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Cardiovascular Risk and the Effect of CPAP Therapy in Patients with Obstructive Sleep Apnea Syndrome

DISSERTATION ABSTRACT

of a dissertation thesis for the award of the educational and scientific degree "Doctor"

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The dissertation thesis is written on 158 typewritten pages, including 14 tables, 31 figures. The bibliography contains 277 references, of which 1 in Cyrillic and 276 in Latin script.

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The dissertation materials are available to interested parties at the Library of MU Pleven and on the university website – www.mu-pleven.bg.

The public defense of the dissertation thesis will take place on 02 Oct 2026 at 14:30 in hall..... , Medical University-Pleven.

CONTENTS

ABBREVIATIONS USED

AH – arterial hypertension

BP – blood pressure

AHI – apnea-hypopnea index

BQ – Berlin Questionnaire

SCD – sudden cardiac death

UAW – upper airways

IHD – ischemic heart disease

ODI – oxygen desaturation index

IS – ischemic stroke

OAI – obstructive apnea index

BMI – body mass index

MAI – mixed apnea index

HI – hypopnea index

CAI – central apnea index

SDB – sleep-disordered breathing

OSA – obstructive sleep apnea

EDS – excessive daytime sleepiness

AF – atrial fibrillation

HR – heart rate

CSA – central sleep apnea

EF – left ventricular ejection fraction

NC – neck circumference

MRI – magnetic resonance imaging

EDSS - Expanded Disability Status Scale

ESS - Epworth Sleepiness Scale

NIHSS - National Institutes of Health Stroke Scale

SD - Standard deviation

SO2 – oxygen saturation

AHI – apnea-hypopnea index, the sum of all apneas and hypopneas per hour of recording

ASP – average sleep propensity

AAI – Autonomic Arousal Index, calculation of the autonomic microarousal index
AF – atrial fibrillation
ABPM – 24-hour ambulatory blood pressure monitoring
ACE inhibitor – angiotensin-converting enzyme inhibitors
ARB – angiotensin receptor blocker
BP – blood pressure
BNP – natriuretic peptide
CRI – Cardiac Risk Index, the cardiovascular risk index
CCB – calcium antagonists, calcium channel blockers
CKD – chronic kidney disease
CRT – cardiac resynchronization therapy
DBP – diastolic blood pressure
EF – ejection fraction
HBPM – home blood pressure monitoring
HMOD – Hypertension-Mediated Organ Damage, organ damage mediated by arterial hypertension
HFpEF – heart failure with preserved ejection fraction
HFmrEF – heart failure with mid-range ejection fraction
LA – left atrium
LAVI – left atrial volume index
LV – left ventricle
LVH – left ventricular hypertrophy
LVMI – left ventricular mass index
LVESV – left ventricular end-systolic volume
LVEDV – left ventricular end-diastolic volume
LVEF – left ventricular ejection fraction
MAP – mean arterial blood pressure
NT-proBNP – N-terminal pro-B-type natriuretic peptide
PVCs – supraventricular extrasystoles
RA – right atrium
RV – right ventricle
SBP – systolic blood pressure
SCORE - Systematic COronary Risk Evaluation
VT – ventricular tachycardia
TAPSE – tricuspid annular plane systolic excursion
PAD – peripheral arterial disease

Introduction

Sleep-disordered breathing (SDB) encompasses several conditions: habitual snoring, obstructive sleep apnea (OSA), central sleep apnea, obstructive sleep apnea syndrome (i.e., OSA with daytime symptoms), Cheyne-Stokes breathing, and sleep hypoventilation syndrome.

Obstructive sleep apnea is a common but still insufficiently recognized and diagnosed respiratory problem related to sleep, which affects mainly middle-aged men. It disrupts the quality of sleep and the health of approximately 2–4% of adults (Georgiev, 2013).

Sleep-disordered breathing is often underestimated as a risk factor for systemic complications and therefore remains undiagnosed in primary outpatient care (Kramer et al., 1999). Although OSA was defined as a syndrome more than three decades ago, only in the last ten years has the problem attracted serious attention from both the medical community and the public (Chervin et al., 1996). Even with increasing awareness among medical specialists, a large proportion of patients with treatable but undetected OSA remains untreated (Chervin et al., 1996; Redline et al., 1998; Silverberg et al., 1998). The prevalence of the disease among middle-aged men is between 1% and 5%, and among women of the same age group – between 1.2% and 2.5% (Young et al., 1993; Olson et al., 1995; Lavie et al., 1983; Stradling et al., 1991; Gislason et al., 1993). Observations show that prevalence increases with advancing biological age (Bixler et al., 1982; Catterall et al., 1985). A strong correlation has been established between age and the apnea index (Ancoli-Israel et al., 1987).

Obstructive sleep apnea syndrome is defined by recurrent interruptions (apneas) or reduction (hypopneas) of airflow by more than 50% for over 10 seconds during sleep, accompanied by desaturation ≥4%, due to obstruction of the upper airways (D'Andrea et al., 2020). The strongest risk factors are obesity and male gender (Drager et al., 2013). Frequent awakenings lead to non-restorative sleep, excessive daytime sleepiness, reduced work capacity, problems with memory, attention, and concentration. Cessation of breathing causes oxygen deficit and increased stress, which damages all organs and systems, with the cardiovascular and endocrine systems being the most affected. Characteristic is the alternation of respiratory pauses with loud snoring. This is a condition of recurrent partial or complete collapse of the upper airways during sleep with ineffective respiratory effort. OSA is associated with numerous multisystem complications, including cardiovascular diseases.

Obstructive sleep apnea is associated with various forms of cardiovascular diseases (CVD) – hypertension, stroke, heart failure (HF), ischemic heart disease (IHD), and atrial fibrillation (AF) (Shahar et al., 2001). Adults with OSA not only have an increased risk of developing comorbid CVD but also worse outcomes related to them. The most commonly described cardiovascular complications of OSA include coronary disease, heart failure, arterial hypertension, and various arrhythmias. The main pathophysiological mechanisms are endothelial dysfunction, coagulation disorders, increased sympathetic activity, oxidative and inflammatory stress. Detailed observations provide grounds for OSA to be considered an independent, modifiable cardiovascular risk factor. Numerous studies show that the application of continuous positive airway pressure (CPAP) improves the clinical condition of these patients and slows disease progression. Therefore, patients with CVD should be purposefully screened for OSA, and vice versa.

The mechanisms underlying OSA are complex and multifactorial – a combination of anatomical, physiological, and neurological factors that interact and lead to collapse of the

airways and subsequent respiratory disturbances during sleep. Anatomical anomalies, decreased muscle tone, negative intrathoracic pressure, intermittent hypoxia (IH), sympathetic activation, and changes in neural control play a key role. Understanding these mechanisms is essential for developing targeted diagnostic and therapeutic strategies. Intermittent hypoxia is a characteristic feature of OSA. There is compelling evidence that this factor is central in the pathophysiology of CVD. The model of IH in OSA – with recurrent short cycles of desaturation followed by rapid reoxygenation – substantially differs from chronic sustained hypoxia in other respiratory or cardiac diseases and leads to different pathophysiological reactions.

Among the leading factors for OSA are anatomical anomalies or changes in the structure of the upper airways – excessive soft tissue in the throat (enlarged tonsils, long soft palate, large tongue), which narrows the airways and predisposes to collapse during sleep (Tsai et al., 2022; Xiao et al., 2022; Schwab et al., 2003). Also, anomalies in the facial and cervical skeleton, such as a small or retruded jaw (micrognathia or retrognathia), further reduce the space for airflow (Cistulli et al., 1996).

With frequent obstructions of the upper airways during sleep, hypoxia and recurrent changes in intrathoracic pressure are observed. Negative intrathoracic pressure increases afterload and impairs relaxation of the left ventricle. Contractility decreases, leading to volume overload in both systole and diastole. The hypoxia itself damages energy processes in cardiomyocytes and further reduces contractility. As a result, the sympathetic nervous system is activated, which increases heart rate and peripheral vasoconstriction and further increases the preload on the left ventricle (Lattimore et al., 2003; Javaheri et al., 2017).

OBJECTIVE

The aim of the present study is to evaluate the cardiovascular risk in patients with obstructive sleep apnea (OSA) and to analyze the effect of long-term CPAP therapy on the clinical, anthropometric, hemodynamic, and echocardiographic parameters, as well as on the cardiovascular prognosis.

Tasks

1. To analyze the clinical and anthropometric characteristics of patients with OSA in the Bulgarian population.
2. To evaluate the diagnostic value of screening questionnaires (Epworth Sleepiness Scale) for detecting patients at high risk of OSA.
3. To determine the presence of comorbid cardiovascular diseases at the time of diagnosis of obstructive sleep apnea and the cardiovascular events that occurred (newly diagnosed AH, HF, tachyarrhythmias) in patients on CPAP therapy compared with the control group over a period of three years.
4. To monitor changes in arterial pressure in patients with and without CPAP therapy, as well as the need for antihypertensive therapy.
5. To monitor changes in left ventricular and left atrial function in patients with and without CPAP therapy.
6. A group of patients in whom NTproBNP levels are to be determined at the time of diagnosis of obstructive sleep apnea and six months after CPAP therapy.
7. To monitor changes in left ventricular and left atrial function in patients with and without CPAP therapy, to develop a risk stratification model, as well as predictors for a more severe course of the disease.

Methods

The study began in 2017 and is ongoing. A total of 114 patients were included, divided into two groups depending on whether a CPAP device was used or not. Our study was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice Guidelines, and the ethical rules of the institutional committee of the Medical Faculty of Trakia University, Stara Zagora, Bulgaria. All patients signed informed consent approved by the institutional review board, protocol 16/2021.

All patients had diagnosed obstructive sleep apnea, confirmed using the SOMNO check Cardio – a multichannel device measuring airflow, snoring, saturation, pulse rate, plethysmography, and pulse wave analysis. Patients were divided into two groups depending on whether or not they used CPAP therapy in the treatment of OSA. Both groups of patients were followed up for 36 months, at the time of diagnosis, and at the 6th, 12th, 24th, and 36th month.

Blood pressure was measured using a sphygmomanometer according to the instructions of the European Society of Hypertension.

The telediastolic pressure (E/E') was determined by echocardiography.

The morphometric parameters weight and height were used to calculate the BMI.

The main criterion according to which patients were divided into groups was whether CPAP was applied as treatment for sleep apnea together with the remaining therapy, or whether the device was not applied and the patient was treated only with the respective medication for the cardiovascular disease. Thus, two groups were formed: a control group and a group undergoing CPAP therapy.

1. Inclusion and Exclusion Criteria for the Formation of Study and Control Groups

1.1 Inclusion Criteria:

- Age > 18 years;
- Signed informed consent;
- Diagnosed obstructive sleep apnea through performed ambulatory polygraphy;

1.2 Exclusion Criteria:

- Age < 18 years;
- Refusal to sign informed consent;
- Diagnosed HF with reduced ejection fraction < 40%
- Diagnosed permanent atrial fibrillation.

Patients with HF with reduced ejection fraction < 40%, as well as patients with permanent atrial fibrillation at the time of diagnosis are subject to exclusion from the study due to the high risk of the presence of central sleep apnea and Cheyne-Stokes respiration.

Patients must be divided into two groups:

- Group on Regular CPAP Therapy
- Control Group of Patients without CPAP Therapy.

2. Follow-up

Patients were planned to be followed up at the 6th, 12th, 24th, and 36th month from diagnosis, with cardiovascular risk monitored through:

- assessment of sleepiness
- clinical examination;
- measurement of arterial pressure;
- electrocardiogram (ECG);
- transthoracic echocardiography (TTE);
- BMI;
- occurred cardiovascular complications (arterial hypertension, arrhythmias, ischemic heart disease, heart failure);

2.1 Epworth Sleepiness Scale (ESS) for Assessment of Sleepiness

All patients with suspected OSA answered the questionnaire – Epworth Sleepiness Scale (ESS) for assessment of sleepiness, see Table 3, with which the risk for the presence of OSA was evaluated.

ESS is a self-administered questionnaire with 8 questions. Respondents were asked to rate on a 4-point scale (0–3) their usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in these activities at least from time to time, although not necessarily every day. The ESS score (the sum of 8 item scores, 0–3) can range from 0 to 24. The higher the ESS score, the higher the average sleep propensity in daily life (ASP) of that person, or their 'daytime sleepiness'.

It was initially reported in 1991 that the 'normal' range of ESS scores was from 2 to 10 (Johns, 1991). With more data, this proved to be incorrect. Adults in Australia who have no evidence of chronic sleep disturbance (including frequent snoring) have a mean ESS score of 4.6 (95% confidence intervals from 3.9–5.3) with a standard deviation of 2.8 and a range from zero to 10 (Johns and Hocking, 1997). By this criterion, the reference range of 'normal' ESS scores is from zero to 10. This is the same as the range defined by the 2.5 and 97.5 percentiles.

A similar 'normal' range has been reported from the United Kingdom (mean = 4.5 +/- 3.3 (SD), n = 188) (Chervin at al, 1995), Italy (4.4 +/- 2.8, n = 54) (Manni et al, 1999), and Turkey (3.6 +/- 3.0, n = 60) (Izci et al, 2008). However, more evidence is needed to be certain that such a reference range applies to other populations as well.

Many ESS scores reported from the general population, without taking into account the presence or absence of sleep disorders, are higher than this 'normal' range. This is probably because sleep disorders that increase ASP, especially the various forms of sleep-disordered breathing, are common in the community (Mihăicută et al, 2013). However, it should not be assumed that sleep-disordered breathing is the only factor influencing ESS scores. Other causes, including depression, are also important. Gender and age have a small effect on ESS scores among adults, but ethnicity does. African Americans have significantly higher ESS scores than white Americans (Mihăicută et al, 2013; Sanford et al, 2006).

ESS scores from 11–24 represent increasing levels of 'excessive daytime sleepiness' (EDS). The percentage of people with EDS varies considerably between different groups, from about 10 to 40% or more (Johns and Hocking, 1997; Sanford et al, 2006). Almost all patients suffering from narcolepsy have severe or moderate EDS according to these ESS criteria, as expected (Parkes et al, 1998; Johns, 2000; van der Heide et al, 2015).

Overall, ESS results can be interpreted as follows:

- 0-5 Lower normal daytime sleepiness
- 6-10 Higher normal daytime sleepiness

- 11-12 Mild excessive daytime sleepiness
- 13-15 Moderate excessive daytime sleepiness
- 16-24 Severe excessive daytime sleepiness

Table 3 Epworth Sleepiness Scale (ESS) – Sleepiness Scale

Situation	**Likelihood of dozing**			
	never	**Sometimes**	**often**	**always**
Sitting and reading	0	1	2	3
Watching TV	0	1	2	3
Sitting quietly in a public place, for example in a theater, cinema, meeting, etc.	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after a lunch (without alcohol)	0	1	2	3
In a stopped car due to traffic jam or red light.	0	1	2	3

Results greater than 10 are considered pathological with respect to excessive daytime sleepiness.

2.2 SOMNO check Cardio

All patients were examined using the SOMNO check Cardio – a multichannel device measuring respiratory flow, snoring, saturation, pulse rate, plethysmogram, and pulse wave analysis (PWA).

The following are calculated by the device:

- apnea–hypopnea index (AHI) – the sum of all apneas and hypopneas per hour of recording;
- minimum and mean saturation, desaturation index, minimum, mean, and maximum pulse rate;
- determination of the Cardiac Risk Index (CRI) and its presentation in the form of a radar diagram;
- automatic recognition of absolute arrhythmia (atrial fibrillation) and Cheyne-Stokes breathing;
- calculation of the Autonomic Arousal Index (AAI)

2.3 Polysomnography

Polygraphy has great diagnostic value, is more convenient for the patient, is significantly less expensive, and can be performed at home. The latter is of enormous importance because the patient is much more relaxed at home and the results are much closer to reality. One of the major disadvantages of polysomnographic examination is that it is performed in specialized laboratories where the sleeping conditions differ from those in the patient's home. The results show only the momentary state for the particular night, and this is absolutized as the main indicator for determining the severity of obstructive sleep apnea syndrome and thus the treatment modality (i.e., the results do not always truly reflect the actual condition).

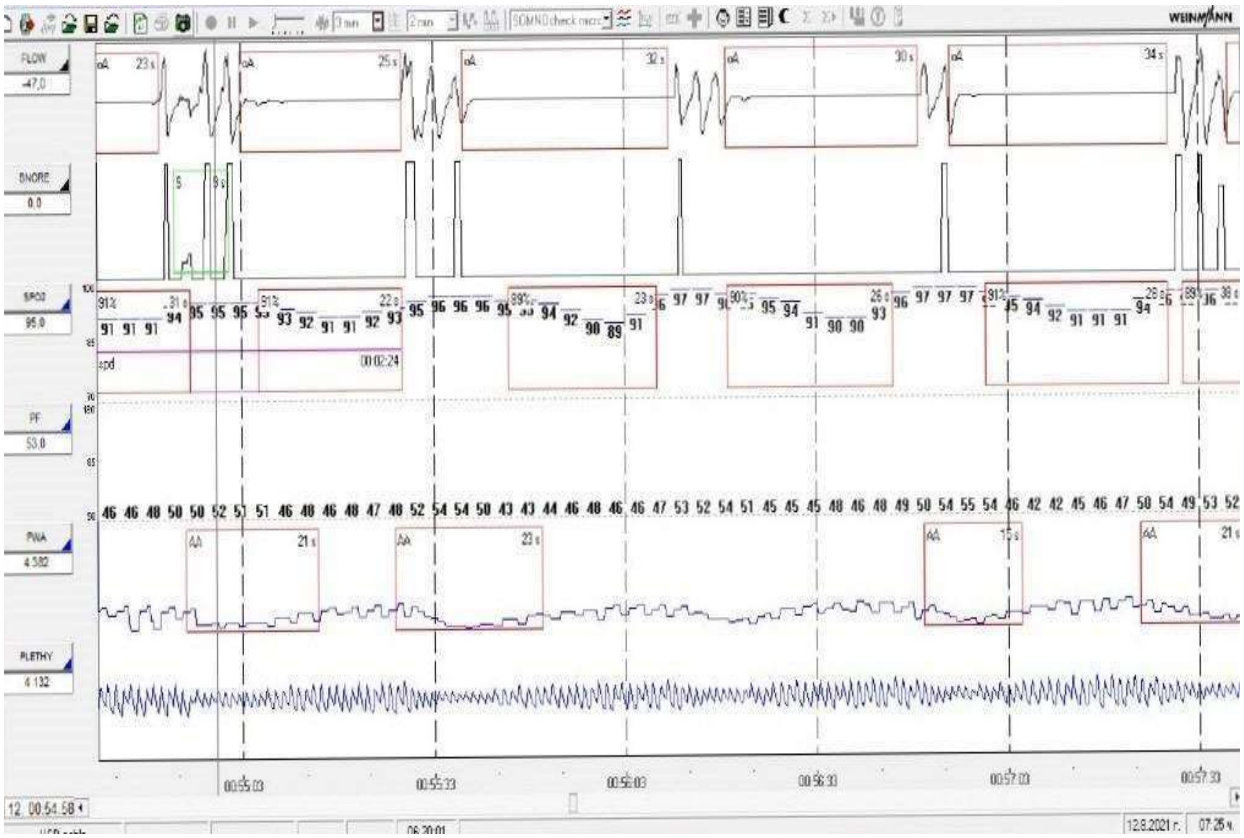


Fig. 4. Polygraphic recording of a patient with obstructive sleep apnea syndrome, apneic pauses with maximum duration of 34s and drop in spO2 to 89%

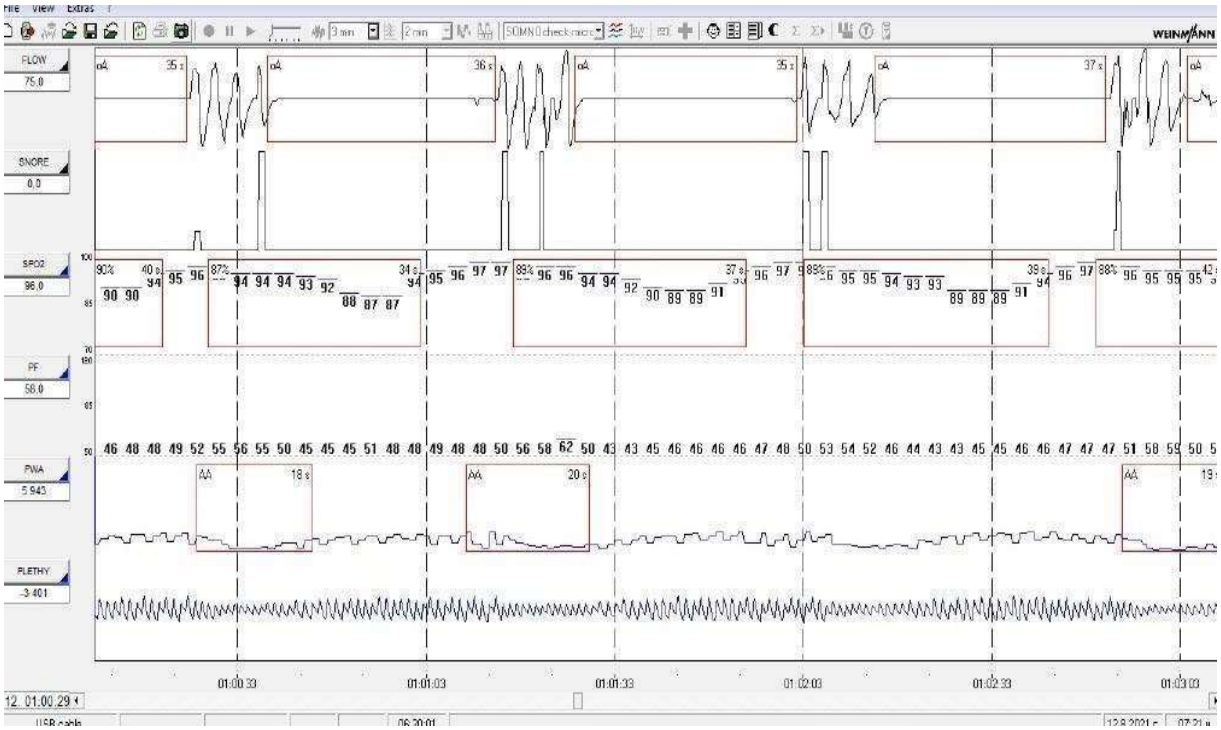


Fig. 5 Polygraphic recording of a patient with obstructive sleep apnea syndrome, apneic pauses with maximum duration of 37s and drop in spO2 to 87%.

Risk summary

Cardiovascular risk

Your risk for sleep apnea (AHI (apnea/hypopnea index))

Risk for fragmented sleep (AAI)

Cardiovascular risk

Cardiac risk index (CRI)	0.48

Respiration

AHI (apnea/hypopnea index)	30,0/ h (• en	oAHI (obstructive AHI)	35,5 / h
AT (ap nea index)	34.6 / h	cAHI (central AHI)	0.S / h
HI (hypopnea index)	1.7 / h	snoring	25 'A
longest apnea	66 s	flattening	8 °/
mean apnea duration	25 s		

Oxygen

Oxygen desaturation index	34,3/ h	Tim e below 95 °A	02:01:45 [S3 %]
lowest saturation	66 % (90-96 %)	Time below 90 °4	00:28:19 [08 %]
mean saturation	94 % (94-98 %)	Time below 85 °4	00:08:03 [02 %]
		Total hypoxem ia duration (SpO2 <90°4 for >S min.)	00:00:00 [00 %]

Heart rate

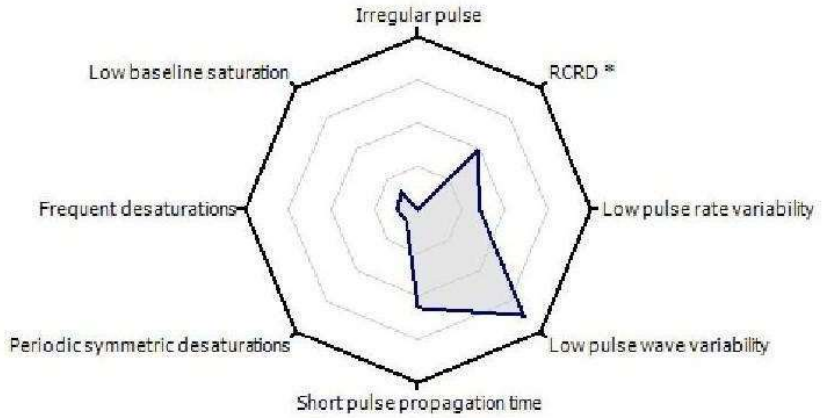
mean pu1se rate	52 / min	highest pulse rate	80/ mln tao-so/ aj
		lowest pulse rate	42/ min (€0-7o/ mnj

Sleep fragmentation

AAI (autonom ous arousal index)	29,4/ h (• 80/ h)	RERA	K2 ?h
AAI resp (AAI with respiratory events)	24,6 / h	AAI non resp (AAI wJhout respiratory evenls)	4,8 / h

Fig. 6 Automatic analysis of the SOMNO check Cardio device

Individual risk pattern



Irregular pulse	0,0
RCRD *	0,5
Low pulse rate variability	0,4
Low pulse wave variability	0,9
Short pulse propagation time	0,6
Periodic symmetric desaturations	0,1
Frequent desaturations	0,1
Low baseline saturation	0,1

Findings

Moderate risk indicators:
- Reduced chronotropic reaction to desaturations

Fig. 7 Radar diagram of the individual cardiovascular risk in a patient with obstructive sleep apnea

2.4 Other Examinations

Patients were followed up through clinical examination, measurement of arterial pressure, electrocardiography, echocardiography, BMI, in order to evaluate the presence of cardiovascular complications (arterial hypertension, arrhythmias, ischemic heart disease, heart failure).

2.4.1 Assessment of Arterial Hypertension

Hypertension is defined as office SBP values ≥140 mmHg and/or DBP values ≥90 mmHg. Based on office BP, the global prevalence of hypertension in 2015 is estimated at 1.13 billion, including more than 150 million in Central and Eastern Europe. The overall prevalence of hypertension in adults is approximately 30–45%. This high prevalence persists worldwide, regardless of income, i.e., in low-, middle-, and higher-income countries. Hypertension becomes increasingly common with advancing age and is >60% in persons aged >60 years. With population aging, adoption of a more sedentary lifestyle, and increasing body weight, the prevalence of hypertension worldwide continues to rise. Elevated BP is the leading global factor contributing to premature death. It is important to emphasize that despite advances in diagnosis and treatment over the past 30 years, disability-adjusted life years attributed to hypertension have increased by 40% since 1990. Responsible for the majority of mortality and disability (~70%) is

SBP ≥140 mmHg, and the largest number of SBP-related deaths annually are due to ischemic heart disease (4.9 million), hemorrhagic stroke (2.0 million), and ischemic stroke (1.5 million). Both office and out-of-office BP show an independent and continuous relationship with the incidence of several types of cardiovascular events [hemorrhagic stroke, ischemic stroke, myocardial infarction, sudden death, heart failure, and peripheral arterial disease (PAD)], as well as with end-stage kidney disease. Data are growing on the close association of hypertension with an increased risk of developing atrial fibrillation (AF), and evidence is emerging that links early elevation of BP with an increased risk of cognitive changes and dementia. A continuous relationship between BP and the risk of events has been demonstrated for all ages and all ethnic groups, and spans from high BP levels to relatively low values. S...

Hypertension is defined as resistant to treatment when the recommended treatment strategy fails to lower office SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively, and inadequate BP control is confirmed by ABPM (24-hour ambulatory blood pressure monitoring) or HBPM (home blood pressure monitoring) in patients with confirmed adherence to therapy. The recommended treatment strategy should include appropriate lifestyle measures and treatment with optimal or well-tolerated doses of three or more drugs, which should include a diuretic, typically an ACE inhibitor or ARB and a CCB.

Pseudoresistant hypertension must be excluded, and secondary causes of hypertension must also be ruled out. Studies on the prevalence of resistant hypertension are limited by differences in the definitions used, and the reported prevalence varies between 5 and 30% in patients with treated hypertension. After applying a strict definition and after excluding the causes of pseudoresistant hypertension, the actual prevalence of resistant hypertension is most likely <10% of treated patients. Patients with resistant hypertension have a higher risk of HMOD (Hypertension-Mediated Organ Damage), CKD (chronic kidney disease), and premature CV events.

Pseudoresistant hypertension – several possible causes of pseudoresistant hypertension must be assessed and excluded before concluding that the patient has resistant hypertension:

- Poor adherence to prescribed medications is a common cause of pseudoresistant hypertension, occurring in <50% of patients assessed through medication therapy monitoring, and is directly related to the number of prescribed tablets;
- The white-coat phenomenon (in which office BP is elevated, but BP on ABPM or HBPM shows good control) is not rare among patients, which is why before confirming the diagnosis of resistant hypertension, it is recommended that office hypertension be confirmed by hypertension on ABPM or HBPM.
- Poor technique of office BP measurement, including the use of cuffs that are too small for the arm circumference, can lead to falsely elevated BP.
- Pronounced calcification of the brachial artery, especially in older patients with severely calcified arteries.
- Clinician inertia leading to insufficient doses or irrational combinations of antihypertensive drugs.
    - Other Causes of Resistant Hypertension
- Lifestyle-related factors, such as obesity or significant weight gain, excessive alcohol consumption, and high sodium intake.
- Use of vasopressor or sodium-retaining substances, medications prescribed for conditions other than hypertension, some herbal preparations, or use of stimulants (cocaine, anabolic steroids, etc.)

- Obstructive sleep apnea (usually, but not necessarily, associated with obesity).
- Undetected secondary forms of hypertension.
- Chronic HMOD, especially CKD or hardening of the large arteries.

Resistant hypertension is associated with older age (especially >75 years), male sex, black African origin, higher initial BP values at the time of diagnosis, the highest BP values ever reached throughout the patient's life, frequent outpatient visits, obesity, diabetes, atherosclerotic disease and HMOD, CKD, and 10-year Framingham coronary risk <20% (Table 3).

Secondary hypertension is hypertension due to an identifiable cause that can be treated with an intervention specific to the respective cause. A high level of suspicion and early detection of secondary causes of hypertension are important because interventions could lead to cure, especially in younger patients [e.g., corrective surgery for aortic coarctation, renal angioplasty in younger patients with fibromuscular dysplasia of the renal artery, reversal of an endocrine cause of hypertension (e.g., by removal of an adrenal adenoma), or drug treatment of a monogenic disease affecting a specific drug-sensitive ion channel (e.g., selective use of amiloride in Liddle syndrome). Interventions that treat the cause of secondary hypertension later in life are less likely to lead to cure (i.e., to eliminate the need for antihypertensive prescriptions), because long-standing hypertension leads to damage to the vessels and other organs that maintain elevated BP, but the intervention is still important because it often leads to much better BP control with fewer drugs (Figure 3).

2.4.1.1 Blood Pressure Monitoring

Arterial pressure is monitored with an automatic blood pressure device Microlife BP A6 Plus with AFIB technology; the device features:

-MAM technology – automatic triple measurement for medically accurate results, according to WHO recommendations

-AFIB – measuring blood pressure (single or triple), the device monitors for the presence of atrial fibrillation

In patients with difficult-to-control arterial pressure, suspected resistant hypertension, as well as suspected lack of nocturnal dipping of arterial pressure, 24-hour Holter monitoring of arterial pressure is performed. For this purpose, a blood pressure Holter Contec ABPM50 is used, with the capability of measuring: systolic blood pressure (SYS), diastolic blood pressure (DIA), mean arterial blood pressure (MAP), pulse (PR), as well as specialized software for in-depth analysis of NIBP, trends, and graphs.

2.4.1.2 Electrocardiography

Electrocardiography is performed on a 6-channel ECG device ECG Contec 600G Touch Screen, equipped with automatic analysis and interpretation, automatic calculation of parameters such as HR, P-R interval, QRS complex, Q-T interval, Q-Tc, P axis, QRS axis, T axis, R(V5), S(V1), R(V5) + S(V1), etc.

Table 4 Characteristics of Resistant Hypertension, Secondary Causes, and Contributing Factors (adapted from Williams et al, 2018)

Characteristics of patients with resistant hypertension	Causes of secondary resistant hypertension	Drugs and substances that may cause elevated BP
Demographics •Older age (especially >75 years) •Obesity •More common in Black individuals •Excessive dietary salt intake •High baseline BP and chronic uncontrolled hypertension	More common causes •Primary aldosteronism •Atherosclerotic renovascular disease •Sleep apnea • CKD	Prescribed medications •Oral contraceptives •Sympathomimetic agents (e.g., decongestants in proprietary cold medications) •Nonsteroidal anti-inflammatory drugs •Cyclosporine •Erythropoietin •Steroids (e.g., prednisolone and hydrocortisone) •Some oncological therapies
Comorbidities •HMOD: LVH and/or CKD •Diabetes •Atherosclerotic vascular diseases •Aortic stiffening and isolated systolic hypertension	Less common causes •Pheochromocytoma •Fibromuscular dysplasia •Aortic coarctation •Cushing's disease •Hyperparathyroidism	Over-the-counter medications •Energy drugs (e.g., cocaine, amphetamines, and anabolic steroids) •Excessive licorice intake •Herbal medicines (e.g., ephedra and ma huang)

BP = blood pressure; CKD = chronic kidney disease; HMOD = hypertensive organ damage; LVH = left ventricular hypertrophy

2.4.1.3 Transthoracic Echocardiography

Transthoracic echocardiography (TTE) is the method of choice for assessing myocardial systolic and diastolic function. The modified biplane Simpson's rule is used for evaluation of left ventricular systolic function. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured in the apical four-chamber view. The Teichholz method for calculating LVEF from linear dimensions was used only in patients without segmental wall motion abnormalities.

Doppler methods were used to calculate hemodynamic parameters, such as stroke volume index and cardiac output, based on the time-velocity integral in the LV outflow tract region. In all patients, left ventricular diastolic function was assessed using Doppler methods. Diastolic dysfunction is considered the underlying pathophysiological disturbance in patients with HFpEF, and possibly also HFmrEF, and for this reason its evaluation plays an important role in diagnosis.

A mandatory element of the echocardiographic examination is the assessment of right ventricular (RV) structure and function, including RV and right atrial (RA) dimensions, evaluation of RV systolic function, and pulmonary arterial pressure. Among the parameters reflecting RV systolic function, the following measures are of particular importance: tricuspid annular plane systolic excursion (TAPSE); pathological TAPSE values < 17 mm indicate RV systolic dysfunction. Systolic pressure in the pulmonary artery is obtained with optimal recording of the maximum tricuspid regurgitant jet and tricuspid systolic gradient, together with assessment of RA pressure based on the diameter of the inferior vena cava (IVC) and its respiratory collapse.

Transthoracic echocardiography (TTE) was performed on a Mindray MX7 echocardiography system. The system has the following capabilities:

Pulse Wave Doppler - Pulsed-wave Doppler;

PW with HPRF for high-velocity blood flows

Color Doppler Flow Imaging – Color Doppler
Power Doppler Flow Imaging – Power Doppler
Directional Power Doppler Flow Imaging – Power Doppler with directional blood flow indication
M-mode; Color M-mode;
Duplex in real time;
Triplex in real time, CW, TDI.

2.4.1.4 Determination of BMI

For the calculation of BMI, an online calculator was used, based on the formula:
$BMI = W/h^2$, where:

BMI – body mass index;
W – weight in kilograms;
h – height in meters.

2.4.2 Assessment of Heart Failure

For the purposes of the study, the NYHA functional classification was used – describing the severity of symptoms and exercise intolerance.

The diagnosis of HFpEF requires fulfillment of the following criteria:

- Presence of symptoms and/or signs of HF
- "Preserved" EF (defined as LVEF ≥50% or 40–49% for HFmrEF);
- Elevated natriuretic peptide levels (BNP >35 pg/mL and/or NTproBNP >125 pg/mL);
- Objective data for other cardiac functional changes underlying HF;
- In case of uncertainty, a stress test or invasive measurement of elevated LV filling pressure may be performed to confirm the diagnosis.
- In-depth diagnostics are necessary in cases with initial data for HFpEF/HFmrEF and consist of objectifying structural and/or functional cardiac abnormalities that are the underlying cause of the clinical picture. Key structural abnormalities are left atrial volume index (LAVI) >34 mL/m² or left ventricular mass index (LVMI) ≥115 g/m² in men and ≥95 g/m² in women. Key functional changes are E/e' ≥13 and mean e' of the septal and lateral walls.

2.4.3 Arrhythmias

The frequency of cardiac arrhythmias, mainly nocturnal, increases with the severity of sleep apnea-hypopnea syndrome. The most common rhythm disturbances observed in patients with sleep apnea-hypopnea syndrome are sinus bradycardia, sinus pause, first-degree AV block and second-degree Mobitz I AV block, and an increased number of PVCs (Guilleminault et al, 1983). A circadian pattern of AF occurrence and a higher frequency of SCD during sleep time (from midnight to 6 a.m.) have been demonstrated.

Obstructive sleep apnea is associated with reduced mean nocturnal oxygen saturation <93%, while the lowest nocturnal saturation <78% has been shown to be an independent risk factor for SCD (P< 0.0001). Therefore, the presence of obstructive sleep apnea should be included in the list of investigations for SCD risk stratification (Gami et al, 2013).

Currently, there are no data suggesting that a different approach from the standard one should be applied to AF in patients with sleep apnea-hypopnea syndrome; furthermore, the value of continuous positive airway pressure for the prevention of AF and SCD remains undefined. Whether appropriate treatment of obstructive sleep apnea can alter clinical manifestations and lead to avoidance of the need for pacemaker therapy in patients whose arrhythmias are related only to obstructive respiratory events is unknown. Newer innovative pacemaker therapy methods for the treatment of central sleep apnea-hypopnea syndrome are under investigation, utilizing phrenic nerve stimulation and upper airway stimulation in obstructive forms.

2.4.4 NT pro BNP

The natriuretic peptide BNP is secreted from the cardiac chambers in response to increased wall stress, initially as the pro-hormone pro-BNP. Subsequently, as a result of enzymatically controlled reactions, BNP and NT-proBNP are produced from pro-BNP. The effects of BNP are:

- Nocturnal natriuresis.
- Diuretic effect.
- Vasodilation.
- Inhibition of renin-aldosterone secretion.
- Blocking of the sodium-retaining properties of aldosterone.

BNP and NT-pro-BNP are secreted not only in response to increased pressure in the cardiac chambers, but also with minimal damage to cardiomyocytes as a result of ischemia. NT-pro-BNP has a longer half-life than BNP, better in vitro stability, and higher concentration in the blood, which suggests greater sensitivity during determination. Elevated levels of BNP and NT-proBNP are found in individuals with initial heart damage – cases with "silent" ischemia, left ventricular hypertrophy, enlarged LA dimensions, and atrial fibrillation. Moreover, they are present even in cases that develop these conditions after several years. In this sense, determination of NT-proBNP levels can be used for the diagnosis of these conditions.

NT-pro-BNP in our patients is measured at the clinical laboratory "Ramus". In a group of 10 patients, NT-pro-BNP will be measured at the time of diagnosis of obstructive sleep apnea and six months after initiation of CPAP therapy. Correlation analysis showed the dependence of NT-pro-BNP on left ventricular systolic stress and left ventricular dysfunction.

2.4.5 Overall Assessment of Cardiovascular Risk

Hypertension is rarely encountered in isolation and is often combined with other CV risk factors, such as dyslipidemia and impaired glucose tolerance. This clustering of metabolic risk factors exerts a multiplying effect on CV risk. Accordingly, quantitative assessment of total CV risk (i.e., the probability that a given individual will develop a CV event over a defined period of time) is an important part of the risk stratification process in patients with hypertension. There are many systems for CV risk assessment, and most determine 10-year risk.

After 2003, the European guidelines for CVD prevention recommended the use of the SCORE system (Systematic COronary Risk Evaluation), because it is based on large representative European cohort data. The SCORE system calculates the 10-year risk of a first fatal atherosclerotic event depending on age, sex, smoking, total cholesterol level, and SBP. The SCORE system allows for consideration of different levels of CV risk in a number of European countries, for which external validation has been performed. One of the previous limitations of the SCORE system was that it was applicable only to patients aged 40–65 years; recently, however, the SCORE system has been adapted for patients over 65 years of age. Hypertensive patients with documented CVD, including asymptomatic atherosclerotic disease on imaging diagnostics, type 1 or type 2 diabetes, very high levels of individual risk factors (including grade 3 hypertension), or chronic kidney disease (CKD; stages 3–5), are automatically assigned to the very high (i.e., ≥10% CVD mortality) or high (i.e., 5–10% CVD mortality) 10-year CV risk category (Figure 8). Such patients do not require special CV risk calculation to determine their needs for treatment of their hypertension and other CV risk factors. In all other hypertensive patients, calculation of 10-year CV risk using the SCORE system is recommended. The assessment should be supplemented by evaluation for hypertensive organ damage (HMOD), which can also increase CV risk to a higher level, even when asymptomatic. Evidence has also emerged that elevation of serum uric acid to levels lower than those typical for gout is independently associated with increased CV risk in the general population, as well as in hypertensive patients. The SCORE system calculates only the risk of fatal CV events.

The total risk of CV events (fatal and non-fatal) is approximately three times higher than the frequency of fatal CV events in men and four times higher in women. This multiplier is reduced to less than three times in older people, since in them there is a greater probability that the first event will be fatal. There are important general modifiers of CV risk (Figure 9), as well as specific modifiers of CV risk in patients with hypertension. CV risk modifiers are particularly

important at borderline CV risk and especially in patients with moderate risk, where a single risk modifier can convert moderate risk into high risk and influence the choice of treatment aimed at affecting CV risk factors.

Cardiovascular risk is strongly influenced by age (i.e., older people invariably have higher absolute CV risk). Conversely, absolute risk in younger individuals, especially younger women, is invariably lower, even in those with a markedly elevated risk profile. In them, relative risk is elevated, even at low absolute risk. The use of the term "CV risk age" has been proposed as a suitable way of denoting risk and choosing treatment, especially in younger people with low absolute but high relative risk. This is done by illustrating how a younger patient (e.g., aged 40 years) with risk factors but low absolute risk has a CV risk corresponding to that of a much older person (60 years) with optimal risk factor levels; and thus, the CV risk age of the younger patient is 60 years. CV risk age can be calculated automatically using HeartScore (www.heartscore.org).www.heartscore.org

A second circumstance is that the presence of comorbid disease is often recorded in a binary manner in CV risk assessment systems (e.g., diabetes, yes/no). This does not reflect the importance of the severity or duration of comorbidities on total CV risk. For example, long-standing diabetes is clearly associated with high risk, whereas in recently onset diabetes the risk is less clear.

The third specific conundrum for hypertension is which BP values should be used in CV risk assessment in a patient receiving treatment for hypertension. If treatment has started recently, it is most likely appropriate to use the BP values before treatment initiation. If treatment has been ongoing for a prolonged period, using the current BP value under treatment will invariably lead to underestimation of risk, because it does not reflect the prolonged preceding exposure to higher BP levels, and antihypertensive treatment does not lead to complete risk reversal, even with good BP control. If treatment has been prolonged, then the "treated BP value" should be used with the caveat that the calculated CV risk will be lower than the actual risk in the patient. The fourth conundrum is how to use out-of-office BP values in risk calculators calibrated according to office BP values. These various limitations should be taken into account when calculating CV risk in clinical practice.

Normally, BP decreases during sleep. The cutoff value for defining patients as "dippers" is if their nocturnal BP falls by >10% from the mean daytime BP value; however, "dipping" status often shows large variations between different days and therefore has poor reproducibility. Sleep disturbances, obstructive sleep apnea, obesity, high dietary salt intake in salt-sensitive individuals, the presence of orthostatic hypotension, autonomic dysfunction, CKD, diabetic neuropathy, and advanced age are the main causes of lack of nocturnal dipping (decrease) of BP. Studies reporting daytime and nocturnal BP using the same statistical model have established that nocturnal BP is a stronger predictor of clinical outcome than daytime BP. The night-to-day BP ratio is also a significant predictor of clinical outcome, and patients with reduced nocturnal BP dip (i.e., 0.9) have increased cardiovascular risk. Moreover, those with no nocturnal BP dip or higher mean BP values at night than during the day are at strongly increased risk. A number of additional indicators derived from ABPM recordings have some prognostic value, including 24-hour BP variability and morning BP surge.

Classification and Regression Tree Method (CART)

The Classification and Regression Trees method (Classification and Regression Trees, CART), developed by Leo Breiman et al. (Breiman et al., 1984), is a statistical approach for analyzing the relationship between an outcome (e.g., presence of disease) and multiple clinical indicators. CART creates a so-called "decision tree", in which the studied group of patients is divided into subgroups based on specific values of clinical variables (e.g., body mass index, apnea-hypopnea index, age, etc.). At each step, the algorithm selects the indicator and cutoff value that best discriminate patients according to the outcome. The method works by sequentially dividing patients into increasingly homogeneous groups until terminal subgroups with clearly expressed risk or probability for the respective condition (e.g., severe sleep apnea) are reached. The result is a visual structure (tree) that can be interpreted as a series of clinical rules of the type:

- if AHI > a certain value → increased risk
- if BMI > a certain value → additional increase in risk

Advantages in Medical Research

- easy interpretation as clinical rules
- identification of threshold values with practical significance
- ability to detect interactions between factors
- does not require specific assumptions about data distribution

Limitations

- "overfitting" is possible in small samples
- results may vary across different samples
- requires verification by additional methods or validation.

In the present study, the CART model was used to identify key clinical predictors and cutoff values associated with the severity of sleep apnea. Through this approach, clear and practically applicable rules for risk stratification in patients are derived. To assess changes in BMI over time and the effects of CPAP treatment, sex, and age group, a general linear model with repeated measures was applied using IBM SPSS Statistics, version 26.

The model included four time points (BMI 0, BMI 12, BMI 24, and BMI 36), defined as a within-subject factor with polynomial structure, and three between-subject factors – CPAP (user/non-user), sex, and age group. Main effects and interactions between factors (including CPAP × sex × time and CPAP × sex × age) were evaluated.

Multivariate tests (Wilks' lambda, Pillai's trace), univariate effects, interaction effects, and estimates of effect size (partial eta-squared) and test power (observed power) were calculated. Bonferroni correction was used for multiple comparisons.

Results

Of the patients participating in the study, 78.95% are male and 21.05% are female. Approximately the same ratios are maintained in the individual groups. The control group is composed of 21.3% (n=10) women and 78.7% (n=47) men. In the CPAP group, women are slightly more numerous – 32.6% (n=14), and men are 68.4% (n=43). These ratios confirm the higher morbidity frequency in males.

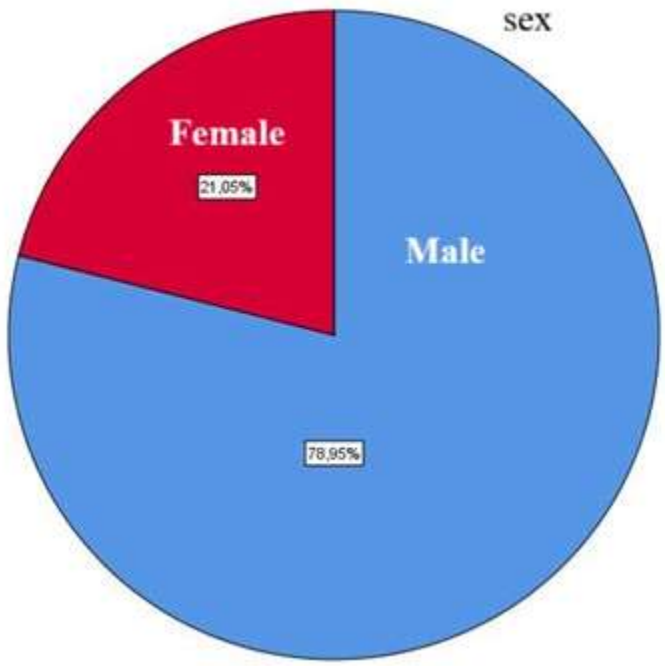
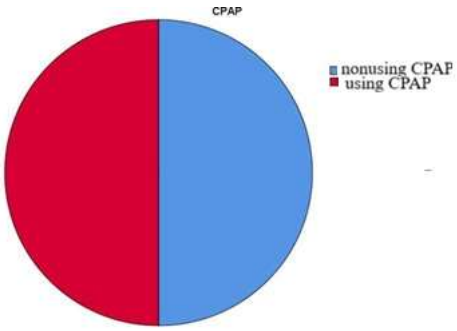


Fig. 10 Distribution of patients by sex

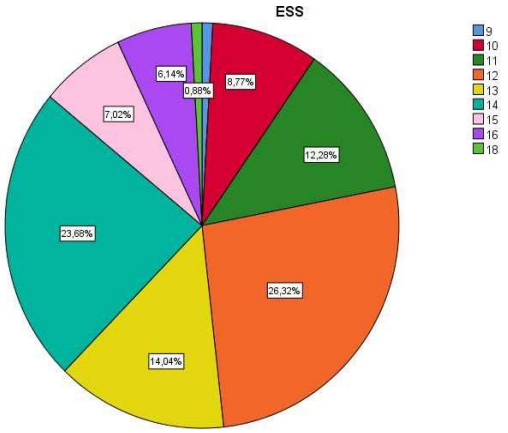
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	male	90	78,9	78,9	78,9
	female	24	21,1	21,1	100,0
	Total	114	100,0	100,0	



CPAP

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Неползващи CPAP	57	50,0	50,0	50,0
	Ползващи CPAP	57	50,0	50,0	100,0
	Total	114	100,0	100,0	

Fig. 11 Distribution of patients into two groups: using and not using a CPAP device



Фиг. 12 Epworth sleeping scale за оценка на сънливостта

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	9	1	,9	,9	,9
	10	10	8,8	8,8	9,6
	11	14	12,3	12,3	21,9
	12	30	26,3	26,3	48,2
	13	16	14,0	14,0	62,3
	14	27	23,7	23,7	86,0
	15	8	7,0	7,0	93,0
	16	7	6,1	6,1	99,1
	18	1	,9	,9	100,0
	Total	114	100,0	100,0	

Table 5 Results of the questionnaire- Epworth sleeping scale for the assessment of sleepiness, with which the risk of OSA was evaluated

In all patients with newly diagnosed sleep apnea there is increased daytime sleepiness (ESS≥10), with the severity of OSA correlating with a higher score on the questionnaire- Epworth

sleeping scale. In the examination of the patients with newly diagnosed sleep apnea, a mean AHI=42.35 was established.

	N		Mean	Std. Error of Mean	Median	Std. Deviation	Range	Minimum	Maximum
	Valid	Missing							
Age	114	0	55,59	1,102	55,00	11,766	57	25	82
BMI	114	0	35,8596	0,33496	36,150	3,57637	17,90	26,40	44,30
Neck circumference	114	0	40,54	0,356	40,00	3,805	22	27	49

Fig. 6 Anthropometric parameters

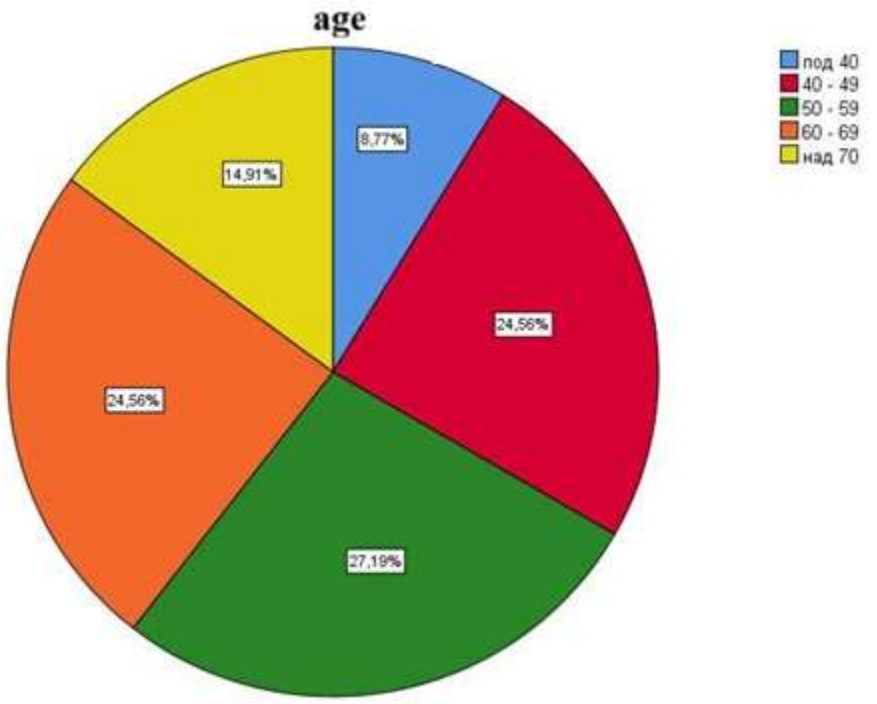


Fig. 13 Distribution by age

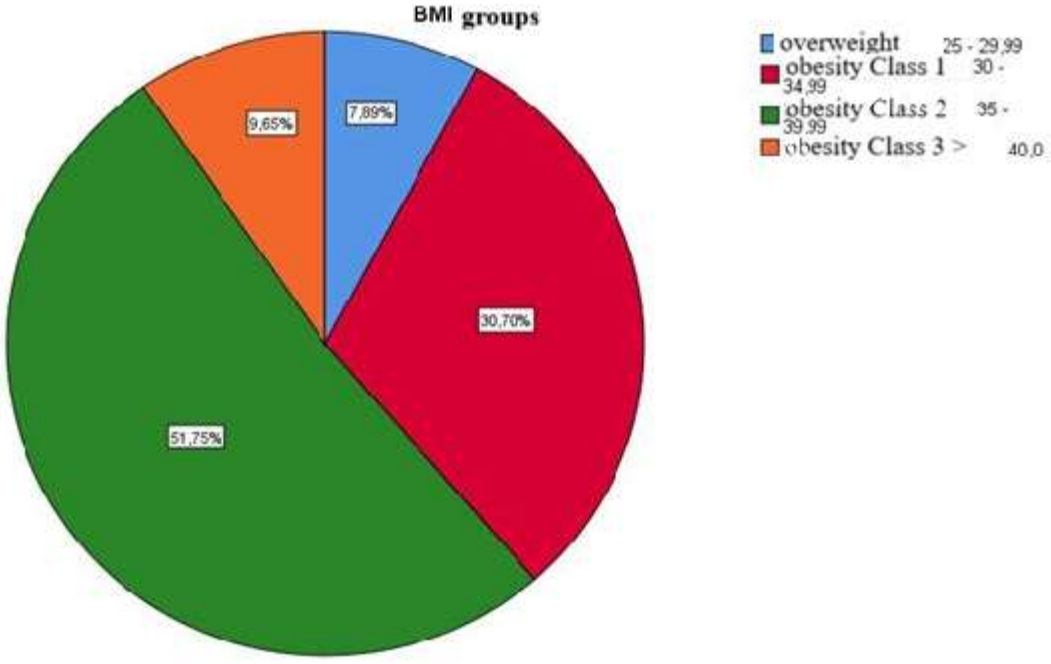


Fig. 14 Distribution by BMI

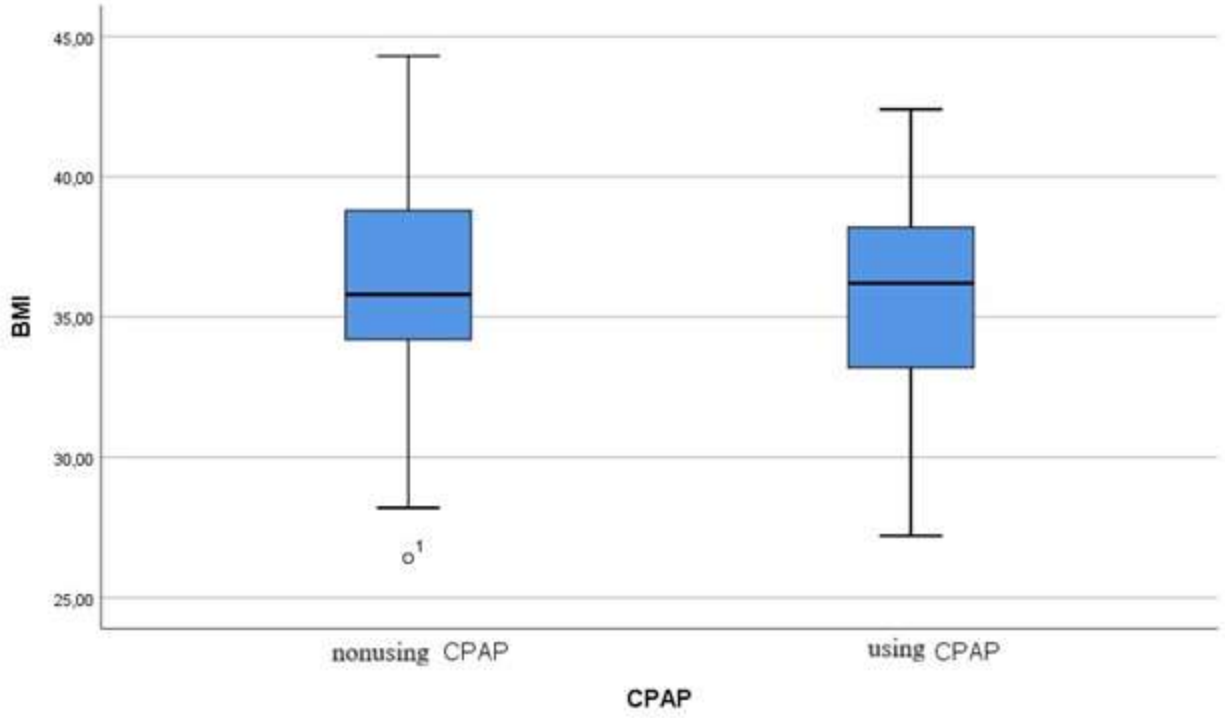


Fig. 16 Distribution by BMI

	N								
	Valid	Missing	Mean	Std. Error of Mean	Median	Std. Deviation	Range	Minimum	Maximum
AHI	114	0	42,35	1,978	40,00	21,120	89	8	97
lowest Sat	114	0	67,59	1,234	70,00	13,173	54	37	91
Mean Sat	114	0	90,02	0,456	91,50	4,872	23	73	96
ODI	114	0	38,97	2,260	36,50	24,131	101	1	102

Table 7 Results of the diagnostic polygraphic study performed

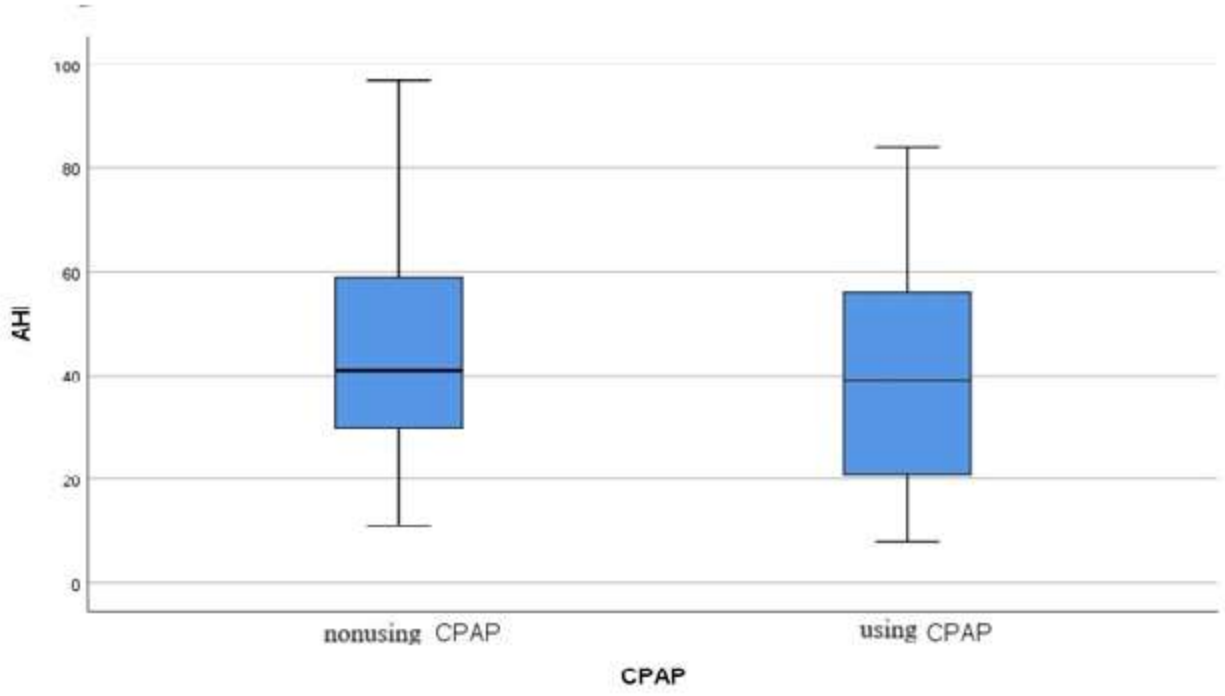


Fig. 16 Results of the polygraphic study - AHI

Analysis of the results from the polygraphic studies performed shows that the two groups are comparable with respect to the severity of obstructive sleep apnea. The values of the AHI (Apnea–Hypopnea Index) demonstrate similar distribution, with median values in the CPAP-using group and the non-CPAP-using group being close. The absence of substantial differences in AHI distribution suggests that the two groups are initially comparable in disease severity, which allows subsequent analyses to be interpreted without significant influence of differences in sleep apnea severity.

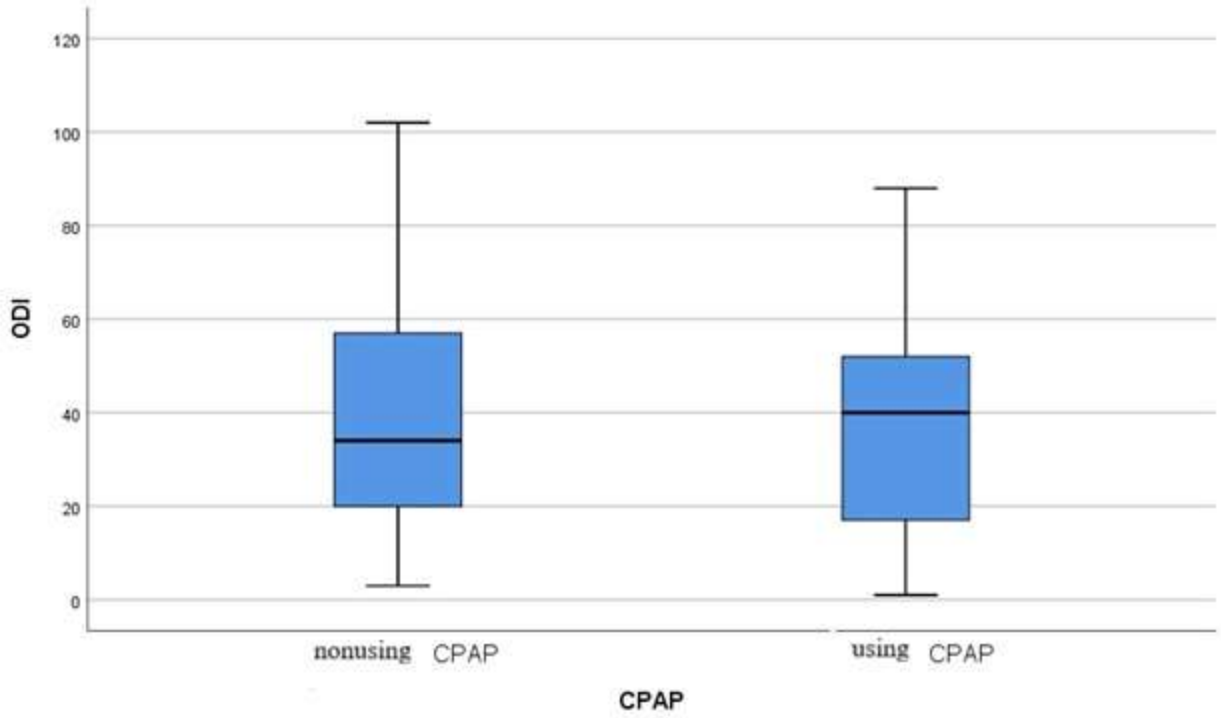
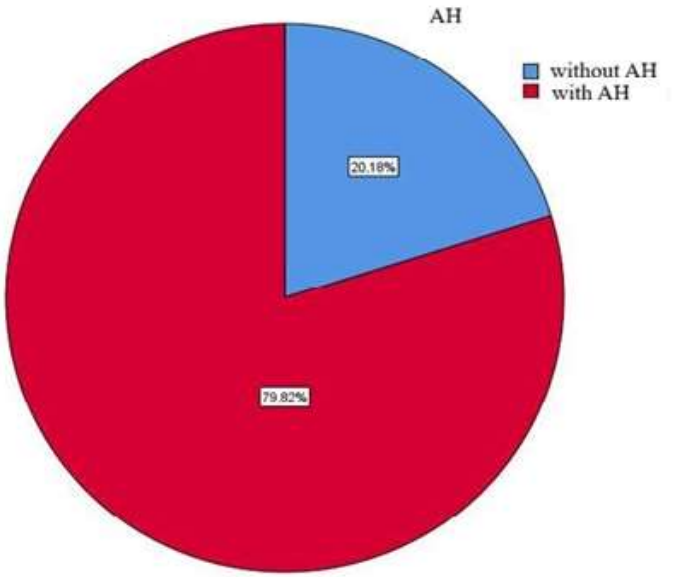


Fig. 17 ODI - Oxygen Desaturation Index, desaturation index

	N								
	Valid	Missing	Mean	Std. Error of Mean	Median	Std. Deviation	Range	Minimum	Maximum
Systolic BP	114	0	152,38	1,454	155,50	15,528	62	126	188
Diastolic BP	114	0	85,79	0,548	85,00	5,847	32	70	102
EF-0	114	0	59,25	0,561	60,50	5,989	25	42	67
LA area-0	114	0	19,77	0,237	19,00	2,535	14	16	30
Systolic BP-6	114	0	141,72	0,849	142,00	9,069	38	126	164
Diastolic BP-6	114	0	83,01	0,358	84,00	3,827	22	70	92
EF-6	114	0	59,24	0,540	61,00	5,769	22	44	66
LA area-6	114	0	19,76	0,238	19,00	2,543	14	16	30
Systolic BP-12	114	0	139,95	1,176	136,00	12,561	58	124	182
Diastolic BP-12	114	0	82,53	0,385	82,00	4,112	28	70	98
EF-12	114	0	58,88	0,578	61,00	6,173	23	42	65
LA area-12	114	0	20,13	0,254	19,00	2,712	14	16	30
Systolic BP-24	114	0	141,23	1,283	138,00	13,700	54	122	176
Diastolic BP-24	114	0	82,19	0,440	82,00	4,700	22	72	94
EF-24	114	0	58,23	0,634	61,00	6,768	34	35	69
LA area-24	114	0	20,66	0,270	20,00	2,887	14	16	30
Systolic BP-36	113	1	137,02	0,939	136,00	9,983	50	116	166
Diastolic BP-36	113	1	81,60	0,346	82,00	3,678	19	70	89
EF-36	113	1	58,04	0,565	60,00	6,001	21	44	65
LA area-36	113	1	20,89	0,278	20,00	2,956	14	16	30

Table 9 Followed parameters at 6th, 12th, 24th, and 36th month.



		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No hypertension	23	20,2	20,2	20,2
	Registered hypertension	91	79,8	79,8	100,0
	Total	114	100,0	100,0	

Fig. 18 Arterial hypertension in patients with established OSA.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	23	20,2	20,2	20,2
	1	4	3,5	3,5	23,7
	2	19	16,7	16,7	40,4
	3	41	36,0	36,0	76,3
	4	23	20,2	20,2	96,5
	5	4	3,5	3,5	100,0
	Total	114	100,0	100,0	

Table 10 Medications used

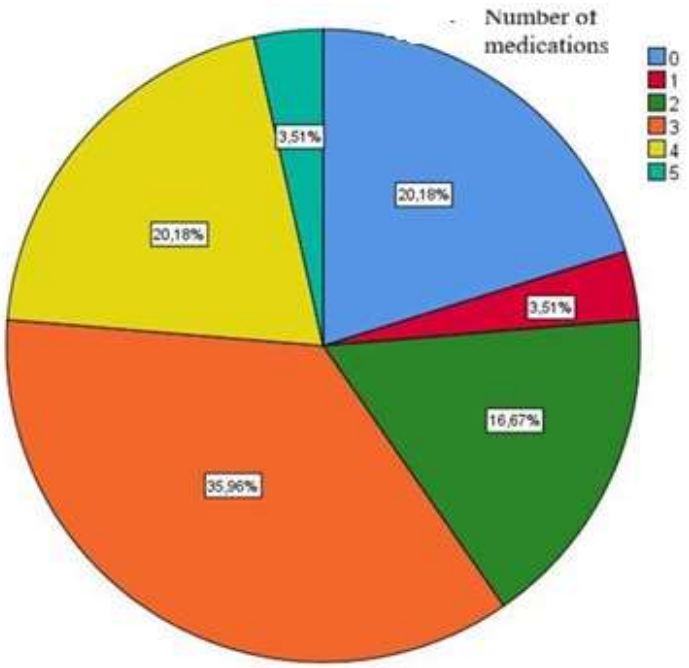
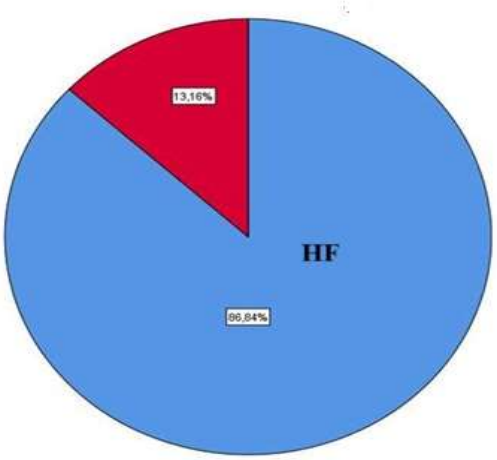


Fig. 19 Number of medications used

Heart failure

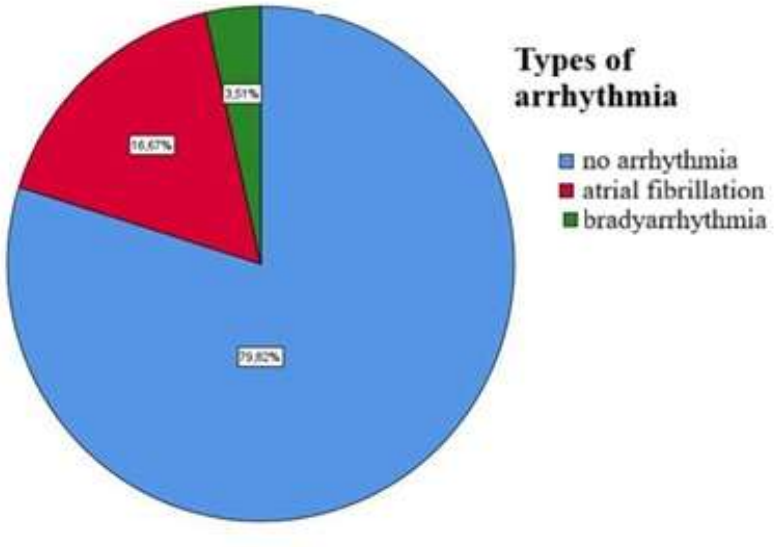


		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No heart failure	99	86,8	86,8	86,8
	Heart failure present	15	13,2	13,2	100,0
	Total	114	100,0	100,0	

Fig. 20 Heart failure in patients with OSA

Arrhythmias

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	91	79,8	79,8	79,8
	Yes	23	20,2	20,2	100,0
	Total	114	100,0	100,0	



		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No arrhythmia	91	79,8	79,8	79,8
	Atrial fibrillation	19	16,7	16,7	96,5
	Bradyarrhythmias	4	3,5	3,5	100,0
	Total	114	100, 0	100,0	

Fig. 21 Arrhythmias in patients with OSA.

A large proportion of the patients turned out to be polymorbid with respect to cardiovascular diseases, with 91 of them having arterial hypertension, 23 having an existing arrhythmia (19 atrial fibrillation, 4 with bradyarrhythmias), and 15 having heart failure.

The relationship between obstructive sleep apnea and hypertension is well documented, especially regarding nocturnal hypertension. Obstructive sleep apnea may be responsible for a large proportion of cases of elevated arterial pressure or lack of its decrease during the night

BMI

The percentage distribution of patients by degree of obesity is presented in Fig. 22

Of all patients participating in the study, 92.11% have varying degrees of obesity. It turns out that the highest – 51.75% – is the percentage of those with grade II obesity, whose BMI ranges from 35 to 39.99. Grade I obesity is represented in 30.70% with BMI 30–34.99. The least represented group is grade III obesity (BMI >40).

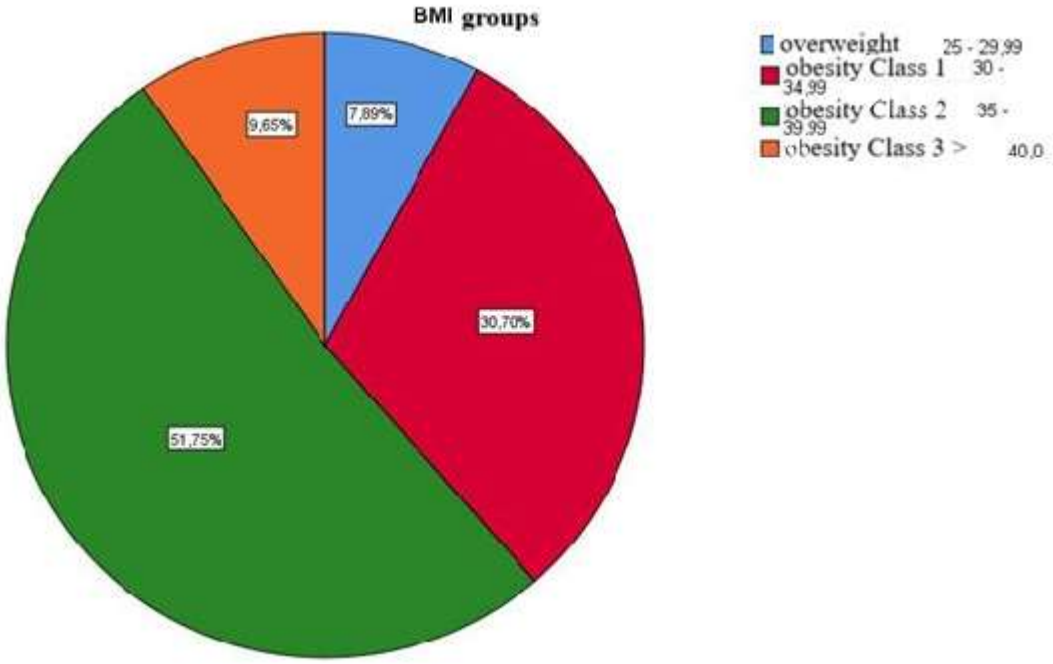


Fig. 22 Percentage distribution of patients by degree of obesity

BMI by months

Fig. 23 Change in BMI in patients with and without CPAP therapy

Analysis of the dynamics of body mass index (BMI) in patients using and not using CPAP therapy

The present graphical analysis presents the dynamics of mean body mass index (BMI) in two groups of patients – those using CPAP therapy and those not using it – within a 36-month observation period. The data cover four time points: baseline (0 months), 12th, 24th, and 36th

month from the start of follow-up.

Observed trends

In the group of patients using CPAP therapy, a statistically significant decrease in BMI is observed already within the first 12 months – from 35.64 to 32.37 (Δ = -3.27). In subsequent periods, the decrease continues, albeit with lower intensity – to 31.60 at the end of the 36-month period. The total decrease over the three years amounts to -4.04 BMI units, which can be interpreted as clinically significant.

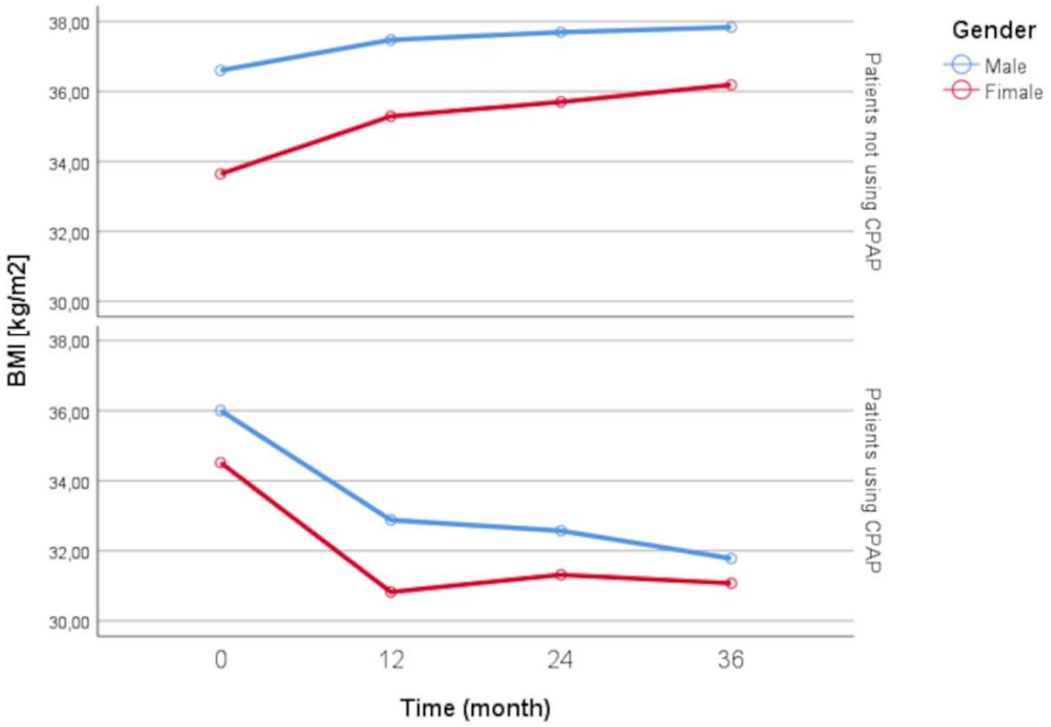
Conversely, in patients not using CPAP, a steady trend toward weight gain is observed: from 36.08 at baseline to 37.55 at month 36. This corresponds to a total increase of +1.47 BMI units over the same period. The rate of increase is linear and constant, without indications of spontaneous stabilization or weight reduction.

Between-group difference

The difference in BMI between the two groups deepens over time. While baseline values are close, at month 36 a difference of approximately 6 units is observed in favor of the CPAP group. This difference is particularly important, since epidemiological data show that a decrease of more than 5 BMI units is associated with reduced risk of cardiovascular diseases, type 2 diabetes, and sleep apnea.

Clinical interpretation

The trends in the CPAP group demonstrate not only stabilization of body mass but also sustained improvement over time. The effect is most pronounced during the first year of therapy, after which the decrease "plateaus" but is maintained. This suggests that CPAP therapy exerts a favorable influence not only on respiratory function during sleep but also on the metabolic profile and body weight of patients. Such results may be explained by reduced chronic inflammation, improved hormonal balance (including ghrelin and leptin), and increased energy efficiency of the organism.



Groups	Sex	Baseline measurement	12 months	24 months	36 months
Non-CPAP users	Men	36.6±3.5	37.47±3.2	37.69±3.3	37.83±3.5
	Women	33.64±3.0	35.29±3.0	35.70±2.7	36.19±2.4
	Total	36.08±3.6	37.09±3.3	37.34±3.2	37.55±3.4
CPAP users	Men	36.0±3.6	32.88±3.2	32.57±3.4	31.77±4.1
	Women	34.5±3.1	30.82±2.9	31.31±3.0	31.07±3.1
	Total	35.6±3.6	32.37±3.2	32.26±3.3	31.60±3.8

Fig. 26 Change in BMI in patients with and without CPAP therapy – men and women

To assess changes in BMI at four time points: baseline, 12 months, 24 months, and 36 months, a general linear model with repeated measures was applied. The model includes time as a within-subject factor and CPAP use, sex, and age group as between-subject factors.

Mauchly's test shows that the assumption of sphericity is violated, $W=0.411$, $\chi^2(5)=86.939$, $p<0.001$. Therefore, for the interpretation of within-subject effects, Greenhouse-Geisser corrected results were used.

A significant main effect of time was found, $F(2.005, 198.510)=9.822$, $p<0.001$, partial $\eta^2=0.090$, indicating that BMI changed significantly over the follow-up period in the total sample. More importantly, the interaction between time and CPAP use was statistically significant, $F(2.005, 198.510)=64.040$, $p<0.001$, partial $\eta^2=0.393$. This result shows that the trajectory of BMI over time differs substantially between patients who used CPAP therapy and those who did not.

Initially, the mean BMI values were similar in both groups. In patients who did not use CPAP, BMI increased from 36.08±3.61 kg/m² at baseline to 37.09±3.26 kg/m² at 12 months, 37.34±3.24 kg/m² at 24 months, and 37.55±3.35 kg/m² at 36 months. In contrast, patients using CPAP showed a significant decrease in BMI from 35.64±3.56 kg/m² at baseline to 32.37±3.23 kg/m² at 12 months. This lower BMI level was maintained at 24 and 36 months, with mean values of 32.26±3.29 kg/m² and 31.60±3.84 kg/m², respectively.

The between-subject effect of CPAP use was also statistically significant, $F(1,99)=8.194$, $p=0.005$, partial $\eta^2=0.076$. The estimated marginal means show that over the follow-up period, BMI was significantly higher in non-CPAP users compared to CPAP users: 35.69 kg/m² versus 32.68 kg/m², respectively. The Bonferroni-corrected mean difference was 3.014 kg/m², 95% CI [1.369; 4.658], $p<0.001$.

A significant interaction between time and sex was also observed, $F(2.005, 198.510)=3.205$, $p=0.043$, partial $\eta^2=0.031$, indicating that the dynamics of BMI differ to some extent between men and women. However, the interaction between time, CPAP device use, and sex was not statistically significant, $F(2.005, 198.510)=0.375$, $p=0.688$, partial $\eta^2=0.004$. Therefore, the favorable effect of CPAP on BMI dynamics was observed in both men and women, with no evidence of a statistically different response associated with CPAP depending on sex. The interaction between time, CPAP device use, and age group was not significant, $F(6.015, 198.510)=0.566$, $p=0.758$, partial $\eta^2=0.017$. Similarly, the four-way interaction between time, CPAP use, sex, and age group was not significant, $F(4.010, 198.510)=0.769$, $p=0.547$, partial $\eta^2=0.015$. These findings show that the effect of CPAP on BMI reduction was not substantially modified by age group.

Overall, the results show a clear divergence between the two groups. Patients who do not use CPAP demonstrate a gradual increase in BMI over the 36-month observation period, whereas CPAP users show a marked decrease during the first 12 months, followed by stabilization and slight further decrease until the end of follow-up. In the analysis of morphometric parameters at the beginning of the study, there is no statistically significant difference between the male subgroups, nor between the two female subgroups. The control group has a BMI of 36.08±3.6 kg/m², with a statistically significant difference ($p<0.05$) attributable to sex: men – BMI 36.6±3.5 kg/m², and women – BMI 33.6±3.0 kg/m². The baseline parameters of the groups using CPAP therapy are similar. The overall BMI is 35.6±3.6 kg/m², with men – BMI 36.0±3.6 kg/m² and

women – BMI 34.5±3.1 kg/m². The dynamic change in BMI during the study at 12, 24, and 36 months is presented in Table 1 and Fig. 26.±3 ± ±3 ± 3 ±

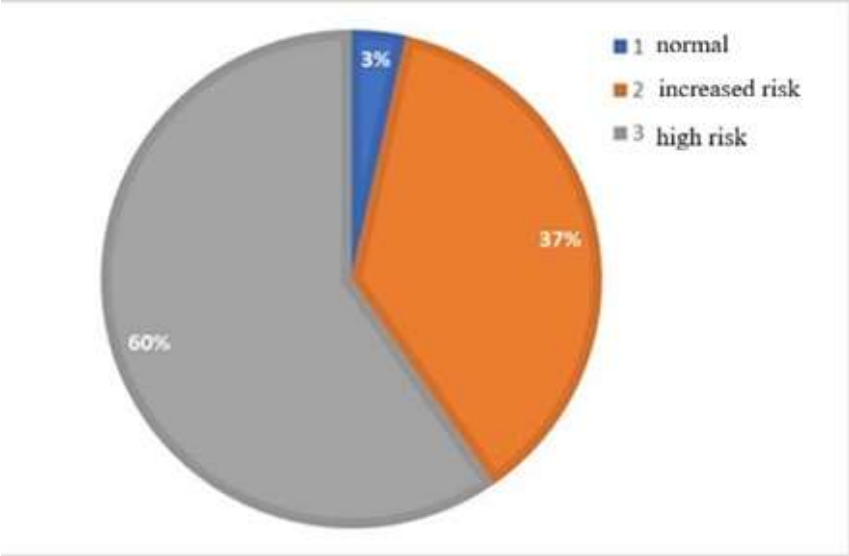
Fig. 26 Change in BMI in patients with and without CPAP therapy - women

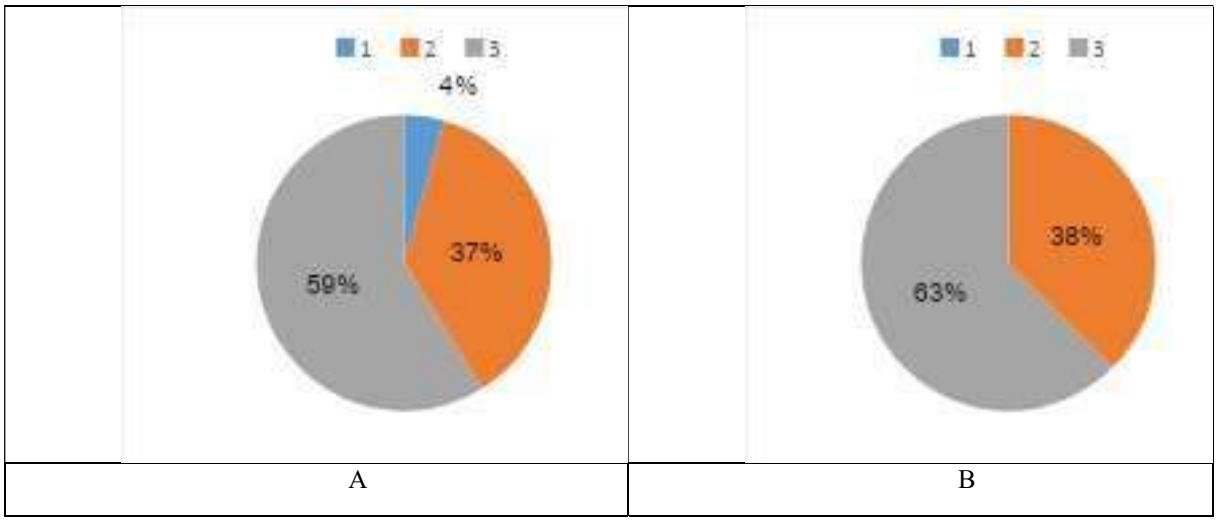
Tracking the dynamic changes that occurred during the three-year observation, a statistically significant reduction in BMI at 12 months is clearly outlined, in both men and women between the two main groups. After the initial change in BMI, no further tendency toward reduction is observed; instead, a stable state with slight fluctuations occurs.

Neck circumference

The percentage distribution of patients by obesity status, based on neck circumference, is presented in Fig 2 7 . Patients with high risk/central obesity and neck circumference for men ≥40 cm and for women ≥37 cm account for 60%. Increased risk, neck circumference between 37–40 cm for men and 34–37 cm for women, accounts for 30%. Only 3% of patients have a normal value, representing an insignificant.

From the distribution presented in Fig. 27, it can be seen that there is no sexual dimorphism in the studied group.





A B

Fig. 27 Percentage distribution of patients by obesity status, based on neck circumference, total distribution and distribution in men (A) and women (B).

EF – left ventricular ejection fraction

The dynamics of changes in LVEF were measured at five time points: 0, 6, 12, 24, and 36 months. The observed changes are presented in Table 11.

Groups	sex	Baseline measurement	6 months	12 months	24 months	36 months
Non-CPAP users	Men	59.72±5.56	59.55±5.44	58.72±6.33	57.51±6.97	57.76±5.78
	Women	58.40±5.70	58.60±6.38	57.30±5.90	55.30±7.20	54.30±6.78
CPAP users	Men	58.91±6.83	59.05±6.08	59.26±6.30	59.05±6.64	58.70±6.13
	Women	59.29±5.24	59.21±6.00	59.36±5.84	60.21±5.73	59.57±5.12

Table 11 Dynamics of changes in LVEF

Men

In men, both CPAP users and non-users, no statistically significant difference in LVEF was found. The mean values at baseline are identical (59.72±5.56 in group 1 and 58.91±6.83 in group 3). At 36 months, the values remain close (57.76±5.78 versus 58.70±6.13).

This shows that in men, the use of CPAP does not lead to a substantial change in left ventricular function within the observed period.

Women

At the initial time points (0–24 months), women using and not using CPAP have similar LVEF values. However, at 36 months, a distinct difference is observed:

- Women without CPAP: LVEF = 54.30±6.78
- Women with CPAP: LVEF = 59.57±5.12

This is the only statistically significant difference established in the analysis. It indicates a substantial change toward reduction in women who do not use CPAP at the end of the follow-up period, as well as stability in the parameter throughout the entire study period in those undergoing therapy.

E/E' - Analysis of the dynamics of the E/E' parameter depending on CPAP therapy and sex

To assess changes in the E/E' parameter during follow-up, a General Linear Model (GLM) for repeated measures was applied. The within-subject factor was follow-up time with five levels (0, 6, 12, 24, and 36 months), and the between-subject factors were sex and CPAP therapy use.

Before conducting the analysis, the assumption of sphericity was checked using Mauchly's test. The results showed a statistically significant violation of sphericity (Mauchly's $W = 0.515$, $\chi^2 = 71.339$, $p < 0.001$); therefore, Greenhouse–Geisser corrected degrees of freedom ($\varepsilon = 0.712$) were used in interpreting the results. Descriptive analysis shows that the mean E/E' values vary over the follow-up period. The mean value is 9.50 ± 2.63 at baseline, decreases to 9.12 ± 2.22 at six months, after which a gradual increase to 9.88 ± 2.44 at 36 months is observed. Although the absolute changes are not large, they indicate the presence of dynamics in the parameter over time. A statistically significant main effect of time on E/E' values was found (Greenhouse–Geisser: $F(2.846; 310.246) = 9.502$, $p < 0.001$). This result shows that the E/E' parameter undergoes significant changes during the follow-up period.

Of particular interest is the interaction between time and CPAP therapy. The analysis identified a strongly statistically significant Time × CPAP interaction (Greenhouse–Geisser: $F(2.846; 310.246) = 36.896$, $p < 0.001$). This result shows that changes in E/E' during the observation period proceed differently in patients treated with CPAP compared to patients without CPAP therapy. Therefore, the effect of CPAP is expressed not only as a difference between groups at a given moment, but primarily as a different long-term trajectory of change in the parameter. No statistically significant interaction between time and sex was found (Greenhouse–Geisser: $F(2.846; 310.246) = 2.476$, $p = 0.065$). Although the result is close to the threshold of statistical significance, the available data do not allow us to conclude that the dynamics of E/E' differ substantially between men and women.

Similarly, the three-way interaction Time × Gender × CPAP did not reach statistical significance (Greenhouse–Geisser: $F(2.846; 310.246) = 2.459$, $p = 0.066$). This indicates that the influence of CPAP therapy on the dynamics of E/E' is similar in both sexes. In the analysis of between-subject effects, no statistically significant main effect of sex ($F(1;109) = 0.854$, $p = 0.357$) or of CPAP therapy ($F(1;109) = 2.673$, $p = 0.105$) was found. No significant interaction between sex and CPAP therapy was established either ($F(1;109) = 0.793$, $p = 0.375$).

The lack of a significant main effect of CPAP shows that the mean E/E' values, averaged over the entire follow-up period, do not differ substantially between the two groups. At the same time, the significant Time × CPAP interaction shows that therapy influences the way the parameter changes over time. Therefore, the clinical effect of CPAP on E/E' manifests primarily through a change in the long-term dynamics of the parameter, rather than through a constant difference between groups.

During follow-up, one patient did not reach the final 36-month visit; therefore, data for the last time point are available for 113 participants. The proportion of missing data is below 1% and is not expected to substantially affect the reliability of the results.

Changes in E/e' values for the total sample show opposite trends between the two main groups. At the initial time point (month 0), values are statistically significantly higher in CPAP users – 10.28±2.61 versus 8.71±2.42 in non-users. After 6 months of observation, a substantial decrease is registered in the CPAP therapy group to 9.25±2.08, while the control group shows a slight increase to 8.91±2.36. At month 12, the observed trends continue, with the control group not using CPAP showing a statistically significant increase to 9.59±2.25, whereas in the group treated with CPAP, the parameter values statistically significantly decrease to 9.12±1.28. The unfavorable trend toward permanent increase, and a statistically significant one compared to controls, continues in non-users in the subsequent time intervals at 24 months and 36 months: 10.7±2.73 and 10.8±2.54, respectively. Opposite changes are seen in patients using CPAP therapy in the same intervals: at 24 months – 8.77±1.61, and at 36 months – 8.95±1.93. The overall change over 36 months is –1.33 for the CPAP group and +2.11 for the control group – a difference of almost 3.5 units, which is clinically significant.

Women using CPAP demonstrate a marked decrease in E/e' from 10.50±1.99 to 8.86±1.77 ($p<0.05$); at the end of the period, the reduction is 1.64. In women without therapy, there is a statistically significant increase from 9.50±2.5 to 12.20±2.04, i.e., +2.70. The difference between groups at 36 months is over 3.3 units, with the control group showing particularly the highest rate of increase between 12 and 24 months.

Men demonstrate an even clearer and more linear response to therapy. The initial E/e' value in users is 10.21±2.81, and at the end of the period – 8.98±2.05 (statistically significant decrease of –1.23). In non-CPAP users, an increase from 8.54±2.38 to 10.52 (+1.98) is observed. Similar to the dynamics in women, the maximum difference ($p<0.05$) between groups occurs around 24–36 months.

In our study regarding left ventricular telediastolic pressure, differences were observed only between the two patient groups at the beginning of the study. In both sexes using CPAP, a significant improvement in left ventricular telediastolic pressure (E/e') values is observed, with women demonstrating a slightly stronger decrease compared to men. On the other hand, in women from the control group, the strongest increase in pressure is also observed, which highlights the tendency toward deterioration of cardiac function in the absence of CPAP therapy.

NTproBNP

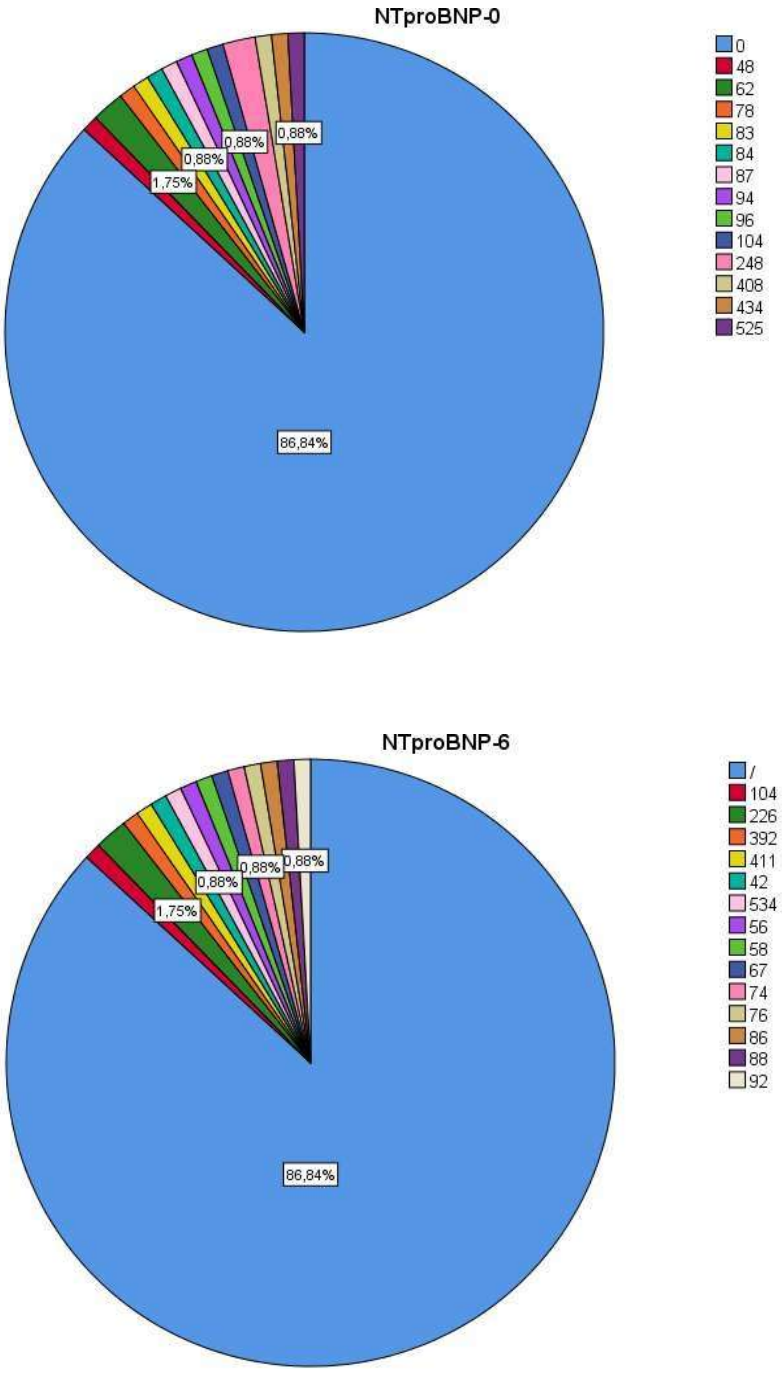


Fig. 28 Group of patients in whom NT-pro BNP was followed at diagnosis and at 6 months.

In a group of patients, NT-pro-BNP was investigated at the time of diagnosis of obstructive sleep apnea and six months after initiation of CPAP therapy. Correlation analysis showed that NT-pro-BNP depends on left ventricular systolic stress and left ventricular dysfunction, but not on the use of CPAP therapy.

Arterial pressure – Analysis of the dynamics of systolic arterial pressure

To assess changes in systolic arterial pressure, a General Linear Model (GLM) for repeated measures was applied. The within-subject factor was time with five levels: 0, 6, 12, 24, and 36 months. The between-subject factors were CPAP therapy and sex.

The sphericity check using Mauchly's test showed a significant violation of this assumption: $W = 0.481$, $\chi^2(9) = 78.652$, $p < 0.001$. Therefore, the results for effects involving time are interpreted using the Greenhouse–Geisser correction. A statistically significant main effect of time on systolic pressure was found: $F(2.935, 319.915) = 20.250$, $p < 0.001$, $\eta^2p = 0.157$. This shows that systolic pressure changes substantially during the 36-month follow-up.

The key result is the significant time × CPAP interaction: $F(2.935, 319.915) = 19.113$, $p < 0.001$, $\eta^2p = 0.149$. This means that the change in systolic pressure over time is not the same in patients with and without CPAP therapy. Therefore, the effect of CPAP manifests precisely as a different trajectory of arterial pressure throughout the follow-up. No significant time × sex interaction is found: $F(2.935, 319.915) = 0.268$, $p = 0.845$, $\eta^2p = 0.002$. The three-way interaction time × CPAP × sex is also not significant: $F(2.935, 319.915) = 0.539$, $p = 0.652$, $\eta^2p = 0.005$. Therefore, the dynamics of systolic pressure do not differ substantially between men and women, and the effect of CPAP on temporal change does not depend on sex.

In the between-subject effects, a significant overall effect of CPAP is found: $F(1,109) = 10.386$, $p = 0.002$, $\eta^2p = 0.087$. This shows that the mean systolic pressure values over the entire period differ between the CPAP group and the control group. Sex has no statistically significant main effect: $F(1,109) = 2.974$, $p = 0.087$, $\eta^2p = 0.027$. The CPAP × sex interaction is also not significant: $F(1,109) = 0.947$, $p = 0.333$, $\eta^2p = 0.009$. The two main groups show changes in systolic arterial pressure values similar to those of telediastolic pressure. At the initial time point 0, the values in the CPAP-using group are statistically significantly higher – 156.80 ±14.57 mmHg versus 147.94±15.31 mmHg in non-users. After the 6-month period, values in both groups are almost identical, with a tendency toward decrease in controls – 142.23±9.82 mmHg, and a statistically significant decrease compared to baseline in patients with CPAP therapy to 141.21±8.30 mmHg. At month 12, changes continue in patients undergoing CPAP treatment; values reach 133.89±14.17 mmHg, with a statistically significant difference both compared to the initial measurement time point and to month 6. During the subsequent two registration time points, a stable state is achieved: at 24 months 133.19±7.87 mmHg, and at 36 months – 132.95±8.41 mmHg.

Changes in women using CPAP follow the same trends as in the total group, with a marked decrease from 156.43 ±14.62 mmHg to 133.50±7.95 mmHg ($p<0.05$); at the end of the period, the reduction is 22.93 mmHg. In women without therapy, there is an unfavorable tendency toward an increase in systolic blood pressure values at 12, 24, and 36 months.

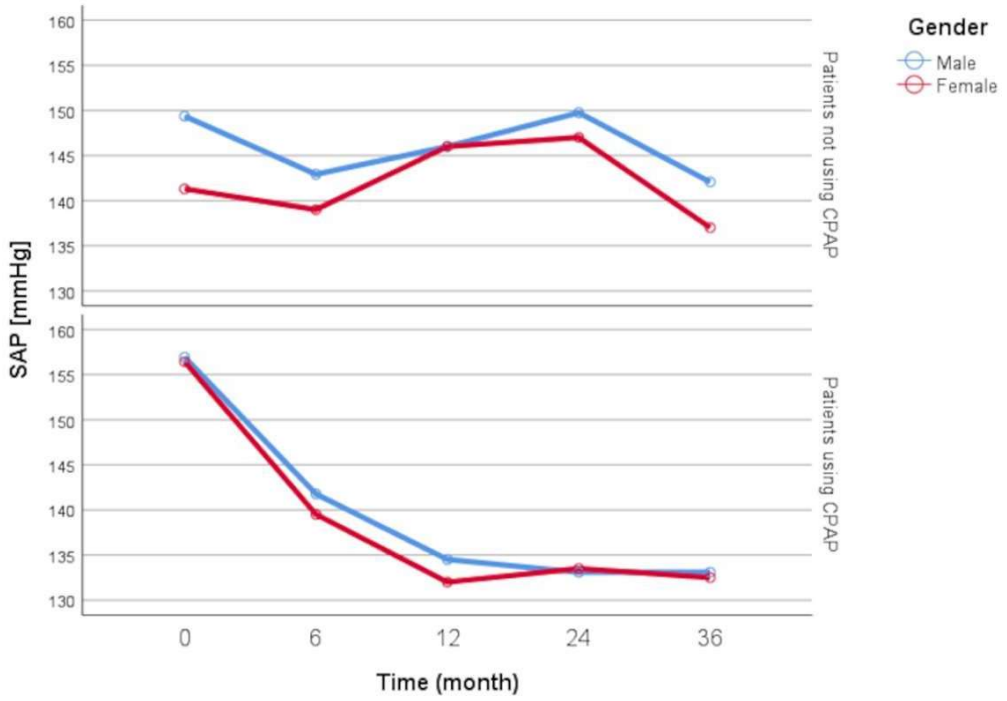


Fig. 29 Changes in SBP during 36-month follow-up

Men show an analogous response to CPAP therapy. The initial systolic pressure value in users is 156.93±14.72 mmHg, and at the end of the period, a stable equilibrium of close values is achieved – 134.51±6.62 mmHg, 133.09±8.47 mmHg, and 133.09±8.65 mmHg (statistically significant decrease of –23.84 mmHg). In non-CPAP users, a lack of variation is observed across the individual follow-up periods, with no tendency toward increase or decrease.

In both sexes using CPAP, a significant improvement in systolic pressure values is observed. On the other hand, in women from the control group, a deterioration of hypertension is registered, due to an increase in systolic values.

Analysis of the dynamics of diastolic arterial pressure

For diastolic arterial pressure, an analogous General Linear Model (GLM) for repeated measures with the same structure was applied: time as a within-subject factor with five levels, and CPAP therapy and sex as between-subject factors.

Mauchly's test again showed a violation of sphericity: $W = 0.756$, $\chi^2(9) = 30.030$, $p < 0.001$. Therefore, the results are interpreted using the Greenhouse–Geisser correction. A statistically significant main effect of time on diastolic pressure was found: $F(3.497, 381.220) = 8.582$, $p < 0.001$, $\eta^2p = 0.073$. This shows that diastolic pressure also changes significantly during the follow-up period, but the effect size is smaller than that for systolic pressure. The time × CPAP interaction is statistically significant: $F(3.497, 381.220) = 9.083$, $p < 0.001$, $\eta^2p = 0.077$. This means that the dynamics of diastolic pressure over time differ between patients with CPAP

therapy and patients without CPAP. Therefore, for diastolic pressure as well, CPAP is associated not so much with a constant overall difference between groups, but with a different course of change over time. No significant time × sex interaction is found: $F(3.497, 381.220) = 0.745$, $p = 0.545$, $\eta^2p = 0.007$. The three-way interaction time × CPAP × sex is also not significant: $F(3.497, 381.220) = 1.512$, $p = 0.205$, $\eta^2p = 0.014$. This shows that sex does not substantially alter the temporal dynamics of diastolic pressure and does not modify the effect of CPAP.

Unlike systolic pressure, no significant overall between-subject effect of CPAP is found for diastolic pressure: $F(1,109) = 1.542$, $p = 0.217$, $\eta^2p = 0.014$. Sex also has no significant main effect: $F(1,109) = 2.356$, $p = 0.128$, $\eta^2p = 0.021$. The CPAP × sex interaction is not statistically significant: $F(1,109) = 2.671$, $p = 0.105$, $\eta^2p = 0.024$. The results show that both systolic and diastolic arterial pressure change significantly over time. For both parameters, the time × CPAP interaction is statistically significant, which is the main argument that the observed dynamics of arterial pressure differ between patients with and without CPAP therapy. The effect is more pronounced for systolic pressure. This is evident both from the higher η^2p value for the effect of time on SBP (0.157 versus 0.073 for DBP) and from the stronger time × CPAP interaction for SBP ($\eta^2p = 0.149$) compared to DBP ($\eta^2p = 0.077$). Furthermore, only for systolic pressure is there a significant overall between-subject effect of CPAP, whereas for diastolic pressure this effect does not reach statistical significance.

Thus, the results support the conclusion that CPAP therapy is associated with a more favorable long-term dynamic of arterial pressure, with the effect being more clearly expressed for systolic pressure. Sex does not show a substantial influence on this dynamic and does not alter the effect of CPAP.

Groups	Sex	Baseline measurement	6 months	12 months	24 months	36 months
Non-CPAP users	Men	85.32±5.01	84.36±3.25	83.87±4.57	83.74±5.17	82.78±3.23
	Women	80.60±6.33	82.00±2.67	83.80±4.76	82.30±5.03	82.20±3.82
CPAP users	Men	87.07±5.95	81.81±4.51	81.37±3.10	80.72±3.77	80.74±3.87
	Women	87.14±6.12	82.86±2.68	80.64±3.22	81.43±4.18	79.93±3.34

Table 12: Comparative summary of GLM results for SBP and DBP – Time, Time × CPAP, Time × Gender, Time × CPAP × Gender, CPAP main effect

It is obvious that the trends observed in systolic values are identical in diastolic values as well, with some minor differences. Diastolic values do not exceed the reference limits, unlike

systolic values, and vary within the high-normal blood pressure range. In addition, we could note that their variations have a smaller range.

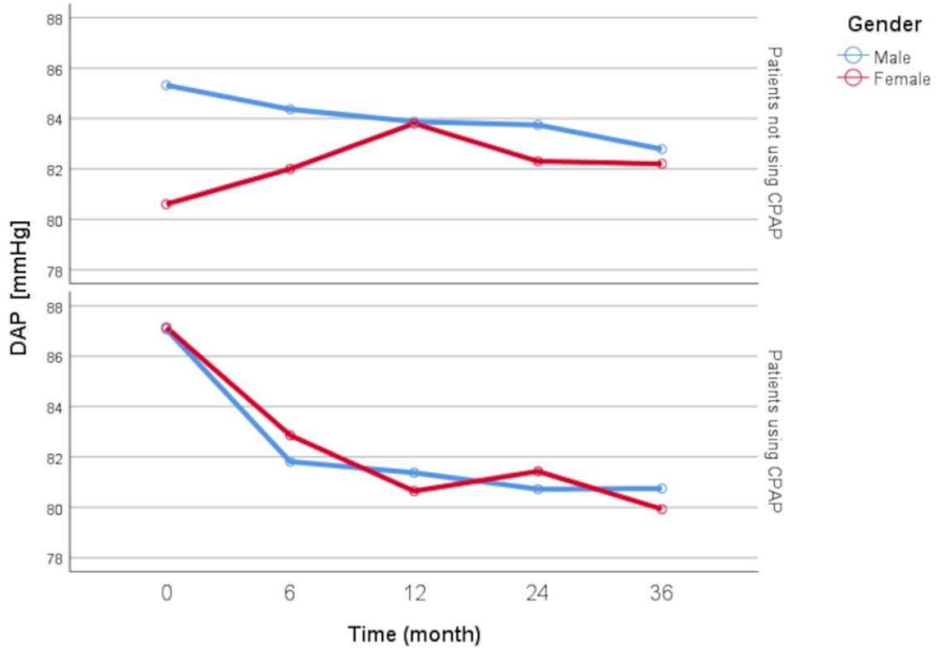


Fig. 30 Changes in DBP during 36-month follow-up

LA, Table 13 Dynamics of left atrial (LA) area at five time points (0, 6, 12, 24, and 36 months)

Groups	Sex	Baseline measurement	6 months	12 months	24 months	36 months
Non-CPAP users	Men	19.72±2.30	19.74±2.32	20.40±2.71	21.26±2.86	21.50±2.84
	Women	19.20±1.62	19.20±1.62	20.10±1.97	21.40±2.12	22.00±2.31
CPAP users	Men	20.09±2.96	20.07±2.95	20.09±2.92	20.21±2.99	20.40±3.10
	Women	19.36±2.50	19.29±2.55	19.36±2.62	19.50±2.77	19.64±2.79

Data presenting the dynamics of left atrial (LA) area at five time points (0, 6, 12, 24, and 36 months) in both sexes and in both groups, CPAP users and non-users, are presented in Table 13.

In men not using CPAP, LA area increases from 19.72 cm² to 21.50 cm² over 36 months, with a total increase of +1.78 cm². The standard deviation also increases from 2.30 to 2.84, indicating greater variability. In women who do not use CPAP, the process follows an analogous course, but is slightly more pronounced; from 19.20 cm², the increase over the entire period is 2.80 cm², reaching 22.00 cm². Groups applying CPAP therapy demonstrate greater LA stability.

The area in both groups undergoing CPAP therapy remains practically stable: from 20.09 cm² to 20.40 cm², with a minimal increase of +0.31 cm², and in women from 19.36 cm² to 19.64 cm², giving an increase of +0.28 cm², the smallest of all groups.

Medications used

The dynamics of medications used, presented as mean values and standard deviation, are shown in Table ... The number of medications taken demonstrates clear differences between groups according to sex and CPAP therapy use. In patients who do not use CPAP, a clearly expressed tendency toward progressive increase in medication burden over time is observed. Men without CPAP increase the number of medications from 2.19±1.39 at baseline to 3.39±1.02 at 36 months, representing the largest increase among all groups. Women without CPAP also show a significant increase (1.90±1.10 → 3.10±1.20), with the greatest change occurring between 6 and 12 months.

Conversely, in patients who use CPAP, stabilization or reduction in the number of medications is established. Men on CPAP reduce the medication burden from 2.70±1.63 to 2.44±1.16 at 36 months, while women on CPAP demonstrate the most favorable dynamic with a reduction from 2.79±1.31 to 2.36±0.84 and stable values after 12 months.

The statistical interpretation of the observed trends suggests the presence of a significant main effect of CPAP therapy, as CPAP patients maintain a stable or decreasing number of medications, unlike those without therapy. There is also a significant effect of time, expressed as a progressive increase in medications in non-CPAP users. The data also suggest an interaction between time and CPAP status, as well as a probable effect of sex, since men without CPAP show the most unfavorable dynamic, while women on CPAP – the most favorable. The described trends are clearly demonstrated in the table with statistical indicators (Table 14).

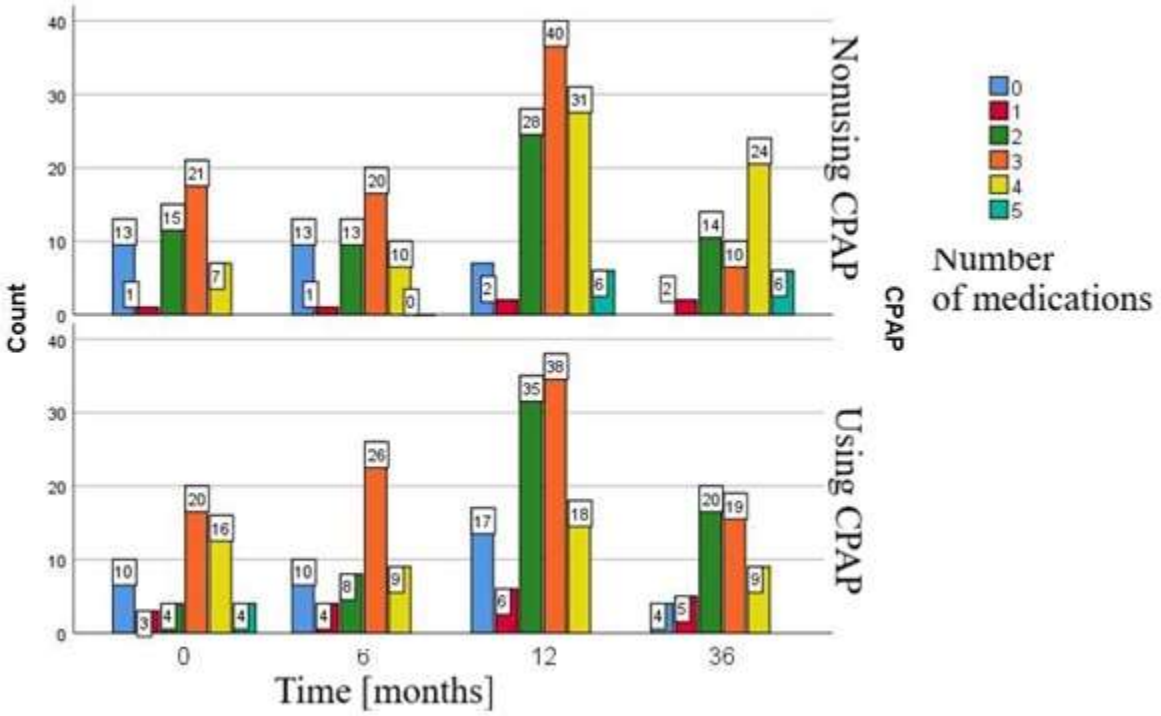


Table 31 Number of medications used during follow-up at five time points (0, 6, 12, 24, and 36 months)

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	15,306[a]	5	,009
Likelihood Ratio	17,409	5	,004
Linear-by-Linear Association	4,425	1	,035
N of Valid Cases	114		

a. 4 cells (33,3%) have expected count less than 5. The minimum expected count is 2,00.

Number of medications/ CPAP

These results underscore the role of CPAP therapy in limiting multimorbidity and reducing pharmacological burden in patients with obstructive sleep apnea.

Groups	Sex	Baseline measurement	6 months	12 months	24 months	36 months
Non-CPAP users	Men	2.19±1.39	2.30±1.46	2.57±1.36	3.19±0.97	3.39±1.02
	Women	1.90±1.10	1.90±1.10	2.70±0.82	3.40±0.84	3.10±1.20
CPAP users	Men	2.70±1.63	2.33±1.39	2.33±1.34	2.35±1.29	2.44±1.16
	Women	2.79±1.31	2.43±1.16	2.07±1.07	2.29±0.99	2.36±0.84

Table 14 Number of medications used during follow-up at five time points (0, 6, 12, 24, and 36 months)

Model results

Indicator	Training	Cross-validation
RMSE	1,64	1,93
MAE	1,29	1,51
R^2	0,48	0,37
nodes / terminal	11 / 6	–

- **First splitter: E/E'-0 ≥ 9.5 → strongest single predictor (Relative importance = 1.00).**
- **Second splitter (low E/E'-0 branch): BMI ≥ 34.2 kg/m² → further increases risk by ΔE/E' ≈ +2.1.**
- **Secondary splitter (high E/E'-0 branch): Neck circumference ≥ 41 cm or absence of CPAP → prediction for highest values (E/E'-36 ≈ 12.3 ± 1.0).**
- **CPAP therapy appears as a splitter only at the third level, but reduces median E/E'-36 by ~1.4 (clinically relevant).**
    - **Predictor importance (normalized %)**

E/E'-0 (100) › BMI (63) › CPAP (41) › LA area-0 (32) › Neck circumference (29) › Age (18) › Number of medications (12) › Sex (5)

Discussion

This 36-month prospective study shows that long-term CPAP therapy exerts significant and clinically meaningful benefits on BMI, left ventricular diastolic function, and arterial blood pressure in patients with obstructive sleep apnea. The results provide convincing evidence that prolonged CPAP use contributes not only to improved respiratory function during sleep, but also to favorable cardiovascular remodeling and hemodynamic stabilization. Importantly, the magnitude and persistence of these effects underscore the value of long-term adherence to treatment, an aspect that has not been sufficiently addressed in previous studies.

BMI

Basoglu and colleagues conduct a multicenter, prospective study of patients with OSA who use CPAP therapy. The authors track changes in anthropometric parameters for 1.1 ± 1 years. They note a slight decrease in BMI in patients with obesity and a corresponding increase in those with BMI >30 kg/m². This shows the critical importance of the BMI cutoff value of 30 kg/m². A similar study is conducted by Garcia et al. (2011), with a study duration of 6 months. They track changes in appetite and metabolism. For the relatively short study they conduct, they do not find substantial changes in body weight. After one-year follow-up of patients of both sexes with BMI above and below 30 kg/m², Redenius et al. (2007), testing their initial hypothesis of weight reduction under the influence of CPAP therapy, surprisingly find a significant weight increase in patients without obesity and no substantial changes in those with obesity. Several authors seek the explanation for this phenomenon in the leptin response to CPAP therapy, namely – the reduction of its secretion and corresponding concentration in the blood. The consequence of this is the understandable reduction of its suppressive effect on appetite. In the study conducted by us, a very good effect of CPAP therapy on body weight is found. In the control group of patients without CPAP therapy, there is a linear rate of weight increase, albeit minimal, with no tendency toward stabilization or decrease. Patients with CPAP therapy not only reduce their weight but also reach a stable state that remains stable during the later years of observation. Notably, these changes occur right from the beginning during the first 12 months. The rate of weight reduction is pronounced in the initial period. Our results underscore those obtained by authors who studied similar patient groups with BMI >30 kg/m². As we also see from...

E/E'

OSA causes changes in the structure and function of the left ventricle; available literature reports conflicting results. One of the main parameters of left ventricular status is telediastolic pressure. But and colleagues investigate 120 subjects, of whom 40 have confirmed sleep apnea, 40 have hypertensive disease, and 40 are healthy controls. OSA patients are subjected to CPAP treatment for 26 weeks. They find a favorable effect of CPAP therapy on E/e' values. Improvement in left ventricular function is also found by Arias et al. (2005) in a study of men undergoing CPAP therapy for 12 weeks due to sleep apnea. Unfortunately, data on the effects of CPAP therapy on left ventricular function, and especially on telediastolic pressure, are not only scarce but also contradictory. In our study, in both sexes using CPAP, a significant improvement in left ventricular telediastolic pressure (E/e') values is observed, more strongly expressed in women. CPAP therapy has a distinctly favorable effect on E/e' – an indicator of diastolic dysfunction – in both men and women. In the absence of therapy, the parameter deteriorates progressively. The analysis underscores the need for timely initiation of CPAP in patients with obstructive sleep apnea and cardiac comorbidity. The positive changes could be explained by

improved myocardial metabolism during CPAP treatment and, as a result, remodeling of the myocardial wall.

Arterial blood pressure

In patients with OSA accompanied by other comorbidities, resistant hypertension develops, which is refractory or poorly responsive to usual therapeutic regimens. In this regard, the effect of CPAP therapy is extremely favorable. It has been established that it lowers both systolic and diastolic pressure values. Phillips et al. (2008) report that after 8 weeks of CPAP treatment, a reduction occurs in both central systolic and peripheral arterial pressure. It is known that OSA contributes to a substantial increase in arterial wall rigidity, which is one of the factors for stable maintenance of high blood pressure and risk of cardiovascular incidents. The use of CPAP therapy significantly reduces rigidity and lowers blood pressure values (Doonan et al., 2011). The data reported by Saito et al. (2010) are also unambiguous regarding the lowering of blood pressure in both hypertensive and normotensive patients after 6 months of CPAP treatment. In the patients studied by us, opposite changes in systolic pressure response are observed between the two main groups, and no differences between women and men are present. The rate of change toward reduction is fastest during the first 12 months, when CPAP therapy is applied. Reaching the minimum during the remaining 24 months, values are stable and lack variation. Our data confirm the results of Pedrosa et al. (2013) in the follow-up of systolic pressure over a six-month period in a control group with OSA and in the group treated with CPAP. Diastolic pressure varies to a significantly lesser degree, with the maximum effect in men achieved at 6 months, and in women at 12 months. Differences on the order of 12–14 mmHg systolic value indicate a reduction in afterload on the heart. We could hypothesize that the change after CPAP treatment is due to reduced sympathetic overactivity in ...

It is known that OSA contributes to a substantial increase in arterial wall rigidity, which is one of the factors for stable maintenance of high blood pressure and risk of cardiovascular incidents. The use of CPAP therapy significantly reduces rigidity and lowers blood pressure values (Doonan et al., 2011).

LA

Untreated obstructive sleep apnea (OSA) is a well-established risk factor for structural changes in the cardiac chambers. Recurrent episodes of hypoxia, fluctuations in intrapleural pressure, and chronic sympathetic activation lead to increased preload and diastolic dysfunction, which stimulates dilation of the left atrium.

This is confirmed by our data, where both men and women without CPAP show a clearly progressive increase in LA area. Women without CPAP show the largest increase (+2.80 cm^2), which may reflect greater sensitivity to the hemodynamic effects of OSA. "Recurrent intermittent hypoxia leads to structural changes in the atrial myocardium." (Lin et al., 2019)

CPAP therapy stabilizes the upper airways, reduces fluctuations in intrapleural pressure, and reduces nocturnal hypoxia. This leads to improved diastolic function and reduced atrial load. Statistical analysis clearly shows that in both men and women using CPAP, LA area remains practically unchanged for 36 months. This is in full accordance with published data. [Jane Colish et al. Obstructive Sleep Apnea: Effects of Continuous Positive Airway Pressure on Cardiac Remodeling as Assessed by Cardiac Biomarkers, Echocardiography, and Cardiac MRI, Chest, 2012.]

Sex differences in remodeling. An interesting observation is that women without CPAP have a greater increase in LA area compared to men without CPAP. This may be due to: differences in vascular reactivity, loss of hormonal protection after the onset of menopause, and later diagnosis of OSA in women. On the other hand, women on CPAP show the least remodeling, which may indicate a better therapeutic response. [Federica Moscucci et al. Obstructive sleep apnea syndrome (OSAS) in women, 2025].

Untreated OSA leads to progressive increase in LA area, especially in women.

- CPAP therapy stabilizes LA dimensions and practically prevents remodeling.
- Sex influences the degree of remodeling, with women being more vulnerable in the absence of therapy, but also more responsive to CPAP.

These results underscore the importance of early diagnosis of OSA and adherence to CPAP therapy as a key factor for preventing atrial remodeling and potentially reducing the risk of atrial arrhythmias. CPAP therapy shows a sex-specific effect on left ventricular function. While no significant changes are observed in men, CPAP leads to a statistically significant improvement in LVEF in women at 36 months. These results highlight the need for an individualized approach in assessing the effect of CPAP and for additional studies directed at sex differences in hemodynamic response.

LVEF – left ventricular ejection fraction

The present study demonstrates a sex-specific effect of CPAP on left ventricular function. While no significant changes are observed in men, CPAP leads to a late-occurring improvement in LVEF in women, which reaches statistical significance at 36 months. CPAP increases intrapleural pressure, which leads to a reduction in venous return (preload) and reduction of transmural pressure of the left ventricle (afterload). This improves stroke volume and reduces myocardial oxygen consumption. These effects are well described in the literature and are associated with improvement of left ventricular function in patients with obstructive sleep apnea (OSA) and heart failure. CPAP reduces episodes of intermittent hypoxia and sympathetic hyperactivation, characteristic of OSA. This leads to lower arterial pressure, reduced myocardial load, and improved diastolic function.

Women demonstrate a different profile of autonomic regulation, vascular reactivity, and hormonal status, which may influence the response to CPAP. Estrogens improve endothelial function and vasodilation, which may enhance the effect of reduced afterload with CPAP. This may explain why only women show significant improvement in LVEF in our study. The observed statistically significant difference in women at 36 months suggests that CPAP may have a stronger and later-manifesting effect on left ventricular function in women. This may be due to a combination of hemodynamic, autonomic, and hormonal mechanisms.

Medications

The present follow-up of the number of medications taken over a period of 36 months shows clearly distinguishable trajectories between the groups according to gender and CPAP

therapy use. The data demonstrate that the absence of CPAP is associated with progressive increase in medication burden, while CPAP therapy leads to stabilization or reduction in the number of medications, regardless of gender. This underscores the systemic effect of CPAP on the control of comorbid conditions.

In men who do not use CPAP, the most unfavorable dynamics are observed. The number of medications increases from 2.19±1.39 at baseline to 3.39±1.02 at month 36, representing the largest increase among all groups. This trend likely reflects progression of hypertension, deterioration of metabolic control, and accumulation of cardiovascular risk factors characteristic of untreated obstructive sleep apnea. Chronic intermittent hypoxia and increased sympathetic activity in these patients may explain the need for adding new medications over time. Women without CPAP also show a significant increase in medication burden (1.90±1.10 → 3.10±1.20), with the greatest change occurring between months 6 and 12. This may reflect later-diagnosed comorbidities, hormonal changes (perimenopause/menopause), and more atypical clinical presentation of OSA in women, which often leads to delayed treatment and later accumulation of therapeutic needs.

Conversely, in patients using CPAP, stabilization or reduction in the number of medications is observed. Men on CPAP reduce medication burden from 2.70±1.63 to 2.44±1.16, suggesting improved blood pressure control, reduction in the need for antihypertensive combinations, and stabilization of metabolic parameters. Women on CPAP demonstrate the most favorable dynamics – reduction from 2.79±1.31 to 2.36±0.84 and stable values after month 12. This likely reflects better therapeutic response, lower OSA severity at baseline, and faster improvement in sleep quality and daytime functionality.

Statistical interpretation of the observed trends suggests the presence of a significant main effect of CPAP therapy, as patients on CPAP maintain a stable or decreasing number of medications, unlike those without therapy. There is also a significant effect of time, expressed as progressive increase in medications among non-CPAP users. The data also suggest an interaction between time and CPAP status, as well as a probable effect of gender, since men without CPAP show the most unfavorable dynamics, while women on CPAP show the most favorable.

From a clinical perspective, these results underscore the significance of CPAP therapy as an intervention that not only improves OSA symptoms but also limits multimorbidity, reduces pharmacological burden, and potentially reduces the risk of drug interactions. This has a direct impact on quality of life, treatment adherence, and long-term patient prognosis.

- Untreated OSA leads to progressive increase in LA area, especially in women.
- CPAP therapy stabilizes LA dimensions and practically prevents remodeling.
- Gender influences the degree of remodeling, with women being more vulnerable in the absence of therapy, but also more responsive to CPAP.

These results underscore the significance of early diagnosis of OSA and adherence to CPAP therapy as a key factor for preventing atrial remodeling and potentially reducing the risk of atrial arrhythmias. CPAP therapy shows a sex-specific effect on left ventricular function. While no significant changes are observed in men, CPAP in women leads to a statistically

significant improvement in LVEF at month 36. These results highlight the need for an individualized approach in assessing the effect of CPAP and for additional studies directed at sex differences in hemodynamic response.

CART model – Clinical interpretation

1. Baseline E/E′ is the strongest determinant factor – patients with OSA starting with ≥ 9.5 have more than 70% probability of remaining in the pathological range (> 10) in the third year.
2. Obesity (BMI ≥ 34) modifies the risk even with low baseline E/E′, underscoring the role of metabolic load on diastolic relaxation.
3. CPAP shows an independent protective effect, but only in the subgroup with high baseline risk.
4. The combination of "high E/E′ at disease diagnosis + non-use of CPAP + wide neck circumference" characterizes the most unfavorable cluster – a target for aggressive intervention.

Comparison with the literature

- Our coefficient of determination (R^2 = 0.37 CV) is comparable to published multivariate linear models (0.30–0.45) in similar populations.
- Previous studies (Li et al., 2023; Hoshide et al., 2024) also demonstrate that improvement in diastolic function with CPAP is limited to patients with baseline diastolic abnormality – a finding confirmed by the present tree.
    - Strengths and limitations

Strengths:

- Interpretable algorithm, fast for clinical implementation;
- Cross-validation was used → control of overfitting;
- Both morphological and therapeutic predictors are included.

Limitations:

- Modest R^2 indicates that > 60% of variation remains unexplained – likely due to lack of dynamic variables (blood pressure, AHI indices, biomarkers);
- Relatively small sample → risk of unstable split points;
- Ensemble method was not used to check stability (Random Forest).

- Practical implications

- Algorithm for early stratification: in patients with E/E′-0 ≥ 9.5, thorough echocardiography and early initiation of CPAP are recommended, especially if BMI ≥ 34 kg/m².
- Integration into electronic records: the tree can be implemented as a clinical "alert" warning of progressive diastolic dysfunction.

Conclusion – The CART model provides a clinically transparent and statistically validated tool for predicting E/E′ at the end of the third year. In a dissertation context, this proves that early echocardiographic parameters, combined with anthropometric data and CPAP status, enable reliable risk stratification and outline pathways for personalized therapy in OSA.

Discussion – place of the obtained CART model in the context of modern ML approaches in OSA.

The results of the present tree for predicting E/E′ at the third year in adults with OSA fit into the growing body of studies applying decision trees and ensemble algorithms for various clinical purposes in apnea in the adult population. First, the obtained model shows that baseline E/E′-0 and BMI are key splitters of risk for diastolic dysfunction. Similar dominance of anthropometric and cardiac parameters has been reported in the large study by Han et al. (2023), where XGBoost/LightGBM models classify OSA severity with ~88% accuracy mainly by BMI, neck circumference, and blood pressure. We extend these observations by showing that the same predictors retain their prognostic value even when the target variable is echocardiographic rather than a clinical index.

Second, the protective effect of CPAP in the model tree (reduction of median E/E′ ≈ –1.4) corresponds with the work of Lo, Liang and Kuo (2025), who demonstrate that Random Forest models constructed with clinical and physiological parameters predict lower residual AHI in patients with good CPAP efficacy. This suggests that the diastolic benefits of CPAP are reflected distinctly at the echocardiographic level when the model includes both anatomical and therapeutic factors.

Third, R^2 (0.37 after cross-validation) is comparable to the accuracies reported by Russo et al. (2024) and Yan et al. (2022), who use XGBoost/Random Forest for OSA stratification and achieve AUC 0.92–0.98. The difference that in the obtained model we predict a continuous cardiac parameter partially explains the more moderate determination – echocardiographic parameters by nature have wider biological noise.

Finally, the data of Pei et al. (2025) for predicting subclinical myocardial strain through a combined LR + CART model with AUC ≈ 0.91 underscore the potential of tree-based algorithms to detect early cardiac dysfunction. The present study contributes by showing that even at baseline E/E′ ≥ 9.5, patients can be targeted for early echocardiographic follow-up and therapeutic escalation.

In summary, the present CART model:

- confirms the leading role of obesity and baseline diastolic function in future deterioration;
- demonstrates that CPAP has an independent beneficial effect on diastolic parameters;
- expands the use of ML in OSA by shifting the focus from AHI prediction to prospective echocardiographic remodeling.

This positions the model as a clinically interpretable tool for personalized stratification, consistent with the findings of the latest tree-based algorithms in the literature.

There are partially comparable analogous models in the literature

Study	Population	Objective/Model	Main highlights
Pei et al., 2025 – retrospective LR + QUEST model	312 adults with OSA	Prediction of reduced LV strain (early myocardial dysfunction)	The tree uses BMI, CT90 and biochemistry; AUC ≈ 0.91 pmc.ncbi.nlm.nih.govpmc.ncbi.nlm.nih.gov
You et al., 2023 – Random Forest	250 patients with initial normal BP	Incident hypertension in OSA	Pure oximetry model, AUC = 0.84 cdt.amegroups.orgcdt.amegroups.org
Zhang et al., 2024 – Random Forest	798 individuals with suspected OSA	Screening for moderate/severe OSA (AHI ≥ 15)	Sens. 94.7% / Spec. 73.1% pmc.ncbi.nlm.nih.govpmc.ncbi.nlm.nih.gov
Lo et al., 2025 – Random Forest	427 CPAP patients	**Residual AHI and optimal pressure**	RF outperforms linear regression for residual AHI acc.orgacc.org
Yan et al., 2022 – RF + logistic nomogram	1044 patients	Nominal moderate/severe OSA	AUC = 0.976, 6 easy predictors researchgate.netresearchgate.net

No study has used CART/Regression Tree to predict the diastolic parameter E/E′ over time in OSA. This is the first systematic application of a tree-based algorithm for long-term echocardiographic prognosis in this field.

First in the literature integration of baseline E/E′, BMI, neck, LA area, and CPAP status in Regression-CART for the third year.

Validation with 10-fold cross-validation → proven stability (RMSE 1.93; R^2 0.37).

Identification of a threshold value E/E′-0 ≥ 9.5 as a dominant splitter for future diastolic dysfunction – a threshold not previously indicated in the OSA context.

Evidence that CPAP lowers predicted E/E′ among high-risk patients, independently of BMI (new argument for early initiation of therapy).

Creation of a simple clinical index (OSADRI – OSA Diastolic Risk Index), derived from the tree nodes, which can be calculated without software.

Proposal for a clinical algorithm (three risk levels) for referral to echocardiography and CPAP.

The proposed index – OSADRI

Criterion (outcome data)	**Points**
E/E′-0 ≥ 9.5	2
BMI ≥ 34 kg/m²	1
Neck circumference ≥ 41 cm	1
LA area-0 ≥ 34 cm²	1

Range: 0–6 pts.

Categories:

- 0 – 1 pt. → Low risk (annual follow-up)
- 2 – 3 pts. → Moderate risk (echo + consultation < 6 mo.)
- ≥ 4 pts. → High risk → immediate echocardiography and CPAP

How the index serves in practice

1. Rapid stratification in outpatient settings – all variables are collected during the primary examination.
2. Action algorithm (included in electronic record):
    - At OSADRI ≥ 4, the system automatically generates a referral for diagnostic polysomnography/echocardiography and a CPAP trial night.
3. Communication tool – the visual "tree" facilitates explaining to the patient why they are at risk.
4. Monitoring – reduction of OSADRI by ≥2 pts. after weight loss or initiation of CPAP can be used as an objective metric for therapeutic success.

Next steps

- External validity in an independent cohort (multicenter).
- Integration into a mobile application for primary care physicians.
- Prospective trial – whether application of an OSADRI-guided algorithm reduces the incidence of cardiac events.

Conclusion: the absence of an analogous published CART model for E/E′ in OSA distinguishes this work as an innovative contribution both in echocardiographic and somnological literature and provides a practical tool for early referral to CPAP therapy.

An OSA Diastolic Risk Index (OSADRI) was developed – the first index based on a Regression-CART model that uses only baseline clinical and echocardiographic data to predict the risk of diastolic dysfunction in patients with OSA and its modification by CPAP therapy. The index is easily calculable (0–6 pts.), validated by 10-fold cross-validation, and proposes a three-tier clinical scheme for referral. Published analogues are lacking, which constitutes an original methodological and practical contribution.

Conclusions

1. Of the patients participating in the study, 78.95% are male and 21.05% are female. 30.7% of the patients have class I obesity, 51.75% have class II obesity, 9.65% have class III obesity. This confirms male gender, obesity, and neck circumference as the most important predictors for the development of OSA.
2. All patients with newly diagnosed sleep apnea have increased daytime sleepiness (ESS≥10), and the severity of OSA correlates with a higher score on the Epworth Sleepiness Scale questionnaire. In examination of patients with newly diagnosed sleep apnea, a mean AHI=42.35 was established.
3. In 79.8% of diagnosed patients with OSA, AH is established; 20.1% have confirmed arrhythmia, with AF being the most common arrhythmia in patients with OSA (17.5%); 14.0% of patients have HF. Patients with obstructive sleep apnea are at increased cardiovascular risk.
4. Patients without CPAP therapy are at a statistically significantly higher risk of developing cardiovascular diseases (AH, HF, arrhythmias).
5. Long-term CPAP therapy leads to a statistically significant reduction in systolic and diastolic blood pressure, with the effect being more pronounced for systolic pressure.
6. Regular use of CPAP improves control of arterial hypertension and leads to a statistically significant reduction in antihypertensive therapy.
7. CPAP therapy limits the progression of diastolic dysfunction, stabilizes left atrial dimensions, and improves left ventricular function, especially in women.
8. CPAP therapy does not lead to a statistically significant change in NT-proBNP values, which confirms its role as a marker for assessing heart failure.
9. The developed CART model enables reliable risk stratification and identification of patients at highest risk of progressive diastolic dysfunction.

Contributions

Scientific-theoretical:

1. For the first time in the Bulgarian population, anthropometric and clinical parameters and their relationship with OSA were evaluated.

2. For the first time, prospective data on cardiovascular diseases in patients with OSA in the Bulgarian population were presented.

3. For the first time in Bulgaria, OSA questionnaires were used in patients with cardiovascular diseases, and their role as a screening tool for diagnosis was evaluated.

4. CPAP lowers predicted E/E′ among high-risk patients, independently of BMI (new argument for early initiation of therapy).

Scientific-applied

1. A model was developed, including anthropometric and clinical parameters, combined with questionnaires, to assist in the diagnosis of OSA.

2. A risk profile for the presence of OSA was determined and a practically applicable algorithm for risk stratification was proposed.

Methodological contributions (confirmatory)

1. The high prevalence of cardiovascular diseases in patients with OSA was confirmed.

2. Known risk factors from the literature in patients for the development of OSA were confirmed.

Summary

Cardiovascular Risk Assessment and the Effect of Continuous Positive Airway Pressure Therapy in Patients with Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is one of the most common sleep-related breathing disorders and represents an independent risk factor for cardiovascular morbidity and mortality. Recurrent episodes of upper airway obstruction during sleep result in intermittent hypoxia, sympathetic nervous system activation, oxidative stress, systemic inflammation, endothelial dysfunction, and adverse cardiac remodeling. These pathophysiological mechanisms contribute to the development and progression of arterial hypertension, atrial fibrillation, heart failure, coronary artery disease, pulmonary hypertension, and cerebrovascular disease. Continuous positive airway pressure (CPAP) therapy is currently considered the treatment of choice for moderate and severe OSA. Although its beneficial effects on respiratory function are well established, its long-term impact on cardiovascular structure and function remains incompletely defined.

Aim -The present study aimed to evaluate cardiovascular risk in patients with obstructive sleep apnea and to investigate the long-term effects of CPAP therapy on clinical characteristics, blood pressure control, cardiac structure and function, and cardiovascular risk stratification.

Materials and Methods -This prospective observational study included 114 consecutive adult patients diagnosed with obstructive sleep apnea by home sleep polygraphy. Clinical assessment comprised medical history, anthropometric measurements, office blood pressure, laboratory testing, Epworth Sleepiness Scale, Berlin Questionnaire, and comprehensive transthoracic echocardiography. Patients were followed for three years. According to adherence to treatment, they were allocated to either a CPAP-treated group or a non-CPAP group. Longitudinal changes in clinical, anthropometric, hemodynamic, and echocardiographic parameters were evaluated. Statistical analysis included descriptive statistics, repeated-measures General Linear Models (GLM), correlation analyses, multivariable modelling, and Classification and Regression Tree (CART) analysis for cardiovascular risk stratification.

Results- The study population consisted predominantly of overweight or obese middle-aged men with a high prevalence of arterial hypertension and other cardiovascular risk factors. Increasing body mass index and neck circumference were significantly associated with greater severity of obstructive sleep apnea. Patients receiving long-term CPAP therapy demonstrated significant reductions in both systolic and diastolic blood pressure compared with untreated patients. CPAP treatment was also associated with stabilization of left atrial remodeling and improvement in indices of left ventricular diastolic function, particularly the E/e′ ratio, suggesting reduced left ventricular filling pressure. Longitudinal analysis demonstrated that the beneficial cardiovascular effects of CPAP persisted throughout the three-year follow-up period. A sex-related difference was observed, with female patients showing greater improvement in selected echocardiographic parameters. A CART predictive model integrating anthropometric, clinical, and echocardiographic variables successfully identified patients at increased risk of progressive left ventricular diastolic dysfunction and adverse cardiovascular remodeling.

Conclusions - Obstructive sleep apnea is strongly associated with an increased cardiovascular risk profile characterized by obesity, hypertension, and subclinical cardiac dysfunction. Long-term CPAP therapy contributes to improved blood pressure control, attenuation of cardiac remodeling, and preservation of left ventricular diastolic function. These findings support the role of CPAP not only as a treatment for sleep-disordered breathing but also as an important component of cardiovascular risk reduction. The proposed risk stratification model may facilitate earlier identification of patients at high cardiovascular risk and improve individualized therapeutic decision-making in routine clinical practice.

Scientific Contributions

- A comprehensive prospective evaluation of cardiovascular changes in Bulgarian patients with obstructive sleep apnea was performed over a three-year follow-up period.
- The study demonstrated the favorable long-term effects of CPAP therapy on blood pressure regulation and cardiac remodeling.
- A predictive CART model integrating anthropometric, clinical, and echocardiographic parameters was developed for cardiovascular risk stratification in patients with OSA.
- The findings provide practical evidence supporting early diagnosis, individualized risk assessment, and timely initiation of CPAP therapy in patients at increased cardiovascular risk.

Keywords: obstructive sleep apnea, polygraph examination, cardiovascular complications.

LIST OF PUBLICATIONS AND PARTICIPATIONS RELATED TO THE DISSERTATION TOPIC

Publication of scientific results in full-text articles and/or reports:

1. **Simonov D.,** Dimitrova A. Influence of obstructive sleep apnea syndrome on cardiovascular risk. Proceedings – Varna Medical Forum, vol. 10, 2021, suppl. 3, 39-44.

2. **Simonov D.,** Dimitrova A. Covid-19, obstructive sleep apnea syndrome, influence of hypoxia on cardiovascular risk – Proceedings of reports and abstracts – scientific conference "Covid 19 – multidisciplinary scientific overview" – Medical College – TrU, Stara Zagora 01-02.10.2021. ISBN 978-954-338-180-7, 15-25.

3. **Darko Simonov**, Radost Dimitrova, Antoaneta Yordanova, Mario Milkov, Anna Tolekova, Anelia Dimitrova - RISK FACTORS FOR OBSTRUCTIVE SLEEP APNEA – CLINICAL STUDY AND CART BASED ANALYSIS. Supplement of Jubilee Joint Forum 35 IMAB & 15 SEEC, Section Medicine, ISSN: **1312 773X** (Online), 192-195, https://doi.org/10.5272/jimab.2025v31Supplement-M

Participation in scientific forums

1. **Simonov D.,** Dimitrova A. Influence of obstructive sleep apnea syndrome on cardiovascular risk – Jubilee scientific conference – 60 years of Pathophysiology – "Medical University – Varna" 24 – 25 September 2021.

2. **Simonov D.,** Dimitrova A. Covid-19, obstructive sleep apnea syndrome, influence of hypoxia on cardiovascular risk – Scientific conference "Covid 19 – multidisciplinary scientific overview" – Medical College – TrU, Stara Zagora 01-02.10.2021.

3. **Simonov D.,** Dimitrova A. **„**Effects of obstructive sleep apnea syndrome on cardiovascular risk- treatment options" **-** 11th South-East European Conference of Chemotherapy, Infections and Cancer and 31st Annual Assembly of International, 28-31 October 2021- Medical University-Plovdiv, Bulgaria

4. **Darko Simonov,** MD; Anelia Dimitrova MD, PhD, Prof.; Mario Milkov MD, PhD, Prof. Arterial hypertension in patient with obstructive sleep apnea – 12-th South-East European Conference of chemotherapy, infections and cancer & 32-st Annual Assembly of International Medical Association Bulgaria, 20-23 October, 2022, Trakia University – Stara Zagora

5. **Darko Simonov, MD**; Anelia Dimitrova MD, PhD, Prof,; Mario Milkov MD, PhD, Prof. CARDIAC ARRHYTHMIAS IN PATIENTS WITH SLEEP APNEA SYNDROME - INTERNATIONAL CONFERENCE OF THE BULGARIAN SOCIETY OF PHYSIOLOGICAL SCIENCES, 30 October-1 November 2022, Stara Zagora Mineral Springs.

6. **Darko Simonov**, Danail Dimitrov, Martin Koriykov, Ventsislav Grigorov, Lilyana Mircheva, Petar Uzov, Vladimir Kornovski, Toni Vekov, PULMONARY REGURGITATION IN 32 -YEAR -OLD GUCH - XXVIII World congress of echocardiography and allied techniques, 29 september – 01 october 2023, Sofia, Bulgaria

7. **Darko Simonov**, MD, Anelia Dimitrova MD, PhD, Prof. – CARDIAC ARRHYTHMIAS IN PATIENTS WITH SLEEP APNEA SYNDROME /poster/ – XVIII National Congress of Cardiology, 10-13 October 2024, Plovdiv, Bulgaria**.**

8. **Darko Simonov,** Gergana Sandeva, Pavlina Parusheva, Desislava Baltadzhieva, Kosara Kopraleva, Pavlina Gidikova - PSYCHOSOCIAL RISK FACTORS IN HEALTHCARE WORKERS DURING THE PANDEMIC /report/ - Anniversary Scientific Conference 50th Anniversary of Medical University Pleven, 01-03 November, Pleven, Bulgaria.

9. **Darko Simonov**, Radost Dimitrova, Antoaneta Yordanova, Mario Milkov, Anna Tolekova, Anelia Dimitrova, RISK FACTORS FOR OBSTRUCTIVE SLEEP APNEA – CLINICAL STUDY AND CART BASED ANALYSIS **35-th Jubilee Annual Assembly of Intl. Med. Assoc. Bulgaria (IMAB)** and 15-th South-East European Conference (SEEC) 9-12 October 2025 Trakia University, Stara Zagora, Bulgaria

Participation in a research project

- Research project 12/2021, Medical Faculty-TrU, Stara Zagora - Influence of obstructive sleep apnea syndrome on cardiovascular risk.