JCSM
Journal of Clinical Sleep Medicine

CASE REPORTS

Ticagrelor-Associated Shift From Obstructive to Central Sleep Apnea: A Case Report

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Ticagrelor, a P2Y12 receptor antagonist, is used in combination with aspirin in patients with coronary artery disease. Recent reports suggest that ticagrelor might induce central sleep apnea (CSA) by increasing chemosensitivity to hypercapnia. We herein describe the case of a patient with positive airway pressure (PAP)-treated obstructive sleep apnea (OSA), in whom PAP-telemonitoring revealed the emergence of CSA and Cheyne-Stokes respiration (CSR) after initiation of ticagrelor for an acute coronary syndrome with preserved left ventricular ejection fraction. Ticagrelor-associated shift from OSA to CSA was confirmed by respiratory polygraphy after PAP withdrawal, and was associated with an increased chemosensitivity to hypercapnia. Ticagrelor discontinuation was associated with the recurrence of pure OSA and the normalization of hypercapnic ventilatory response. A transient recurrence of CSA and CSR was identified by PAP-telemonitoring after accidental reintroduction of the drug. Further studies are required to determine the mechanisms, incidence, and consequences of ticagrelor-associated CSA.

Keywords: central sleep apnea, remote positive airway pressure-telemonitoring, ticagrelor

Citation: Paboeuf C, Priou P, Meslier N, Roulaud F, Trzepizur W, Gagnadoux F. Ticagrelor-associated shift from obstructive to central sleep apnea: a case report. *J Clin Sleep Med*. 2019;15(8):1179–1182.

INTRODUCTION

Ticagrelor, a P2Y12 receptor antagonist, is used in combination with aspirin in patients with acute coronary syndrome.[1] Recent case reports and data from the VigiBase suggested that ticagrelor therapy may induce central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR).[2–4] We describe here the case of a patient in whom ticagrelor therapy for acute coronary syndrome was associated with a shift from obstructive sleep apnea (OSA) to CSA.

REPORT OF CASE

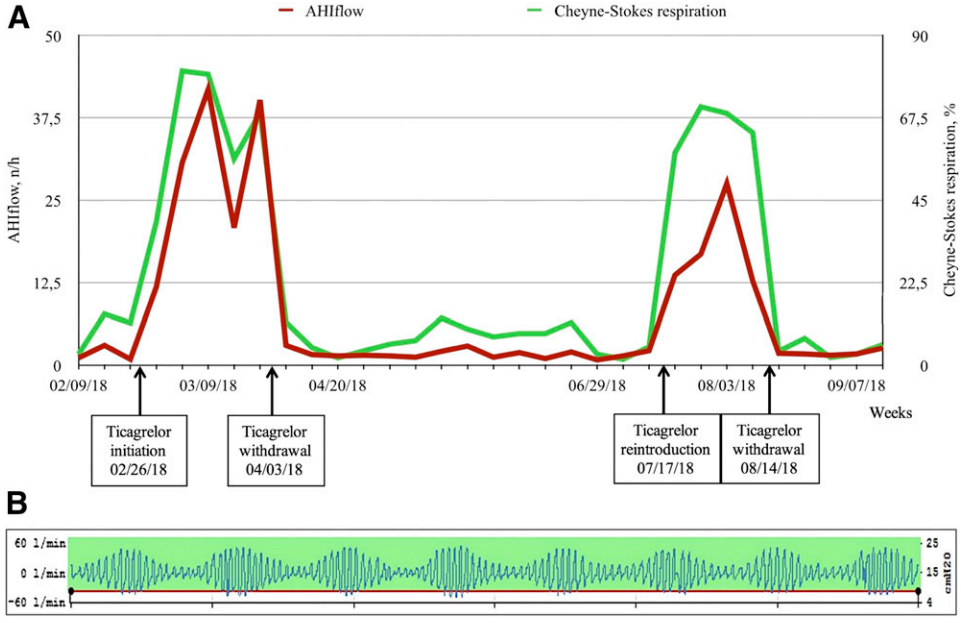
A 71-year-old man with medical history of systemic hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, and ischemic stroke in 2014 received a diagnosis of severe OSA in 2014. The patient was treated with metoprolol, gliclazide, aspirin, pravastatin, enalapril-hydrochlorothiazide, and metformin-sitagliptin. Overnight in-laboratory respiratory polygraphy (RP) demonstrated an apnea-hypopnea index (AHI) of 45 events/h with 91% of obstructive apneas (**Table 1**). The patient was minimally symptomatic with an Epworth Sleepiness Scale score of 5/24. Positive airway pressure (PAP) therapy (System One RemStar Auto A-Flex, Philips Respironics, Pittsburgh, Pennsylvania, United States) was initiated in the auto-adjusting mode for 2 months then switched to a fixed pressure of 8 cmH_20. Follow-up visits showed good treatment adherence ($\geq$ 5 h/night) and efficacy with residual events detected by the device (AHI_{FLOW}) $\leq$ 5 events/h. With patient agreement, remote PAP-telemonitoring was implemented in February 2018. On February 26, 2018, the patient was admitted for a non-ST-segment elevation coronary syndrome with a peak troponin level of 1,397 ng/L. After successful tritroncular revascularization of the proximal circumflex coronary artery, the first obtuse marginal artery, and the right coronary artery with implantation of drug-eluting stents, ticagrelor was added to aspirin. In the following days, PAP-telemonitoring revealed a rapid increase in the AHI_{FLOW} (up to 42 events/h) and in the percentage of CSR (up to 80%) (**Figure 1**), with no change in treatment adherence and PAP mask leaks. The RP without PAP (March 30, 2018) showed an AHI of 66 events/h with a marked predominance of central (28%) and mixed (64%) apneas, and 29% of CSR (**Table 1** and **Figure 2**). Increased chemo-sensitivity to hypercapnia was demonstrated with a 4.4 L/min/mmHg hypercapnic ventilatory response (HCVR) and hypocapnia on arterial blood gases performed in the sleep laboratory in the morning following RP (**Table 1**). A comprehensive cardiac assessment showed no cardiac arrhythmia on 24-hour Holter electrocardiogram recording. Echocardiography showed a preserved left ventricular ejection fraction and no increase in left ventricular wall thickness or left atrial size, suggesting heart failure with preserved ejection fraction. Biological assessment showed no sign of renal failure and the patient had no clinical symptom of neuromuscular or endocrine disease such as acromegaly. Immediately after ticagrelor discontinuation and a switch to clopidogrel (April 3, 2018), remote PAP-telemonitoring showed a rapid reduction, to normal values of both AHI_{FLOW} and CSR (**Figure 1**). When the prescription was renewed, the general practitioner was not yet informed that ticagrelor had been replaced by

Table 1—Patient's clinic and polygraphic data at diagnosis and during follow-up.

	At Diagnosis	Under Ticagrelor	After Ticagrelor Withdrawal
Dates	09/22/2014	03/30/2018	09/05/2018
Age, years old	66	69	69
Body mass index, kg/m^2	28.4	28.7	29.4
Epworth Sleepiness Scale score	5	6	4
Respiratory polygraphy			
Apnea-hypopnea index, events/h	45	66	50
Apnea index, events/h	17	47	23
Obstructive sleep apneas, %	90.8	7.5	94.7
Central sleep apneas, %	4.9	28.0	0.0
Mixed sleep apneas, %	4.3	64.5	5.3
Hypopnea index, events/h	28	19	27
CSR, %	3	29	3
Mean SaO_2, %	91	93	89
3%ODI, events/h	48	67	53
T90, %	30	22	57
Supine position, %	29	56	74
LVEF, %	–	63	62
HCVR, L/min/mmHg	–	4.4	2.6
Arterial blood gases			
pH	–	7.43	7.41
PaO_2, mmHg	–	102	84
$PaCO_2$, mmHg	–	33	37

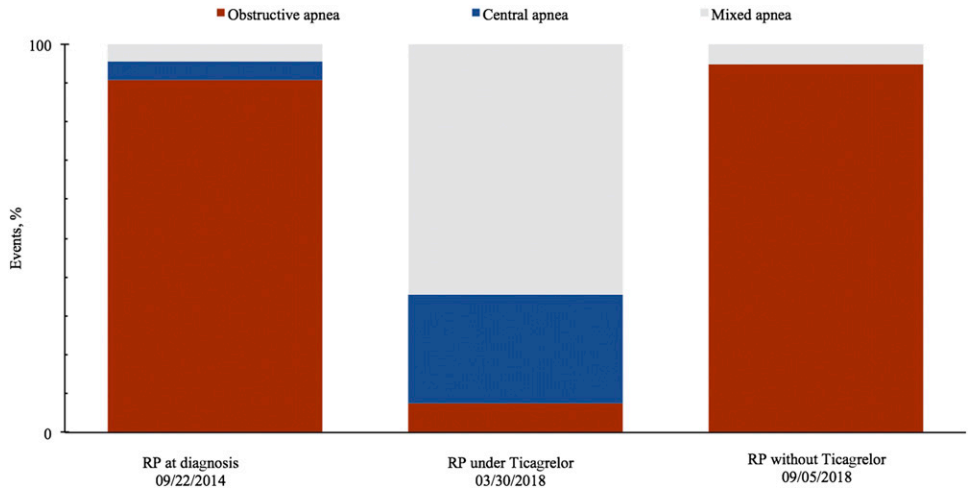
CSR = Cheyne-Stokes respiration, HCVR = hypercapnic ventilatory response, LVEF = left ventricular ejection fraction, ODI = oxygen desaturation index, SaO_2 = oxygen saturation, T90 = percentage of recording time with oxygen saturation below 90%.

Figure 1—AHI_{FLOW} and Cheyne-Stokes respiration measured by PAP device.



(A) Report of the evolution of apnea-hypopnea index (AHI_{FLOW}) and Cheyne-Stokes respiration detected by remote positive airway pressure (PAP)-telemonitoring during the patient follow-up. **(B)** Cheyne-Stokes respiration over a 6-minute period recorded by the PAP device under ticagrelor therapy.

Figure 2—Distribution of obstructive, central, and mixed apneas on full-night respiratory polygraphy (RP) at diagnosis, under ticagrelor and after ticagrelor withdrawal.



clopidogrel due to CSA. The accidental reintroduction of the drug between July 17 and August 14, 2018 resulted in a transient recurrence of apneas, hypopneas, and CSR (**Figure 1**). Four weeks after the final discontinuation of ticagrelor, arterial blood gases and HCVR were normalized, and RP without PAP (09/05/2018) showed an AHI of 50 with 95% of obstructive apneas and no CSR (**Table 1** and **Figure 2**).

DISCUSSION

To the best of our knowledge this is the first report of an association between ticagrelor and the onset of CSA with CSR under PAP therapy for OSA. PAP treatment-emergent CSA was excluded by the demonstration of CSA on RP after PAP withdrawal. Cardiac arrhythmias and heart failure were also excluded. The patient did not take any other treatment known to induce CSA such as opioids or baclofen.[5,6] Furthermore, the recurrence of CSA and CSR after accidental reintroduction of the drug reinforces the hypothesis that ticagrelor was responsible for the onset of central sleep-disordered breathing.

In most circumstances, CSA and CSR are a consequence of hypersensitive ventilatory chemoreflex response to CO_2.[7] There is increasing evidence in support of a considerable overlap between OSA and CSA.[7,8] Indeed, high loop gain is present in approximately 30% of patients with OSA, and is related to OSA severity.[7,9] The overlap is particularly evident in patients with chronic heart failure in whom the shift from OSA to CSA is associated with a reduction in pCO_2.[10] In our patient, the switch from pure OSA to a combination of central/mixed apneas under ticagrelor was associated with an increased chemosensitivity to hypercapnia that disappeared after drug discontinuation. It has been hypothesized that ticagrelor may increase chemosensitivity as a consequence of antagonism of microglial P2Y12 receptors.[2,4] The effects of ticagrelor on pulmonary C fibers might also contribute to the development of unstable respiratory control during sleep.[4]

Unlike the previous case reports of ticagrelor-associated CSA, our patient did not report dyspnea when the treatment was initiated. Furthermore, there was no change in treatment adherence and Epworth Sleepiness Scale score. In line with recent data,[11,12] this highlights the potential value of PAP-telemonitoring for early identification of emergent CSA under PAP therapy.

Given the increasing number of patients treated with ticagrelor for acute coronary syndrome, and the high prevalence of OSA in patients with coronary artery disease,[13] clinicians should be aware that these patients may be affected by the acute onset of CSA or switch from OSA to CSA. Further studies are required to determine the mechanisms, incidence, and consequences of ticagrelor-associated sleep-disordered breathing.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February 23, 2019
Submitted in final revised form April 16, 2019
Accepted for publication April 17, 2019
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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.