ONLINE FIRST

FOLIA CARDIOLOGICA

ISSN: 2353-7752

e-ISSN: 2353-7760

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DOI: 10.5603/FC.a2019.0074

Article type: Original Papers

Submitted: 2018-10-01

Accepted: 2019-01-15

Published online: 2019-07-02

Valvular heart disease and different circadian blood pressure profiles

Wady zastawkowe serca i różne profile dobowe ciśnienia tętniczego

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Abstract

Valvular heart diseases (VHD) increase the risk of cardiovascular morbidity and mortality. Little is known about correlation between circadian blood pressure profile and VHD. The aim of the study was to clarify the association of dipping status and VHD prevalence.

103 consecutive patients (male: 50.5%), who underwent 24-hour ambulatory BP measurement and ECG-Holter simultaneously were analysed. We divided patients into 3 groups: dipping was defined as 10–20% (28.2%), non-dipping as < 10% (50.5%) fall in nocturnal BP and reverse-dipping as higher nocturnal than diurnal BP (21.4%). VHD was assessed by transthoracic echocardiography and described as mild, moderate or severe regurgitation or stenosis accordingly. Further we compared severity of VHD, nocturnal fall pattern and ABPM features in all groups.

We found no statistically significant associations between dipping pattern and frequency of VHD. We also found no statistical association between dipping status and severity of VHD. Our study showed some correlations between VHD severity and different ABPM parameters. Though dipping status obtained by ABPM did not influence severity of VHD, there were associations between ABPM outcomes and VHD. This finding may have important implications on care of patients with hypertension and VHD, though further studies are needed.

Key words: circadian rhythm; hypertension; valvular heart disease;

Introduction

Hypertension is a growing problem, and currently, there are over 1 billion hypertensive individuals worldwide]. In 1978 Millar-Craig et al. described circadian variation of blood

pressure (BP) using continuous intra-arterial monitoring [3]. Nowadays ambulatory blood pressure measurement (ABPM) is a noninvasive method to obtain circadian blood pressure profile (CBPP) [4].

Studies prove that non-dipping pattern in hypertensive individuals might be associated with increased cardiovascular risk [5–7]. The lower or lack of fall in nocturnal BP values could also cause target organ damage. Literature brings evidence that non-dipping pressure profile is connected with left ventricle hypertrophy (LVH), cardiac functional alteration, renal damage, carotid artery abnormalities and cerebrovascular diseases [8–15] . Valvular heart disease (VHD) may be not as common as coronary artery disease (CAD) or heart failure , but remains significant, since it frequently requires interventions [16, 17]. The aim of the study was to assess if there are associations between VHD prevalence as well as occurrence and either CBPP or ABPM parameters.

Materials and methods

Study population

This was a retrospective study analyzing data of 103 patients hospitalized in the Department of Cardiology and Hypertension in Central Research Hospital of the Ministry of Interior and Administration in Warsaw between January 2012 and December 2013. All consecutive patients, who simultaneously underwent ABPM and 24-hours ECG Holter (ECG-Holter), were included in further analysis. According to nocturnal fall pattern we divided patients into three groups. Dipping was defined as a 10–20% fall in nocturnal systolic BP (SBP), non-dipping as less than 10%, and reverse-dipping as higher average SBP during the night than during the day [6, 18]. Collected data were analyzed retrospectively and Local Ethics Committee gave consent to conduct the trial.

Measurements

In the study Treacker NIBP2 SpaceLabs Healthcare and ABP 90217-7Q SpaceLabs Healthcare devices were used to obtain ABPM and Lifecard CF Reynolds Medical device to assess ECG-Holter. Measurements of BP were performed every 10 minutes during awake hours and every 30 minutes at night. Additionally, all patients had transthoracic echocardiography (TTE) using Phillips IE-33 and EPIQ Ultrasound machines and rest-ECG performed. In TTE VHD severity was described as none (0), mild (+), moderate (++) or severe (+++).

Statistics

Statistical analysis was performed on R version 3.1.2 [19]. Continuous variables are presented as number of observations and mean with standard deviation; categorical variables are reported as frequencies and percentages. The distribution of continuous variables was first analysed with Shapiro-Wilk test of normality and then according to the results ANOVA test or Kruskal-Wallis test were used. Categorical variables were compared using Fisher's exact test. The significance level was set at 0.05.

Results

One hundred three consecutive patients (male: 50.5%) with mean age 63.9 (± 17.7) years simultaneously underwent ABPM and ECG-Holter were included in further analysis. According to ABPM outcomes 29 (28%) patients were dippers, 52 (50%) were non-dippers and 22 (21%) were reverse-dippers respectively. The reverse dipper group was the oldest, with mean age 74.9 ± 10.9 years, and differences in age between groups were statistically significant ($p < 0.001$). Study population characteristic is presented in Table 1. There were significant differences between groups in occurrence of diagnosis of chronic kidney disease (CKD) and peripheral artery disease (PAD), with the higher prevalence of those diseases in non–dipper and the highest in reverse-dipper group. Mean systolic and diastolic pressure, both diurnal and nocturnal, which differed statistically significantly between subgroups in our study population, is presented also in Table 1.

Echocardiography parameters assessed in our study population are given in Table 2. From those results only left atrium diameter (LAD) differed significantly regarding CBPP (40.2 ± 4.8 mm; 43.8 ± 6.2 mm; 41.8 ± 5.2 mm; $p = 0.026$; dippers, non-dippers, reverse-dippers, respectively). We found no statistically significant difference between neither prevalence nor occurrence of VHD regarding CBPP in our study population. Parameters are given in Table 2 and Table 3.

List of drugs administered in our study population is given in Table 4. Both: β- and α-adrenolytics were more commonly used in non-dipper and reverse-dipper than in dipper population (α-adrenolytics: 0%; 13.04%; 30%; $p = 0.009$; β-adrenolytics: 57.69%; 69.57%; 95%; $p = 0.011$; dippers, non-dippers, reverse dippers, respectively). There were no statistically significant differences in drugs doses (Table 5).

Our study showed that severity of aortic stenosis (AS) correlated positively with maximal nocturnal systolic blood pressure (SBP) ($\rho = 0.208$; $p = 0.038$) and that severity of aortic regurgitation (AR) correlated negatively with diastolic blood pressure (DBP) during the

nighttime (ρ = -0.214; p = 0.033). Additionally we found that severity of AR was connected with lower maximal heart rate (HR) at night (ρ = -0.197; p = 0.050), while AS correlated with lower maximal HR during awake hours (ρ = -0.202; p = 0.044). Tricuspid stenosis correlated negatively with both awake (ρ = -0.199; p = 0.047) and nightly DBP (ρ = -0.207; p = 0.039) and with maximal DBP during awake hours (ρ = -0.198; p = 0.048). During awake hours both minimal SBP (ρ = -0.197; p = 0.050) and maximal DBP (ρ = -0.236; p = 0.018) correlated negatively with pulmonary regurgitation.

Discussion

Heart is one of the organs damaged by hypertension. Some authors described LVH and higher left ventricle mass index (LVMI) in non-dipper patients group compared to dippers [8, 20–22]. Those data are inconclusive, because others failed to prove those outcomes [23–25]. It may be due to different methods used in those studies, i.e. Cuspidi et al., who proved statistically significant differences in LVH prevalence and higher LVMI in never-treated non-dippers with reproducible non-dipper pattern of hypertension comparing to those with reproducible dipper pattern of hypertension, used multiple ABPM measurements in order to divide patients into groups, while others used only 1 measurement [8]. Cuspidi et al. [9] described that fact as the reason of different outcomes in comparison with other studies. This fact may be relevant, but other authors reported high reproducibility of ABPM outcomes regarding CBPP in their study population (hemodialysis patients) after 6 and 12 months [20]. Ferrara et al. [26] reported that differences in echocardiography outcomes may be significant in dippers comparing to non-dippers only in recently discovered hypertension and showed similar changes in both groups in long-standing hypertension. Additionally, Sokmen et al. [27] found that there was no statistically significant difference between dippers and non-dippers hypertensive patients, who had adequate BP control regarding LVH, LVMI. We also assessed presence of LVH and in our population we found that non-dippers had higher both posterior wall end-diastolic diameter (PWDd) and interventricular septal end-diastolic dimension (IVSd). Additionally, we found that there was an inverse tendency in reverse-dipper group, what was in contra position to Wang et al. [28] results. Although, in all those parameters we did not reach statistical significance, what might be due to relatively smaller study population than in cited studies. Additionally, in another original article recently submitted for publication, we analyzed factors determining CBPP and nightly fall of SBP. We found that patients who were older, diagnosed with peripheral artery disease or dilated cardiomyopathy and who used α-adrenolytics had lower fall in nocturnal SBP. Also, we found

that patients who had lower hemoglobin concentration, higher CK-MB values or lower maximal heart rate had lower fall in nocturnal SBP. We assessed higher prevalence of altered CBPP in patients who used β- or α-adrenolytics or torasemide. Though according to our results none of TTE parameters (including LVH) determined CBPP and nightly fall of SBP. Looking further into analysis of TTE measurements, in the context of CBPP larger LAD, was already described by others in non-dipper group [9]. Our results proved those outcomes regarding differences between dippers and non-dippers. Surprisingly we found that this tendency was not continued in reverse-dipper group, although we found no studies to compare our outcomes with. Regarding detailed analysis of VHD in the context of CBPP we found only one study in which authors assessed VHD (in that particular study only aortic valve disease was considered) influence on CBPP. Authors found that aortic valve disease was connected with altered CBPP. Our outcomes did not prove that fact. It may be due to smaller population in the cited Jensen et al. study (13 patients with either aortic regurgitation or aortic stenosis) [29] .

Above-mentioned Jensen's study may also be considered as one of the reasons why there was a correlation between AS severity and higher maximal SBP at night. They found that there was higher activity of renin-angiotensin system in patients with aortic valve disease [29]. Others described higher sympathetic nervous system activity in patients diagnosed with AS [30]. Further studies are needed, because our outcomes regarding other correlations were not proved by other studies.

As we already mentioned, limitation of our study may be the fact that we used only one ABPM outcome in order to define and divide our study population. Additionally relatively large reverse dipper population may be considered both, limitation and strength of our study. It could be limitation, because there are not enough data regarding reverse dipper population in literature, so we had little opportunity to compare our results. It may be considered strength because it gives information about population, which has not been precisely described so far.

Conclusion

To conclude, we found influence of neither occurrence nor severity of VHD on CBPP in our study population. Though we found some interesting associations between ABPM parameters and severity of VHD. Further studies are needed, but these outcomes may have implications on care on patients with hypertension.

Konflikt interesów

Autorzy nie zgłaszają konfliktu interesów

Streszczenie

Wady zastawkowe serca (z ang. valvular heart disease — VHD) zwiększają ryzyko zachorowań i zgonów z przyczyn sercowo-naczyniowych. Niewiele jest wiadomo na temat zależności pomiędzy profilem dobowym ciśnienia tętniczego (z ang. circadian blood pressure profile), a VHD. Celem tej pracy było wyjaśnienie związku pomiędzy CBPP, a VHD.

103 kolejnych pacjentów (mężczyźni: 50,5%), którzy wykonany mieli równocześnie całodobowy pomiar ciśnienia tętniczego i 24-godzinny zapis EKG metodą Holtera byli włączeni do badania. Podzielono pacjentów na 3 grupy: „dippers" zdefiniowani zostali jako osoby mające ciśnienie tętnicze w nocy o 10–20% niższe niż w ciągu dnia (28,2%), „non-dippers" jako osoby mające spadek ciśnienia tętniczego w nocy mniejszy niż 10% (50,5%), natomiast „reverse-dippers" stanowily osoby mające wyższe wartości ciśnienia w nocy, niż w ciągu dnia (21,4%). VHD oceniana była przy pomocy echokardiografii przezklatkowej i oceniana jako mała, umiarkowana lub ciężka. Następnie porównywano ciężkość VHD, CBPP i dane z całodobowego pomiaru ciśnienia tętniczego we wszystkic grupach.

Nie znaleziono istotnej statystycznie zależności pomiędzy CBPP i częstością występowania VHD. Co więcej, nie znaleziono również istotnej statystycznie zależności pomiędzy CBPP, a ciężkością VHD. Znaleziono korelację pomiędzy ciężkością VHD, a niektórymi parametrami ocenianymi w trakcie całodobowego pomiaru ciśnienia tętniczego.

Pomimo, że CBPP nie wpływał na ciężkość VHD istnieją zależności pomiędzy wynikami całodobowego pomiaru ciśnienia tętniczego i VHD. Dalsze badania są konieczne.

Słowa kluczowe: rytm okołodobowy; nadciśnienie tętnicze; wady zastawkowe serca

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Table 1. Population characteristics

	Dipper	**Non–dipper**	**Reverse dipper**	
Age [years]	55.24 ± 17.83	63.98 ± 17.46	74.91 ± 10.86	**p < 0.001**
Gender [M/F]	16/13	30/22	6/16	**p = 0.052**

SBP day [mmHg]	129.72 ± 11.30	127.48 ± 13.81	125.77 ± 15.32	p = 0.575
SBP night [mmHg]	111.55 ± 9.16	121.58 ± 13.73	133.00 ± 18.04	**p < 0.001**
SBP fall	13.93 ± 2.83	4.63 ± 2.91	-5.61 ± 3.71	**p < 0.001**
DBP day [mmHg]	74.41 ± 8.19	71.23 ± 8.67	67.45 ± 6.53	**p = 0.009**
DBP night [mmHg]	61.34 ± 6.67	65.29 ± 7.87	67.86 ± 8.05	**p = 0.009**
DBP fall	17.46 ± 3.93	8.21 ± 5.32	-0.53 ± 5.35	**p < 0.001**
HF	8 (27.59%)	17 (32.69%)	11 (52.38%)	p = 0.188
HF-REF	0 (0.00%)	1 (1.92%)	0 (0.00%)	p > 0.999
HF-PEF	6 (20.69%)	15 (28.85%)	10 (47.62%)	p = 0.126
CKD	1 (3.70%)	9 (17.65%)	6 (30.00%)	**p = 0.045**
PAD	1 (4.00%)	3 (5.88%)	5 (26.32%)	**p = 0.031**
DCM	0 (0.00%)	2 (3.85%)	2 (10.00%)	p = 0.175
CAD	6 (20.69%)	8 (15.38%)	7 (35.00%)	p = 0.178
Post MI	2 (7.14%)	2 (3.85%)	3 (15.79%)	p = 0.212
Post CABG	0 (0.00%)	0 (0.00%)	1 (5.26%)	p = 0.192
OSAS	7 (25.00%)	13 (25.00%)	2 (9.09%)	p = 0.302
DM	4 (14.29%)	7 (13.73%)	2 (10.00%)	p > 0.999
Hyperlipidemia	14 (50.00%)	30 (57.69%)	13 (61.90%)	p = 0.720
COPD	0 (0.00%)	0 (0.00%)	1 (5.00%)	p = 0.213
AF	3 (10.34%)	15 (29.41%)	8 (36.36%)	p = 0.055
NT-proBNP [pg/mL]	332.40 ± 359.33	1490.38 ± 2507.92	1414.30 ± 2919.21	p = 0.650
CK [µg/L]	109.56 ± 38.57	92.66 ± 49.09	119.62 ± 65.23	p = 0.103
CK–MB [µg/L]	16.56 ± 5.09	18.75 ± 9.88	24.82 ± 16.82	**p = 0.030**

AF — Atrial Fibrillation; CAD — Coronary Artery Disease; CK — creatine kinase; CK—MB — CK MB isoenzyme; CKD — Chronic Kidney Disease; COPD — Chronic Obstructive Pulmonary Disease; DBP — Diastolic Blood Pressure; DCM — Dilated Cardiomyopathy; DM — Diabetes Mellitus; HF — Heart Failure; HF—PEF — HF with Preserved Ejection Fraction; HF—REF — HF with Reduced Ejection Fraction; NT-proBNP — N-terminal of the prohormone brain natriuretic peptide; OSAS — Obstructive Sleep Apnea Syndrome; p — overall p-value for 3-group comparison of means (ANOVA test) or distributions (Kruskal-Wallis test) for continuous variables and percentages ($\chi 2$ test) for categorical variables; PAD

— Peripheral Artery Disease; Post CABG — Post Coronary Artery Bypass Graft; Post MI — Post Myocardial Infarction; SBP — Systolic Blood Pressure.

Table 2. Echocardiography parameters

	Dipper	**Non–dipper**	**Reverse dipper**	
EF [%]	62.39 ± 4.69	61.35 ± 7.23	59.86 ± 6.23	p = 0.127
LVDd [mm]	50.31 ± 4.43	50.18 ± 5.88	50.10 ± 5.94	p = 0.700
RVDd [mm]	31.50 ± 4.53	32.73 ± 4.86	31.45 ± 6.11	p = 0.475
LAD [mm]	40.21 ± 4.80	43.75 ± 6.15	41.76 ± 5.22	**p = 0.026**
IVSd [mm]	10.59 ± 1.21	10.94 ± 1.77	10.11 ± 3.00	p = 0.676
PWDd [mm]	10.34 ± 1.34	10.76 ± 1.73	10.14 ± 1.53	p = 0.260
TAPSE	22.00 ± 4.24	23.00 ± 5.89	21.83 ± 2.99	p = 0.901
IVC [mm]	16.00 ± 4.58	20.50 ± 5.45	15.46 ± 7.98	p = 0.663
VHD:				
AR	7 (25.00%)	18 (35.29%)	6 (28.57%)	p = 0.632
AS	0 (0.00%)	2 (3.92%)	0 (0.00%)	p = 0.717
MR	20 (68.97%)	36 (70.59%)	18 (85.71%)	p = 0.370
MS	0 (0.00%)	0 (0.00%)	0 (0.00%)	NA
TR	10 (35.71%)	28 (54.90%)	12 (57.14%)	p = 0.236
TS	0 (0.00%)	2 (3.92%)	0 (0.00%)	p = 0.712
PR	0 (0.00%)	1 (1.96%)	1 (4.76%)	p = 0.454
PS	0 (0.00%)	0 (0.00%)	0 (0.00%)	NA

AR — aortic regurgitation; AS — aortic stenosis; ; EF — ejection fraction; IVC — inferior vena cava; IVSd— intraventricular septum end-diastolic diameter; LAD — left atrium diameter; LVDd — left ventricle end diastolic dimension; MR — mitral regurgitation; MS — mitral stenosis; p — overall p-value for 3-group comparison of means (ANOVA test) or distributions (Kruskal-Wallis test) for continuous variables and percentages ($\chi 2$ test) for categorical variables; PR — pulmonary regurgitation; PS — pulmonary stenosis; PWDd — posterior wall end-diastolic diameter; RVDd — right ventricle end diastolic dimension; TAPSE — tricuspid annular plane systolic excursion; TR — tricuspid regurgitation; TS — tricuspid stenosis; VHD — valvular heart disease.

Table 3. Valvular heart disease severity.

	Severity	**Dipper**	**Non-dipper**	**Reverse dipper**	
AR	0	21 (75.00%)	33 (64.71%)	15 (71.43%)	p = 0.869
	1	7 (25.00%)	17 (33.33%)	6 (28.57%)	
	2	0 (0.00%)	1 (1.96%)	0 (0.00%)	
AS	0	28 (100.00%)	49 (96.08%)	21 (100.00%)	p > 0.999

	Severity	Dipper	Non-dipper	Reverse dipper	
	1	0 (0.00%)	1 (1.96%)	0 (0.00%)	
	3	0 (0.00%)	1 (1.96%)	0 (0.00%)	
MR	0	9 (31.03%)	15 (29.41%)	3 (14.29%)	p = 0.422
	1	19 (65.52%)	28 (54.9%)	15 (71.43%)	
	2	1 (3.45%)	7 (13.73%)	2 (9.52%)	
	3	0 (0.00%)	1 (1.96%)	1 (4.76%)	
TS	0	28 (100.00%)	49 (96.08%)	21 (100.00%)	p = 0.712
	1	0 (0.00%)	2 (3.92%)	0 (0.00%)	
TR	0	18 (64.29%)	23 (45.10%)	9 (42.86%)	p = 0.280
	1	10 (35.71%)	23 (45.10%)	10 (47.62%)	
	2	0 (0.00%)	5 (9.80%)	2 (9.52%)	
PR	0	28 (100.00%)	50 (98.04%)	20 (95.24%)	p = 0.454
	1	0 (0.00%)	1 (1.96%)	1 (4.76%)	

AR — aortic regurgitation; AS — aortic stenosis; MR — mitral regurgitation; p — overall p-value for 3-group comparison of percentages ($\chi 2$ test) for categorical variables; PR — pulmonary regurgitation; TR — tricuspid regurgitation; TS — tricuspid stenosis.

Table 4. Drugs administered in study population

	Dipper	Non–dipper	Reverse dipper	
β-adrenolytics	15 (57.69%)	32 (69.57%)	19 (95.00%)	**p = 0.011**
α-adrenolytics	0 (0.00%)	6 (13.04%)	6 (30.00%)	**p = 0.009**
Ca-antagonists	9 (34.62%)	26 (56.52%)	9 (45.00%)	p = 0.196
ACE–i	16 (61.54%)	22 (47.83%)	13 (65.00%)	p = 0.388
ARB	3 (11.54%)	14 (30.43%)	6 (30.00%)	p = 0.164
Amiodarone	0 (0.00%)	1 (2.17%)	0 (0.00%)	p > 0.999
Digoxine	0 (0.00%)	2 (4.35%)	0 (0.00%)	p = 0.714
Aldosterone antagonists	0 (0.00%)	7 (15.22%)	1 (5.00%)	p = 0.073
Furosemide	0 (0.00%)	8 (17.39%)	2 (10.00%)	p = 0.057
Torasemide	1 (3.85%)	2 (4.35%)	7 (35.00%)	**p = 0.002**
Kaldyum	0 (0.00%)	6 (13.04%)	0 (0.00%)	**p = 0.047**

Kalipoz	4 (15.38%)	19 (41.3%)	12 (60.00%)	**p = 0.006**
Hydrochlorotiazide	1 (3.85%)	8 (17.02%)	0 (0.00%)	p = 0.065
Indapamide	5 (19.23%)	9 (19.57%)	3 (15.00%)	p = 0.941
ASA	7 (26.92%)	12 (26.09%)	8 (40.00%)	p = 0.524
VKA	3 (11.54%)	10 (21.74%)	3 (15.00%)	p = 0.593
LMWH	0 (0.00%)	1 (2.17%)	1 (5.00%)	p = 0.467
Statin	18 (69.23%)	30 (65.22%)	15 (75.00%)	p = 0.732

ACE-i — Angiotensin-Converting-Enzyme inhibitor; ARB — Angiotensin *II* receptor blocker; ASA — Acetylsalicylic Acid; LMWH — Low-Molecular-Weight Heparin; p — overall p-value for 3-group comparison of percentages ($\chi 2$ test) for categorical variables; VKA — Vitamin K Antagonist.

Table 5. Drugs doses in study population

	Doses	**Dipper**	**Non–dipper**	**Reverse dipper**	
β-adrenolytics	0	11 (44.00%)	14 (31.11%)	1 (5.26%)	p = 0.082
	1	9 (36.00%)	22 (48.89%)	12 (63.16%)	
	2	5 (20.00%)	7 (15.56%)	5 (26.32%)	
	3	0 (0.00%)	2 (4.44%)	1 (5.26%)	
ACE-i	0	10 (38.46%)	24 (52.17%)	7 (35.00%)	p = 0.073
	1	0 (0.00%)	5 (10.87%)	3 (15.00%)	
	2	6 (23.08%)	2 (4.35%)	4 (20.00%)	
	3	10 (38.46%)	15 (32.61%)	6 (30.00%)	
ARB	0	23 (88.46%)	32 (71.11%)	14 (70.00%)	p = 0.612
	1	1 (3.85%)	2 (4.44%)	1 (5.00%)	
	2	2 (7.69%)	7 (15.56%)	3 (15.00%)	
	3	0 (0.00%)	4 (8.89%)	2 (10.00%)	

1 — small doses; 2 — medium doses; 3 — high doses*;* ACE-i — Angiotensin-Converting-Enzyme inhibitor; ARB — Angiotensin *II* receptor blocker*;* p — overall p-value for 3-group comparison of percentages ($\chi 2$ test) for categorical variables.