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CASE REPORT
Other

Ticagrelor-associated ventricular pauses: a case report and literature review

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Background Ticagrelor is an oral anti-platelet agent that is a reversible and direct inhibitor of the adenosine diphosphate P2Y12 receptor. Ticagrelor's brady-arrhythmic potential was investigated in a sub-study of the PLATO trial, which concluded that the effects were transient and not clinically significant beyond the acute initiation phase. Since then, there have been emerging reports of ticagrelor-associated high-degree heart block, requiring drug discontinuation and pacemaker insertion. We present a case of symptomatic ventricular pauses in a patient loaded with ticagrelor post-percutaneous coronary intervention (PCI) for non-ST elevation acute coronary syndrome (NSTEACS) and review the literature relating to ticagrelor and its brady-arrhythmic potential.

Case summary A 59-year-old female presented to our hospital with NSTEACS and received an oral load of ticagrelor 180 mg following PCI to her mid-left circumflex coronary artery. Three hours after, four pauses were observed on telemetry over a 20 min period, the longest being 18.5 s in duration. Ticagrelor was ceased and clopidogrel commenced in place. No arrhythmic events were recorded on loop recorder interrogation following ticagrelor discontinuation.

Discussion The exact mechanism of ticagrelor-induced brady-arrhythmia is unclear, although inhibition of adenosine reuptake is proposed as likely due to structural similarities between ticagrelor and adenosine. In the setting of acute coronary syndrome treated with ticagrelor, extracellular adenosine concentrations are amplified by the ischaemic milieu with myocardial adenosine release and blunted cellular reuptake. This leads to enhanced agonism of adenosine A1 receptors, causing negative chronotropy and dromotropy. This case report highlights ticagrelor's brady-arrhythmic potential even in the absence of baseline conduction disease or concurrent confounding medications.

Keywords Ticagrelor • Acute coronary syndrome • Brady-arrhythmia • Ventricular pauses • Case report

Learning points

- Current ESC guidelines recommend the use of ticagrelor along with aspirin in patients with acute coronary syndrome regardless of initial treatment strategy.
- Ticagrelor can cause rare, brady-arrhythmic effects in patients with acute coronary syndrome.
- Augmented adenosine release in the ischaemic context, with blunted cellular re-uptake by Ticagrelor competition are likely culprit mechanisms, with downstream effects of negative dromo- and chronotropy.
- Patients with pre-existing conduction abnormalities may have a higher brady-arrhythmic risk, however, this case report highlights ticagrelor's brady-arrhythmic potential even in the absence of baseline conduction disease or concurrent confounding medications.

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Introduction

Dual anti-platelet therapy (DAPT) is the mainstay treatment of patients with acute coronary syndrome (ACS) and following percutaneous coronary intervention (PCI) for stable coronary disease. Ticagrelor is an oral anti-platelet agent that is a reversible and direct inhibitor of the adenosine diphosphate $P2Y_{12}$ receptor. Unlike clopidogrel and prasugrel which require hepatic activation, ticagrelor, and its metabolite are biologically active following gastrointestinal absorption, have a more rapid onset of action and a higher degree of platelet inhibition.[1] The PLATO (Platelet Inhibition and Patient Outcomes) trial first demonstrated superiority of ticagrelor over clopidogrel when used in conjunction with aspirin, in reducing rates of cardiovascular death and recurrent myocardial infarction in patients with ACS.[2] However, ticagrelor is associated with a greater risk of minor and major bleeding (including intracranial haemorrhage), brady-arrhythmias, and dyspnoea, which are major causes of medication discontinuation.[2]

A sub-study of the PLATO trial[3] further explored the risk of brady-arrhythmias, and showed that ticagrelor (compared with clopidogrel) was associated with an increased risk of ventricular pauses of more than 3 s in the first week of treatment. Nonetheless, the study concluded that ticagrelor's brady-arrhythmic 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 follow-up.[3] Since then, there have been emerging case reports of ticagrelor-associated high-degree heart block, requiring drug discontinuation and in some cases, pacemaker insertion (*Table 1*).

We present a case of symptomatic ventricular pauses in a patient loaded with ticagrelor post-PCI for non-ST elevation ACS (NSTEACS) and review the literature relating to ticagrelor and its brady-arrhythmic potential.

Case presentation

A 59-year-old female with no prior cardiac diagnosis presented to our hospital with 3 days of intermittent chest pain. Her cardiac risk factors included hypertension, hypercholesterolaemia, elevated body mass index, and impaired glucose tolerance. Her medical history was also significant for asthma, gastro-oesophageal reflux disease and depression. Cardiovascular examination was unremarkable with no signs of heart failure.

Her admission electrocardiogram (ECG) showed sinus rhythm, normal axis, narrow QRS (80 ms) with no ischaemic change or conduction defects (*Figure 1*). The patient's serum troponin recorded a peak measurement of 0.31 μg/L (cTnI $n < 0.04$ μg/L). Her biochemistry and blood panels were otherwise unremarkable with normal renal and liver function. Echocardiography showed normal biventricular size and systolic function, with normal valves.

Radial approach coronary angiography was performed and the culprit vessel was shown to be the left circumflex artery (non-dominant) with a long 80% stenosis in the mid-portion. This was treated with deployment of a Synergy 3.0 ×24 mm drug eluting stent and restoration of TIMI 3 flow (*Figure 2*). Medical management was elected for the patient's residual moderate diffuse left anterior descending artery disease. The right coronary artery was non-obstructed.

At conclusion of the procedure, an oral load of ticagrelor 180 mg was administered. Three hours after, whilst convalescing in the coronary care unit, she began complaining of dyspnoea and four pauses were observed on telemetry over a 20 min period (*Figure 3*), the longest being 18.5 s in duration (*Figure 4*). Correspondingly, the patient had intermittent lapses of consciousness and underwent emergency right femoral venous temporary pacing wire insertion.

Ticagrelor was considered as the probable cause for the pauses, for that reason no additional ticagrelor was given after the loading dose and clopidogrel was commenced in place. No further brady-arrhythmias were detected in the subsequent 24 h and the un-utilized temporary pacing wire was removed. The patient was also

Timeline

Time		Progress
Day 1	1120	Coronary angiography and left circumflex percutaneous coronary intervention
	1330	Oral 180 mg ticagrelor load; transfer to coronary care unit
	1545	Onset of dyspnoea
	1632	Intermittent ventricular pauses of up to 3 s observed on telemetry
	1653	Patient found unresponsive; corresponding 18.5 s ventricular pause on telemetry
	1900	Temporary pacing wire inserted; no pacing requirement or brady-arrhythmic recurrence post
Day 2		No further ticagrelor given after loading dose; clopidogrel commenced in place
		Normal echocardiogram
		No further events on telemetry; temporary pacing wire removed
Day 3		Discharged home after insertion of an implantable loop recorder

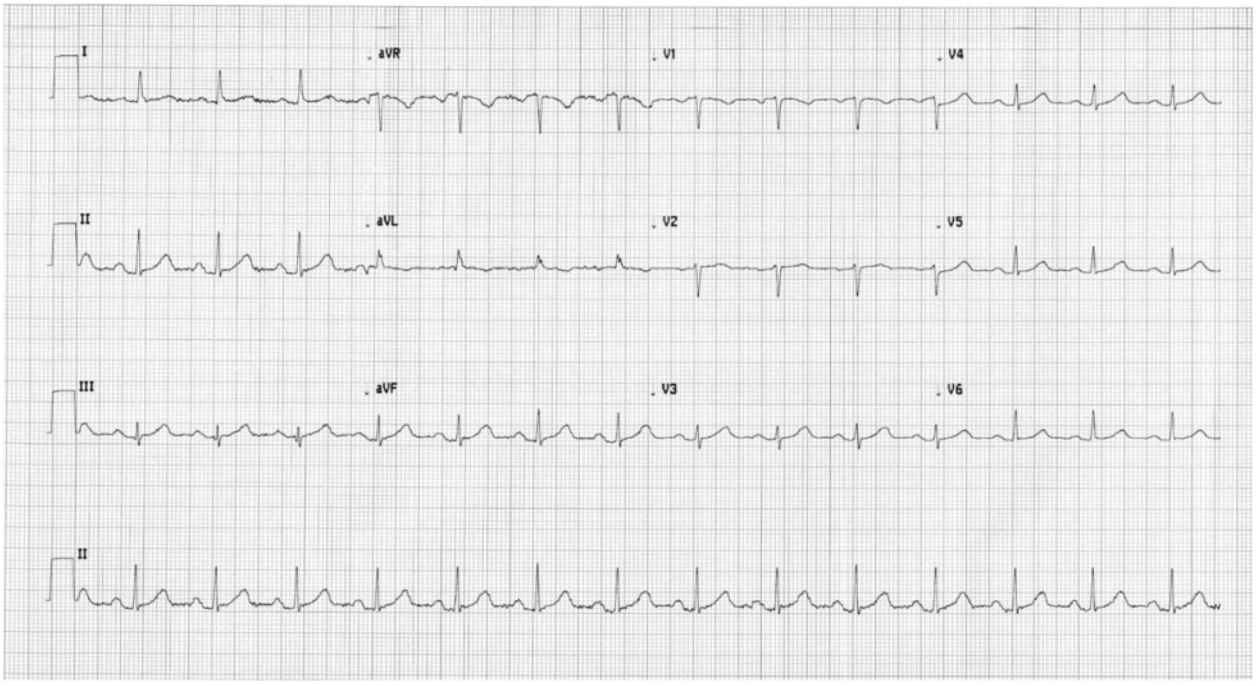

Figure 1 Baseline electrocardiogram.

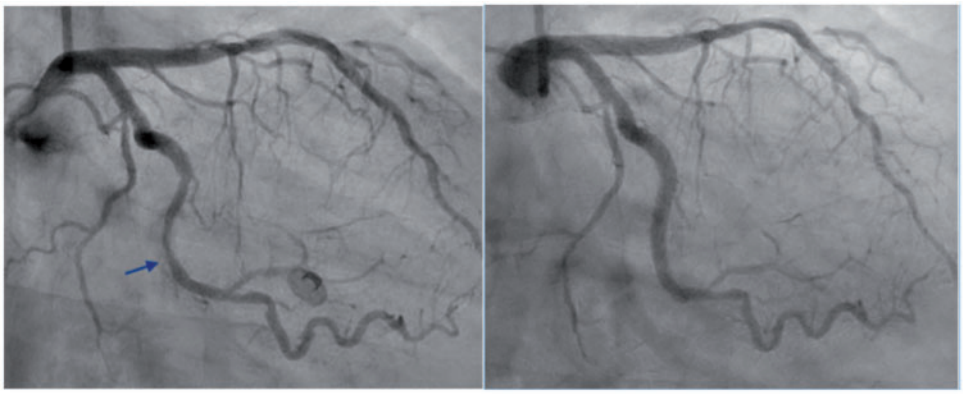

Figure 2 Mid-left circumflex artery culprit stenosis—pre- (left) and post-percutaneous coronary intervention (right).

discharged with aspirin, atorvastatin, perindopril, and amlodipine. A loop recorder (Medtronic Reveal LINQ) was implanted. Beta-blocker therapy was not prescribed in view of preceding events. Notably, there had not been a prior personal or family history of syncope.

No cardiorespiratory symptoms were raised during regular follow-up over 12 months with no arrhythmic events recorded on loop recorder interrogation.

Discussion

We present a case of symptomatic ventricular pauses in a patient loaded with ticagrelor post-PCI for NSTEACS.

Ticagrelor is rapidly absorbed with 36% bioavailability, reaching peak plasma concentration 1.5 h after oral dosing and achieving peak (90%) inhibition of platelet aggregation at 2 h following a loading dose of 180 mg.[1] Elimination is via the liver with a half-life of approximately

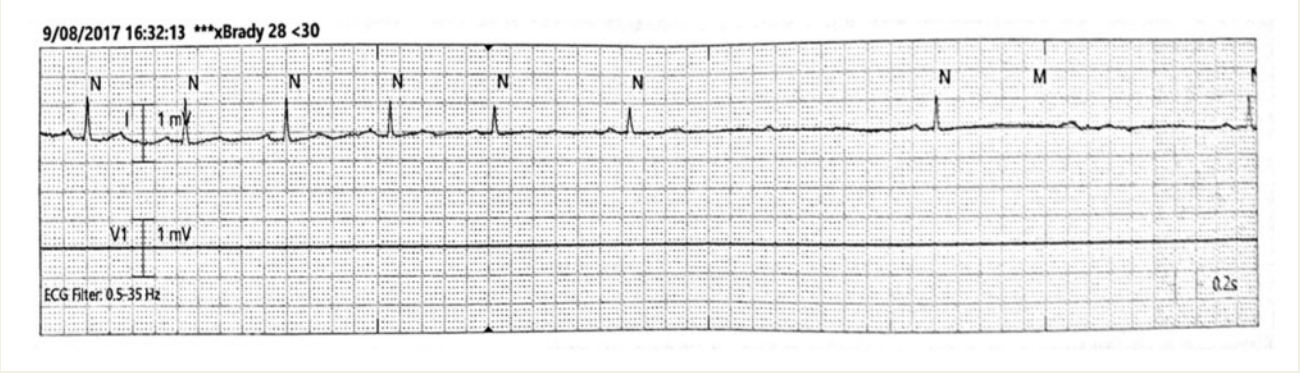

Figure 3 Ventricular pauses of 3 s. N: normal beat; M: missed beat.

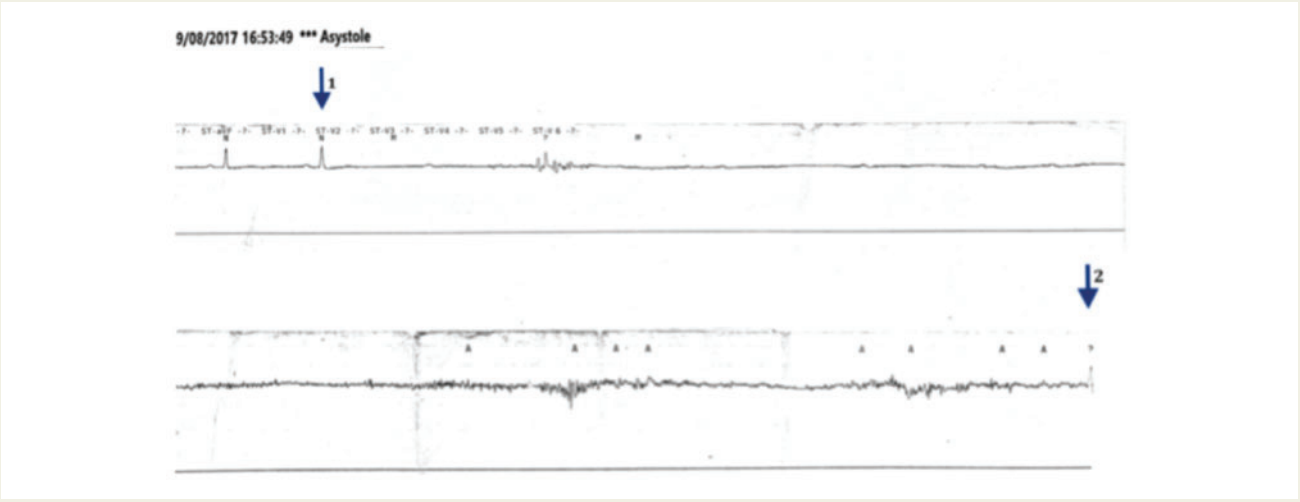

Figure 4 Rhythm strip showing ventricular pause of 18.5 s between arrows marked (1) and (2).

7 h. The 2017 European Society of Cardiology focused update on DAPT in coronary artery disease[4] recommends the use of ticagrelor along with aspirin in patients with ACS regardless of initial treatment strategy.

Several factors in our case suggest ticagrelor culpability. 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 dromo/chronotropic potential. Bradycardic symptom onset was 3 h following oral ticagrelor loading, consistent with its anticipated drug peak plasma concentration. Lastly, there was no acute or late brady-arrhythmic recurrence with discontinuation of ticagrelor.

The exact mechanism of ticagrelor-induced brady-arrhythmia is unclear, although inhibition of adenosine reuptake is proposed as likely. Extracellular adenosine has a half-life of several seconds due to rapid cellular uptake through sodium independent equilibrative nucleoside transporters (ENTs) and sodium dependent concentrative nucleoside transporters (CNTs). ENTs are ubiquitous, present on erythrocytes as well as the liver, heart, spleen, kidneys, lungs, intestines, and brain, while CNTs are found primarily in the liver, kidneys, and small intestine.[5]

Ticagrelor shares structural similarity with adenosine, binding to ENT1 receptors on erythrocytes, and competitively inhibiting cellular adenosine uptake. Three adenosine receptor subtypes (A_1, A_{2a}, and A_3) have cardiac expression with agonism resulting in bradycardia, coronary vasodilatation, and activation of multifaceted cardioprotective mechanisms, respectively.[1,6]

The earliest coronary response to myocardial ischaemia of any aetiology is vasodilatation; mediated by A_{2a} receptors on vascular smooth muscle cells and adenosine release from the ischaemic myocardium.[6] In the setting of ACS treated with ticagrelor, extracellular adenosine concentrations are amplified both by the ischaemic milieu with myocardial adenosine release and blunted cellular reuptake. This leads to enhanced agonism of adenosine A_1 receptors, highly expressed in cardiac conduction tissue, causing negative chronotropy via suppression of sinoatrial node automaticity and negative dromotropy via impulse conduction delay at the atrioventricular node.

Table 1 summarizes 10 published case reports of ticagrelor-associated brady-arrhythmia. All cases occurred in patients with ACS. Notably, 7 of 10 patients had pre-exisiting conduction disease on baseline ECG, with concurrent beta-blocker therapy in most.

Table 1 Summary of published case reports of ticagrelor-associated brady-arrhythmias

Cases	Indication for ticagrelor	Baseline ECG	Pre-existing medications	Time from ticagrelor administration to symptoms/ arrhythmia	Symptoms/ECG	Outcomes
Sharma *et al.*[7]	55-year-old male with unstable angina; PCI to LCx	Sinus rhythm, borderline 1st-degree AV block, RBBB	Metoprolol	2 months	Dizziness 2nd-degree Mobitz type 2 AV block	Ticagrelor ceased; 2nd-degree AV block resolved after 2 days; clopidogrel commenced; and discharged with loop recorder
Yurtdas and Ozdemir[8]	47-year-old female with NSTEACS; PCI to LCx	Sinus rhythm, infero-lateral ST depression	Nil	2 days	Complete AV block	Ticagrelor ceased; complete AV block resolved after 2 days; prasugrel commenced; and nil events at 3 months
Goldberg *et al.*[9]	52-year-old male with NSTEACS; PCI to distal LM and ramus intermedius	RBBB	Bisoprolol	4 h	Syncope Complete AV block and ventricular pause of 11 s	Temporary pacing wire inserted; ticagrelor ceased; heart block resolved after 4 days; clopidogrel commenced; and no recurrence at 6 months
Nicol *et al.*[10]	39-year-old male with anterior STEMI; PCI to LAD	ST elevation in leads V1-4	Atenolol	1 h	Ventricular pause of 8 s	Beta-blocker discontinued; and unclear if ticagrelor was continued
Ünlü *et al.*[11]	ACS; PCI to LCx	First-degree AV block	Bisoprolol	4 days	Mobitz type II AV block	Bisoprolol and ticagrelor ceased; AV block persisted after 10 days; and dual-chamber PPM inserted
Baker *et al.*[12]	56-year-old male with NSTEACS, PCI to proximal LAD	Sinus rhythm, no conduction abnormalities	Nil	3 h	Sinus bradycardia followed by sinus arrest and complete heart block	Ticagrelor ceased; temporary pacing wire inserted then removed 12 h later; and asymptomatic at 4 weeks
De Maria *et al.*[13]	82-year-old male with NSTEACS; PCI to LAD	First-degree AV block	Bisoprolol	2–3 days	Syncope 2:1 AV block	Bisoprolol ceased, episodes persisted, ticagrelor ceased, and no further events at 6 months
De Maria *et al.*[13]	76-year-old male with NSTEACS; PCI to LCx	RBBB, left anterior fascicular block and borderline 1st-degree AV block	Nil	Within 2 weeks	Syncope Complete AV block	Ticagrelor ceased; prasugrel commenced; brady-arrhythmia persisted; and dual-chamber PPM inserted
Ozturk *et al.*[14]	62-year-old male with NSTEACS; stent to RCA	First-degree AV block	Metoprolol	7 h	Mobitz type II AV block	Ticagrelor and metoprolol ceased; AV block resolved on day 3; and no further events after 1 month
Goldberg *et al.*[15]	71-year-old female with NSTEACS; PCI to proximal LAD	LBBB	Bisoprolol	2 days, 3 h after bisoprolol (new)	Syncope complete AV block with ventricular pause	Ticagrelor and bisoprolol ceased; temp wire inserted; and no recurrence at 6 months

AV: atrioventricular; DAPT: dual anti-platelet therapy; LAD: left anterior descending coronary artery; LBBB: left bundle branch block; LCx: left circumflex coronary artery; LM: left main coronary artery; NSTEACS: non-ST elevation acute coronary syndrome; RBBB: right bundle branch block; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction.

Ticagrelor was ceased in all patients and substituted with either clopidogrel or prasugrel. Two patients with pre-morbid ECG conduction abnormalities required permanent pacemaker insertion due to persistence of heart block despite discontinuation of ticagrelor.

In conclusion, we present a case of symptomatic and profound ventricular pauses in a patient loaded with ticagrelor post-PCI for NSTEACS. This was observed in our patient even in the absence of baseline conduction disease or concurrent confounding medications, unlike most cases in the published literature (*Table 1*), and highlights the need for broader awareness of ticagrelor's not-insignificant brady-arrhythmic potential.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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