The Influence of Sleep Apnea on 24-Hour and Nocturnal ECG and Blood Pressure Parameters in Patients with Acute Heart Failure

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Significance of the Study

- This study investigated the influence of sleep apnea (SA) on 24-hour ECG and blood pressure (BP) parameters in stabilized acute heart failure patients. The results confirm the negative effects of severe SA on BP behavior and arrhythmogenesis, reinforcing also the recommendation of complex routine monitoring of these patients for therapeutic and prognostic reasons before hospital discharge.

Keywords

Heart failure · Sleep apnea · Arrhythmia · Blood pressure monitoring

Abstract

Objective: To investigate the influence of sleep apnea (SA) on ECG and blood pressure (BP) monitoring parameters in patients with acute heart failure (AHF). **Methods:** A total of 51 hospitalized patients with AHF (13 women, 38 men, mean age 60.8 years) underwent 24-hour combined monitoring of ECG and BP and SA testing before discharge. Heart rhythm (mean heart rate, arrhythmias, pauses, QT interval, heart rate variability) and BP (mean systolic and diastolic values, variability, circadian variation) parameters were obtained for the whole day and for nighttime (22:00–06:00). Depending on SA severity, the patients were divided into two groups (respiratory event index, REI, <15/h and ≥15/h). Comparisons

of parameters between the two groups were performed using t test and χ^2 test (alpha <0.05 for significance). **Results:** A total of 29 (56.9%) patients had REI ≥15/h. In this group, the systolic and diastolic BP values (24-hour and nighttime) were significantly higher ($p < 0.05$). BP variability did not differ, and a markedly blunted circadian variation of both the systolic and diastolic values was observed. In the group with REI ≥15/h, we found a higher nocturnal versus diurnal mean heart rate ratio ($p = 0.046$) and a greater occurrence of nocturnal versus diurnal ventricular premature beats ($p = 0.0098$). **Conclusion:** The presence of significant SA was found to influence the BP values and nocturnal ventricular ectopy in patients with stabilized AHF. SA, 24-hour ECG, and BP monitoring could provide important information with potential impact on patient management.

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Introduction

Acute heart failure (AHF) is a clinical entity with important prognostic and disease management implications. Thus, independently of the actual clinical scenario, beyond the acute management, there are some compulsory tasks which have to be completed on every patient hospitalized with AHF: (1) establishing the cardiac substrate and the trigger factor(s) of decompensation, (2) rethinking chronic management, including the need for invasive interventions (e.g., coronary, valvular, etc.) and implantable devices, (3) prognostic evaluation using multiple parameters (clinical and laboratory data, biomarkers, echocardiographic and Holter-derived data, etc.), (4) diagnosis and treatment (strategy) of noncardiac comorbidities, and (5) reinforcing treatment adherence and integrated patient monitoring [1, 2].

Generally, identification and efficient control of noncardiac comorbidities, e.g., chronic obstructive pulmonary disease, anemia, iron deficiency, diabetes, sleep apnea (SA), etc., could improve significantly the quality of life and prognosis of patients with heart failure (HF) [1].

In the above context, patients admitted to our clinic with AHF when already in stable clinical condition, undergo 24-hour combined ambulatory monitoring (Holter ECG and ambulatory blood pressure monitoring, ABPM) and SA testing before discharge. The former is performed primarily for arrhythmia, ischemia, and blood pressure (BP) profile analysis, and based on monitoring results, for prognostic evaluation. The aim of SA testing is the diagnosis and quantification of comorbid SA, a condition frequently associated with HF, the HF-SA relationship being bidirectional, with known impact on quality of life, prognosis, and treatment [3].

Keeping in mind the effects of SA on heart rhythm and BP behavior, with potential practical implications, and the relatively limited literature regarding this subject in HF, we investigated the influence of SA on 24-hour and nocturnal Holter ECG and ABPM parameters in patients with AHF. Our main goal was to demonstrate a deleterious effect of SA, providing new arguments for routine SA monitoring in this setting.

Materials and Methods

Patient Population

A total of 51 consecutive cases (13 women, 38 men, mean age 60.8 years) were included in the study, from the patients hospitalized with AHF in the Department of Cardiology of the Clini-

cal County Hospital Mures, Tirgu Mures, Romania. AHF was a manifestation of acute decompensated chronic HF in all patients. At admission, the patients signed the general consent form used in our institution, agreeing to anonymous data collection for scientific purposes. Approval of the local Ethics Committee was obtained for confidential collection and processing of data. The exclusion criteria were: severe hemodynamic instability during hospitalization, significant insomnia, and chronic treatment for obstructive SA with continuous positive airway pressure (CPAP) therapy. During admission, the patients received the usual care applied to patients with AHF in our department, including common diagnostic and therapeutic procedures.

In-Hospital SA Testing

At the end of hospital admission, when already in stable clinical condition, the patients underwent overnight polygraphy (Stardust II®, Alice NightOne®, Philips Respironics, USA – type III monitoring devices) for assessing the presence, type, and severity of SA. The device was applied at bedtime by a member of the medical staff (physician or nurse), and during nighttime the properly trained night shift nurse supervised the registration. Monitoring consisted of recording of the following six signals: nasal airflow, oxygen saturation, heart rate, thoracic movements, body position, and snoring. The recordings were edited and corrected manually. The episodes of apnea and hypopnea were defined according to the criteria of the American Academy of Sleep Medicine. The overall type of SA was labeled as central or obstructive depending on the predominance (more than 50% of all episodes) of the central or obstructive events. Central events also included the periods with Cheyne-Stokes respiration, which were defined as at least three consecutive cycles of respiration with crescendo-decrescendo pattern interrupted by central hypopnea or apnea. The level of severity was expressed using the respiratory event index (REI) – the number of hypopneas and apneas/registration hours [4, 5]. Depending on the REI values (<15/h and ≥15/h), the patients were divided into two groups to evaluate the influence of SA on Holter-ABPM parameters.

Combined 24-Hour Holter ECG and ABPM

The monitoring was performed together with SA testing, using the EC-3H/ABP Cardiospy® system (Labtech Ltd., Hungary) capable of combined ECG and BP recordings.

Before final analysis, the ECG registrations were edited for verification of template and elimination of artifacts. Then, the Holter ECG parameters (Table 1) were determined by the proprietary algorithm of the software. Special emphasis was placed on the study of nocturnal (22:00–06:00) heart rate, arrhythmias, and heart rate variability (HRV, time domain analysis, global and vagally mediated components) – parameters with a possible relationship to the presence of significant SA.

The automatic BP measurements were performed on the dominant arm of the subjects and were set at every 20 min during the day and at 30 min during nighttime (22:00–06:00). The patients were instructed about proper position of the arm and body (while awake) during measurements. During the review and analysis of BP values, artifacts were eliminated manually by an experienced examiner. The diverse ABPM parameters calculated (Table 2) also included those referring to BP variability.

Table 1. Holter ECG parameters and their description

Parameter	Description
MHR	24-hour mean heart rate (beats/min)
NMHR	Nocturnal mean heart rate (beats/min)
N/D MHR	Nocturnal/diurnal mean heart rate ratio
VPB	24-hour ventricular premature beats (% of total beats)
NVPB	Nocturnal ventricular premature beats (% of nocturnal beats)
N/D VPB >1	NVPB/diurnal ventricular premature beats (%) ratio >1 (<i>n</i> of patients)
NVR/T	Nocturnal ventricular run or tachycardia (<i>n</i> of patients)
SVPB ^a	24-hour supraventricular premature beats (% of total beats)
NSVPB ^a	Nocturnal supraventricular premature beats (% of nocturnal beats)
N/D SVPB >1 ^a	NSVPB/diurnal supraventricular premature beats (%) ratio >1 (<i>n</i> of patients)
NSVR/T ^a	Nocturnal supraventricular run or tachycardia (<i>n</i> of patients)
NAF ^a	Nocturnal atrial fibrillation (<i>n</i> of patients)
NP	Nocturnal pause >2,400 ms (<i>n</i> of patients)
NQTlong	Nocturnal QTc max >500 ms (<i>n</i> of patients)
SDNN ^a	Standard deviation of normal (sinusal) RR intervals, for 24 h (ms) <i>Time domain parameter of global HRV</i>
NSDNN ^a	SDNN calculated for nighttime (ms)
rMSSD ^a	Root mean square successive (normal, sinusal, RR intervals) difference, for 24 h (ms) <i>Time domain parameter of vagally mediated component of HRV</i>
NrMSSD ^a	rMSSD calculated for nighttime (ms)

^a Not considered in patients with atrial fibrillation. HRV, heart rate variability.

Table 2. ABPM-derived parameters and their description

Parameter	Description
MSBP	24-hour mean systolic blood pressure (mm Hg)
MSBP <110	24-hour mean systolic blood pressure <110 mm Hg (<i>n</i> of patients)
NMSBP	Nocturnal mean systolic blood pressure (mm Hg)
NMSBP <110	Nocturnal mean systolic blood pressure <110 mm Hg (<i>n</i> of patients)
MDBP	24-hour mean diastolic blood pressure (mm Hg)
MDBP <70	24-hour mean diastolic blood pressure <70 mm Hg (<i>n</i> of patients)
NMDBP	Nocturnal mean diastolic blood pressure (mm Hg)
NMDBP <70	Nocturnal mean diastolic blood pressure <70 mm Hg (<i>n</i> of patients)
SDSBP	24-hour standard deviation of systolic blood pressure (mm Hg)
NSDSBP	Nocturnal standard deviation of systolic blood pressure (mm Hg)
SDDBP	24-hour standard deviation of diastolic blood pressure (mm Hg)
NSDDBP	Nocturnal standard deviation of diastolic blood pressure (mm Hg)
DISBP	Diurnal index of systolic blood pressure (difference of diurnal and nocturnal mean systolic pressure/diurnal mean systolic pressure, %)
DISBP <10	Diurnal index of systolic blood pressure <10% (<i>n</i> of patients)
DIDBP	Diurnal index of diastolic blood pressure (difference of diurnal and nocturnal mean diastolic pressure/diurnal mean diastolic pressure, %)
DIDBP <10	Diurnal index of diastolic blood pressure <10% (<i>n</i> of patients)

Table 3. Characteristics of SA in the study population

REI	<5/h	5–14.9/h	15–29.9/h	≥30/h	Total
Patients, <i>n</i>	9 (17.6%)	13 (25.4%)	17 (33.3%)	12 (23.5%)	51
Predominantly obstructive, <i>n</i>	9 (100%)	10 (77%)	9 (52.9%)	6 (50%)	34 (66.6%)
Predominantly central, <i>n</i>	0	3 (23%)	8 (47.1%)	6 (50%)	17 (33.3%)
Patients in the two groups, <i>n</i>	22 (43.1%)		29 (56.9%)		

Table 4. Main characteristics of the patient population with respect to the severity of SA

Characteristics	Total	REI <15 (<i>n</i> = 22)	REI >15 (<i>n</i> = 29)	<i>p</i> value
Sex, women/men, <i>n</i>	13/38	5/17	8/21	0.1555
Mean age, years	60.82±11.25	61.5±12.44	60.31±10.46	0.5869
Main substrates of heart failure				
Ischemic heart disease, <i>n</i>	19	8	11	1.0000
Dilated cardiomyopathy, <i>n</i>	33	13	20	0.5590
Significant mitral regurgitation, <i>n</i>	24	13	21	0.3772
Significant aortic stenosis, <i>n</i>	5	3	2	0.6407
Significant aortic regurgitation, <i>n</i>	14	10	4	0.0246
Other valvular, <i>n</i>	28	10	18	0.2689
Primary right heart disease/pulmonary hypertension, <i>n</i>	3	1	2	1.0000
Systemic hypertension, <i>n</i>	24	8	16	0.2588
Atrial fibrillation, <i>n</i>	13	5	8	0.7555
Mean LVEF, %	34.9±13.9	35.45±14.13	34.48±12.66	0.9619
Patients with LVEF <30%, <i>n</i>	18	8	10	1.0000
Mean systolic pulmonary pressure, mm Hg	59.66±15.53	58.43±15.43	60.52±15.89	0.5355
Mean BMI	29.51±5.14	29.1±5.12	29.82±5.22	0.6248
BMI > 30, <i>n</i>	20	8	12	0.7780
Diabetes, <i>n</i>	17	5	12	0.2326
Renal dysfunction (creatinine >1.5 mg%), <i>n</i>	7	2	5	0.6841
Anemia (Hb <11 g%), <i>n</i>	9	4	5	1.0000

Values are mean ± SD for continuous variables, except where otherwise indicated. LVEF, left ventricular ejection fraction.

Statistics

We used descriptive statistics for the characterization of patient population and the prevalence, type, and severity of SA. Comparisons between clinical characteristics, Holter ECG and ABPM parameters in the two groups (REI <15/h and ≥15/h) were performed using *t* test (in the case of continuous variables) and χ^2 test (in the case of categorical variables). Statistical significance was set at $\alpha < 0.05$ (statistical tool used – GraphPad InStat 3.0).

Results

Qualitative and quantitative data related to SA in the study population are presented in Table 3. More than half (56.9%) of the patients had significant SA (REI ≥15/h),

the obstructive form being predominant in the whole cohort, but the central form becoming more and more prevalent in the case of patients with REI ≥15/h. The main characteristics of the study population according to the severity of SA are presented in Table 4. There were no significant differences except for the increased prevalence of significant aortic regurgitation in the group with the more severe form. Tables 5 and 6 present the ABPM and Holter ECG parameters in the two groups. We found significantly larger systolic and diastolic BP values (both for 24 h and nighttime) in the group with more severe SA ($p < 0.05$, except for one parameter, MSBP <110 [$p = 0.0964$]). BP variability parameters did not differ significantly in the two groups and a blunted circadian variation

Table 5. Comparison of ABPM-derived parameters in the two groups

Parameter	REI <15 (n = 22)	REI ≥15 (n = 29)	<i>p</i> value
MSBP	110.36±11.07	118.89±17.74	0.0444
MSBP <110	13	10	0.0964
NMSBP	105.77±13.53	117.92±19.7	0.0178
NMSBP <110	16	9	0.0047
MDBP	63.11±10.5	72.58±9.22	0.0016
MDBP <70	17	10	0.0042
NMDBP	59.95±12.05	69.88±9.81	0.0031
NMDBP <70	19	15	0.0155
SDSBP	11.91±3.93	12.78±4.63	0.4844
NSDSBP	9.3±4.17	10.47±5.08	0.3905
SDBBP	10.18±3.53	11.18±3.7	0.3382
NSDBP	8.24±4.12	9.98±5.26	0.2114
DISBP	5.44±4.72	3.33±5.28	0.2614
DISBP <10	15	26	0.0789
DIDBP	7.79±7.02	4.3±3.4	0.1554
DIDBP <10	13	19	0.7717

Values are expressed as mean ± SD or *n*.

of both the systolic and diastolic values (decreased diurnal indices) was found in the whole patient population. In the group with REI ≥15/h, the nocturnal versus diurnal mean heart rate ratio was significantly higher (*p* = 0.046), and significantly more patients had a greater proportion of nocturnal versus diurnal ventricular premature beats (*p* = 0.0098). Nocturnal HRV did not show a significant difference in relation to SA severity.

Discussion

SA, both the obstructive and central types, is one of the most frequently occurring comorbidities in HF, being present in over 50% of patients, regardless of the type of HF (with reduced or preserved left ventricular ejection fraction) [6–8]. SA proved to be prevalent in our patient population (unselected cases hospitalized with acute HF), being predominantly of the obstructive type.

SA in HF could appear independently or/and facilitated by cardiac decompensation, as the HF-SA relationship is bidirectional. Both the obstructive and central forms are favored by the presence of HF, nocturnal rostral fluid shift with peripharyngeal edema and decreased circulation velocity favoring marked oscillations of CO₂ lev-

Table 6. Comparison of Holter ECG parameters in the two groups

Parameter	REI <15 (n = 22)	REI ≥15 (n = 29)	<i>p</i> value
MHR	73.27±11.25	73.51±11.83	0.5924
NMHR	69.68±11.72	71.6±12.22	0.5762
N/D MHR	0.91±0.06	0.95±0.06	0.0460
VPB	1.34±3.75	1.04±1.26	0.6969
NVPB	1.16±3.34	2.7±8.46	0.4345
N/D VPB >1	4	16	0.0098
NVR/T	3	8	0.3116
SVPB ^a	1.48±0.9	1.36±1.73	0.8705
NSVPB ^a	1.3±0.76	1.69±0.87	0.5404
N/D SVPB >1 ^a	5	11	0.1972
NSVR/T ^a	1	1	1.0000
NAF ^a	3	2	0.6396
NP	1	2	1.0000
NQTlong	6	7	1.0000
SDNN ^a	62.64±28.46	64.26±34.87	0.9042
NSDNN ^a	48.24±28.34	60.57±32.25	0.4978
rMSSD ^a	26.38±11.31	44.83±13.44	0.4190
NrMSSD ^a	27.3±11.62	51.77±15.96	0.3506

Values are expressed as mean ± SD or *n*. ^a Patients with atrial fibrillation were excluded.

els being the main mechanisms involved [9]. Several individual studies and meta-analyses have established the negative effects of SA on quality of life and prognosis of patients with HF [10, 11]. Nocturnal (e.g., restless sleep, awakenings with choking) and diurnal (e.g., excessive daytime sleepiness) symptoms could seriously affect the everyday life of patients, and also have considerable effects on perception disease and adherence to therapy. SA could contribute to the progression of HF by various mechanisms: (1) autonomic imbalance characterized by sympathetic overactivity (caused mainly by the repetitive arousals), with its multiple consequences; (2) negative intrathoracic pressure during obstructive apneas, causing increased preload for the right heart and increased afterload for the left heart; (3) boosts of hypoxemia and myocardial ischemia, and (4) long-term myocardial damage caused by oxidative stress, hypercatecholemia, and chronic inflammation [11, 12].

Beyond its immediate practical value, SA testing during hospital admission has prognostic importance too, as the presence of significant SA is independently related to postdischarge mortality and hospital readmissions [13, 14].

In HF patients, heart rate, rhythm, and BP values and their variations are determined primarily by the current

hemodynamic status, together with cardiac autonomic control (the latter being in close relationship with the former). These factors could be influenced by the multiple negative effects of SA. Higher values and blunted circadian variations (lack of physiological decrease during nighttime) of BP are known phenomena associated with significant SA in normal and hypertensive subjects. The best example in this regard is resistant hypertension associated with severe forms of (mainly obstructive) SA in the majority of cases, with a decreased diurnal index as a rule [15].

The ABPM results of our patients, with already stabilized AHF, revealed significantly higher BP values (both diurnal and nocturnal, systolic and diastolic) in the group with more severe SA; however, the mean BP values were relatively low in both groups. The latter phenomenon could be explained by the decreased cardiac output, together with the BP lowering effects of HF medication. Regarding BP variability and variations, beyond the lack of significant differences between the two groups, we noticed a severely blunted systolic and diastolic diurnal index in both groups, with smaller values in the group with more severe SA, phenomena which could be explained by the HF-related autonomic imbalance (sympathetic overactivity and decreased vagal control), which is further augmented by the presence of SA. The latter mechanism could also explain the relatively higher BP values in the group of patients with more severe SA [11, 12]. This finding could have a double significance: one negative (the higher left ventricular afterload) and one positive (the more BP “reserve” for up-titration of cardioactive medication). The relatively little data in the literature dealing with 24-hour BP monitoring in patients with HF, although the studies are heterogeneous regarding the study populations, support our results: generally, low BP values are associated with blunted circadian variation [16–18]. Moreover, BP values and circadian BP behavior-related parameters were found to have prognostic value in patients with HF [19, 20].

The increase in incidence of nocturnal arrhythmias has been described in the setting of significant SA in various categories of patients, including those with HF [21, 22]. In the seminal Sleep Heart Health Study, after adjusting the results for age, sex, body mass index, and the presence of coronary artery disease, the risk for atrial fibrillation and ventricular ectopy was significantly greater in patients with more severe obstructive SA [23]. In a longitudinal study on 10,701 adults, during a 5-year follow-up period, the incidence of sudden cardiac death was directly related to the severity of SA and nocturnal oxygen de-

saturation [24]. In a large cohort ($n = 2,911$) of elderly men, the more severe forms of SA were associated with increased incidence of atrial fibrillation (mostly in the case of central forms – this tendency being present also in patients with HF) and complex ventricular ectopy (mostly in the case of obstructive forms) [25].

In a study recruiting 81 ambulatory men with stable HF, those patients with SA had significantly more episodes of atrial fibrillation and a higher number of premature ventricular depolarizations [26]. Furthermore, many other studies support the increased incidence of malignant ventricular arrhythmias and sudden cardiac death, especially during nighttime, in patients with HF and comorbid SA [27, 28].

Bradyarrhythmias (including asystole and 2nd and 3rd degree AV blocks) are related primarily to apneas. Prolonged apneas cause hypoxemia, which, by increasing the activity of peripheral chemoreceptors, triggers an enhanced vagal tone in the absence of ventilation. The mechanisms and factors behind SA-related tachyarrhythmias are more complex: hypoxemia together with myocardial ischemia, autonomic triggers (sympathetic overactivity caused by arousals), parietal stretch induced by negative intrathoracic pressure in the case of obstructive SA, and chronic cardiac structural alterations. Specifically, ventricular arrhythmias and nocturnal atrial fibrillation paroxysms, including recurrences after successful cardioversion, are characteristic in this regard [29].

Our study population consisted of patients with already stabilized AHF, and the general prevalence of arrhythmias (bradycardias and ectopy) was relatively low. In the group with more severe SA, we observed a slightly lower decrease of nocturnal heart rate, and an increased number of nighttime (vs. diurnal) ventricular and supraventricular ectopies. The lack of a striking difference between the two groups could have many explanations: e.g., sample size, current use of betablockers, already reaching a stable clinical condition, etc. However, the blunted circadian variation of heart rate in the group with more severe SA could herald a poorer prognosis [30]. The two-time domain HRV parameters had low values, as expected for patients with systolic HF [12].

Conclusion

Our study is a contribution to the understanding of the importance of SA in the setting of HFs. We assessed the influence of SA on 24-hour and nocturnal BP, heart

rate, and rhythm behavior, as these variables have important therapeutic and prognostic implications. Our results confirmed significantly higher BP values and more nocturnal ectopic activity in stable AHF patients with more severe SA. Although, these findings suggest an increased risk in these patients, their potential clinical value has to be determined on a larger patient population. Routine use of 24-hour BP monitoring could have a similar practical value in the setting of HF (both acute and chronic) as Holter ECG monitoring: fine-tuning of therapy on the basis of BP values and using parameters of BP variability and circadian variation for prognostic purposes.

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Statement of Ethics

This study received approval of the Ethical Committee of the Clinical County Hospital Mures (No. 3865/01.03.2016).

Disclosure Statement

The authors have no conflicts of interest to declare.

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