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The severity of chronic heart failure and the parameters of daily blood pressure profile in patients with coronary heart disease

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Abstract

Aim: Although the prevalence of coronary heart disease (CHD) and hypertension which are the most common causes of the development and progression of chronic heart failure (CHF) is high, 24-hour ambulatory blood pressure (BP) monitoring (ABPM) in patients with CHF is not mandatory to be performed. The growing number of evidence suggests that excessive decrease in BP which clearly reflects increased BP variability (BPV) affects the survival of patients with heart failure (HF). The objective of the study was to investigate the relationship between the parameters specific to CHF severity and features of daily BP profiles in patients with ischemic CHF and hypertension.

Methods: Ninety patients with functional class II–IV of CHF and CHD (the main group) and 50 non-CHF patients with hypertension (the comparative group) were examined. The transthoracic echocardiography (TTE) [atrial end-systolic dimension (ESD), ventricular end-diastolic dimension (EDD), left ventricular mass index (LVMI), and left ventricular ejection fraction (LVEF)] and 24-hour ABPM (BPV parameters and proportions of hypotensive episodes) were performed. The relationships between the abovementioned parameters were evaluated using the univariate correlation analysis and stepwise multiple linear regression.

Results: Higher functional class of CHF is found to be associated with a higher incidence of daytime systolic BP (SBP) decline and nighttime SBP and diastolic BP (DBP) variability while higher LVEF is related to the hypotensive episodes regardless of CHF.

Conclusions: It appears that the larger trials involving CHF patients with reduced LVEF should be conducted to clarify the obtained results.

Keywords

Coronary heart disease, chronic heart failure, hypertension, blood pressure variability, 24-hour ambulatory blood pressure monitoring, proportion of hypotensive episodes

Introduction

To date, coronary heart disease (CHD) and hypertension remain one of the leading causes of the development and progression of chronic heart failure (CHF) [1–4]. Arterial hypertension is one of the most important modifiable risk factors for the development of cardiovascular complications. High blood pressure (BP) is associated with the risk of cardiovascular events and mortality in general [5]. The epidemiological studies [6–12] report that the prevalence of CHF in developed countries is about 1% in subjects over 55 years old but exceeds 10% in patients over 70 years old. The incidence of CHF in subjects older than 45 years old is doubled every 10 years. At this time, the number of subjects with coronary atherosclerosis and consequently with CHD and CHF is progressively increasing. It should be noted that this is partly explained by the improved long-term results of medical and surgical treatment of cardiovascular diseases and subjects' prolonged life expectancy in the developed countries which contributes to an increase in the proportion of patients with CHF signs in the global population [13]. In general, the large epidemiological and multicenter clinical studies currently report that the proportion of ischemic CHF is 60–75% [14]. Moreover, in recent years, more and more evidence has appeared indicating that not only increased BP but also its variability is involved in the relationship between hypertension and risk of end-organ damage and occurrence of cardiovascular events [15]. In addition, much attention is currently being paid to excessive BP reduction in CHF patients. In particular, there is data in the literature on the negative impact of hypotension, including orthostatic hypotension, on the development of outcomes in patients with CHF with reduced ejection fraction [16]. BP variability (BPV) is defined as BP fluctuations exceeding the physiological limits [17]. The BP fluctuations are caused by a number of causes: emotional, physical (e.g., body posture, physical activity), and activity of cardiovascular regulatory mechanisms [18]. It should be noted that currently, 24-hour ambulatory BP monitoring (ABPM) for patients with CHF and CHD is not mandatory to be performed [8, 9, 19]. However, several studies have proven the negative impact of BP values outside the "safe" or "critical" lower limit on the survival of patients with circulatory insufficiency [20–25]. Thus, Lee et al. [26] demonstrated that CHF patients had a U-shaped mortality curve depending on the BP values and the survival decreased already when systolic BP (SBP) values were lower than 120 mmHg. Serov et al. [27] reported that daily hypotensive episodes were observed in almost three-quarters of CHF patients while the transient systolic and diastolic hypotensive episodes were associated with the risk for myocardial infarction in CHF patients. Studies by Gorelik et al. [28] have shown an increased risk of death in patients with CHF with low SBP. However, the author emphasizes that high SBP indicates an earlier phase of CHF with preserved ejection fraction [28]. There are other studies on the adverse effect of low BP values on the prognosis in patients with CHF and preserved ejection fraction [25, 29].

Also noteworthy are the results of a study by Cautela et al. [16], confirming the data on the negative impact of hypotension, including orthostatic, on the development of outcomes in patients with CHF with reduced ejection fraction [16].

Therefore, the investigation of the relationship between the CHF severity and daily BPV pattern in CHF patients seems actual and well-timed. It seems that a more detailed study of the relationship between ABPM parameters and factors characterizing CHF would expand the understanding of the pathogenesis of cardiovascular and extracardiac disorders in CHF and further optimize the diagnostic and therapeutic approach in patients suffering from this pathology.

Materials and methods

The study was conducted in accordance with the Good Clinical Practice principles and approved by the Local Ethics Committee at Federal State Budgetary Educational Institution of Higher Education V.I. Razumovsky Saratov State Medical University of the Ministry of Healthcare of the Russian Federation. The

inclusion criteria were as follows: CHF in patients with confirmed CHD and age from > 45 to < 65 years old. The patients who had acute or subacute CHD, myocarditis, diabetes mellitus, acute cerebrovascular accident (including in history), alcohol abuse, thyroid dysfunction, severe valvular heart disease, and laboratory evidence of severe hepatic and renal impairment were excluded from the study. The diagnosis and treatment of CHF, CHD, and hypertension were verified in accordance with the current clinical guidelines [19, 30, 31]. The medical history and physical exam data were documented in a formalized case history. All study procedures were performed in the morning after the informed consent was signed. The assessments were performed on a voluntary basis in accordance with the international ethical requirements for medical research involving human subjects (Declaration of Helsinki, 1975; revised at the 64th World Medical Association General Assembly, Fortaleza, Brazil, 2013) [32]. In total, 90 patients with the New York Heart Association (NYHA) functional class II–IV of CHF of ischemic origin (due to CHD) were included in the study (the main group) and 50 non-CHF patients with hypertension (matched for gender and age) were included in the comparative group. In addition to the routine clinical examinations and tests, the patients underwent Doppler echocardiography [EchoCG, Vivid 3 PRO ultrasound system (GE HealthCare, USA)] with measurement of the left atrial end-systolic dimension (LA ESD), right atrial ESD (RA ESD), left ventricular end-diastolic dimension (LV EDD), right ventricular EDD (RV EDD), left ventricular ejection fraction (LVEF), and left ventricular mass index (LVMI). A comprehensive transthoracic ultrasound examination was performed on the Vivid 3 PRO ultrasound system in M-modal and two-dimensional modes at rest in standard echocardiographic positions. Moreover, all patients had 24-hour ABPM, and variability and proportions of hypotensive episodes for daytime and nighttime SBP and diastolic BP (DBP) were calculated. The 24-hour ABPM was performed with an oscillometric device "Cardiotechnika-07-AD-Z/12R" (developed by INCART LLC, St. Petersburg, Russia) with a cuff of the appropriate size. When analyzing the data, only those results of a 24-hour BP measurement were taken into account, at which at least 36 correct and successful BP measurements were made during the day. Participants were instructed to engage in normal activities but to refrain from strenuous exercise and to keep the arm extended and still at the time of cuff inflation. Participants were instructed to keep the position they were in when the measurement started. A detailed conversation was conducted with patients about the need to fill out an individual diary correctly during the study. It was pointed out that it is necessary to clearly reflect in the diary activity levels, bedtime, wake-up time, sleep quality, time of taking medications and food, and the appearance of any symptoms. The day and night hours were determined from the records of the periods of wakefulness and sleep in the individual diaries of patients. BPV was defined as the within-subject standard deviation (SD) of all SBP and DBP recordings during the 24-hour, daytime, and nighttime measurement periods. Based on previous studies [24, 33–37], hypotension was defined as systolic BP < 105 mmHg and/or diastolic < 65 mmHg with daytime ABPM, < 90 mmHg and/or < 50 mmHg with nighttime ABPM. Episodes of arterial hypotension recorded after eating and within 3 min after switching to the orthostatic position of the body were not taken into account (according to the data of the patient's individual diary). The percentage of BP measurements corresponding to the hypotonic values described above to the total number of BP measurements during the day was calculated.

Statistical analysis

The statistical analysis was performed using Statistica version 8.0 (TIBCO Software, USA). Patient groups were described depending on the type of data distribution. To describe quantitative traits with a normal distribution, the mean ± SD was used; for traits with a non-normal distribution, the median and interquartile range (25th and 75th percentiles) were used. In accordance with the type of data, either analysis of variance or non-parametric methods were used: the Wilcoxon paired test, and the Kruskal-Wallis test. Frequencies were compared using crosstabulation. The relationship between the CHF severity, EchoCG characteristics, and daily BP parameters was evaluated using non-parametric correlation (Kendall and Spearman) and stepwise multiple linear regression. Statistical significance was defined as P value < 0.05. The univariate analysis of variance was used to compare the groups by clinical characteristics. The study of group comparability in terms of the possible impact of concomitant therapy received by patients on ABPM parameters was performed using a two-way analysis of variance. The dependent variables were

BPV and hypotension time indices SBP and DBP during daytime and nighttime. The presence/absence of CHF, as well as the groups of drugs taken by patients, were considered independent variable factors. To describe the relationship between variables and exclude indirect and false relationships, including those with concomitant therapy of patients, the method of multiple stepwise linear regression analysis, as well as multivariate analysis of variance, was used.

The main clinical characteristics of the examined patients are presented in Table 1.

Table 1. The main clinical characteristics of the study population (median and quartiles)

Parameter	Patients with ischemic CHF and hypertension (*n* = 90)	Non-CHF patients with hypertension (*n* = 50)	*P* value
Age, years	63 (59, 68)	58 (52, 63)	0.22
Males, *n* (%)	46 (51)	30 (60)	0.04
Females, *n* (%)	44 (49)	20 (40)	0.03
LA ESD, cm	4.2 (3.7, 4.6)	3.7 (3.4, 3.8)	0.01
RA ESD, cm	3.8 (3.6, 4.5)	3.5 (3.3, 3.7)	0.01
LV EDD, cm	5.2 (4.8, 5.5)	4.9 (4.8, 5.1)	0.04
RV EDD, cm	3.0 (2.7, 3.2)	2.7 (2.6, 3.0)	0.01
LVMI, g/m^2	103 (83, 128)	88.5 (79.8, 104.5)	0.03
LVEF, %	46 (38, 63)	70 (66, 75)	0.01
Daytime SBP variability, mmHg	17 (15, 20)	16 (14, 19)	0.06
Nighttime SBP variability, mmHg	12 (9, 18)	11 (8, 13)	0.11
Daytime DBP variability, mmHg	12 (10, 13)	12 (10, 14)	0.07
Nighttime DBP variability, mmHg	8 (8, 11)	11.5 (9, 12)	0.09
Daytime SBP hypotensive episodes, %	6 (0, 11)	3 (0, 5)	0.11
Nighttime SBP hypotensive episodes, %	0 (0, 0)	0 (0, 0)	0.06
Daytime DBP hypotensive episodes, %	8 (1, 18)	11 (0.00, 22.75)	0.08
Nighttime DBP hypotensive episodes, %	8 (0, 15)	0 (0, 0)	0.03
Duration CHD, months	60.1 (35.7, 86.1)	-	-
Duration CHF, months	46.2 (20.6, 68.7)	-	-

-: not applicable. Data presented as median with low and upper quartiles

It is also important to study the comparability of groups in terms of the possible impact of concomitant therapy on the studied ABPM parameters. Information about the drugs taken by patients in both study groups is presented in Table 2.

Table 2. Classes of antihypertensive drugs used by surveyed participants

Group of antihypertensive drugs	Number of patients, *n* (%)	
	Main group	Comparison group
ACE inhibitors/ARA II	90 (100)	36 (72)
Diuretics	59 (66)	25 (50)
Calcium channel blockers	47 (52)	22 (44)
Beta-blockers	75 (83)	18 (36)
Other antihypertensive drugs (alpha-blockers, centrally acting drugs)	4 (4)	4 (8)

ACE: angiotensin-converting enzyme; ARA II: angiotensin II receptor antagonists

Results

When studying the comparability of the examined groups in terms of the possible effect of concomitant therapy on the studied ABPM parameters the following results were obtained during the two-way analysis of variance.

A significant relationship was found between daytime SBP variability and the intake of beta-blockers in patients with CHF that developed against the background of coronary artery disease and arterial hypertension (P = 0.04, R = 0.85): In this cohort of patients, this indicator was significantly higher. When analyzing the relationship of the same parameters among patients in the comparison group, no significant associations were found. The use of drugs from other groups—calcium antagonists and diuretics also did not affect the variability of SBP during wakefulness among all study participants. The variability of SBP at night did not depend on the intake of beta-blockers, calcium antagonists, and diuretics in all groups of examined participants. Daytime DBP variability did not depend on the use of beta-blockers and diuretics, however, among patients in the comparison group receiving calcium antagonists, it was significantly lower (P = 0.04, R = –0.41). No significant significance of any group of drugs in relation to DBP variability during sleep has been established.

When evaluating the effect of the use of beta-blockers, calcium antagonists, and diuretics on the indices of hypotension time of SBP and DBP during the waking period, no significant associations were found in the groups of patients examined.

A significant relationship was found between the indices of DBP hypotension time at night and taking drugs from the group of calcium antagonists (P = 0.05, R = –0.67): When calcium antagonists were used in patients with CHF and CHD, lower indices of DBP hypotension time at night were recorded. Treatment with beta-blockers and diuretics did not have a significant effect on episodes of lower DBP at night. Indices of SBP hypotension time during sleep did not depend on the intake of antihypertensive drugs.

The weak statistically significant correlations were observed when EchoCG and 24-hour ABPM variables were compared in CHF patients using pairwise correlation analysis.

A higher functional class of CHF is associated with higher proportions of daytime SBP and nighttime DBP hypotensive episodes (R = 0.37 and 0.26, respectively). A similar relationship was also observed for LA ESD and proportions of nighttime SBP and DBP hypotensive episodes (R = 0.22 and 0.27, respectively). Probably, in CHF patients, the hypotensive events, especially if they are nocturnal, can impact the organ and tissue perfusion aggravating the existing circulatory insufficiency. With regard to LVEF, it doesn't work that way. In CHF patients, statistically significant positive correlations between daytime SBP and DBP variability and LVEF were revealed (R = 0.33 and 0.34, respectively). Moreover, in CHF patients we determined a significant positive correlation (R = 0.38 and 0.32, respectively) between LVEF and proportions of nighttime SBP and DBP hypotensive episodes. The similar relationship was determined in the comparative group, namely, the higher LVEF values were associated with larger proportions of daytime SBP and DBP hypotensive episodes (R = 0.51 and 0.50, respectively), which at first glance is quite controversial. However, the revealed relationships should be additionally confirmed. In order to eliminate the known limitations of the univariate methods, we applied widely used stepwise multiple linear regression, among other things, to describe the dependence between variables, determine the causal relationship between them, as well as construct predictive values of the dependent variable [38]. In accordance with the purposes of the study, EchoCG parameters and primary measure of clinical severity (functional class of CHF) were selected as independent variables, and 24-hour ABPM parameters were used as dependent variables. The statistically significant regression models are identified as follows.

The close relationship between the functional class of CHF, RA ESD, and RV EDD and nighttime DBP variability is determined (R = 0.84). The obtained results are provided in Table 3. The functional class of CHF has the greatest influence on the daytime DBP variability (P = 0.047).

In non-CHF patients, the significant correlations between the daytime DBP variability and LV EDD, RV EDD, and LVMI were identified (R = 0.72), notably, the daytime DBP variability was dependent on the RV EDD to a greater extent (P = 0.035). The daytime DBP variability was significantly associated with the functional class of CHF, RA ESD, LVMI, and LVEF (R = 0.68) while the daytime DBP variability was "influenced" by RA ESD to a greater extent (P = 0.039). In addition, significant relationships between the nighttime SBP variability and functional class of CHF, LA ESD, and RV EDD were observed (R = 0.60). The functional class of CHF had the greatest influence on the nighttime SBP variability (P = 0.027).

Table 3. The results of regression analysis of the dependence of the variability of DBP at night on echocardiographic parameters and functional class of CHF

Variable	Standardized coefficients		Non-standardized coefficients		*t*	*P* level
	Beta	Str.Err.	Beta	Str.Err.		
Intercept	-	-	36.17093	6.365803	5.68207	< 0.001
FC of CHF	–0.745443	0.151638	–8.18534	1.665057	–4.91595	< 0.001
RA ESD	–0.459399	0.185459	–3.38723	1.367422	–2.47709	0.027
RV EDD	0.296437	0.189023	3.80125	2.423857	1.56826	0.139

FC: functional class; Str.Err.: standard error; -: not applicable. The multiple correlation coefficient *R* is 0.84; *F* test is 11.110, *P* = 0.005

As shown in Table 4, in non-CHF patients, there was a close correlation between the proportion of daytime DBP hypotensive episodes and LVEF, RA ESD, and LVMI (R = 0.84). The LVEF had the greatest effect (P = 0.005). Significant correlations between the proportion of daytime SBP hypotensive episodes and functional class of CHF, RA ESD, and LVMI were found (R = 0.63). The functional class of CHF and LVMI had the greatest effect (P = 0.028 and 0.018, respectively). In non-CHF patients, the proportion of daytime SBP hypotensive episodes was significantly associated with LVEF and LVMI (R = 0.67), notably, LVEF had the greatest effect (P = 0.021).

Table 4. The results of regression analysis of the dependence of the time index of hypotension DBP during the day on echocardiographic parameters in patients with hypertension without CHF

Variable	Standardized coefficients		Non-standardized coefficients		*t*	*P* level
	Beta	Str.Err.	Beta	Str.Err.		
Intercept	-	-	–213.532	49.33815	–4.32792	0.002
RA ESD	0.409000	0.189456	19.059	8.82848	2.15881	0.059
LVMI	0.315478	0.187720	0.349	0.20770	1.68057	0.127
LVEF	0.673136	0.183051	1.816	0.49372	3.67731	0.005

Str.Err.: standard error; -: not applicable

Discussion

Therefore, the controversial information, at first glance, was obtained during the study: On the one hand, functional class, which is a key clinical parameter of CHF severity, is significantly higher with a larger number of hypertensive episodes. However, on the other hand, LVEF, which is one of the most important instrumental parameters of CHF severity, has higher values with an increase in the proportion of hypertensive episodes according to 24-hour ABPM regardless of CHF. The logical explanation probably exists. Firstly, only a small proportion of patients included in the main group had reduced LVEF, therefore, based on the obtained results, it becomes clear the relevance of conducting a similar study where the primary inclusion criterion would be reduced LVEF. Secondly, we should not forget that LVEF (for all its important prognostic significance) is an instrumental variable of cardiac pump function, whereas functional class along with a clinical assessment of CHF severity allow us to some extent to represent both the peripheral circulation, and, in particular, degree of compensation for affected pump function which is mainly reflected by LVEF.

The regression analysis revealed that LVEF did not significantly affect the 24-hour ABPM variables in CHF patients. On the contrary, the functional class of CHF was significantly associated with such dependent variables as nighttime SBP and DBP variability (positive correlation) and proportion of daytime SBP hypotensive episodes (negative correlation). In the comparative group, the proportion of daytime SBP hypotensive episodes depended most on LVEF.

Certainly, the obtained results require further confirmation. This pilot study justifies that larger trials involving CHF patients with reduced LVEF values should be conducted.

The analysis of the obtained results performed using both univariate pairwise correlation and stepwise multiple linear regression demonstrated that the functional class of CHF was higher with larger proportions

of hypotensive episodes, especially with regard to daytime SBP. Obviously, this correlation is not accidental and reliably confirms that in patients with ischemic CHF hypotensive episodes can aggravate the patient's clinical status. It should be noted that if pairwise correlation analysis revealed single weak correlations between the LVEF values and 24-hour ABPM variables, then multiple analyses excluded the "influence" of LVEF in this correlation.

On the contrary, in the comparative group, the 24-hour ABPM variables were significantly dependent on LVEF values, and, unlike patients with CHF and CHD, larger proportions of hypotensive episodes corresponded to the best LVEF values.

Study limitations

It should be noted that in this work we have analyzed data from a relatively small number of patients, and therefore it is necessary to perform a larger study. At this stage of our work, the mechanistic aspects of the identified associations were not investigated. Among these, for example, changes in vagal tone, changes in catecholamine secretion, secretion of factors by the heart muscle, such as brain natriuretic peptide (BNP), the formation of nitric oxide by vascular endothelial cells, as well as other indicators that can affect vascular tone, and myocardial angiogenesis.

Also, the results obtained in the course of the work do not answer the question of whether the correction of episodes of hypotension of BPV will have a positive effect on the prognosis of patients with CHF.

Conclusions

Previous studies provide a large amount of information about the significance of arterial hypertension in the development and progression of CHF. The present study also shows the relationship between episodes of hypotension and variability in BP during the day with parameters characterizing the severity of CHF. A higher functional class of CHF is found to be associated with a higher incidence of daytime SBP decline and nighttime SBP and DBP variability while higher LVEF is related to the hypotensive episodes regardless of CHF. Perhaps it is explained by the fact that in patients with significantly decreased LVEF in the absence of circulatory insufficiency caused by atherosclerotic cardiovascular disease, the possibilities of myocardial contractile function do not "interfere" with daily BP fluctuations. Decreased myocardial contractile function is known to be associated with greater vascular wall rigidity which can also contribute to the rigidity of 24-hour BP fluctuations [39, 40]. As a result, the positive correlations established between LVEF values and proportions of hypotensive episodes may be of a secondary nature. The statistically significant positive correlations observed in this study between the daytime variability of systolic and DBP and LVEF values confirm this assumption.

Abbreviations

ABPM: ambulatory blood pressure monitoring

BP: blood pressure

BPV: blood pressure variability

CHD: coronary heart disease

CHF: chronic heart failure

DBP: diastolic blood pressure

EchoCG: echocardiography

LA ESD: left atrial end-systolic dimension

LV EDD: left ventricular end-diastolic dimension

LVEF: left ventricular ejection fraction

LVMI: left ventricular mass index

RA ESD: right atrial end-systolic dimension

RV EDD: right ventricular end-diastolic dimension

SBP: systolic blood pressure

Declarations

Author contributions

NSA: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing—original draft. YGS: Formal analysis. NDM and TYL: Investigation. ARK: Methodology, Investigation, Resources. LEK: Visualization, Writing—review & editing. OVB: Data curation, Investigation. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The conduct of this study was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education V.I. Razumovsky Saratov State Medical University of the Ministry of Healthcare of the Russian Federation.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The datasets that support the findings of this study are available from the author upon reasonable request. If someone wants to request the data you should contact Oksana V. Bugaeva, bugaeva.ov@staff.sgmu.ru.

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