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Original Article

Central sleep apnea after acute coronary syndrome and association with ticagrelor use

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ABSTRACT

Study objectives: By modifying the apneic threshold, the antiplatelet agent ticagrelor could promote central sleep apnea hypopnea syndrome (CSAHS). We aimed to assess the association between CSAHS and ticagrelor administration.
Methods: Patients were prospectively included within 1 year after acute coronary syndrome (ACS), if they had no heart failure (and left ventricular ejection fraction $\geq$ 45%) and no history of sleep apnea. After an overnight sleep study, patients were classified as "normal" with apnea hypopnea index (AHI) < 15, "CSAHS patients" with AHI $\geq$ 15 mostly with central sleep apneas, and "obstructive sleep apnea hypopnea syndrome (OSAHS) patients" with AHI $\geq$ 15 mostly with obstructive sleep apneas.
Results: We included 121 consecutive patients (mean age 56.8 $\pm$ 10.8, 88% men, mean body mass index 28.3 $\pm$ 4.4 kg/m^2, left ventricular ejection fraction 56 $\pm$ 5%, at a mean of 67 $\pm$ 60 days (median 40 days, interquartile range: 30–80 days) after ACS. In total, 49 (45.3%) patients had AHI $\geq$ 15 (27 [22.3%] CSAHS %, 22 [18.2%] OSAHS).
For 80 patients receiving ticagrelor, 24 (30%) had CSAHS with AHI $\geq$ 15, and for 41 patients not taking ticagrelor, only 3 (7.3%) had CSAHS with AHI $\geq$ 15 (chi-square = 8, p = 0.004). On multivariable analysis only age and ticagrelor administration were associated with the occurrence of CSAHS, (p = 0.0007 and p = 0.0006).
Conclusion: CSA prevalence after ACS is high and seems promoted by ticagrelor administration. Results from monocentric study suggest a preliminary signal of safety.
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1. Introduction

The prevalence of central sleep apnea hypopnea syndrome (CSAHS) after acute coronary syndrome (ACS) is unclear. Indeed, most of studies focusing on sleep-disordered breathing in this condition do not distinguish central and obstructive apnea [1,2]. Moreover, a few studies [3,4] classified individuals with sleep disordered breathing but did not exclude patients with Heart Failure (HF), which could be an important confounding factor because HF is one of the main causes of CSAHS [5]. Furthermore, CSAHS could be promoted by the use of ticagrelor, a relatively new drug that modifies the apneic threshold [6]. We aimed to investigate the prevalence of central CSAHS in patients without HF after ACS, and identify associated factors, including ticagrelor use.

2. Methods

2.1. Patients

This was a prospective monocentric study. Between January 2018 and March 2020, all consecutive patients hospitalized in our cardiac rehabilitation center 1 week to 1 year after an ACS were screened. We included patients with left ventricular ejection fraction (LVEF) $\geq$ 45% on the day of inclusion.

2.2. Exclusion criteria

We excluded patients with a known history of sleep apnea (ie patients already treated with continuous positive airway pressure

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and patients who had refused such a treatment after a previous sleep study)

We excluded all patient with any episode of HF. Formally, HF is a "clinical syndrome characterized by typical symptoms (eg breathlessness, ankle swelling and fatigue) that may be accompanied by signs (eg elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality" [7]. However, the term Heart failure includes HFrEF (Heart Failure with reduced ejection fraction: EF<40%), HFmrEF (Heart failure with middle range ejection fraction: EF 40–49%) and HFpEF (heart failure with preserved ejection fraction: EF $\geq$ 50%).

To avoid modifications of our results by patients with HFpEF we excluded these patients as follows: HFpEF was defined according to the ESC Guidelines [7]: symptoms ± signs of heart failure and LVEF $\geq$ 50% and elevated levels of natriuretic peptides and at last one of the additional criterion: Left ventricular hypertrophy and/or left atrial enlargement and diastolic dysfunction estimated by the E/e'ratio. Furthermore, because high systolic pulmonary artery pressure is common in HF, we excluded patients with (sPAP) > 45 mm Hg.

Other exclusion criteria were history of cerebrovascular accident or central neurological disease, opioid or baclofene therapy, hypothyroidism and hemodialysis.

All patients gave their informed consent to be in the study. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

We initially planned to include 100 patients. This population was reached in December 2019, but, at that time, the control group of patients not taking ticagrelor was only 20 patients. Thus, we decided to continue the study, by including only patients not taking ticagrelor until this group reached at least 40 patients. Finally, due to the COVID 19 crisis, the inclusion was stopped on March 1, 2020. At that time the non ticagrelor group included 41 patients.

2.3. Sleep study

Patients underwent an overnight sleep study with a Nox T3 portable sleep monitor (Nox Medical, Reykjavik, Iceland). The following signals were recorded during the portable monitor recordings: nasal pressure, rib cage and abdominal movement by inductance plethysmography, snoring, body position, activity, heart rate and oxygen saturation by pulse oximetry. The portable monitor recordings were initially scored automatically by using Noxturnal software. The software program defined apneas as $\geq$ 90% reduction in airflow from baseline for at least 10 s. Obstructive apnea was defined as apnea associated with respiratory effort, and central apneas was defined as apnea during which respiratory effort was absent. Mixed apnea was defined as apnea during which respiratory effort was initially absent but appeared during the latter part of the event. Hypopnea was defined as $\geq$ 30% reduction in a respiratory signal for $\geq$10 s associated with $\geq$3% reduction in oxygen saturation. Cheyne-Stokes breathing was scored with both of the following [1]: episodes of $\geq$3 consecutive central apneas and/or central hypopneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 s, and [2] five or more central apneas and/or central hypopneas per hour associated with the crescendo/decrescendo breathing pattern recorded over a minimum of 2 h of monitoring. The recordings were then manually edited by an experienced polygraphy technologist (blinded to treatment) according to the 2012 American Academy of Sleep Medicine scoring criteria [8]. When the portable monitor recording's nasal pressure signal was absent or not able to be scored throughout the recording or during portions of the recording, the flow signal derived from the rib cage and abdominal respiratory inductance plethysmography signals was used for scoring. Automatic analysis of snoring involved Noxturnal software.

The AHI was calculated as the average number of apneas and hypopneas per hour of analysis time. The oxygen desaturation index (ODI) was calculated as the: number of times that the oxygen saturation decreased from baseline by $\geq$ 3 percentage points (ODI $\geq$ 3%).

Patients with AHI <15 were considered "normal". Patients with AHI $\geq$15 considered to have sleep disordered breathing and were classified as CSAHS or OSAHS according to the percentage of central and/or obstructive apneas: > 50% of central apneas for CSASH and >50% of obstructive apneas for OSAHS.

2.4. Doppler echocardiography

M-mode, 2D images, and flow and tissue Doppler recordings were obtained for all patients with use of a Doppler transthoracic echocardiograph (GE Vivid 6S or 7, Horten, Norway). 2D imaging was performed as usual in parasternal long- and short-axis views and apical 4- and 2-chamber views. Doppler recordings were obtained in the apical 4-chamber view.

LV systolic and diastolic volumes and LVEF were derived from biplane apical (2- and 4-chamber) views with a modified Simpson rule algorithm. sPAP was calculated from tricuspid or pulmonary insufficiency according to the Bernouilli law.

Left ventricular hypertrophy was estimated by measuring interventricular septum width (normal: 6–10 mm) with a 2D-guided M-mode imaging [9].

Left atrial enlargement was estimated by measuring left atrial anteroposterior diameter in the parasternal long-axis view using 2DE [10] Normal AP dimension is 2.7–3.8 cm in women and 3.0–4.0 cm in men.

Pulsed Doppler was used to record transmitral inflow in the apical four chamber view. Tissue Doppler velocities were then acquired at lateral annular site. The early diastolic (e′) velocity by tissue Doppler at the lateral annular site was measured and the E/e′ ratio computed (normal <13) [7].

2.5. Exercise tests

All patients underwent a bicycle exercise test with 10 Watts/min workload increments up to exhaustion. Resting heart rate, maximal heart rate at peak of exercise and peak exercise workload (in watts) were collected.

2.6. Statistical analysis

Because we excluded 15 patients with already known and treated OSA, we could not stastically analyse OSA. Personal data security was guaranteed by assigning each patient a trial number. Data are reported as mean ± SD or median (interquartile range [IQR]) for continuous variables and number (percentage) for categorical variables. Unpaired Student's *t* test or ANOVA (and Kruskal–Wallis test for non-normal distributed variables) and Chi square test were used to compare continuous and categorical variables, respectively. To determine factors associated with CSA we used univariable and multivariable logistic regression models. $P < 0.05$ was considered statistically significant. All analyses involved use of STATVIEW 5.0 (StatView Software).

To check the absence of modification of our results by patients with HFmrEF, we performed a subgroup analysis in patients with LVEF $\geq$ 50%

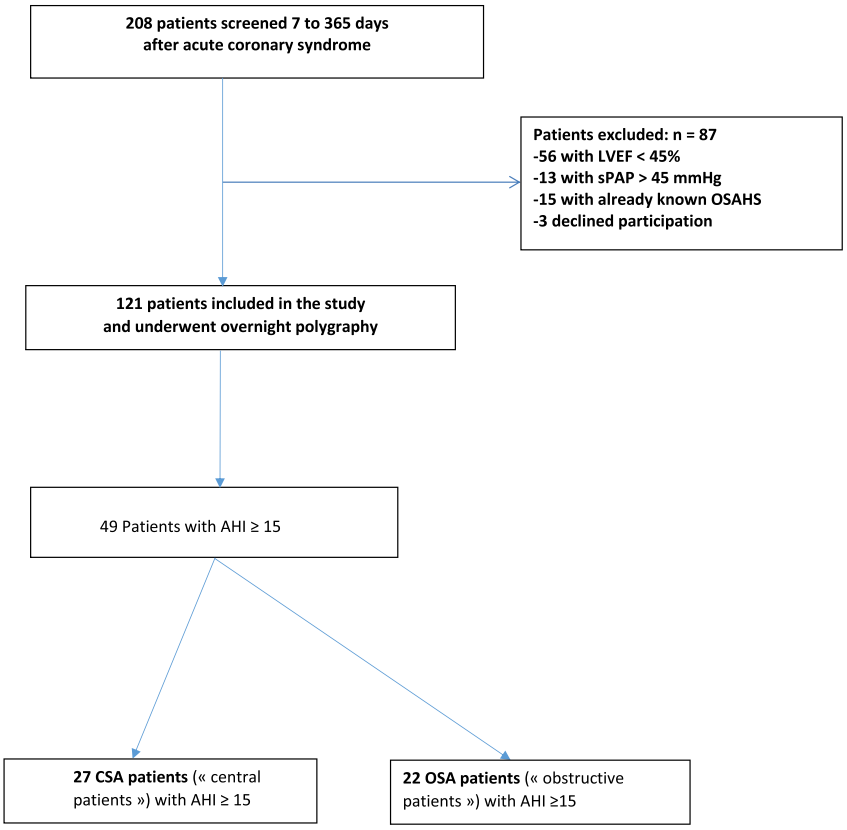

Fig. 1. Flow of participants in the study. OSAHS: obstructive sleep apnea hypopnea syndrome. LVEF: left ventricular ejection fraction. sPAP: systolic pulmonary artery pressure. AHI: apnea hypopnea index. CSA: central sleep apnea. OSA: obstructive sleep apnea.

3. Results

3.1. Patients

Between January 1, 2018 and March 1, 2020, among 208 post-ACS consecutive patients, 87 were excluded (Fig. 1), mainly patients with the least suspicion of heart failure. Finally, 121 patients were included at mean of 66.7 ± 60.5 days after ACS onset (median 40 days [IQR 30–80]). The mean age was 56.8 ± 10.8 years, and 88.4% were men (Table 1). Mean body mass index was 28.3 ± 4.4 kg/m^2. All patients underwent coronary angiography; 112 (92.5%) had primary percutaneous intervention with stenting and 9 (7.5%) coronary artery bypass grafting. All patients except one (99.2%) received aspirin (75–160 mg/day) and 115 (95%) received a thienopyridine (clopidogrel, n = 28; prasugrel, n = 7; ticagrelor, n = 80). Characteristics of patients with and without ticagrelor administration were similar (Table 2).

The global medical therapy was in keeping with Guidelines (betablockers: 88.4%, statins: 99.2%, angiotensin converting enzyme inhibitor/angiotensin 2 antagonist 76.0%), the mean LVEF was 56.2 ± 5.0%. Heart failure treatments were very rare: sucabitril-valsartan (n = 0), ivabradine (n = 1), and diuretic (n = 3) which confirms the good adherence to exclusion criteria. Mean LA diameter, Mean Interventricular septum width and E/e' ratio were normal (Tables 1 and 2).

According to the ESC Guidelines [7], no patients had HFrEF, HFmrEF or HFpEF.

Patients had rather good exercise capacity: mean peak exercise workload 124 ± 41 W.

3.2. Sleep-disordered breathing

In total, 27 of the 121 patients had CSAHS (with AHI ≥ 15), for a prevalence of 22.3%: 24/80 (30%) in the ticagrelor group and 3/41 (7.3%) in the non ticagrelor group (p = 0.004) (Fig. 2). CSAHS was usually asymptomatic or pauci-symptomatic: the mean Epworth score was 3.3 ± 1.2, which indicated no somnolence, and only 2 patients had moderate dyspnea.

A total of 22 of the 121 (18.2%) patients had OSAHS (with AHI ≥ 15): 13/80 (16.2%) in the ticagrelor group and 9/41 (21.9%) in the non ticagrelor group.

Among the 112 patients with LVEF ≥50%, 75 were taking ticagrelor and 37 were not. The rate of patients with CSA and AHI >15 was of 28% in patients taking ticagrelor (n = 21) and 8.1% (n = 3) in the control group (p = 0.01).

On univariable analysis and multivariable analysis (Table 3), only age and ticagrelor administration were significantly associated with CSAHS (p = 0.0007 and p = 0.0006).

4. Discussion

CSAHS prevalence and its clinical consequences in individuals with coronary artery disease, especially ACS, without systolic LV dysfunction and/or heart failure, have not been assessed. Furthermore, CSAHS could be promoted by the use of ticagrelor, a relatively new drug that modifies the apneic threshold. Among our 121 patients, 49 (40.5%) had AHI ≥ 15; 22.3% with CSAHS and 18.2% with OSAHS. CSAHS prevalence was rare in patients not taking ticagrelor (3/41:7.3%), but was high in patients taking ticagrelor (24/80: 30%).

Table 1
Characteristics of patients.

	All patients (n = 121)	CSAHS patients (n = 27)	OSAHS patients (n = 22)	AHI < 15 (n = 72)	p
Age, years, mean ± SD	56.8 ± 10.8	61.8 ± 8.8	55.2 ± 10.5	55.4 ± 11.2	0.02
Gender Sex n (%)	107 (88)	26 (96)	19 (86)	62 (86)	0.4
Delay ACS-PG (days) [IQR]	40 [30–80]	57 [25–95]	35 [20–58]	47 [30–77]	0.1
Coronary angioplasty, n (%)	112 (93)	27 (100)	20 (90)	65 (90)	0.25
Coronary Artery Bypass Graft, n (%)	9 [7]	0	2 [9]	7 (9.8)	0.25
Current smoker n (%)	49 (40)	9 (32)	12 (52)	30 (42)	0.3
Diabetes, n (%)	27 [22]	8 (29)	3 [15]	16 [22]	0.4
Known hypertension, n (%)	41 (34)	9 (33)	9 (40)	24 (72)	0.9
Hypercholesterolemia, n (%)	55 (45)	12 (44)	9 (40)	33 (47)	0.7
BMI, kg/m^2, mean ± SD	28.3 ± 4.4	28.7 ± 4.6	30.2 ± 4.2	27.6 ± 4.2	0.04
atrial fibrillation, n (%)	2 (2%)	0	0	2 (3%)	0.5
LVEF, n (%)	56.2 ± 5.0	55.6 ± 5.1	55.5 ± 5.9	56.7 ± 4.7	0.4
LAD (mm), mean ± SD	36.4 ± 4.8	36.6 ± 4.3	38.06 ± 6	35.6 ± 4.3	0.4
ISW (mm), mean ± SD	9.6 ± 1.07	9.4 ± 0.7	9.3 ± 1.3	9.8 ± 1.1	0.6
E/e' ratio	7.9 ± 2.0	7.7 ± 1.8	8.2 ± 2.1	7.9 ± 2.0	0.5
sPAP (mm Hg)	30. ± 3	31 ± 3	29 ± 6	27 ± 8	0.09
BNP (pg/ml) [IQR 25–75]	86 [35–212]	101 [27–200]	94 [42–220]	86 [35–224]	0.9
Drug therapy					
Aspirin, n (%)	120 (99)	27(100)	21 (95)	72 (100)	0.1
Clopidogrel, n (%)	28 (23)	2 [7]	8 (36)	18 (25)	0.05
Prasugrel, n (%)	7 (5.8)	1 [4]	1 [4]	5 [8]	0.3
Ticagrelor, n (%)	80 (66)	24 (89)	13 (59)	44 (61)	0.01
Beta-blocker, n (%)	107 (88)	23 (85)	19 (86)	65 (90)	0.7
Ivabradine, n (%)	1 [1]	0	0	1 [1]	0.7
ACE-I/AAII n (%)	92 (76)	20 (74)	17 (77)	55 (76)	0.9
Statin, n (%)	120 (99)	27 (100)	22 (100)	71 (99)	0.9
MRA, n (%)	9 [7]	2 [7]	2 [9]	5 [7]	0.9
Sacubitril valsartan,n (%)	0	0	0	0	0.9
Benzodiazepine, n (%)	11 [9]	3 [11]	4 [18]	4 [6]	0.18
Diuretic, n (%)	3 [2]	0	2 [9]	1 [1]	0.08
Exercise test results					
Rest Heart Rate (bpm)	67 ± 10	65 ± 10	69 ± 12	67 ± 11	0.4
Maximal heart rate (bpm)	117 ± 23	110 ± 22	110 ± 21	121 ± 23	0.1
Maximal load (watts)	124 ± 41	131 ± 38	108 ± 37	126 ± 42.6	0.1
Polygraphy results Mean ± SD					
AHI	17.8 ± 15.8	33.1 ± 15.6	31.9 ± 15.4	7.8 ± 3.9	<0.0001
AI	7.8 ± 12.1	15.2 ± 14.5	18.1 ± 16.4	1.9 ± 1.6	<0.0001
OAI	4.2 ± 8.6	3.0 ± 3.2	15.6 ± 15.6	1.3 ± 1.4	<0.0001
CAI	3.1 ± 6.5	11.3 ± 10.3	1.4 ± 1.2	0.5 ± 0.7	<0.0001
MAI	0.4 ± 1.2	1.0 ± 1.7	1.0 ± 1.7	0.6 ± 0.2	<0.0001
HI	16.6 ±	17.8 ± 9.3	13.8 ± 7.3	5.4 ± 3.1	0.9
Cheynes-Stokes breathing duration (min)	75.7 ± 69.3	130.1 ± 97.7	68.3 ± 50.4	57.3 ± 48.2	<0.0001
ODI	17.4 ± 15.4	27.9 ± 15.3	27.5 ± 12.5	10.0 ± 11.7	<0.0001
Mean SaO_2 (%)	93.0 ± 2.0	93.1 ± 1.6	91.6 ± 2.5	93.4 ± 1.9	0.002
% SaO_2 < 90%	4.6 ± 9.5	5.9 ± 10.8	12.5 ± 15.5	1.7 ± 3.2	<0.0001
Snoring duration (min)	47 ± 53	26 ± 23	102 ± 70	39 ± 44	<0.0001
Epworth score	3.8 ± 2.2	3.3 ± 1.2	5.8. ± 3.7	3.4 ± 1.5	<0.0001

ACS: acute coronary syndrome. PG: polygraphy. OSAHS: obstructive sleep apnea hypopnea syndrome. CSAHS: central sleep apnea hypopnea syndrome. BMI: body mass index. Bpm: beat per minute. BNP: B-type natriuretic peptide. LVEF: left ventricular ejection fraction. LAD: Left atrial anteroposterior diameter. ISW: interventricular septum width. sPAP: systolic pulmonary artery pressure. ACE-I angiotensin converting enzyme inhibitor. AAI: angiotensin antagonist inhibitor. MRA: mineralocorticosteroid receptor antagonist. AHI: apnea hypopnea index. AI: apnea index. OAI: obstructive apnea index. CAI: central apnea index. MAI: mixed apnea index. HI: hypopnea index. ODI: oxygen desaturation index. SaO_2: oxygen saturation % SaO 2 < 90%: % of time with SaO_2 < 90%.

On multivariable analysis, only age and ticagrelor administration were associated with the occurrence of CSAHS.

Classical CSAHS risk factors are older age, male sex, heart failure, cerebrovascular accident, hemodialysis, and hypothyroidism. This is a strength of our study that all these confounding factors, especially the least suspicion of heart failure were exclusion criteria.

A safety signal for ticagrelor and sleep apnea syndrome (without differenting between OSAHS and CSAHS) was recently raised [6] by a disproportionality analysis in VigiBase, the World Health Organization Global Individual Case Safety Reports database including more than 16 million reports collected from 127 countries. The analysis showed a significant relative odds ratio (ROR) (4.16 [95% CI, 2.87–6.03]), but this disproportionality was not found for other antiplatelet agents (clopidogrel: ROR = 0.55, prasugrel: ROR = 1.08, aspirin: ROR = 0.57). So far, only a few cases of CSAHS in patients taking ticagrelor have been published [11–14] in France [11,12] and the United States [13,14]. Whenever the drug was withdrawn, (n = 5) the central sleep apnea greatly decreased [11–14], and, whenever the drug was reintroduced (n = 3), this side effect reoccurred [11,12]. A recent observational study [15] including 30 patients taking ticagrelor, performed 1 week after ACS, showed a prevalence of severe CSA (AHI ≥ 30) in 50% of the patients.

In a recent attempt to exonerate ticagrelor, Sabatine et al. [16] performed a post-hoc analysis of all randomized double-blinded clinical trials with ticagrelor and found no sleep apnea cases excess with ticagrelor. However, one can find only what one sets out to look for: a non-prespecified asymptomatic (or paucisymptomatic) adverse event such as CSA cannot emerge from a post hoc analysis. Therefore, in this study, the rate of sleep apnea (CSA + OSA) was much smaller than that usually observed in the general population after ACS (0.2% vs about 25%).

Table 2
Characteristics of patients with or without ticagrelor.

	Ticagrelor Group (n = 80)	No Ticagrelor Group (n = 41)	p
Age	55.6 ± 10.1	59.1 ± 12.0	0.08
Sex, male,n (%)	68 (80)	39 (95)	0.18
Delay ACS-PG (days), median [IQR]	55 [33–80]	40 [30–75]	0.53
BMI (kg/m2), mean ± SD	28.0 ± 4.3	29.0 ± 4.5	0.2
Diabetes, n (%)	16 [20]	11 (27)	0.32
High blood pressure, n (%)	23 (28)	18 (44)	0.78
LVEF (%), mean ± SD	56.4 ± 4.5	55.8 ± 5.9	0.54
LAD (mm) mean ± SD	36.1 ± 4.6	37.0 ± 5.1	0.3
IVS (mm) mean ± SD	9.5 ± 0.9	9.8 ± 1.3	0.2
E/e' ratio	7.8 ± 1.9	8.0 ± 2.0	0.7
BNP (pg/ml), median [IQR]	67 [36–169]	182 [35–277]	0.10
sPAP (mmHg), mean ± SD	31 ± 3	30 ± 4	0.25
Exercise test results, mean ± SD			
Resting heart rate (bpm)	65 ± 10	71 ± 11	0.003
Maximal heart rate (bpm)	118 ± 23	114 ± 21	0.36
Workload (watts)	129 ± 40	113 ± 43	0.06
Drugs			
Beta-blocker, n (%)	74 (92)	33 (80)	0.052
ACEI AAI, n (%)	62 (77)	30 (73)	0.6
MRA, n (%)	5 [6]	4 [10]	0.49
Diuretic, n (%)	0 (0)	3 [7]	0.01
Statin, n (%)	80 (100)	40 (97)	0.16
Ivabradin, n (%)	0 (0)	1 (2.5)	0.16
Benzodiazepin, n (%)	6 (7.5)	5 [12]	0.4
Polygraphy results, mean ± SD			
AHI	19.8 ± 17.8	13.9 ± 10.2	0.05
AI	9.4 ± 14	4.8 ± 6.5	0.004
HI	10.4 ± 8.7	9.2 ± 6.0	0.4
CAI	4.0 ± 7.4	1.3 ± 4.0	0.03
OAI	4.7 ± 10.2	3.3 ± 4.3	0.39
ODI	18.8 ± 17.2	14.5 ± 10	0.17
Mean SaO 2 (%)	93 ± 2.1	92.8 ± 0.6	0.6
Cheyne-Stokes score (min)	79 ± 76	69 ± 52	0.46

ACS: acute coronary syndrome, PG: polygraphy, BMI: body mass index, LVEF: left ventricular ejection fraction, Left atrial anteroposterior diameter, ISW: interventricular septum width, BNP: B-type natriuretic peptide sPAP: systolic pulmonary arterial pressure, RHR: resting heart rate, Max HR: maximal heart rate (during the exercise test), ACE-I angiotensin converting enzyme inhibitor. AAI: angiotensin antagonist inhibitor MRA: mineralocorticosteroid receptor antagonist, AHI apnea hypopnea index, AI: apnea index, HI: hypopnea index, CAI: central apnea index OAI: obstructive apnea index, ODI: oxygen desaturation index, SaO_2: oxygen saturation %.

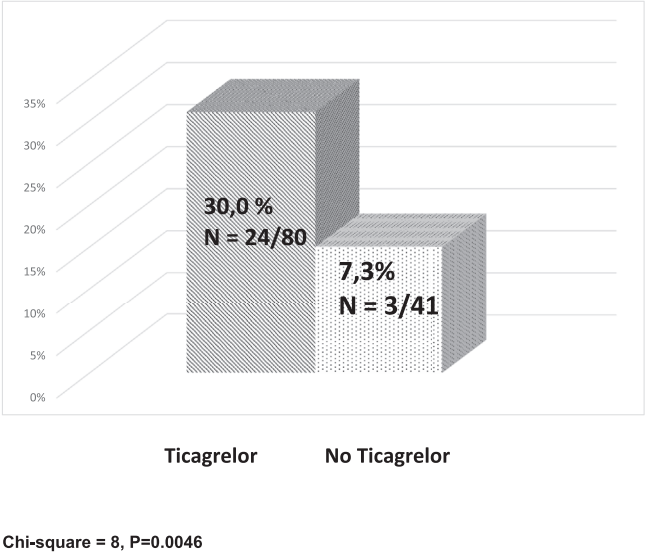

Fig. 2. Central sleep apnea (AHI > 15) rate: ticagrelor versus no ticagrelor. Chi-square = 8, P = 0.0046.

Regarding underlying mechanisms, the most probable explanation seems to be increased chemo-sensitivity to hypercapnia by a direct P2Y12 inhibitory effect on the central nervous system [13,17]. Moreover, ticagrelor seems to increase adenosine concentration and its biological activity [18], which stimulates pulmonary vagal C fibers, mediating the sensation of dyspnea, and thus provoking episodes of hyperventilation. Whatever the mechanism, the

Table 3
Univariable and multivariable analysis: factors associated with central sleep apnea.

	r	p
A Univariate analysis		
Age, years, mean ± SD	0.26	0.004
Gender Sex n (%)	0.1	0.2
Delay ACS-PG (days) [IQR]	0.06	0.5
Current smoker n (%)	0.1	0.2
Diabetes, n (%)	0.09	0.3
Known hypertension, n (%)	0.01	0.9)
BMI, kg/m^2, mean ± SD	0.05	0.6
LVEF, n (%)	0.08	0.41
LAD (mm), mean ± SD	0.01	0.8
IVS (mm), mean ± SD	0.1	0.3
E/e' ratio	0.05	0.5
sPAP (mm Hg)	0.07	0.5
BNP (pg/ml) [IQR 25–75]	0.09]	0.6
Ticagrelor, n (%)	0.25	0.005
Beta-blocker, n (%)	0.05	0.5
ACE-I/AAII n (%)	0.03	0.7
Benzodiazepine, n (%)	0.03	0.7
B Multivariate analysis		
Age	0.12	0.0007
Ticagrelor	0.26	0.0006

ACS: acute coronary syndrome. PG: polygraphy. OSAHS: obstructive sleep apnea hypopnea syndrome. CSAHS: central sleep apnea hypopnea syndrome. BMI: body mass index. Bpm: beat per minute. BNP: B-type natriuretic peptide, LVEF; left ventricular ejection fraction, Left atrial anteroposterior diameter, ISW: interventricular septum width, sPAP: systolic pulmonary artery pressure,ACE-I angiotensin converting enzyme inhibitor. AAI: angiotensin antagonist inhibitor.

Table 4
Imputability score determination [from Ref. [20]].

	Yes	No	Do not know	Score	References
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1	[6,8–12]
2. Did this adverse event appear after the suspected drug was administered?	+2	−1	0	+2	[6,8–12] + our results
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	−1	0	+1	[8–11]
4. Did the adverse reaction reappear when the drug was readministered?	+2	0	0	+2	[8,9]
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2	HF patients excluded in our study
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0	
10. Was the adverse event confirmed by any objective evidence[a]?	+1	0	0	+1	
TOTAL SCORE	**NA**	**NA**	**NA**	**9**	

Score ≤0: doubtful, 1 ≤ score ≤4: possible, 5 ≤ score ≤8: probable, score ≥9: sure.
HF: heart failure. NA: not applicable.
[a] Objective evidence (question 10) was polygraphy results.

subsequent ventilation overshoot elicits sufficient hypocapnia to cause apnea [19]. Once the central respiratory drive is withdrawn, apnea persists until PaCO2 increases above the apneic threshold.

Finally, to assess a drug's responsibility for the occurrence of an adverse reaction, an imputability score [20] can be calculated (Table 4). The score can range from zero (no imputability) to 13. For scores 5 to 8, the imputability is “probable” and from 9 to 13 “sure”. After examining the medical literature and our results, we calculated the imputability score for ticagrelor in causing CSAHS at 9 (“sure”).

Regarding, the severity of this ticagrelor adverse reaction, we must be cautious not to overestimate it and not have the same reasoning as for OSASH.

Indeed, the high prevalence and clinical significance of OSAHS in patients with coronary artery disease (whatever the disease stage) is well known and has been extensively studied: OSAHS has been found involved in endothelial dysfunction, inflammation and sympathetic activation which may promote ischemic events. Furthermore, this syndrome has been associated with worse prognosis [21]. However, this association is much less clear in patients with CSAHS, especially those without heart failure [19]. Furthermore, in the PLATO study [22], in patients with ACS with or without ST-segment elevation, as compared with clopidogrel, ticagrelor significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke. Because in this study more than 9000 patients received ticagrelor for 12 months, CSAHS, (even if it seems frequent in our study), did not seem to impair the good efficacy/tolerance balance of the drug. Therefore, in asymptomatic CSAHS patients, switching from ticagrelor to another P2Y12 inhibitor does not seem appropriate.

4.1. Limitations

Although the polygraphy reader was blinded to the treatment, our survey was monocentric and no central core reanalysis was performed. Furthermore, we did not no test after ticagrelor withdrawal (which would have been unethical in our opinion) and/or reintroduction.

Clearly our study was not designed to assess OSAHS prevalence after ACS. Indeed [1] OSA prevalence in the 69 patients excluded for heart failure, systolic LV dysfunction or high sPAP was not known and [2] we excluded patients with already treated OSA.

In conclusion, asymptomatic central sleep apnea may be associated with ticagrelor administration after ACS. Further multicentric studies should investigate the exact incidence, sustainability, and potential consequences of this side effect.

Authorship statement

PM planned, designed and conducted the study. He analysed the Data and has written the draft of the article. All authors co-designed the

Study during several meetings. All authors have co-conducted the study. All

Authors had full access to the data. All authors participated in the final

Writing of the paper. PM, JYT and ABD paid special attention to statistical analysis.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.01.026.

References

[1] Ludka O, Stepanova R, Vyskocilova M, et al. Sleep apnea prevalence in acute myocardial infarction. The sleep apnea in post-acute myocardial infarction patients study. Int J Cardiol 2014;176:13–9.
[2] Huang Z, Zheng Z, Luo Y, et al. Prevalence of sleep-disordered breathing in acute coronary syndrome: a systemic review and meta-analysis. Sleep Breath 2017;21:217–26.
[3] Hayashi H, Fukuma N, Kato K, et al. Clinical backgrounds and the time course of sleep disordered breathing in patients after myocardial infarction. J Nippon Med Sch 2013;80:192–9.
[4] Buchner S, Greimel T, Hetzenecker A, et al. Natural course of sleep disordered breathing after acute myocardial infarction. Eur J Respir 2012;40:1173–9.
[5] Mookadam F, Calvin AD, Somers VK. Prevalence and management of central sleep apnea in heart failure patients. Curr Heart Fail Rep 2008;5:233–7.
[6] Revol B, Jullian-Desayes I, Tamisier R, et al. Ticagrelor and central sleep apnea. J Am Coll Cardiol 2018;71:2378–9.
[7] Ponikowski P, Voors AA, Anker SD, et al., ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200. 2016 May 20.
[8] Berry R, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of sleep medicine. J Clin Sleep Med 2012;8:597–619.
[9] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American

Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imag 2015;16:233–70.
[10] Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009 Mar;10:165–93.
[11] Puel V, Theophile H, Godard I, et al. Ticagrelor and central sleep apnea: impact of withdrawal and reintroduction. Br J Clin Pharmacol 2019;85:1855–8.
[12] Paboeuf C, Priou P, Meslier N, et al. Ticagrelor-associated shift from obstructive to central sleep apnea: a case report. J Clin Sleep Med 2019:1179–82.
[13] Giannoni A, Emdin M, Passino C. Cheyne-Stokes respiration, chemo reflex , and Ticagrelor Related Dyspnea. N Engl J Med 2016;375(10):1004–6.
[14] Kado JMD, Farrehi P, et al. Central Sleep Apnea with Cheyne-Stokes breathing induced by use of ticagrelor. Sleep 2018;41. Abstract Supplement abstract n° 1139.
[15] Giannoni A, Borrelli C, Gentile F, et al. Central apnoeas and ticagrelor related dyspnoea in patients with acute coronary syndrome. Eur Heart J Cardiovasc Pharmacother 2020. https://doi.org/10.1093/ehjcvp/pvaa089. Jul 15:pvaa089 Epub ahead of print. PMID: 32667975.
[16] Sabatine M, Hiatt W, Goto S, et al. No significant relationship between ticagrelor and sleep apnea in large randomized blinded trials. JACC Cardiovasc Interv 2020;27(13):1012–4.
[17] Ortega-Paz L, Ariotti S, Akkerhuis KM, et al. Adenosine and ticagrelor plasma levels in patients with and without ticagrelor related dyspnea. Circulation 2018;138:646–8.
[18] Cattaneo M, Schulz R, Nylander S. Adenosine mediated effects of T icagrelor. J Am Coll Cardiol 2014;63:2503–9.
[19] Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. J Am Coll Cardiol 2017;69:841–58.
[20] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reaction. Clin Pharmacol Ther 1981;30:239–45.
[21] Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005 r 19-25;36:1046–53.
[22] Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.