

Prognostic value of daytime heart rate, blood pressure, their products and quotients in chronic heart failure

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Abstract

Background: *Chronic heart failure (CHF) is an important epidemiological and therapeutic issue with poor prognosis. The aim of the study was to estimate the prognostic value of daytime heart rate (HR), blood pressure (BP), their products and quotients in patients with CHF.*

Methods: *The study included 80 stable patients with CHF and reduced left ventricular ejection fraction (LVEF \leq 35%). Physical examination, laboratory blood tests, electrocardiogram, chest X-ray, echocardiography, 6-minute walk test, telemetry monitoring and BP measurements were performed in all participants. We estimated mean daytime: BP, HR, their products and quotients. The follow-up period was 6 months. Major adverse cardiac events (MACE) included: death, cardiovascular death, hospitalization due to CHF exacerbation.*

Results: *The analysis involved all recruited patients with CHF (91% men) aged 59 ± 12 years, in New York Heart Association class 2.15 ± 0.57 and reduced LVEF (mean LVEF: $23 \pm 6\%$). The 3-month and 6-month mortality rates were 4% and 6%, respectively. There was a significant correlation between diastolic blood pressure (DBP), all-cause mortality ($p = 0.048$) and CHF decompensation ($p = 0.0004$) after 3-month observation period. No relationship was found between HR or systolic blood pressure (SBP) and MACE. Both higher $SBP \times HR$ and $DBP \times HR$ products were related to lower risk of heart failure exacerbations during 6-month follow-up. None of the analyzed products or ratios had an impact on mortality in this study group.*

Conclusions: *Diastolic blood pressure, $SBP \times HR$ and $DBP \times HR$ products may be useful in subsequent heart failure exacerbation risk stratification. Moreover, DBP value may predict short-term mortality in patients with CHF. (Cardiol J 2019; 26, 1: 20–28)*

Key words: chronic heart failure, heart rate, blood pressure, diastolic blood pressure, double product

Introduction

The management of patients suffering from chronic heart failure (CHF) is one of the most challenging issues in cardiology today. Due to the ageing of world populations, advances in acute coronary syndrome treatment and effective secondary prevention, the prevalence of CHF increases systematically [1]. The incidence of CHF is particularly high in elderly people. More than 50%

of patients with new onset HF is ≥ 75 years old [2]. Despite improvements in pharmacological and invasive therapy of HF the prognosis still remains poor. There are many risk factors leading to HF development and progression [1]. Nevertheless, the search for biomarkers and factors are useful in CHF outcome prediction not only to be able to stratify the risk but also to improve quality of life, decrease the number of subsequent hospitalizations and mortality rates [3].

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Hypertension (HTN) is a most important cardiovascular risk factor and apart from stroke, heart failure (HF) is one of the most frequent complications of HTN [1]. Optimal blood pressure (BP) control in hypertensive patients may significantly delay HF onset and is possible using pharmacological and non-pharmacological treatment. Unfortunately, the rate of successful implementation of non-pharmacological treatment is low even in patients with diagnosed HTN [1, 4]. Conversely to the general population, patients with CHF usually do not benefit from intensive antihypertensive therapy [5–7]. As a result of standard pharmacotherapy including angiotensin converting enzyme (ACE) inhibitors or angiotensin receptors blockers (ARB), beta-blockers, mineralocorticoid receptors antagonists (MRA) and diuretics, the majority of patients with HF and reduced left ventricular ejection fraction (HFrEF) have low or even very low BP values. Moreover, the phenomenon of the J-shaped mortality curve in the other group of patients with cardiovascular diseases was observed, which may also be apparent in the HF population. SPRINT Research Group revealed that among patients at high risk for cardiovascular events but without diabetes, targeting systolic blood pressure (SBP) of less than 120 mmHg, as compared with less than 140 mmHg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause. Nevertheless, significantly higher rates of some adverse events were observed in the intensive-treatment group [8]. Bavishi et al. [9] observed that in older hypertensive patients, intensive BP control decreased cardiovascular mortality and HF, although they had increased risk of renal failure. One of the most difficult challenges in the treatment of patients with CHF are recurrent exacerbations of this disease. Prior hospitalization is one of the important risk factors predicting subsequent episodes of CHF decompensation [10]. The relationship between BP and risk for CHF decompensation has not been clearly established. Thus, the influence of BP on prognosis of patients with CHF remains uncertain and requires additional studies.

Heart rate (HR) is an independent cardiovascular risk factor in the general population [11]. Data from many trials demonstrated relationship between increased resting HR and mortality in the majority of cardiovascular diseases [12, 13]. Other studies have confirmed the positive role of HR in lowering cardiac event prevention. Heart failure involves many compensation mechanisms leading to an HR increase. Many authors have observed the correlation between increased HR and higher

risk of major adverse cardiac events (MACE) in patients with CHF [1, 14]. Nevertheless, its role in HF needs further investigation.

Double product (DP), defined as HR multiplied by SBP reflects myocardial oxygen consumption. Thus, it plays an important role in cardiovascular risk stratification during exercise testing in patients with ischemic heart disease [15, 16]. There are many conflicting studies concerning the role of DP in cardiovascular risk stratification in healthy populations and hypertensive patients. According to some data, DP correlates positively with mortality in the general population [17]. However other authors discourage the use of DP as a cardiovascular risk prediction determinant [18]. The impact of DP as well as other HR and BP products and ratios on prognoses in patients with CHF needs further study.

The aim of this prospective study was to evaluate the prognostic value of daytime HR, BP, their products and ratios in stable patients with CHF in providing useful, achievable tools in risk stratification.

Methods

There were 80 stable patients with CHF and HFrEF enrolled in this study. The inclusion criteria were as follows: age 18–80 years, stable clinical status, CHF diagnosed at least 1 year before recruitment into the study, ischemic or dilated cardiomyopathy, LVEF $\leq 35\%$ and optimal medical therapy. The exclusion criteria were as follows: CHF exacerbation within 3 months prior to the study, pregnancy and valvular heart disease as a cause of CHF. All patients recruited were diagnosed and treated at the Cardiology Department according to the recent 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute HF and CHF [1]. All patients underwent following examinations: medical history, physical examination, laboratory tests, 12-lead resting electrocardiogram (ECG), chest X-ray, transthoracic echocardiography and the 6-minute walk test. Laboratory tests including the following parameters were assessed: total blood count with hemoglobin and red blood cell distribution width, sodium, potassium, urea, creatinine, glomerular filtration rate, total bilirubin, cholesterol, triglycerides, uric acid, alanine transaminase, aspartate transaminase, glucose and B-type natriuretic peptide.

Heart rate and BP obtained were mean daytime values as determined through measurements

performed with 24-h telemetry monitoring and OMRON M7 Intelli IT device (Japan), 4 times a day, respectively. BP was measured at rest, each time twice with a 2 min pause at 6.00, 10.00, 16.00 and 20.00 h. For analysis of median value all 8 measurements was taken. Pulse pressure (PP) values were calculated as the difference between SBP and DBP. The following products were also estimated and ratios: HR × SBP (DP), HR × DBP, HR × PP, HR/SBP, HR/DBP, HR/PP. The follow-up period was 6 months. All follow-up data were obtained from visits or by telephone. MACE was defined as: death of all causes, cardiovascular death, hospitalization due to the HF exacerbation. The study protocol was approved by the Local Ethics Committee.

Statistical analysis

All statistical calculations were performed using the statistical package StatSoft. Inc. (2014) STATISTICA (data analysis software system), version 12.0. Quantitative variables were characterized by the arithmetic mean, standard deviation, median, minimum and maximum values (range) and 95% confidence interval (CI). Whereas qualitative variables were presented using frequencies and percentages. To check whether a variable quantitative came from a normally distributed population analysis using the Shapiro-Wilk. In contrast, testing the hypothesis of equal variances test, Leven (Brown-Forsythe) was used. The significance of differences between the two groups (model variables unrelated) examined these test significance differences: Student t or, in the absence of homogeneity of variance, the Welch test or Mann-Whitney U (in cases of non-compliance with the conditions of applicability of the Student t test or for variables measured on the ordinal scale). Tests of independence χ^2 was used for categorical variables (by using Yates correction according to the number of cells below 10, checking conditions of Cochran and the Fisher exact test). In order to establish link strength and direction between variables, correlation analysis was used in calculating the Pearson correlation coefficients and/or Spearman. In all calculations the level of significance was set at $p = 0.05$.

Results

Data of all 80 recruited patients were under analysis. The basic characteristics of the study population are presented in Tables 1 and 2.

The mean age of the study group was 59 ± 11 years and men constituted the majority of the

Table 1. Baseline characteristics of the study group.

Variables	Values
Age [year]	59 ± 12
Men	93 (91%)
BMI [kg/m ²]	28.7 ± 5.4
NYHA class	2.15 ± 0.57
Heart rate [bpm]	75 ± 14.3
SBP [mmHg]	114 ± 14
DBP [mmHg]	70 ± 9.5
DP [bpm × mmHg]	8649 ± 1953.5
HR × DBP [bpm × mmHg]	5368 ± 1303.6
HR × PP [bpm × mmHg]	3272 ± 1066
HR/SBP [bpm/mmHg]	0.67 ± 0.15
HR/DBP [bpm/mmHg]	1.08 ± 0.24
HR/PP [bpm/mmHg]	1.94 ± 0.97
LVEF [%]	23.3 ± 6.7
6MWT distance [m]	351.3 ± 110.3
Ischemic CHF	50 (62.5%)
Prior MI	50 (62.5%)
Prior stroke	10 (12.5%)
Prior CABG	13 (16.25%)
Prior PCI	30 (37.5%)
Prior ICD	49 (61.25%)
Smoking	55 (68.75%)
Qualified to HTX	9 (11%)
BNP [pg/mL]	742 ± 701

Values are presented as means ± standard derivation or as number (percentages); BMI — body mass index; NYHA — New York Heart Association; SBP — systolic blood pressure; DBP — diastolic blood pressure; DP — double product; HR — heart rate; PP — pulse pressure; LVEF — left ventricular ejection fraction; 6MWT — six-minute walk test; CHF — chronic heart failure; MI — myocardial infarction; CABG — coronary artery bypass grafting; PCI — percutaneous coronary interventions; ICD — implantable cardioverter defibrillator; HTX — heart transplantation; BNP — B-type natriuretic peptide

population (91%). Most participants were in New York Heart Association (NYHA) II class (mean: 2.2 ± 0.6). The majority of recruited subjects were nondiabetic (70%) and had CHF of ischemic origin (62.5%). Atrial fibrillation was confirmed in 22% of all study participants. For a majority of study population, comorbidities were reported. Three (4%) patients died during 3-month follow-up, and 5 (6%) during a 6-month observation due to HF deterioration. Ten (12.7%) patients were subsequently hospitalized for CHF decompensation within 3-months and 19 (24%) during 6 month follow-up.

After a 3-month and excluding a 6 month observation period there was a significant correlation

Table 2. Comorbidities and medication use at baseline.

Variables	Values
Hypertension	50 (62.5%)
Atrial fibrillation	16 (22%)
Diabetes mellitus	24 (30%)
Dyslipidemia	26 (32.5%)
COPD	17 (21.25%)
Liver dysfunction	9 (11.25%)
Renal dysfunction	16 (20%)
Thyroid dysfunction	11 (13.25%)
Peptic ulcer disease	7 (8.75%)
Peripheral arterial disease	5 (6.25%)
ASA	41 (51.25%)
Oral anticoagulants	9 (11%)
Beta-blockers	75 (93.75%)
Amiodarone	19 (23.75%)
Ivabradine	5 (6.25%)
Loop diuretics	75 (93.75%)
Aldosterone antagonists	12 (15%)
ACE inhibitors	70 (87.25%)
Statins	55 (68.75%)
ARB	10 (12.5%)
Digoxine	14 (17.5%)

Values are presented as numbers (percentages); COPD — chronic obstructive pulmonary disease; ASA — acetylsalicylic acid; ACE — angiotensin converting enzyme; ARB — angiotensin receptor blockers

between DBP and all-cause mortality ($p = 0.048$) as well as CHF decompensation ($p = 0.0004$) in the whole group. DBP was significantly higher in patients without CHF decompensation as well as in those who survived. No relationship was found between HR or SBP and MACE. Furthermore, it was observed that in patients with higher $HR \times DBP$ product, risk of CHF decompensation was significantly lower in both 3-month ($p = 0.001$) and 6-month ($p = 0.032$) observation periods. Moreover, patients hospitalized for CHF exacerbation in 6-month observation DP was significantly lower than in stable ones. No correlations were found between: DP, $HR \times DBP$, $HR \times PP$ products and 3 or 6 month mortality. None of the following calculated quotients: HR/SBP , HR/DBP , HR/PP significantly influenced the risk of CHF exacerbation or mortality. None of the presented factors were found to be significant for MACE risk stratification in multiple analysis of COX proportional hazard. The most significant correlations are presented in Tables 3 and 4.

Discussion

In this prospective study, it was demonstrated that daytime DBP may be a valuable risk stratification factor for death and HF exacerbation in stable patients with CHF. Within the present study population mean SBP and DBP values were 114 ± 14 mmHg and 70 ± 9.5 mmHg, respectively. It was shown that higher DBP but not SBP was associated with lower risk of death and CHF decompensation in the 3-month observation period. A relationship was not confirmed between DBP and MACE in the 6-month observation period. It was presumed that this fact may be related to patient clinical status improvement during the follow-up period. Similar observations concerning DBP in HF have been reported in other previous studies. Lee et al. [5] in retrospective analysis of Digitalis Investigation Group (DIG) data revealed that in patients with systolic dysfunction ($LVEF \leq 45\%$) and NYHA II and III class, lower SBP and DBP were associated with greater mortality in short and long-term observation. This study supports the suggestion of other authors that patients with $SBP < 110$ mmHg and $DBP < 60$ mmHg had a significantly higher risk of death. These observations have been documented in several studies. According to these authors, patients with $SBP < 110$ mmHg were at higher risk of mortality [19, 20]. The negative correlation between BP and mortality was also observed in a prospective study of patients with acute HF decompensation performed by Ghali et al. [21]. Lip et al. [22] A recent cohort study indicated that patients with incident HF and increased initial SBP and DBP values were at higher risk of adverse cardiovascular events. Similarly, Raphael et al. [6] revealed that contrary to the general population, higher SBP was a favourable prognostic marker in CHF which was not related to etiology, ACE inhibitor or beta-blocker use. Some authors have suggested that low daytime BP variability may also influence prognosis in patients with HF [23]. Sherazi et al. [24] and revealed that the absence of hypertension, as well as elevated urea and lower $LVEF \leq 45\%$ indicate increased risk of short and long-term mortality. The relationship between DBP and MACE has been discussed in other publications concerning this subject [8, 25, 26]. McEvoy et al. [27] revealed an association between $DBP < 60$ mmHg and coronary heart disease events in Atherosclerosis Risk In Communities (ARIC) cohort study population. It has been documented that low DBP was related to subclinical myocardial damage and MACE. The most important conse-

Table 3. Correlations between chosen variables and 3-month mortality rate.

Variable	Survival (n = 77)	Death (n = 3)	P
HR			
Mean (SD)	76.0 (14.0)	69.7 (24.6)	0.8792
Range	51.0–120.0	42.0–89.0	
Median	75.0	78.0	
95% CI	[72.8;79.1]	[8.6;130.7]	
SBP			
Mean (SD)	114.6 (14.7)	103.3 (9.5)	0.1795
Range	90.0–145.0	96.0–114.0	
Median	110.0	100.0	
95% CI	[111.3;118.0]	[79.9;126.8]	
DBP			
Mean (SD)	71.1 (9.4)	59.3 (9.0)	0.0482
Range	50.0–89.0	50.0–68.0	
Median	70.0	60.0	
95% CI	[69.0;73.3]	[36.9;81.7]	
DP			
Mean (SD)	8691.3 (1909.4)	7326.0 (3084.4)	0.5022
Range	5400.0–15600.0	4032.0–10146.0	
Median	8280.0	7800.0	
95%CI	[8258.0;9124.7]	[–336.2;14988.2]	
HR × DBP			
Mean (SD)	5410.5 (1269.6)	4277.3 (2006.5)	0.3488
Range	3000.0–9600.0	2100.0–6052.0	
Median	5304.0	4680.0	
95% ci	[5122.4;5698.7]	[–707.2;9261.8]	
HR × PP			
Mean (SD)	3280.8 (1071.5)	3048.7 (1082.8)	0.8296
Range	900.0–6300.0	1932.0–4094.0	
Median	3000.0	3120.0	
95% CI	[3037.6;3524.0]	[358.9;5738.4]	
HR/SBP			
Mean (SD)	0.68 (0.16)	0.67 (0.20)	0.7903
Mean (SD)	0.41–1.10	0.44–0.78	
Range	0.66	0.78	
Median	[0.64;0.71]	[0.17;1.16]	
HR/DBP			
Mean (SD)	1.09 (0.24)	1.15 (0.27)	0.5861
Range	0.64–1.83	0.84–1.31	
Median	1.07	1.30	
95% CI	[1.03;1.14]	[0.48;1.82]	
HR/PP			
Mean (SD)	1.95 (0.99)	1.60 (0.59)	0.6761
Range	0.98–8.08	0.91–1.95	
Median	1.75	1.93	
95% CI	[1.73;2.18]	[0.12;3.08]	

SD — standard derivation; CI — confidence interval, other abbreviations — see Table 1

Table 4. Correlations between chosen variables and 3-month chronic heart failure (CHF) exacerbations.

Variable	No CHF decompensation (n = 61)	CHF decompensation (n = 19)	P
HR			
Mean (SD)	76.5 (14.3)	69.2 (13.3)	0.2183
Range	51.0–120.0	42.0–89.0	
Median	75.0	70.0	
95% CI	[73.0;79.9]	[59.7;78.7]	
SBP			
Mean (SD)	115.3 (15.1)	107.0 (10.4)	0.1097
Range	90.0–145.0	96.0–130.0	
Median	115.0	102.0	
95% CI	[111.7;118.9]	[99.5;114.5]	
DBP			
Mean (SD)	72.1 (9.3)	60.7 (5.8)	0.0004
Range	50.0–89.0	50.0–70.0	
Median	70.0	60.0	
95% CI	[69.8;74.3]	[56.6;64.8]	
DP			
Mean (SD)	8796.7 (1947.2)	7434.2 (1694.1)	0.0525
Range	5400.0–15600.0	4032.0–10146.0	
Median	8300.0	7 500.0	
95% CI	[8328.9;9264.4]	[6222.3;8646.1]	
HR × DBP			
Mean (SD)	5511.7 (1265.1)	4229.7 (993.3)	0.0011
Range	3000.0–9600.0	2100.0–6052.0	
Median	5394.0	4477.5	
95% CI	[5207.8;5 815.6]	[3519.2;4940.2]	
HR × PP			
Mean (SD)	3285.0 (1107.7)	3204.5 (830.9)	0.9061
Range	900.0–6 300.0	1932.0–4779.0	
Median	3000.0	3 000.0	
95% CI	[3018.9; 3551.1]	[2610.1; 3798.9]	
HR/SBP			
Mean (SD)	0.68 (0.16)	0.65 (0.12)	0.8712
Range	0.41–1.10	0.44–0.78	
Median	0.66	0.67	
95% CI	[0.64;0.72]	[0.56;0.74]	
HR/DBP			
Mean (SD)	1.08 (0.25)	1.14 (0.21)	0.3925
Range	0.64–1.83	0.84–1.47	
Median	1.07	1.17	
95% CI	[1.02;1.14]	[0.99;1.29]	
HR/PP			
Mean (SD)	1.99 (1.03)	1.53 (0.37)	0.1548
Range	0.98–8.08	0.91–1.95	
Median	1.75	1.51	
95% CI	[1.74;2.24]	[1.26;1.80]	

SD — standard derivation; CI — confidence interval, other abbreviations — see Table 1

quence of DBP lowering is coronary blood flow reduction due to a lower perfusion gradient [27]. These mechanisms may be also present in patients with HF of ischemic origin. The present findings support previous hypotheses that excessive hypotensive therapy in patients with HF leading to significant BP lowering may correlate with an increase in mortality rate. Some authors however, have not confirmed DBP association with mortality but only SBP with nonsudden cardiac death [7]. In contrast to our findings concerning the influence of DBP on CHF exacerbations, the most recent report by Voors et al. [28] noted an association between lower SBP but not DBP and hospitalizations owing to HF. Moreover, BP was not one of the strongest predictors of mortality due to HF. According to BARDICHE-index authors lower SBP was associated with higher HF exacerbation rate independently of LVEF [29]. Several authors have demonstrated that higher SBP was independently related to improved cardiovascular survival in patients with CHF [13, 21, 24, 30]. Surprisingly, this study did not confirm the relationship between SBP and MACE in the whole group of patients or in study subgroups. Nevertheless, it should be underlined that in contrast to other studies only mean daytime values of SBP were taken into analysis. Furthermore, the examined group was small and observation period short. In the majority of studies examining this subject follow-up duration exceeded 1 year.

It has been documented that HR is an independent risk factor in patients with HF. Elevated resting HR is associated with unfavourable pathomechanisms including: increased oxygen demand, diminished ventricular relaxation and reduced stroke volume [31]. Many authors have revealed that HR reduction impacted favourably on outcome in patients with HF [31–34]. According to the SHIFT study and substudy results, reduced HR was associated with relative risk reduction for cardiovascular death and/or HF worsening. Furthermore, lower HR was related to reversal of cardiac remodeling [14, 35]. A recent report by Zou et al. [36] noted that HR deceleration and acceleration capacities are independent risk factors for dilated cardiomyopathies. Moreover, HR acceleration may be a valuable HF exacerbation prognostic factor. Nevertheless, HR reduction in patients with chronic HFrEF is not associated with better survival in atrial fibrillation presence [37, 38]. This study did not observe a significant correlation between daytime HR and mortality or HF decompensation rate in short-term observation. It cannot be excluded, however, that prolonged

observation and/or mean whole day HR values would have influenced the final results. Moreover, all patients were on optimal pharmacological treatment affecting BP and HR.

In summary, according to many authors the prognostic role of BP and HR in HF outcome cannot be overestimated. Some authors have suggested that combining HF and SBP constitutes a valuable prognostic factor in older patients with HF [39]. Nevertheless, there are still few reports concerning the prognostic value of HR and SBP combinations, products or quotients in patients with CHF. The results of the present study provide several new findings on this issue. It was found that higher HR \times SBP product (DP) correlated negatively with CHF exacerbation risk in 6-month observation period. Similarly, patients with higher HR \times DBP product were at lower risk of CHF decompensation both in 3-month and 6-month observation periods. The supposition was that those negative correlations are related to previously described reverse relationship between BP and HF outcome. No relationship was observed between: DP, HR \times DBP, HR \times PP products and mortality. There were no publications found which support the present observations. There were few conflicting studies examining the predictive role of DP in healthy or hypertensive populations [17, 18, 40]. Moreover, none of the calculated quotients impacted on MACE during follow up. No publications were found concerning this subject in patients with HF. There are some reports concerning the role of mean arterial pressure and heart rate quotient (PRQ) in myocardium hypoperfusion prediction. Buffington et al. [41] indicated that PRQ is an effective predictor of hypoperfusion of collateral-dependent myocardium. Mereu et al. [42] investigated HR/SBP quotient as predictor of neuromediated syncope. It has been revealed that HR/SBP ratio may be a valuable tool to estimate the occurrence of syncope. Further studies are needed to estimate the prognostic role of combining HR and BP in populations with CHF.

Limitation to the study

The prognostic value strength of proposed risk stratification factors may be diminished by the fact that the majority of patients received pharmacological treatment including antihypertensive drugs (ACE inhibitors or ARB, diuretics, beta-blockers) and negative chronotropic agents (digoxin, beta-blockers). Moreover, BP and HR values were not estimated by ambulatory BP monitoring but only through automatic several daytime BP measure-

ments. However, the intention of this study was to verify the utility of simple BP measurements similar to those performed at home. Finally, the study population was small and the observation period short thus it may be difficult to extrapolate obtained results to general CHF populations.

Conclusions

This study revealed that DBP and DP, $HR \times DBP$ products may be simple, achievable tools in the prediction of HF exacerbations in stable CHF patients in short-term observation. Moreover, a significant relationship was found between DBP value and 3-month mortality in this group of patients. None of the estimated products or quotients influenced mortality in the present study group.

Conflict of interest: None declared

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