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Influence of SARS-COV-2 infection on circadian behavior of blood pressure

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Abstract

This study aimed to investigate the relationship between blood pressure variability using ambulatory blood pressure monitoring (ABPM) and biological outcomes in non-previously hypertensive patients with mild-moderate COVID-19. A total of 20 patients hospitalized with COVID-19 were enrolled in this study. Patients were grouped according to the severity of COVID-19 into mild and moderate. Variables such as mean arterial pressure (MAP), systolic/diastolic (max/mean values), pulse weighted average, and day/night index were analyzed using ABPM. Patients with a drop of more than 10% in nocturnal blood pressure during the circadian rhythm are referred to as dippers, while patients with a smaller decrease are referred to as non-dippers. We compared the level of C-reactive protein (CRP), vitamin D, fasting blood glucose, ferritin, fibrinogen and investigated the relationship among the groups. Moreover, this study aimed to determine the impact of COVID-19 severity on blood pressure (BP) values and variability in 24-hour ABPM. Moderate COVID-19 patients with hypertension were older (61±12 *vs.* 43±10 years; P<0.001), had higher levels of CRP (29.4±9.2 *vs.* 10.3±3.2 mg/dL; P=0.009), ferritin (445±35 *vs.* 300±24 μg/l; P=0.032), fibrinogen (578±48 *vs.* 475±34 mg/dl; p=0.042) and higher non-dipper status (70% *vs.* 30%; P=0.013), than those with mild symptoms. There was a proportional relationship between COVID-19 severity and age, CRP levels, fibrinogen, ferritin and arterial blood pressure variability (day-night index-non dipper status) (all, P<0.05). Moderate COVID-19 patients without previous hypertension developed this disease and were significantly associated with greater non-dipper status and worsened biological outcomes. Advanced age and systemic inflammation are proportional to higher blood pressure and lower night/day index status. Additional attention is needed for COVID-19 patients with new-onset hypertension and high BP values with non-dipper status.

Keywords: COVID-19, dipper, non-dipper, hypertension.

Introduction

In the last two years, we have been inundated with the consequences of COVID-19, and, not surprisingly, all attention has focused on it. We soon learned about the strong relationship between cardiovascular involvement in COVID-19 and thrombotic

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disturbances. Moreover, COVID-19 was considered a viral systemic disorder that impacts the cardiovascular system that is able to unmask or worsen cardiovascular diseases. Coronavirus disease represents a challenge for healthcare systems worldwide. Even prior to the pandemic, we were not successfully controlling cardiovascular risk factors, and some of them, particularly obesity and sedentarism, were getting worse. Male sex, older age, and the coexistence of chronic comorbidities have been described as the most relevant conditions associated with a worse prognosis. Arrhythmias, myocarditis, pericarditis, and angina were common in patients with COVID-19.

In this study, we focused on patients admitted with COVID-19 in the second wave, which had a massive impact in Romania, without previously known cardiovascular disease, who developed high blood pressure. We also tried to seek correlation in these patients with unknown cardiovascular disease who developed systemic hypertension related to the severity of the COVID-19 disease.

Material and methods

We enrolled consecutive patients with mild and moderate disease symptoms in whom we documented high blood pressure during hospitalization for COVID-19. Thus, a total of 20 patients without previous cardiovascular disease hospitalized with COVID-19 were enrolled in this study. Patients were grouped according to the severity of COVID-19 into mild and moderate. Mean arterial pressure (MAP), systolic/diastolic (max/mean values), pulse weighted average, and day/night index were analyzed using ambulatory blood pressure monitoring (ABPM). A patient with a drop of more than 10% in nocturnal blood pressure during the circadian rhythm is referred to as a dipper, and a patient with a smaller decrease is referred to as a non-dipper.

We performed a standard electrocardiogram (ECG), and echocardiographic evaluation in all patients admitted to the COVID-19 positive department, and a more thorough echo evaluation was done after the quarantine period ended. All of them had normal morphologic and functional echo parameters, as expected in previous free-of-disease individuals.

We compared the levels of C-reactive protein (CRP), vitamin D, fasting blood glucose, ferritin, and fibrinogen and investigated the relationship among the groups and the results are shown in Tables 1, and 2; also, baseline group characteristics are shown in Table 3. On the other hand, this study aimed to determine the impact of COVID-19 severity on blood pressure (BP) values and variability in 24-hour ambulatory blood pressure monitoring (ABPM). Each of them was assessed according to our hospital's protocol in this peculiar epidemiologic setting: clinical examination, BP monitoring, standard ECG, thoracic CT scan and lab tests. After discharge from the COVID-19 positive department, 24h ambulatory blood pressure monitoring was performed in each case.

In normal conditions, there is a consensus that home BP measurements, or ABPM should be checked at or before initiation of therapy and then three months after starting therapy for monitoring and documentation of adequate BP control. In these patients, we performed ABPM after discharge and 3–6 months later. None of the patients were previously hypertensive or diabetic. ABPM was performed in recovered patients with normal

Table 1. COVID-19 patients with mild symptoms – lab results.

	Vitamin D (ng/ml)	Fasting blood glucose (mg/dl)	Ferritin (µg/l)	CRP (mg/L)	Fibrinogen (mg/dl)
1	40	112	66.5	3.4	286
2	44	107	85	1.3	291
3	34	98	170	11	391
4	38	76	160	6.9	279
5	40	116	93	1.8	311
6	21	78	195	2.4	280
7	26	86	107	1.4	276
8	50	74	175	1.9	270
9	52	82	201	5.7	305
10	25	89	102	7.5	420

Table 2. COVID-19 patients with moderate symptoms – lab results.

	Vitamin D (ng/ml)	Fasting blood glucose (mg/dl)	Ferritin (µg/l)	CRP (mg/L)	Fibrinogen (mg/dl)
1	27	101	401	2.6	370
2	25	78	289	3.8	390
3	37	98	280	4.1	496
4	30	103	470	6.9	550
5	19	140	360	3.7	625
6	24	93	205	12.7	630
7	18	137	290	10.5	490
8	25	93	404	5.4	355
9	12	156	327	8.7	567
10	26	104	421	7.4	501

saturation in oxygen in a friendly environment of their homes. We did not include patients with sleep apnea and other sleep disorder, long COVID syndrome, or those diagnosed with anxiety.

Statistical analysis was performed using GraphPad Software, Inc. To calculate the statistical significance, we performed comparisons between the two groups using the t-Student test and Fisher exact test. For variables with Gaussian distribution, the values are presented as mean±standard deviation, and the p-value was calculated using the unpaired t-Student test. Correlation has been evaluated with Pearson's test. Statistical significance was considered at $p<0.05$.

Table 3. Baseline group characteristics.

Variable	Moderate COVID-19 N=10	Mild COVID-19 N=10	P-value
Age, years (interval)	61 (45–82)	43 (35–71)	0.001
Sex, masculine, no. (%)	5 (50)	6 (60)	0.81
BMI, Kg/m²	27 (8.5)	28 (5.5)	0.83
Ferritin, ug/l/interval	445 (390–473)	300 (191–540)	0.032
CRP, mg/l/interval	29.4 (18–47)	10.3 (6–18)	0.009
Fibrinogen, mg/dL/interval	578 (467–694)	475 (290–538)	0.042
Vitamin D (ng/ml)	21 (11–32)	32 (9–39)	0.059
High glucose (without previous DM) (%)	6 (60)	4 (40)	0.153
Mild paroxysmal arrhythmias (atrial and ventricular) (%)	8 (80)	6 (60)	0.265
Pulse weighted average, bpm/interval	91 (80–127)	86 (71–98)	0.097
Systolic BP, mmHg/interval	146 (124–158)	141 (110–151)	0.105
Diastolic BP, mmHg/interval	88 (68–94)	84 (61–89)	0.153
Systolic BP max, mmHg/interval	181 (170–192)	178 (169–188)	0.243
Diastolic BP max, mmHg/interval	94 (85–99)	92 (81–98)	0.195
Circadian curve non-dipper, %	70	30	0.013

BMI – body mass index; BP – blood pressure; BPM – beats per minute; CRP – C-reactive protein; DM – diabetes mellitus.

Results and discussion

Moderate COVID-19 patients with hypertension were older (71±12 *vs.* 53±17 years; P<0.001), had higher levels of C-reactive protein (CRP) (; P=0.009), ferritin (300±24 *vs.* 445±35 µg/l; P=0.032), fibrinogen (475±34 *vs.* 578±48 mg/dl; p=0.042) and higher non-dipper status (62.6% *vs.* 32.9%; P=0.013), than those with mild symptoms. There was a proportional relationship between COVID-19 severity and age, levels of CRP, fibrinogen, ferritin and arterial blood pressure variability (day/night index) (all, P<0.05).

New-onset hypertension was observed in all patients at the end of the followed period. These findings suggest that COVID-19 increases systolic and diastolic BP and may cause new-onset hypertension. Large studies are warranted in the near future to affirm the link between hypertension and COVID-19 severity and to achieve better pharmacological management of COVID-19 patients with hypertension. Detecting and adequately treating hypertension remains an important goal. Prognosis depends on blood pressure control, and complications may occur because it should not be ignored that, although initially asymptomatic, hypertension is a progressive disease.

According to our data, non-dipper status correlates with high CRP, ferritin, and fibrinogen levels as markers of the inflammatory impact.

In order to obtain control of blood pressure, patients receive beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers if needed. We did not find any significant statistical differences regarding the treatment received for COVID-19. We appreciate the hemodynamic control in patients with normal oxygen saturation, free of systemic COVID-19 symptoms like fever, headache, nausea, and dizziness.

Early reports suggested that hypertension might represent a risk factor for susceptibility to SARS-CoV-2 infection, a more severe course of COVID-19, and increased COVID-19-related deaths. Nevertheless, the independent role of hypertension remains under debate since hypertension is often associated with older age and other cardiovascular risk factors in the general population, which may also contribute to the SARS-Cov-2 infection. Moreover, the role of antihypertensive drugs, primarily angiotensin-converting inhibitors and angiotensin receptor blockers (ARBs), in COVID-19 development and outcome appeared controversial in the early days of the pandemic. Indeed, preclinical studies using these classes of drugs have suggested a potential up-regulation of angiotensin-converting-enzyme 2 (ACE2), the key binding receptor promoting cell entry of SARS-CoV-2 in the organism. Renin-angiotensin system (RAS) blockers may potentially up-regulate ACE2. Hence, it has been initially hypothesized that these agents might contribute to a higher risk of SARS-CoV-2 infection and a progressive course of COVID-19. However, the early hypothesis describing exacerbation of the disease following the use of antihypertensive medications such as ACEi and ARBs was not clinically proven. To date, there are no clinical data regarding ACEi or ARBs involvement in either improvement or worsening of COVID-19 cases or as a risk factor for COVID-19 infection. Also, there is no substantial evidence to support the discontinuation of ACEi or ARBs or alternate pharmacotherapy to manage hypertension in patients with COVID-19. Therefore, more and more data were gathered to substantiate the relationship between cardiovascular disease, especially in hypertensive patients, circadian behavior, treatment, changing dosage, evolution and prognosis of both hypertension and COVID-19 disease.

Conclusion

Moderate COVID-19 patients without previous hypertension developed this disease and were significantly associated with greater non-dipper status and worsened biological outcomes. Advanced age and systemic inflammation are proportional to higher inflammatory markers and non-dipper status. Additional attention is needed for COVID-19 patients with new onset hypertension and non-dipper status.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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