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CIRCADIAN BLOOD PRESSURE PROFILE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ARTERIAL HYPERTENSION ON BASELINE THERAPY

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Abstract. Circadian blood pressure profile in patients with chronic obstructive pulmonary disease and arterial hypertension on baseline therapy. Konopkina L.I., Dziublyk Ya.O., Babets A.A., Shchudro O.O. *The aim of the study was to analyse the effect of a long-acting muscarinic antagonist and an inhaled corticosteroid on the circadian profile, blood pressure (BP) variability, and circadian rhythm disturbances in patients with chronic obstructive pulmonary disease (COPD) and concomitant arterial hypertension, based on ambulatory blood pressure monitoring (ABPM) data during long-term use of these therapies. A total of 86 patients with COPD of GOLD stage II and III (Global Initiative for Chronic Obstructive Lung Disease) and stage II hypertension (men – 67 (77.9%), women – 19 (22.1%), mean age – 62 (56; 74) years) in a stable phase of the disease were examined. All patients received continuous combined antihypertensive therapy, which remained unchanged for at least 6 months. Depending on the degree of bronchial obstruction and the type of inhalation therapy, patients were divided into three subgroups: subgroup 1 included 34 patients with GOLD stage II airflow limitation who received only a bronchodilator (tiotropium bromide 18 μg per day); subgroup 2 included 23 patients with GOLD stage III airflow limitation who received both a bronchodilator (tiotropium bromide 18 μg/day) and an inhaled corticosteroid (ICS) (beclometasone dipropionate 250 μg twice daily); subgroup 3 included 29 patients with GOLD stage III airflow limitation who received only a bronchodilator (tiotropium bromide 18 μg/day), despite indications for combined therapy. All patients achieved target office blood pressure levels (<140/90 mmHg); however, ABPM revealed elevated mean daily blood pressure (>130/80 mmHg) in 60 out of 86 patients (69.8%), predominantly in subgroup 2 ($p<0.05$). At night, mean diastolic blood pressure in subgroup 2 was 67 (57; 79) mmHg, higher than in subgroup 1 (60 (51; 69) mmHg; $p<0.05$). Blood pressure variability also increased with severe bronchial obstruction: in subgroup 3, night-time systolic BP variability reached 14 (13; 17) mmHg ($p<0.05$ vs. other groups). A normal circadian profile ("dipper") was observed in 25 patients (41.7%), whereas pathological types were recorded in 35 patients (58.3%) – "non-dipper" and "night-peaker" in 33 cases (94.3%) and "over-dipper" in 2 cases (5.7%). Disturbances in nocturnal blood pressure reduction were most frequent in subgroup 2 ($p<0.05$). Thus, patients with COPD and clinically stable (medically compensated) concomitant hypertension generally exhibit normal office blood pressure values. However, nearly 70% of such patients show elevated night-time blood pressure according to ABPM. Patients receiving ICS for COPD therapy predominantly demonstrate pathological circadian BP patterns ("non-dipper" and "night-peaker"), whereas a normal circadian BP pattern ("dipper") is more frequent in patients treated with a long-acting muscarinic antagonist as baseline COPD therapy ($p<0.05$). In patients with COPD and concomitant hypertension, blood pressure should be monitored not only by office measurements but also using ABPM; in cases of ABPM abnormalities, patients require dynamic follow-up by a cardiologist.*

Реферат. Добовий профіль артеріального тиску в пацієнтів із хронічним обструктивним захворюванням легень та гіпертонічною хворобою на тлі базисної терапії. Конопкіна Л.І., Дзюблик Я.О., Бабець А.А., Щудро О.О. *Метою дослідження було проаналізувати вплив холінолітика тривалої дії та інгаляційного кортикостероїда на добовий профіль, варіабельність артеріального тиску (АТ) та циркадні порушення у хворих на хронічне обструктивне захворювання легень із супутньою гіпертонічною хворобою за даними добового моніторингу артеріального тиску (ДМАТ) при тривалому їх застосуванні. Було обстежено 86 хворих на хронічне обструктивне захворювання легень (ХОЗЛ) з II та III ступенем вентиляційних порушень за класифікацію GOLD (Global Initiative for Chronic Obstructive Lung Disease) із гіпертонічною хворобою (ГХ) II стадії (чоловіків – 67 (77,9%), жінок – 19 (22,1%), середній вік – 62 (56; 74) роки) у стабільну фазу патологічного процесу. Усі пацієнти постійно приймали комбіновану антигіпертензивну терапію, що залишалася незмінною щонайменше 6 місяців. Залежно від ступеня бронхообструкції та виду інгаляційної терапії пацієнтів розподілили на три підгрупи: до підгрупи 1 увійшло 34 пацієнти з II ступенем вентиляційних порушень за GOLD, які приймали лише бронходилататор (тіотропію бромід 18 мкг/добу); до підгрупи 2 – 23 пацієнти з III ступенем вентиляційних порушень за GOLD, які приймали як бронходилататор (тіотропію бромід 18 мкг/добу), так й інгаляційний глюкокортикостероїд (ІКС) (беклометазону дипропіонат по 250 мкг/добу двічі на добу); до підгрупа 3 – 29 пацієнтів з III ступенем вентиляційних порушень, які приймали лише бронходилататор (тіотропію бромід 18 мкг/добу), попри показання до комбінованої терапії. За офісним АТ усі пацієнти досягали цільових рівнів (<140/90 мм рт. ст.), проте за даними ДМАТ в 60 з 86 осіб (69,8%) виявлено підвищення середньодобових значень АТ (>130/80 мм рт. ст.), переважно в підгрупі 2 (p<0,05). У нічний час середня величина діастолічного АТ в підгрупі 2 становила 67 (57; 79) мм рт. ст. і була вищою, ніж у підгрупі 1 (60 (51; 69) мм рт. ст.; p<0,05). Варіабельність АТ також зростала при тяжкій бронхообструкції: у підгрупі 3 нічна варіабельність систолічного АТ досягала 14 (13; 17) мм рт. ст. (p<0,05 порівняно з іншими групами). Нормальний циркадний профіль «dipper» відзначався у 25 (41,7%) пацієнтів, тоді як у 35 (58,3%) зафіксовано патологічні типи («non-dipper» та «night-peaker» – 33 (94,3%) випадки; «over-dipper» – 2 (5,7%) випадки). Найчастіше порушення нічного зниження АТ траплялися в підгрупі 2 (p<0,05). Таким чином, у хворих на ХОЗЛ із клінічно стабільним (медикаментозно компенсованим) перебігом коморбідної ГХ зазвичай спостерігаються нормальні показники офісного АТ. Майже в 70% хворих на ХОЗЛ із клінічно стабільним (медикаментозно компенсованим) перебігом коморбідної ГХ за даними ДМАТ спостерігається підвищення рівня АТ в нічний період часу. У пацієнтів, що приймають ІКС для лікування ХОЗЛ, домінують патологічні циркадні ритми АТ «non-dipper» та «night-peaker»; нормальний тип циркадного ритму АТ «dipper» частіше спостерігається в пацієнтів, що в якості базисної терапії ХОЗЛ приймають холінолітик тривалої дії (p<0,05). У хворих на ХОЗЛ із коморбідною ГХ слід контролювати АТ не лише шляхом вимірювання офісного рівня показника, а й за даними ДМАТ; при наявності порушень АТ за ДМАТ пацієнти потребують динамічного спостереження кардіологом.*

One of the key challenges in the management of patients with chronic obstructive pulmonary disease (COPD) is the presence of comorbid conditions that may, through multiple mechanisms, influence the course of the primary disease. Conversely, medications used by patients for the treatment of COPD may affect the course of comorbidities, potentially leading to their decompensation.

Among the comorbidities most frequently observed in patients with COPD is arterial hypertension (AH), which, according to population-based studies, is reported in 50-70% of cases [1, 2]. The presence of such comorbidity may aggravate the overall condition of patients, impair gas exchange, and increase the risk of developing cardiovascular complications [3, 4]. This necessitates monitoring not only the effectiveness of COPD pharmacotherapy but also its cardiovascular safety, particularly during long-term drug use.

The presence of AH in patients with COPD significantly complicates patient management, as both diseases share interrelated pathophysiological mechanisms of development and progression. These include chronic systemic inflammatory response, oxidative stress, activation of the sympathoadrenal system, endothelial dysfunction, and vascular remodelling [5, 6]. In addition, these patients exhibit an increased prevalence of disturbances in the circadian rhythm of blood pressure (BP), which is associated with a higher risk of cardiovascular complications [7, 8].

Ambulatory blood pressure monitoring (ABPM) is recognised as the “gold standard” for assessing hypertension control, determining the type of circadian BP profile, including its variability, identifying nocturnal hypertension, and recording atypical circadian patterns (“non-dipper”, “over-dipper”, “night-peaker”) [9]. It should be noted that, according to a multicentre clinical study by Yang W. et al., disturbances of the circadian blood pressure profile in patients with respiratory pathology are associated with higher mortality, in contrast to clinical situations with isolated elevation of office BP only [10].

It is well known that inhalation therapy, which forms the cornerstone of treatment for patients with COPD, may have varying effects on systemic haemodynamics. It has been demonstrated that both short-acting and long-acting β_2-agonists (LABA) can frequently cause a significant increase in heart rate, whereas long-acting muscarinic antagonists (LAMA),

in particular tiotropium bromide, have only minimal systemic cardiac effects [11]. Inhaled corticosteroids (ICS) have garnered particular attention from researchers: despite their primarily local action, a fraction is absorbed into the systemic circulation, where it may influence adrenal function, vascular tone, and metabolic processes [12]. According to the results of international clinical trials, the use of ICS in combination with bronchodilators by COPD patients leads to improved lung ventilatory function and reduced frequency of COPD exacerbations; however, it may also influence the occurrence of cardiovascular events [13, 14, 15].

Despite the large number of studies devoted to the efficacy and safety of pharmacotherapy for COPD, only a limited number have focused on the impact of inhalation therapy on BP parameters, particularly in patients with concomitant AH. Some publications report the potential for elevated nocturnal BP in patients receiving ICS, although these findings require further clarification [16, 17, 18]. On the other hand, research results indicate a possible reduction in hypertensive load against the background of bronchodilator therapy, owing to improved lung ventilatory function, reduced hypoxia, and secondary normalisation of neurohumoral activity [19, 20].

Thus, investigating the effect of inhalation therapy (inhaled bronchodilators and ICS) on ABPM parameters is not only scientifically justified but also of practical importance for optimising the management of patients with COPD and concomitant AH.

The aim of this study was to analyse the effect of a long-acting muscarinic antagonist and an inhaled corticosteroid on the circadian blood pressure profile, blood pressure variability, and circadian rhythm disturbances in patients with chronic obstructive pulmonary disease and concomitant arterial hypertension, based on ambulatory blood pressure monitoring data during long-term use of these therapies.

MATERIALS AND METHODS OF RESEARCH

A total of 86 patients with COPD with stage II and III ventilatory impairment according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification and stage II AH were examined (67 men (77.9%), 19 women (22.1%), middle age 62 (56; 74) years). The study was conducted between 2018 and 2021.

The clinical diagnosis of COPD was established in accordance with national [21] and international guidelines [22]. The clinical diagnosis of AH was established in accordance with the current national protocol [9].

Patients were eligible for inclusion if they met the following criteria:

1) age over 40 years;

2) confirmed diagnosis of COPD;

3) scheduled use of ICS and/or LAMA for at least the last 6 months;

4) presence of stage II or III ventilatory impairment at the time of examination;

5) confirmed diagnosis of stage II AH;

6) scheduled use of antihypertensive medications for BP stabilisation for at least the last 6 months;

7) signed informed consent to participate in the study and for the processing of personal data.

Patients were excluded from the study if they had any of the following:

1) decompensation of any comorbid condition;

2) infectious exacerbation of COPD at the time of examination or within the previous 6 months;

3) use of LABA during the last 6 months;

4) presence of severe comorbid cardiovascular pathology that could mask or distort the clinical manifestations of COPD;

5) hypertensive crises within the last 6 months;

6) pulmonary thromboembolism at the time of examination or documented in the medical history;

7) presence of other chronic respiratory diseases in medical history (bronchial asthma, idiopathic pulmonary fibrosis, cystic fibrosis, etc.);

8) oncological disease.

At the stage of patient enrolment, complaints were collected; medical history data regarding both COPD and AH were assessed; the volume of prescribed inhalation pharmacotherapy for COPD was evaluated (according to the degree of ventilatory impairment, severity of clinical symptoms, and the number and severity of COPD exacerbations during the year preceding the initiation of planned therapy); the actual COPD therapy received by the patients during at least the last 6 months was assessed; the effectiveness of inhalation pharmacotherapy for COPD (ICS and/or LAMA) was analysed based on clinical symptoms and spirometric parameters; the volume of antihypertensive therapy was assessed; the patients' objective clinical status and the results of general clinical examinations were also evaluated.

Since all patients had the same stage of AH and were receiving comparable antihypertensive therapy for BP control, the distribution into subgroups was based solely on the actual COPD maintenance therapy received and the achieved treatment effectiveness. Thus, the patients were divided into three subgroups.

Subgroup 1 included 34 patients (29 men (85.3%), 5 women (14.7%), middle age 57 (53; 61) years) who, at the time of initiation of therapy, required only a bronchodilator (did not require ICS and had never received it), as they had stage II ventilatory impairment of obstructive type according to the GOLD classification (50% of predicted $<FEV_1<$80% of predicted) [22]. All patients were prescribed a LAMA

(tiotropium bromide – 18 μg per day), which they had been taking continuously for at least 6 months. At the time of enrolment, the median FEV_1 level also corresponded to stage II ventilatory impairment according to GOLD (see below).

Subgroup 2 included 23 patients (16 men (69.6%), 7 women (30.4%), middle age 60 (54; 65) years) who, at the time of initiation of therapy, required both ICS and a bronchodilator, as they had stage III ventilatory impairment of obstructive type according to the GOLD classification (30% of predicted <FEV_1<50% of predicted) [22]. All patients were prescribed combination therapy consisting of ICS (beclometasone dipropionate 250 μg twice daily) and a LAMA (tiotropium bromide – 18 μg per day). After at least 6 months of continuous therapy, the patients achieved a mean FEV_1 level corresponding to stage II obstructive ventilatory impairment according to GOLD (see below).

Subgroup 3 included 29 patients (22 men (75.9%), 7 women (24.1%), middle age 64 (55; 67) years) who, at the time of initiation of therapy, required both ICS and a bronchodilator, as they had stage III ventilatory impairment of obstructive type according to the GOLD classification (30% of predicted <FEV_1<50% of predicted) [22]. As in the previous subgroup, all patients were prescribed combination therapy consisting of ICS (beclometasone dipropionate 250 μg twice daily) and LAMA (tiotropium bromide – 18 μg per day); however, for various reasons, during at least 6 months they received only bronchodilator therapy and did not take ICS. This was due to poor treatment adherence, refusal of ICS because of concerns about adverse effects and/or financial constraints. Thus, the formation of this subgroup was not a result of targeted selection but rather reflected the real-world clinical situation of insufficient adherence to prescribed therapy. After the completion of the study assessments, all patients underwent a follow-up consultation and were once again advised on appropriate combination therapy in accordance with current clinical protocols. At the time of enrolment, the median FEV_1 level still corresponded to stage III obstructive ventilatory impairment according to GOLD (see below).

The subgroups were comparable with respect to age and sex ($p>0.05$).

With regard to stage II arterial hypertension, all patients were on continuous combination antihypertensive therapy (either perindopril/indapamide, losartan/hydrochlorothiazide, or valsartan/hydrochlorothiazide). The therapy had remained unchanged for at least 6 months. Against this background of antihypertensive treatment, the patients remained clinically stable and, according to the results of home BP monitoring performed during daytime, achieved target blood pressure levels (<135/85 mmHg) [9].

The examination of patients included general clinical methods (collection of complaints, medical history, and physical examination), as well as assessment of lung ventilatory function by computerised spirometry with measurement of the flow-volume loop using a Master Screen Body/Diff device (Jager, Germany) in the morning on an empty stomach after 30 minutes of rest. Analysis of the spirometric results was performed in accordance with international [23] and national [24] standards.

To assess cardiovascular safety, specifically the effect of inhalation pharmacotherapy for COPD (ICS and/or LAMA) on BP levels, patients underwent office BP measurements as well as ABPM.

Office BP measurement was performed using a mechanical sphygmomanometer with an upper-arm cuff. ABPM was conducted using the oscillometric method with an ABPpro device (IMESC LLC, Ukraine); the monitoring period lasted 24-27 hours. A standard adult cuff was used, with a deflation rate of 5 mm Hg/sec. The interval between measurements was 15 minutes during the active daytime period (07:00 to 23:00) and 30 minutes during the night-time rest period (23:00 to 07:00).

The main parameters assessed by ABPM were:

- mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values during daytime and night-time periods, which allow evaluation of the baseline level of haemodynamics and the degree of BP control;
- SBP and DBP variability, which is an important indicator of BP stability throughout the period and is associated with the risk of complications;
- time indexes (TI), which characterise the total number of episodes exceeding the reference BP values during daytime and night-time periods, as well as the daily index, by means of which circadian rhythm disturbances could be assessed.

The clinical study was approved by the Bioethics Committee of Dnipro State Medical University (Protocol No. 4 dated 25 October 2017) and was conducted with written informed consent from all participants, in accordance with the principles of bioethics outlined in the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and the "Universal Declaration on Bioethics and Human Rights" (UNESCO).

The obtained results were processed using standard methods of variation series analysis, including calculation of the median (Me) with upper and lower quartiles (25%; 75%). To compare quantitative variables in unrelated samples with non-normal distribution, the Kruskal-Wallis test was used; when a statistically significant difference was detected by this test, Dunn's post hoc test was applied to identify between which medians the difference was significant.

For comparison of quantitative variables in related samples, the Wilcoxon signed-rank test was used. For qualitative variables in unrelated samples, Pearson's χ^2 (chi-squared) test of independence was applied, including Yates' correction for continuity when values were close to 0. Differences between the compared values were considered statistically significant at $p<0.05$. Calculations were performed using Statistica 6.1 software (StatSoft, USA, No. 31415926535897) [25].

RESULTS AND DISCUSSION

When evaluating the clinical effectiveness of inhalation therapy in patients with COPD, we found that the use of LAMA (tiotropium bromide) as monotherapy for at least 6 consecutive months resulted in a reduction in the severity of dyspnoea and cough and an overall improvement in patients' quality of life, although lung ventilatory function parameters changed insignificantly ($p>0.05$). This observation applied to patients with stage II ventilatory impairment according to GOLD (subgroup 1) as well as those with stage III ventilatory impairment according to GOLD (subgroup 3) at the stage of initiation of pharmacological therapy (Table 1).

The use of combination therapy including ICS and LAMA (beclometasone dipropionate + tiotropium bromide) (subgroup 2) promoted a better restoration of lung ventilatory function, which was characterised by a statistically significant increase in FEV_1 levels: prior to the initiation of therapy, the severity of bronchial obstruction in these patients corresponded to stage III according to GOLD, whereas after at least 6 months of treatment it corresponded to stage II according to GOLD (Table 1). It should be emphasised, however, that the marked improvement in spirometric indices in this subgroup of patients does not imply that ICS should be discontinued; rather, it indicates that ICS-containing combination therapy is effective for treating this category of patients and should be continued.

Table 1

Dynamics of Lung Ventilatory Function Parameters in Patients with COPD during Inhalation Pharmacotherapy, Me (25%;75%)

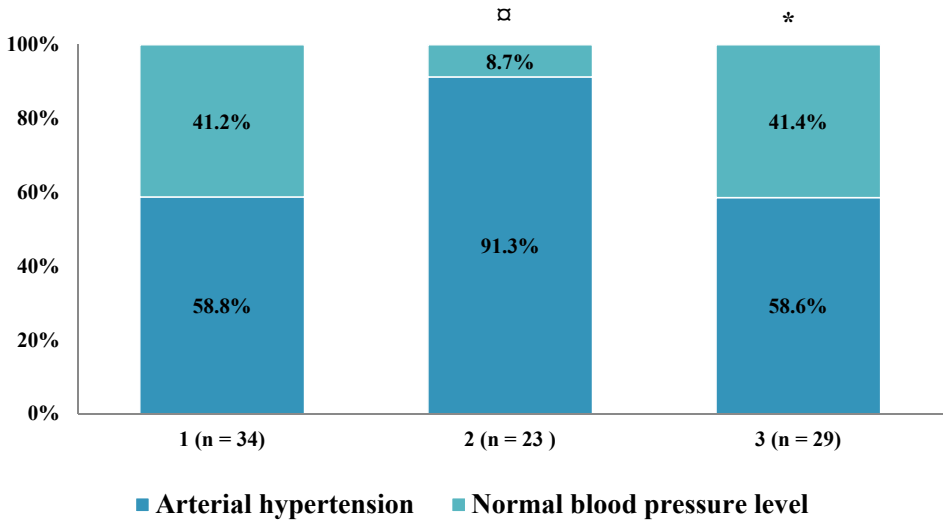
Seq. No.	Parameters	Subgroups of patient					
		1 (n=34)		2 (n=23)		3 (n=29)	
		before initiation of therapy	at the stage of study enrolment	before initiation of therapy	at the stage of study enrolment	before initiation of therapy	at the stage of study enrolment
1.	FEV_1, % of predicted value	56 (52; 62)	60 (55; 67)	45 (42; 49)	54 (51; 59)*	41 (35; 46)	44 (32; 47)
2.	FEV_1/FVC ratio	0.44 (0.40; 0.48)	0.45 (0.41; 0.49)	0.41 (0.37; 0.45)	0.44 (0.39; 0.48)	0.38 (0.32; 0.42)	0.40 (0.33; 0.44)

Note. * – $p<0.05$ according to the Wilcoxon signed-rank test.

When analysing office blood pressure levels, it was found that all examined patients had achieved target BP levels (for office BP, the target level is <140/90 mmHg [9]). In contrast, analysis of ABPM data revealed that in the vast majority of patients with COPD and comorbid arterial hypertension (60 out of 86 patients (69.8%)), target BP levels were not achieved (for ABPM, <130/80 mmHg [9]), with the largest proportion of such patients belonging to subgroup 2 ($p<0.05$) (Fig. 1). Thus, only ABPM results of patients with elevated BP levels were selected for further analysis – a total of 60 individuals: 20 (33.3%) from subgroup 1, 21 (35.0%) from subgroup 2, and 19 (31.7%) from subgroup 3.

The mean SBP and DBP values during the active daytime period were comparable across patient subgroups ($p>0.05$). However, at night, the mean DBP value in subgroup 2 was statistically significantly higher than in subgroup 1 ($p<0.05$) and did not differ from the level observed in subgroup 3 ($p>0.05$) (Table 2).

According to our analysis, during the active daytime period, the medians of SBP and DBP variability did not exceed the reference values and were comparable across all patient subgroups ($p>0.05$). In contrast, during the night-time period, the medians of SBP and DBP variability in subgroup 3 were significantly higher than in subgroups 1 and 2 ($p<0.05$), exceeding the reference values (Table 2).



¤ – $p_{1-2} < 0.05$ between subgroups according to the χ^2 (chi-squared) test; * – $p_{2-3} < 0.05$ between subgroups according to the χ^2 (chi-squared) test.

Fig. 1. Prevalence of elevated BP according to ABPM data in patients with COPD and comorbid AH

The number of episodes of elevated BP, as assessed by SBP and DBP time indexes, was similar across patient subgroups during the active daytime period and remained within the reference range. In contrast, during the night-time period, these parameters in subgroup 1 were significantly lower than in subgroups 2 and 3 ($p<0.05$) (Table 2).

Table 2

Levels of ABPM Parameters in Patients with COPD and Comorbid AH, Me (25%; 75%)

№ з/п	Parameters	Reference values	Subgroups			p
			1 (n=20)	2 (n=21)	3 (n=19)	
1.	Mean SBP (daytime), mmHg	≤135	126 (119; 145)	132 (123; 139)	128 (124; 143)	>0.05
2.	SBP variability (daytime), mmHg	<15	10 (8; 12)	11 (8; 12)	9 (8; 13)	>0.05
3.	Mean SBP (night-time), mmHg	≤120	110 (105; 123)	114 (104; 125)	109 (106; 122)	<0.05
4.	SBP variability (night-time), mmHg	<15	10 (7; 12)	10 (7; 11)	14 (13; 17)*	<0.05
5.	Mean DBP (daytime), mmHg	≤85	70 (65; 73)	75 (63; 89)	67 (62; 76)	>0.05
6.	DBP variability (daytime), mmHg	<14	9 (6; 11)	10 (8; 12)	10 (7; 12)	>0.05
7.	Mean DBP (night-time), mmHg	≤70	60 (51; 69)	67 (57; 79)¤	63 (53; 71)	<005
8.	DBP variability (night-time), mmHg	<12	8 (5; 10)	9 (8; 11)	13 (10; 15)*	<0.05
9.	TI of SBP (daytime), %	<25	15.4 (9.2; 29.4)	22.6 (15.7; 37.5)	23.7 (11.8; 33.3)	>0.05
10.	TI of SBP (night-time), %	<25	27.4 (13.7; 36.6)	46.7 (22.1; 61.2)¤	34.9 (16.8; 49.8)	<0.05
11.	TI of DBP (daytime), %	<15	7.4 (5.9; 10.3)	10.9 (5.7; 13.6)	11.9 (7.2; 17.4)	>0.05
12.	TI of DBP (night-time), %	<15	23.5 (10.1; 37.9)	44.1 (22.1; 59.8)¤	33.8 (37.7; 77.4)*	<0.05

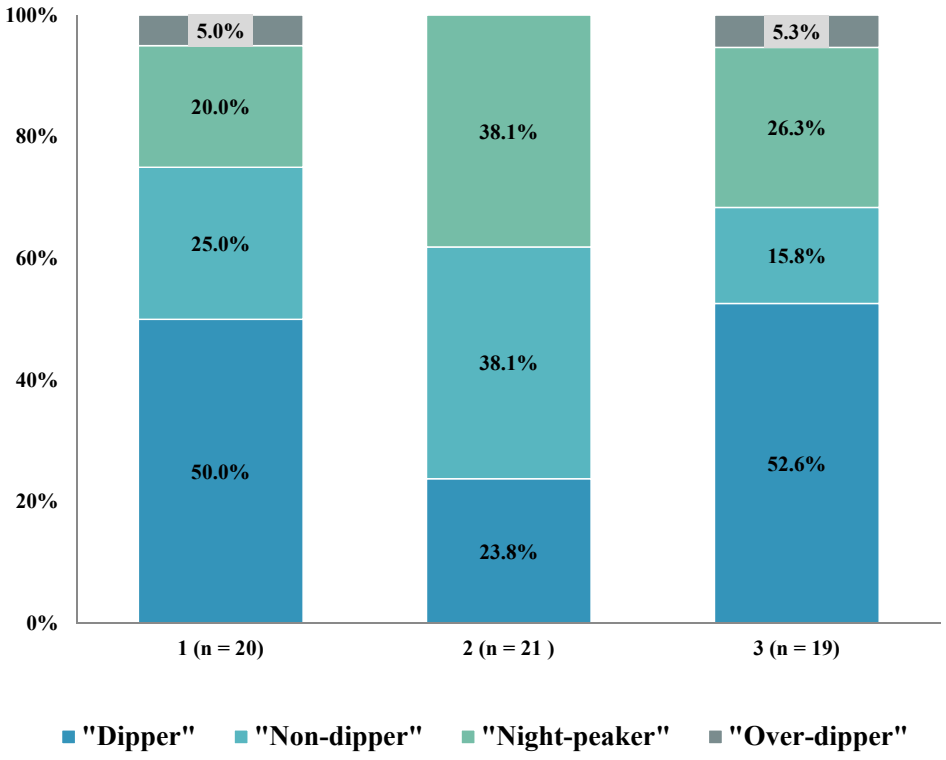
Notes: p – between subgroups according to the Kruskal-Wallis test; ¤ – $p_{1-2} < 0.05$ between subgroups according to Dunn's post hoc test; * – $p_{2-3} < 0.05$ between subgroups according to Dunn's post hoc test.

Thus, while office BP measurements in patients with COPD and comorbid AH receiving antihypertensive therapy demonstrated stabilisation of BP with achievement of target levels, ABPM data revealed haemodynamic disturbances in nearly 70% of patients. Although the haemodynamic profile during the active daytime period was stable regardless of the degree of bronchial obstruction and the type of COPD pharmacotherapy (ICS and/or LAMA), during the night-time period patients with severe bronchial obstruction (stage III according to GOLD) exhibited a marked increase in BP variability. This may be associated with progressive hypercapnia and hypoxaemia occurring specifically at night, which in turn affects sympathoadrenal system activity [12, 17, 20]. In patients with less severe bronchial obstruction (stage II according to GOLD), BP variability did not exceed the reference range; however, those receiving ICS (subgroup 2) more frequently demonstrated increased hypertensive load, which may be related to the partial systemic effect of ICS.

When analysing the daily BP profile according to the degree of nocturnal SBP and DBP reduction, we found that the normal circadian BP type "dipper" was observed in 41.7% of cases overall – in 25 out of 60 patients, including 10 patients each from subgroups 1 and 3 and 5 patients from subgroup 2 (Fig. 2).

A pathological circadian BP rhythm was observed in the majority of the patients examined (35 out of 60 (58.3%)): the predominant types were hypertensive daily BP profiles – "non-dipper" or "night-peaker" (in 33 patients (94.3%)), whereas excessive nocturnal BP reduction ("over-dipper" type) was found in only 2 patients (5.7%) ($p<0.05$).

Subgroup analysis showed that the circadian BP types "non-dipper" and "night-peaker" were most frequently observed in subgroup 2 ($p<0.05$) (Fig. 2).



$p<0.05$ – between subgroups according to the χ^2 (chi-squared) test.

Fig. 2. Circadian BP types according to ABPM data in patients with COPD and comorbid AH

Thus, in patients with COPD and comorbid AH, various circadian rhythm types of the daily BP profile were observed. In patients receiving ICS as part of their maintenance COPD therapy, disturbances of the daily BP profile ("non-dipper" or "night-peaker") occurred more frequently, which may indicate a systemic effect of these drugs and highlight the need for BP monitoring not only during the daytime but especially at night.

Our findings indicate that in most patients with COPD and comorbid AH, despite achieving target office BP values while receiving maintenance antihypertensive therapy, ABPM data demonstrate insufficient BP control, particularly during the

night-time period. The discrepancy between office and BP measurements highlights the necessity of performing ABPM at least once a year or when inhalation therapy is modified in this patient category, since nocturnal hypertension and atypical circadian BP patterns are associated with increased cardiovascular risk.

The most pronounced disturbances of the daily BP profile in patients with COPD, particularly elevated nocturnal BP values and increased hypertensive load, are observed in patients receiving ICS-containing therapy. This is consistent with the literature data on the potential systemic effects of ICS, which may contribute to increased vascular tone, worsening of metabolic changes, and disruption of circadian rhythm regulation [16, 17, 18].

Our clinical study expands the understanding of the potential cardiohaemodynamic consequences of inhalation pharmacotherapy for COPD, particularly under conditions of ICS and/or LAMA use.

In patients with severe bronchial obstruction (stage III according to GOLD), increased BP variability and time indexes were observed during the night-time period. This is likely due to the intensification of hypoxia and hypercapnia in this cohort of patients, particularly at night, which affects sympathoadrenal system activity and leads to impaired vascular reactivity. It cannot be excluded that in some patients with severe obstruction, pulmonary hypertension develops, which has its own pathogenetic mechanisms. According to M.M. Dolzhenko [26], pathological daily BP profile types ("non-dipper" and "night-peaker") are most frequently observed in patients with pulmonary hypertension, which is consistent with our findings and confirms the role of chronic respiratory pathology in the development of circadian BP regulation disorders.

At the same time, in patients with COPD and stage II bronchial obstruction according to GOLD who receive LAMA therapy, the physiological circadian BP profile type – "dipper" – is more frequently observed. This is most likely due to better lung ventilatory function, less pronounced hypoxic impact, and more balanced neurohumoral regulation.

Thus, the combination of COPD and AH requires not only a personalised approach to the prescription of COPD inhalation therapy according to the degree of bronchial obstruction, but also consideration of the potential impact of this therapy on the daily BP profile. Consequently, performing ABPM in this patient category ensures timely diagnosis of latent uncontrolled BP, detection of atypical circadian BP patterns, and enables identification of patients at high risk of cardiovascular events, allowing for timely adjustment of both COPD and antihypertensive therapy.

CONCLUSIONS

1. In patients with chronic obstructive pulmonary disease and clinically stable (pharmacologically compensated) comorbid arterial hypertension, office blood pressure parameters are generally within the normal range.
2. In nearly 70% of patients with chronic obstructive pulmonary disease and clinically stable (pharmacologically compensated) comorbid arterial hypertension, ambulatory blood pressure monitoring reveals elevated blood pressure levels during the night-time period.
3. Among patients receiving inhaled corticosteroids for the treatment of chronic obstructive pulmonary disease, pathological circadian blood pressure rhythms – "non-dipper" and "night-peaker" – predominate, whereas the normal "dipper" pattern is observed more frequently in those receiving long-acting muscarinic antagonist therapy as maintenance treatment for chronic obstructive pulmonary disease ($p < 0.05$). These findings underscore the need for further research to optimise chronic obstructive pulmonary disease management in patients with arterial hypertension, with particular consideration of its impact on circadian blood pressure regulation.
4. In patients with chronic obstructive pulmonary disease and comorbid arterial hypertension, blood pressure should be monitored not only by office measurements but also by ambulatory blood pressure monitoring. In the presence of blood pressure abnormalities detected by ambulatory blood pressure monitoring, patients require dynamic follow-up by a cardiologist.

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