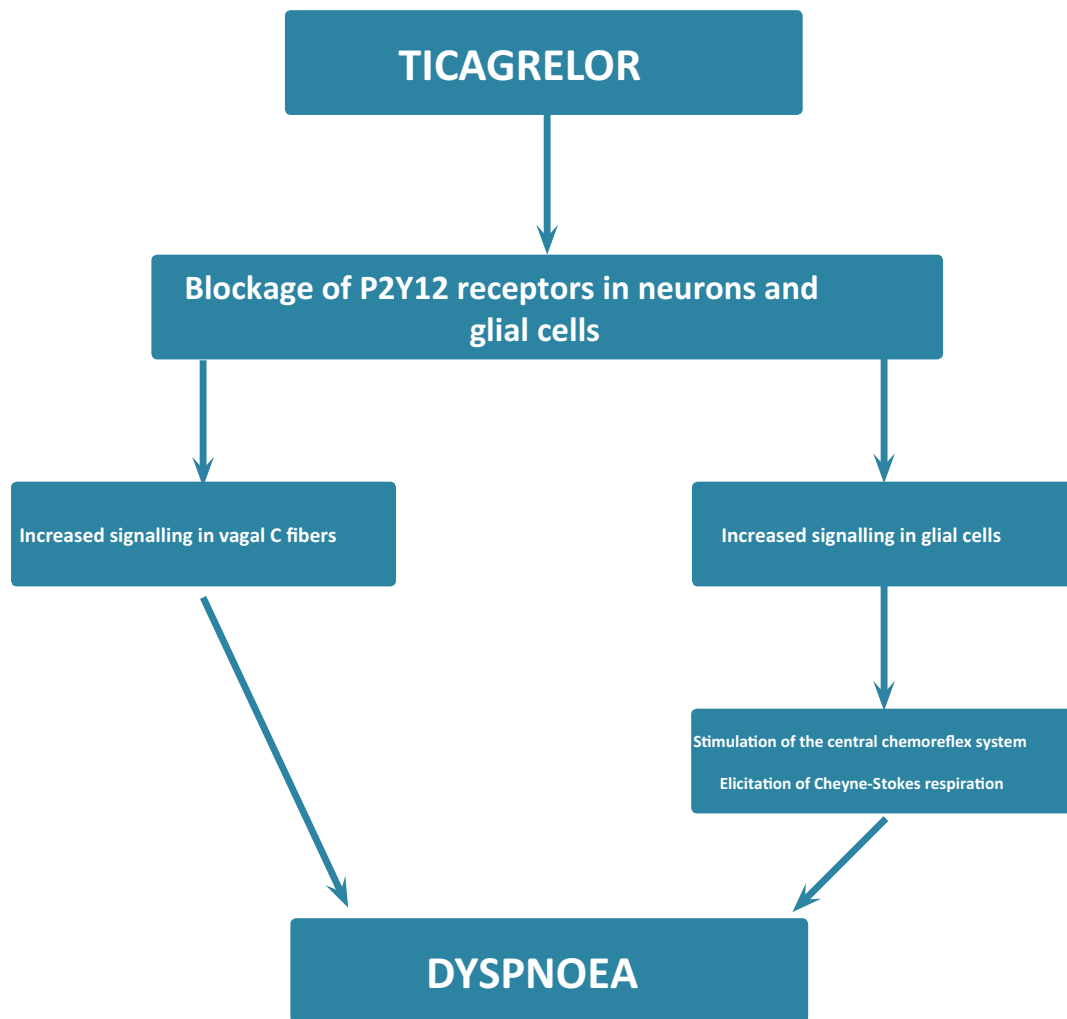


Figure 2. Mechanism of ticagrelor-related dyspnoea – P2Y12 receptors hypothesis.

current and at the same time inhibits calcium-mediated slow channels, decreasing the calcium inward current.³⁷ This leads to depression of automaticity of sinus node and prolongation of A-V conduction, which finally causes bradycardia and conduction disorders.

Other Possible Causes of Dyspnoea and Bradycardia in Patients With ACS and How Do We Know That the Symptoms Are Caused by Ticagrelor?

Dyspnoea can be described as a sudden and unexpected air shortage or unsatisfied inspiration. It is a common symptom with many causes, such as pulmonary, renal, liver, cardiac and metabolic. It is therefore a clinical challenge to find the reason of this symptom. The most common causes of dyspnoea in ACS patients are heart failure exacerbation, pneumonia or acute bronchitis, worsening of pre-existing chronic pulmonary disease, recurrent ischaemia, pulmonary thromboembolism, anaemia, or side effects of beta-blockers or ticagrelor.³⁸

Ticagrelor-related dyspnoea diagnosis is based on exclusion. Taking detailed history and physical examination is very helpful and in most cases enough to diagnose the patient. Sometimes, however, we may additionally commission extra tests such as complete blood count, troponin and CK-MB, D-dimers,

N-terminal pro-brain natriuretic peptide (NT-proBNP), ECG, echocardiography, X-ray and pulmonary function tests.³⁸

Ticagrelor related dyspnoea starts about 2 hours after taking the drug. It appears suddenly, lasts about a minute or 2 and disappears on its own. Typically its intensity increases to a peak and then starts to decrease, reminding Cheyne-Stokes respiration. Between the episodes the patient is asymptomatic, however ‘basic’ dyspnoea due to another reason like pneumonia or heart failure exacerbation may exist. Typically ticagrelor-related dyspnoea is accompanied by strong fear, panic and anxiety. It does not occur with cough and is not related to body position, however in both our cases patients during the attacks chose a sitting position. There are no pathological auscultatory features over the lungs, but heavy bronchial obstruction with drop of blood oxygen may be observed. Sometimes bradycardia co-exists. Episodes of dyspnoea usually return many times during a few hours or even a few days (Table 1).

Patients who suffer from ACS may develop bradycardia due to ischaemia or drugs (beta-blockers, diltiazem, digitalis glycoside and antiarrhythmic drugs like amiodarone). There are also metabolic causes of bradycardia like hyperkalaemia, hypothyroidism or hypothermia.³⁵ Ticagrelor-related bradycardia

Table 1. Features of ticagrelor-related dyspnoea.

How do we know that the dyspnoea is caused by ticagrelor?
Generally based on exclusion
Starts about 2 hours after taking ticagrelor
Accompanied by strong fear, panic and anxiety
Lasts a few minutes and disappears on its own
Between the episodes the patient is asymptomatic
Does not occur with cough and is not related to body position
Remines Cheyne-Stokes respiration
No pathological sounds over the lungs
Theophylline relieves the symptoms
Not typical, but possible – severe bronchospasm and drop in blood oxygen

diagnosis is based on exclusion, there are however some hints indicating that it was caused by ticagrelor. Usually it starts about 2 hours after taking the drug, it lasts a few minutes and disappears without any action, however there are cases of long-lasting bradycardia with the need of temporary or even permanent stimulation.³⁹

Management of Ticagrelor-Related Dyspnoea

Although the attacks of bradycardia and dyspnoea can be shocking, in most of cases they are mild, transient and occur in the first week of treatment.^{1,2} Monitoring the patient for 3 to 4 days without stopping the ticagrelor therapy is recommended, as the attacks will probably disappear after that time.^{1,2,34,40} Sometimes however these side effects are life-threatening or highly intolerable by the patient, which leads to discontinuation of the ticagrelor therapy. Based on published case reports theophylline infusions may have positive effect on those symptoms, causing their remission.⁴¹ Our experiences with the drug are similar, but there is a need for evidence from clinical trials.⁴² As in none of the clinical trials using ticagrelor, patients were treated with theophylline or other methylxanthine drugs, currently there is no recommendation on this aspect neither by European Medicines Agency nor Food and Drug Administration.

Discussion

The aim of this paper was to show that ticagrelor might cause specific side effects such as dyspnoea or bradycardia. It is very important to recognise these side effects and distinguish them from other symptoms like heart failure exacerbation, chronic obstructive pulmonary disease (COPD), pneumonia, anaemia or side effects of other drugs like beta-blockers, because ways of dealing with patients vary depending on the reason. Besides, we are capable of counteracting quickly and effectively through administering antidote or/and changing the treatment.

In the first case dyspnoea and bradycardia started 2 hours after the administration of ticagrelor. During each episode the

patient presented a presyncope, which was not surprising in the situation of reduced left ventricular EF, when the compensation mechanism of tachycardia failed. There were numerous attacks coming suddenly, lasting a few minutes and disappearing spontaneously. There were no clinical, laboratory or instrumental abnormalities which could be the evidence of other cardiac, pulmonary or metabolic diseases. The patient had no stagnation over the lung nor orthopnoea. Echocardiography showed substantially decreased EF, however in the meantime he felt no symptoms except for the fear of the next attack. Ticagrelor was changed to clopidogrel immediately after the first episode of dyspnoea. However severe attacks kept coming back. Only after giving the patient theophylline in slow intravenous infusion made the attacks much weaker and rarer. It was necessary to continue theophylline infusions for 3 days.

Similarly the second patient presented severe dyspnoea with anxiety and fear 2 hours after ticagrelor administration. However in this case dyspnoea was accompanied by auscultatory features of heavy bronchial obstruction and drop of blood oxygen saturation. The patient was a smoker, so firstly we thought about unrecognised COPD or acute spastic bronchitis, but worsening of heart failure was also possible. Beta-mimetics, cholinolytics and corticosteroids had no significant influence of the dyspnoea as the attacks each time resolved spontaneously, but kept coming back. In the meantime the patient felt good, however was afraid of further attacks. Only when the patient was administered theophylline, the episodes of dyspnoea disappeared, and after changing ticagrelor to clopidogrel they did not appear again. Patient went through spirometry which did not point at COPD. After clinical observation and with good results of spirometry, we could diagnose our patient dyspnoea caused by ticagrelor.

Dyspnoea is a common side effect of ticagrelor, but the episodes are usually mild, disappear after a few days and there is no need to change the treatment.^{1,2} In both our cases however, attacks of dyspnoea were severe. They restricted patients' functioning, were very poorly tolerated and were threat to their lives, hence our decision to switch the treatment.^{1,2,34}

There are a few groups of patients that we should be especially careful with. These are patients suffering from COPD, asthma, AV blocks and significantly decreased EF. According to clinical research decreased lungs' functions or low EF are not contraindications for ticagrelor. However, among these patients dyspnoea (and bradycardia) could be life-threatening. As a result, doctors should carefully monitor these groups of patients after ticagrelor administration.^{40,43}

There are 2 main hypotheses concerning the dyspnoea and in our opinion both of them are likely. One is connected with adenosine and its increased tissue or circulating level, the second is related to blockage of P2Y₁₂ receptors. It is possible, that in the first patient the mechanism was connected with P2Y₁₂ receptors and C-fibres or glial cells stimulation, as the patient presented Cheyne-Stoke's respiration pattern with no pathological sounds over the lung. In the second case the patient may have been

sensitive to adenosine as he presented severe bronchospasm. Most researchers suggest, that adenosine stimulates bronchial C-fibres via A1R and A2R, which lead to a sensation of dyspnoea without changing bronchial or pulmonary function.^{24,25} Nevertheless cases of heavy bronchial spasm after systemic adenosine administration, reversed by methylxanthines have been reported.^{26,27} Summarising we believe that different mechanisms responsible for dyspnoea do not exclude each other and one of them may prevail depending on patients susceptibility.

Methylxanthines (amiophylline, theophylline) are antagonists of adenosine receptors. However this class of drugs is also called central nervous system stimulants. Aminophylline interrupts bronchospasm after systemic administration of adenosine.^{26,27} Moreover theophylline reduces dyspnoea in patients with COPD without alteration of their lung function, which could be due to a central effect. The drug as a central nervous system stimulant, reduces apnoeic episodes in premature infants and reduces Cheyne–Stokes respiration.⁴⁴ Thus, the positive influence of theophylline on patients with ticagrelor-related dyspnoea support both, adenosine and P2Y12 hypothesis. The only question that remains is whether theophylline is safe for patients with acute myocardial infarction?

Summary

To summarise, it is important to remember about complications of ticagrelor therapy such as dyspnoea and/or bradycardia. It is worth keeping in mind that ticagrelor-related dyspnoea typically coexists with strong fear and anxiety. In-between the attacks the patient has no problems with breathing, however dyspnoea can overlap on another cause, like heart failure exacerbation. Our observations show, that theophylline interrupts side effects of ticagrelor, which may be helpful in most severe cases.

Author Contributions

All authors reviewed and approved the final manuscript.

Informed Consent

Patient written informed consent has been obtained to publish findings of these 2 case studies.

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