Gasanova A. D., Dragunov D. O., Sokolova A. V., Arutyunov G. P.
N. I. Pirogov Russian National Research Medical University, Moscow, Russia

Risk Assessment of Development of the Major Adverse Cardiac Events in Patients with Chronic Heart Failure with a Preserved and Intermediate Ejection Fraction in the Presence of a Bendopnea Symptom

Aim	To evaluate the risk of major cardiovascular complications (CVC) in patients with chronic heart failure (CHF) with intermediate and preserved ejection fraction (EF) depending on the presence of bendopnea symptom.
Material and methods	The study included 104 patients with stage II CHF and left ventricular EF ≥40%. Mean age of the patients was 72.8±10.6 years. A test for detection of bendopnea symptom was performed for all patients. Two groups were formed: group 1, 69 patients with the bendopnea symptom and group 2, 35 patients with a negative test. Follow-up duration was 24 months. The composite endpoint (CEP) was death and hospitalization for any CVC.
Results	Mean time to the bendopnea symptom was 17.3±6.61 s. At two years of follow-up, the CEP was observed in 36 (34.6%) patients, including 30 (43.5%) patients in group 1 and 6 (17.1%) patients in group 2. 12 patients died, and 9 of them had the bendopnea symptom. 21 patients of group 1 were hospitalized for CVC. Risk of CEP was significantly 1.7 times higher for men (relative risk, RR 1.7 [1.1; 2.6]) than for women. The presence of bendopnea symptom increased the risk of CEP 1.4 times (OP 1.4 [1.1;1.9]) for women and 2.3 times (RR 2.3 [1.4; 3.6]) for men.
Conclusion	Results of the study demonstrated an unfavorable effect of bendopnea symptom on risk of CEP during the two-year follow-up of CHF patients with preserved and intermediate EF.

Keywords	Bendopnea; chronic heart failure; preserved ejection fraction; decompensation; fatal outcome
For citation	Gasanova A. D., Dragunov D. O., Sokolova A. V., Arutyunov G. P. Risk Assessment of Development of the Major Adverse Cardiac Events in Patients with Chronic Heart Failure with a Preserved and Intermediate Ejection Fraction in the Presence of a Bendopnea Symptom. Kardiologiia. 2020;60(4):48–53. [Russian: Гасанова А. Д., Драгунов Д. О., Соколова А. В., Арутюнов Г. П. Оценка риска развития тяжелых сердечно-сосудистых осложнений у пациентов с хронической сердечной недостаточностью с сохраненной и промежуточной фракцией выброса при наличии симптома бендопноэ. Кардиология. 2020;60(4):48–53.]

Corresponding author	Dmitry Olegovich Dragunov. E-mail: tamops2211@gmail.com

The growing quality and availability of medical care in the Russian Federation contribute to the increase in life expectancy, including of comorbid patients. As a result, we are seeing more patients who survive until heart failure. An increasing number of chronic heart failure (CHF) patients present with ejection fraction (EF) greater than 50%. CHF is an outcome of high social and economic relevance that has a significant effect on the rate of hospitalizations, disability, and mortality of patients [1].

Breathing problems are one of the main complaints of patients with CHF. Any breathing problem, whether orthopnea, paroxysmal nocturnal dyspnea, or shortness of breath during physical activity or at rest, is indicative of abnormal intracardiac hemodynamics and the involvement of the heart chambers in a pathological process. In 2014, another breathing problem in patients with CHF was described, bendopnea, i.e., shortness of breath when bending over. It reflects an increased right atrial pressure causing increased pulmonary capillary wedge pressure (PCWP) [2].

Clinical interest in the bendopnea test is high because it is easy to check for this symptom in a doctor's office. The test is simple and requires no additional instruments. However, the use of bendopnea as a symptom to assess the survival prognosis for patients with CHF remains unsettled. Several studies have examined the effect of bendopnea on the risk of adverse outcomes in patients with systolic dysfunction, but the effect of bendopnea on survival and the risk of hospitalization in patients with diastolic dysfunction is not yet well known [4-6].

Our objective was to assess the risk of major cardiovascular complications (CVDs), including myocardial infarction and brain infarction, hospitalization for decompensated CHF, and cardiovascular death, in patients with CHF with intermediate and preserved EF, depending on the presence or absence of bendopnea [3].

ISSN 0022-9040. Kardiologiia. 2020;60(4). DOI: 10.18087/cardio.2020.4.n1043

Material and Methods

The study was carried out under the International Conference on Harmonization guideline for Good Clinical Practice (ICH–GCP). The Long-Term Management of Patients with Comorbidities Register (1 040 outpatient case records) was analyzed, and outpatient case records containing the following data were selected:

1) Diagnosis of CHF;;
2) Echocardiographic findings within 3 mos prior to the study.

Criteria for inclusion in the study were:

Age ≥55 yrs for female patients and ≥60 yrs for male patients; Established and verified diagnosis of stage II CHF; Sustainable therapy under the CHF treatment standards for 3 mos before inclusion; Left ventricular EF 40% or more according to the echocardiographic examination within the previous 3 mos; Signed informed consent form to participate in the study. Criteria for exclusion were: Highly doubtful collaboration with the patient during the study; Low compliance with treatment for social, psychological, economic, or other reasons; Incapacity; Chronic obstructive pulmonary disease, asthma, cancer, anemia of any origin, acquired and congenital valvular heart disease; Alcohol or substance abuse; Surgical intervention within 3 mos of the study.

119 patients met the criteria for inclusion, but only 104 patients could be contacted and included in the final analysis. All included patients were invited to an appointment, during which they were subjected to the bendopnea test, the severity of CHF was established, and other breathing symptoms were detected. The patients were divided into two groups based on the test results: Patients with bendopnea (Group 1, n=69); Patients without bendopnea (Group 2, n=35). These patients were followed for 24 mos, and a composite endpoint (CE) was evaluated: Death/hospitalization for any CVD.

Bendopnea test

For the Bendopnea test, the patient rested on a chair for 5 min, then bent forward as if tying shoelaces or putting on socks. If shortness of breath occurred within 30 sec after the test was started, the patient was required to report this to the physician, who recorded the time in seconds of symptom onset. The test was stopped at 30 sec. If shortness of breath had not occurred within 30 sec while the patient was bending, the test was considered negative, i.e., no bendopnea.

Statistical analysis

The findings were statistically analyzed using the R language and the Rstudio software environment. According to results of Shapiro-Wilk and Kolmogorov-Smirnov tests of data normality, nonparametric or parametric statistical analyses were used. Quantitative values are represented as the mean (M) and standard deviation (SD) or as the median and 25th;75th percentiles. Analysis of variance (ANOVA) was used to verify differences between mean values of variables. The Student's T-test and the Mann–Whitney U-test were used for normal and non-normal distributions, respectively. If the data were on a nominal scale, differences were evaluated with Pearson's chi-squared test. To investigate a risk and/or odds of occurrence of an event, 2×2 tables were constructed, and relative risks (RR) and odds ratios (OR) were calculated The Cox proportional hazard model and Kaplan–Meier curves were applied to evaluate the time dependent risk of an event. The null hypothesis was rejected at the significance level of $p<0.05$.

Results

A positive bendopnea test result was obtained in 69 (66.4%) patients (Group 1) and negative result in 35 (33.6%) patients (Group 2). The mean time to onset of bendopnea was 17.3±6.6 sec.

Major clinical characteristics

All patients included in the study (n=104) initially had similar major, clinical characteristics regardless of the presence of bendopnea (Table 1). The mean age of patients was 72.8±10.6 yrs. In Group 1, the mean waist circumference was 102±12 cm (male patients, 114±13 cm; female patients, 100±9 cm). In Group 2 this circumference was 103± 14 cm (male patients, 102±10 cm; female patients, 105±16 cm) (p=0.682). The disease profile for both groups included coronary artery disease and/or hypertensive heart disease, and/or atrial fibrillation. In Group 1, 25 (36.2%) patients had type 2 diabetes mellitus; in Group 2, 11 (31.4%) had this disease. Fourteen patients received insulin therapy.

Severity of CHF

The breakdown of Group 1 patients by CHF functional class (FC) was 9 FC I (13.0%), 35 FC II (50.7%), 25 FC III (36.2%). In Group 2, this breakdown was 8 FC I (22.9%), 20 FC II (57.1%), 6 FC III (17.1%), 1 FC IV (2.9%) (p=0.09).

In the study cohort of 104 patients, 36 (34.6%) had paroxysmal nocturnal dyspnea, including 27 (75%) with a concomitant symptom of bendopnea. Orthopnea was identified in 82 (78.8%) patients, including 56 (68.3%) with bendopnea. Dyspnea was identified in 99 (95%) patients, including 66 (67%) with bendopnea.

Effect of bendopnea on CE

The median follow-up period was 24.4 mos in both study groups. After two yrs of follow-up, CE was detected

Table 1. Clinical characteristics of the group (at the time of inclusion in the study n=104)

Parameter	Group 1 (n=69)	Group 2 (n=35)	p
Age, yrs	72.2±10.5	72.1±10.7	0.68
Sex, m/f (n)	40/29	18/17	0.67
SBP, mm Hg	128.5±16.2	125.3±20.1	0.36
DBP, mm Hg	77.1±11.2	74.9±11.4	0.23
Pulse BP, mm Hg	50.6±13.2	49.9±15.9	0.62
HR, bpm	70.9±9.8	73.1±11.8	0.8
Waist circumference, cm	101.8±12	103.2±14.3	0.68
BMI, kg/m2	31.5±5.0	29.8±5.5	0.15
Diabetes mellitus, % (n)	36.2 (25)	31.4 (11)	0.78
CAD, % (n)	87 (60)	82.9 (29)	0.78
Hypertensive heart disease, % (n)	97.1 (67)	91.9 (32)	0.42
Atrial fibrillation, % (n)	33.3 (23)	37.1 (13)	0.86
Cerebrovascular disease, % (n)	71 (49)	62.9 (22)	0.53
CKD, % (n)	57.6 (60)	25.9 (27)	0.13
Creatinine, μmol/l	103±42.1	96.9±24.8	0.47
GFR (CKD EPI) ml/min/1.73 m^2	58.2±16.5	61.2±18	0.33
Total cholesterol, mmol/l	4.9±1.4	4.7±1.2	0.41
LDL, mmol/l	2.8±1.2	2.4±0.9	0.4
TG, mmol/l	1.9±1.6	1.5±1.0	0.06
HbA1C, %	6.5±1.3	6.3±1.7	0.24
EF, %	55.3±9.8	49.8±12.3	0.024
LV myocardial mass index, kg/m^2	127.7±43.6	139±41.4	0.21
ACE inhibitors, % (n)	40.5 (28)	40 (14)	0.15
Angiotensin II receptor antagonists, % (n)	45.5 (33)	52 (19)	0.26
Beta blockers, % (n)	69.5 (48)	82.8 (29)	0.38
Mineralocorticoid receptor antagonists, % (n)	44.9 (31)	51.4 (18)	0.29
Diuretics, % (n)	52.2 (36)	57.2 (20)	0.34

SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; HR, heart rate; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; LDL, low-density lipoproteins; HbA1C, glycated hemoglobin; EF, ejection fraction; LV, left ventricle; ACE, angiotensin-converting enzyme.

in 36 (34.6%) patients, including 30 (43.5%) in Group 1 and 6 (17.1%) in Group 2. Twelve patients died, including 9 (75%) with symptom of bendopnea. In Group 1, 21 patients were hospitalized due to cardiovascular complications (CVCs).

Kaplan–Meier curves were applied to analyze CE in patients of both study groups (Figure 1). The risk of CE within 2 yrs was significantly higher in the group of patients with bendopnea. Figure 2 shows that most CEs occurred before Day 200 of follow-up.

In the first step of building the Cox proportional risk model, all predictors with a binary response were included. Later, predictors that did not affect the model were excluded from the analysis.

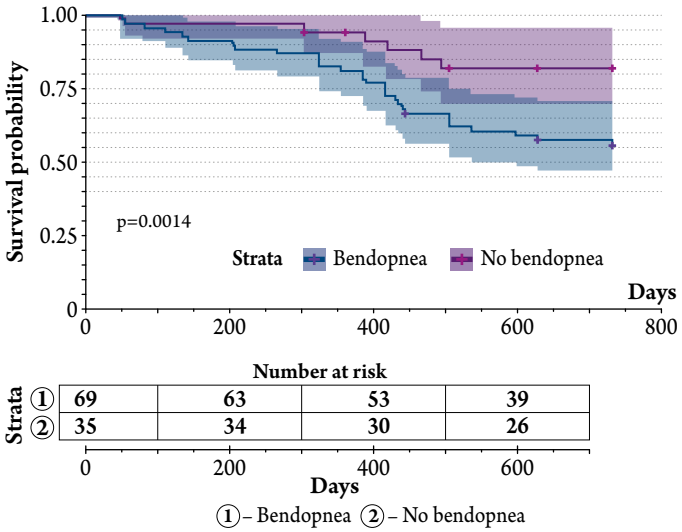
In the second step, a model was built with only significant predictors, which allowed identifying the two predictors with the most significant effect on the increase in the risk of CE, sex and bendopnea (see Figure 2). The risk of CE significantly increased 1.7-fold in male patients (RR 1.7 [1.1; 2.6]) versus female patients (RR 0,5 (0,3; 0,9). The presence of bendopnea increased the risk of CE 1.4-fold (RR 1.4 [1.1; 1.9]), and bendopnea in male patients increased the risk 2.3-fold (RR 2.3 [1.4; 3.6]), in female RR 5,8 (0,82; 41,3) (Figure 3).

Discussion

In 2014, Thibodeau et al. [2] directly compared intracardiac hemodynamics in patients with and without positive bendopnea symptoms. This generated interest in a new symptom of heart failure. Patients with positive bendopnea symptoms had higher right ventricular pressure and PCWP. On the other hand, cardiac index did not change during the bendopnea test in patients with positive symptoms.

ISSN 0022-9040. Kardiologiia. 2020;60(4). DOI: 10.18087/cardio.2020.4.n1043

Figure 1. Survival analysis of patients with CHF and bendopnea



According to current understanding of the physiology of intracardiac hemodynamics, diastolic PCWP corresponds to left atrial filling pressure. Since left atrial diastolic pressure reflects left ventricular diastolic pressure, it possible to use PCWP to assess left ventricular diastolic function, i.e., we can estimate left ventricular overload. Thus, the results of the bendopnea test show if fluid is retained in the pulmonary circulation [2].

According to a meta-analysis [4], the prevalence of bendopnea in patients with systolic CHF ranges from 18 to 33%, regardless of age and sex. Moreover, this meta-analysis showed no significant association between the presence of bendopnea and such concomitant diseases as chronic obstructive pulmonary disease, diabetes mellitus, hypertension, hypertensive heart disease, or atrial fibrillation [3, 5-7].

The effect of abdominal obesity on the risk of bendopnea is often debated, but there is no consensus in the published papers. Some studies showed a relationship between abdominal obesity and bendopnea [6, 7]. However, Thibodeau et al. [2] (28% of patients had bendopnea), and we [8] (42 patients with bendopnea included in the study) did not detect such a relationship. In the present study, the bendopnea and control groups had comparable waist circumference and body mass index (BMI). Mean BMI in Group 1 was 31.5±5.0 kg/m2, and it was 29.8±5.5 kg/m2 in Group 2 (p=0.1585). Thus, we were not able to estimate the effect of obesity on the risk of bendopnea as the groups were homogenous. This issue should be studied individually.

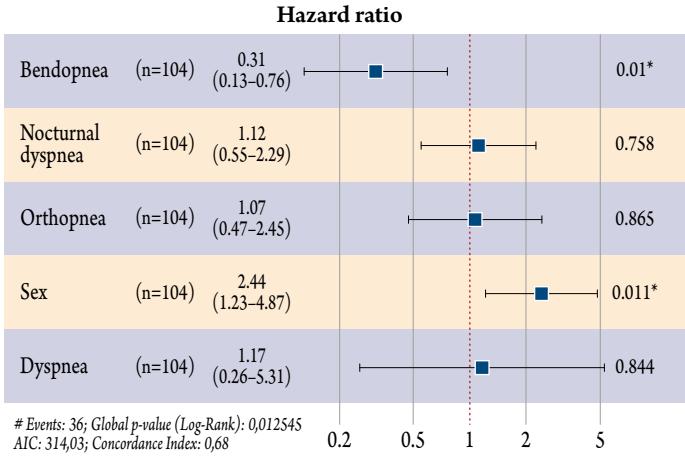
Studyof bendopnea have shown sex differences between patients. The male sex was shown to be intrinsically associated with bendopnea (OR 8.45, 95%

ISSN 0022-9040. Kardiologiia. 2020;60(4). DOI: 10.18087/cardio.2020.4.n1043

АО «АКРИХИН», 142450, Московская область, Ногинский район, г. Старая Купавна, ул. Кирова, 29, телефон/факс: (495) 702-95-03

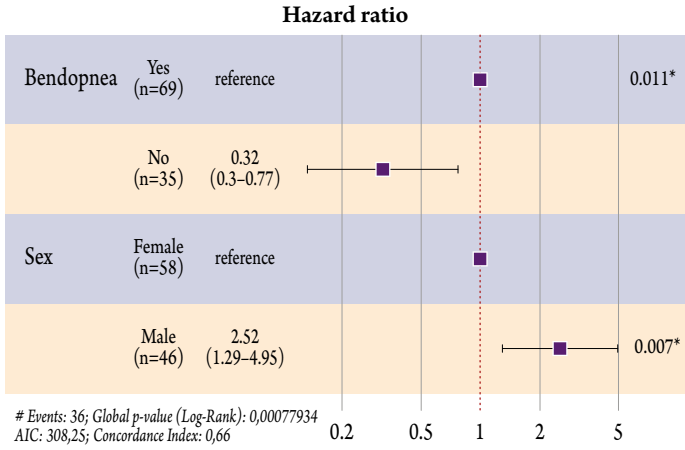
1. По сравнению с плацебо. 2. Инструкция по медицинскому применению препарата Отрио, таблетки 10 мг. 3. Сусеков А.В., Кобалова Ж.Д., Гуревич В.С. и соавт. Возможности клинического применения препарата эзетемиба Отрио (АО «Акрихин», Россия) у пациентов высокого и очень высокого сердечно-сосудистого риска, не достигших целевых значений показателей липидного обмена. Заключение Совета экспертов. Кардиология. 2019;59(5S):47-57. 4. Gagne C et al. Efficacy and Ezetimibe Added to Ongoing TATIN tHERAPY FOR Treatment of Patients With Primary Hypercholesterolemia Am J Cardiol 2002;90:1084-1091.
* ХС ЛНП – холестерин липопротеинов низкой плотности
** ХС – холестерин
Информация для медицинских и фармацевтических работников

Figure 2. Model of the effect of prognostic factors on the risk of occurrence of a composite endpoint



*– p<0.05

Figure 3. Model of the effect of bendopnea and patient's sex on the risk of occurrence of a composite endpoint



*– p<0.05; **– p<0.001.

CI 2.5–28.5) [9] and to have a significant effect on the risk of re-hospitalization [10]. Our findings are comparable to the results of that study. For example, bendopnea increased by 2.3-fold the risk of adverse outcomes in male patients (RR 2.3 [1.4; 3.6]). However, the effect of sex on the development of adverse outcomes in patients with bendopnea should be studied in a larger population.

There are still no large population-based clinical trials to assess adverse outcomes in patients with CHF and bendopnea. For example, Sajeev et al. [10] showed a higher rate of hospitalizations due to CHF in patients with orthopnea versus bendopnea. However, it should be noted that the study group included twice as many patients with orthopnea than with bendopnea.

The association of bendopnea with the risk of death in patients was not studied in that trial, which, according to the authors, was due to a small sample and a short follow-up period of 12 mos. It is worth noting that the published studies of bendopnea did not exceed a 12-mo follow-up period in most cases, whereas the duration of our study was 2 yrs. Baeza-Trinidad et al. [11] studied patients for 6 mos and found that bendopnea was associated with higher mortality.

However, these findings are questionable, because the study included patients with decompensated CHF and a mean age of 81.8±8.3 yrs. All patients had reduced EF, which certainly was associated with more severe conditions [6, 11]. Our study included younger patients with mean age 72.8±10.6 yrs. There were no patients with systolic CHF in the study cohort, and the percentage of patients with decompensated CHF was 30%. Our study also showed a significant 1.4-fold increase (RR 1.4 [1.1; 1.9]) in the risk of CEs (death, hospitalization due to decompensated CHF or other CVCs) in patients with bendopnea.

In 2017, Thibodeau et al. [5] published an observational study that had been carried out in a group of outpatient patients with positive bendopnea symptoms. Unlike in our study, adverse outcomes in the Thibodeau et al. study occurred within the first 3 mos of follow-up. Our findings showed a statistically significant increase in the number of outcomes by Day 200 of the follow-up period. This difference might be due to the fact that, unlike our cohort, Thibodeau et al. mostly included patients with FC III and FC IV CHF [5].

Earlier, we discussed the possibility of using bendopnea as a marker of decompensated CHF. It was shown that the combination of FC III CHF and bendopnea increased by 4.8-fold the risk of decompensation (OR 4.8, 95% CI 1.5–15.1) [8].

Conclusion

Thus, the results of our study demonstrate the adverse effect of bendopnea on the risk of occurrence of a composite endpoint within the 2-yr follow-up of patients with CHF having intermediate and preserved EF.

Limitations of the study

A small number of deaths required us to assess CEs. The research team was not involved in the treatment process; they only observed.

No conflict of interest is reported.

The article was received on 15/01/20

ISSN 0022-9040. Kardiologiia. 2020;60(4). DOI: 10.18087/cardio.2020.4.n1043

REFERENCES

1. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S et al. Heart failure: preventing disease and death worldwide: Addressing heart failure. ESC Heart Failure. 2014;1(1):4–25. DOI: 10.1002/ehf2.12005
2. Thibodeau JT, Turer AT, Gualano SK, Ayers CR, Velez-Martinez M, Mishkin JD et al. Characterization of a novel symptom of advanced heart failure: bendopnea. JACC. Heart failure. 2014;2(1):24–31. DOI: 10.1016/j.jchf.2013.07.009
3. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The Problem With Composite End Points in Cardiovascular Studies: The Story of Major Adverse Cardiac Events and Percutaneous Coronary Intervention. Journal of the American College of Cardiology. 2008;51(7):701–7. DOI: 10.1016/j.jacc.2007.10.034
4. Pranata R, Yonas E, Chintya V, Alkatiri AA, Budi Siswanto B. Clinical significance of bendopnea in heart failure—Systematic review and meta-analysis. Indian Heart Journal. 2019;71(3):277–83. DOI: 10.1016/j.ihj.2019.05.001
5. Thibodeau JT, Jenny BE, Maduka JO, Divanji PH, Ayers CR, Araj F et al. Bendopnea and risk of adverse clinical outcomes in ambulatory patients with systolic heart failure. American Heart Journal. 2017;183:102–7. DOI: 10.1016/j.ahj.2016.09.011
6. Baeza-Trinidad R, Mosquera-Lozano JD, El Bikri L. Assessment of bendopnea impact on decompensated heart failure: Assessment of bendopnea impact on decompensated HF. European Journal of Heart Failure. 2017;19(1):111–5. DOI: 10.1002/ejhf.610
7. Dominguez-Rodriguez A, Thibodeau JT, Abreu-Gonzalez P, Ayers CR, Jimenez-Sosa A, Aranda JM et al. Association Between Bendopnea and Key Parameters of Cardiopulmonary Exercise Testing in Patients With Advanced Heart Failure. Journal of Cardiac Failure. 2016;22(2):163–5. DOI: 10.1016/j.cardfail.2015.12.013
8. Dragunov D.O., Sokolova A.V., Arutyunov G.P., Gasanova A.D., Latyshev T.V. Quality of life in patients with heart failure with preserved ejection fraction and the bendopnea symptom. Kardiologiia. 2019;59(6S):24–32. [Russian: Драгунов Д.О., Соколова А.В., Арутюнов Г.П., Гасанова А.Д., Латышев Т.В. Качество жизни у пациентов с сердечной недостаточностью с сохраненной фракцией выброса и симптомом бендопноэ. Кардиология. 2019;59(6S):24-32]. DOI: 10.18087/cardio.2507
9. Larina V.N., Golovko M.G., Zakharova M.I., Bogush N.L., Poryadin G.V. Clinical and prognostic significance of bendopnea in elderly outpatients. Cardiovascular Therapy and Prevention. 2019;18(6):45–50. [Russian: Ларина В.Н., Головко М.Г., Захарова М.И., Богуш Н.Л., Порядин Г.В. Клиническая и прогностическая значимость бендопноэ у больных пожилого возраста, наблюдающихся в амбулаторных условиях. Кардиоваскулярная терапия и профилактика. 2019;18(6):45-50]. DOI: 10.15829/1728-8800-2019-6-45-50
10. Sajeev CG, Rajan Nair S, George B, Rajesh GN, Krishnan MN. Demographical and clinicopathological characteristics in heart failure and outcome predictors: a prospective, observational study: Prognostic predictors in heart failure. ESC Heart Failure. 2017;4(1):16–22. DOI: 10.1002/ehf2.12119
11. Baeza-Trinidad R, Mosquera-Lozano JD, Gómez-Del Mazo M, Ariño-Pérez de Zabalza I. Evolution of bendopnea during admission in patients with decompensated heart failure. European Journal of Internal Medicine. 2018;51:e23–4. DOI: 10.1016/j.ejim.2018.02.026