DOI: 10.20514/2226-6704-2020-10-1-61-67

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Status of Cardiovascular System in Patients with Chronic Obstructive Pulmonary Disease According to the Results of a Pulse Wave Contour Analysis

Abstract

The combination of chronic obstructive pulmonary disease and cardiovascular disease is an urgent public health problem that determines more severe disease course and poor prognosis for the patient. **The objective of the study** was to evaluate the cardiovascular system state using applanation tonometry in patients with chronic obstructive pulmonary disease depending on the severity of bronchial obstruction. **Material and methods.** Applanation tonometry was performed in 60 patients (56 men, age 63.5 [IQR 59; 70] years) with chronic obstructive pulmonary disease to assess central hemodynamic parameters. The severity of obstructive disorders was determined by spirometry after bronchodilator use. **Results.** In case of progression of bronchial obstruction, a decrease in parameters characterizing coronary blood flow was detected, mainly determined by an increase in heart rate and by a decrease in the duration of diastole. In addition, higher values of augmentation pressure corrected to heart rate of 75 bpm, pulse pressure, central pulse height at the point of maximum rise of direct pulse wave were determined in patients with more severe bronchial obstruction. These parameters indicate higher values of arterial stiffness in this group of patients. **Conclusion.** In patients with chronic obstructive pulmonary disease and high values of bronchial obstruction, there is an imbalance of myocardial load and actual blood supply, and increased arterial stiffness with impaired aortic damping function, which contributes to the development of cardiovascular disease in this group of patients.

Key words: *chronic obstructive pulmonary disease, spirometry, pulse waveform contour analysis, applanation tonometry, central hemodynamics, subendocardial viability ratio*

Conflict of interests

The authors declare no conflict of interests.

Sources of funding

The authors declare no funding for this study.

Article received on 18.11.2019

Accepted for publication on 15.01.2020

For citation: Punin D. A., Milyagin V. A. Status of Cardiovascular System in Patients with Chronic Obstructive Pulmonary Disease According to the Results of a Pulse Wave Contour Analysis. The Russian Archives of Internal Medicine. 2020; 10(1): 61-67. DOI: 10.20514/2226-6704-2020-10-1-61-67

Aix_{75} — augmentation index corrected to HR of 75 beats per minute; C_AP_{75} — augmentation pressure corrected to HR of 75 beats per minute; C_DPTI — central diastolic pressure time index; C_MPD — central mean pressure in diastole; C_MPS — central mean pressure in systole; C_P_{T1h} — central pulse height at the point of maximum rise of direct pulse wave;

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C_SEVR — central subendocardial viability ratio; C_TTI — central tension time index; COPD — chronic obstructive pulmonary disease; CVD — cardiovascular disease; DBP — diastolic blood pressure; DBP_c — central diastolic blood pressure; DD — duration of diastole; $DD_{\%}$ — duration of diastole relative to the period of cardiac cycle; ED — duration of systole; FEV1 — forced expiratory volume in the first second; HR — heart rate; PBP — pulse blood pressure; PBPc — central pulse blood pressure; P_MAX_DPDT — maximum rise rate of peripheral pulse wave; $SatO_2$ — blood saturation; SBP — systolic blood pressure; SBPc — central systolic blood pressure; VC — vital capacity of lungs

Introduction

Today, much attention is paid to the comorbidity of chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVD). This combination of nosologies is an urgent public health problem due to the high prevalence of CVD among patients with COPD, its complex therapy and the high mortality rate of such patients. According to the World Health Organization (WHO), mortality from COPD is ranked 3rd, and according to the TORCH (2007) study, CVD is the cause of death in one in four patients suffering from COPD [1].
A retrospective study of a large group of patients (more than 900 thousand people), conducted by Cazzola M., et al. (2012), showed higher risks of CVD in patients with obstructive diseases such as bronchial asthma and COPD [2]. In addition, a twice as high risk of CVD was proven for patients with COPD in the presence of severe bronchial obstruction [3].
Assessment of the state of the cardiovascular system in patients with COPD is relevant for the detection of CVD and assignment of adequate treatment. One of the state-of-the-art methods of cardiovascular system examination is pulse waveform contour analysis, which allows assessing the levels of central blood pressure and arterial stiffness parameters and revealing an imbalance between the myocardial load and coronary perfusion — parameters that have an effect on the prognosis for the health and life of a comorbid patient [4].

Objective: to assess the state of the cardiovascular system in patients with COPD based on the results of a pulse waveform contour analysis depending on the severity of bronchial obstruction.

Materials and Methods

We examined 60 patients (56 men and 4 women, 63.5 [IQR 59; 70] years) who had been diagnosed with COPD in the pulmonology departments of the Regional State Budgetary Healthcare Institution «Smolensk Regional Clinical Hospital» and the Regional State Budgetary Healthcare Institution «Clinical hospital № 1».
Criteria for the inclusion of patients in this study were the following: confirmed diagnosis of COPD, forced expiratory volume in the first second less than 70%, modified Tiffeneau index less than 0.7.
Exclusion criteria were as follows: heart failure of functional class II-IV, permanent atrial fibrillation, lack of patient cooperation during spirometry.
To evaluate pulmonary function, all patients underwent spirometry 20 minutes after taking salbutamol at the dose of 400 µg. Forced expiratory volume in the first second (FEV_1), vital lung capacity (VC) and modified Tiffeneau index (FEV_1/FVC) were assessed.
Parameters of central hemodynamics were found using applanation tonometry (SphygmoCor). The following parameters were assessed: heart rate (HR), levels of peripheral and central systolic, diastolic and pulse blood pressure (SBP, DBP, PBP, SBPc, DBPc, PBPc), central mean pressure in systole and diastole (C_MPS, C_MPD), maximum rise rate of peripheral pulse wave (P_MAX_DPDT), central pulse height at the point of maximum rise of direct (antegrade) pulse wave (C_P_{T1h}), pressure and aortic augmentation index corrected to the heart rate 75 beats per minute (C_AP_{75}, Aix_{75}), diastole duration (DD), systole duration (ED, ejection duration), ratio of diastole duration to cardiac cycle duration, as a percentage ($DD_{\%}$). The P_MAX_DPDT parameter, according to the literature, reflects myocardial contractility [5]. C_AP_{75} and Aix_{75} were used as parameters of the stiffness of the arterial bed [6]. To assess the load on the myocardium, we used the Central Tension Time Index (C_TTI), which was defined as the area under the systolic part of the pulse curve [7]. The area under the diastolic part of the pulse curve, or Central Diastolic Pressure Time Index

(C_DPTI), was used as a parameter for subendocardial perfusion. The ratio of C_DPTI to C_TTI expressed as a percentage and referred to as the Central Subendocardial Viability Ratio (C_SEVR) characterized the ratio of coronary blood flow to the load on the myocardium (myocardial oxygen demand) [8]. Applanation tonometry was performed in the morning before taking antihypertensive drugs and after the time of action of taken bronchodilators.

Patients were divided into 3 equal groups of 20 people relative to FEV_1 tertiles. Group 1 included patients with FEV_1 less than the first tertile, which amounted to 43.10%; group 3 included patients with FEV_1 more than the second tertile, which equals 56.37%; group 2 included patients with FEV_1 between the first and second tertile.

Data are presented as Me (IQR), where Me is the median, and IQR is the interquartile range: 25th percentile — 75th percentile. To compare hemodynamic parameters in the studied groups, the Kruskal-Wallis test was used. For posteriori pairwise comparisons, Dunn's test was used. For correlation analysis, the Spearman rank correlation coefficient was used. Statistical hypotheses were checked at a significance level of $p<0.05$. Statistical processing was carried out using MS Office Excel 2007 and Statistica 10 software packages.

Results

Characteristics of study group: 56 men and 4 women aged 63.5 [59; 70] years; height — 172 [167; 175.3] cm; body weight — 69.5 [60; 83.3] kg; body mass index (BMI) — 24.4 [21.3; 26.1] kg/m^2; tobacco exposure — 50 [35; 60] packs/years; severity of dyspnea according to mMRC — 2 [1; 2]; severity of symptoms according to the results of COPD Assessment Test (COPD Assessment Test, CAT test) — 19.5 [14; 26] points. Blood saturation ($SatO_2$) at rest was 95 [93; 96] %. According to the history and examination results, hypertension was revealed in 43 patients (71.7%). Parameters of pulmonary function and applanation tonometry are shown in Tables 1 and 2.

Groups of patients with bronchial obstruction of different severity did not differ in age, anthropometric parameters, and tobacco exposure. Groups were comparable in the number of patients with hypertension (15 (75%) patients in group 1, 14 (70%) — in groups 2 and 3). Characteristics of groups of patients with COPD and different severity of bronchial obstruction are shown in Table 3. Hemodynamic parameters in three groups of patients obtained by dividing patients by the level of FEV_1 are presented in Table 4.

Table 1. *Spirometry parameters in patients with chronic obstructive pulmonary disease (n = 60) after the use of bronchodilator*

Parameter	Value, Me (IQR)
FEV_1, L	1.5 [1.1; 1.8]
FEV_1, %	53.1 [38.5; 58.5]
FEV_1/FVC, %	46 [37.3; 52.7]
VC, L	3.5 [3; 4.4]
VC, %	90.3 [80.9; 107.1]

Table 2. *Hemodynamic parameters in patients with chronic obstructive pulmonary disease (n = 60)*

Parameter	Value, Me (IQR)
Peripheral hemodynamic parameters	
SBP, mm Hg	132 [120,8; 145]
DBP, mm Hg	83,5 [75; 90]
PBP, mm Hg	47 [41; 60]
HR, bpm	75 [69; 85]
P_MAX_DPDT, mm Hg/s	729 [610; 978.3]
Central hemodynamic parameters	
SBP_c, mm Hg	121 [110; 130.3]
DBP_c, mm Hg	85 [76; 91]
PBP_c, mm Hg	35.5 [31; 45.3]
C_MPS, mm Hg	112.5 [100.8; 120]
C_MPD, mm Hg	95.5 [85; 102.3]
C_P_{T1h}, mm Hg	26 [23; 34]
C_AP_{75}, mm Hg	9.5 [6; 12]
Aix_{75}, %	25 [19; 30.3]
ED, ms	278 [258.8; 299]
DD, ms	522.5 [454.8; 587.3]
$DD_{\%}$, %	64 [62; 67]
C_TTI, mm Hg*s/min	2,361 [2,054; 2,660]
C_DPTI, mm Hg*s/min	3,701 [3,328; 4,035]
C_SEVR, %	156 [138.8; 179]

Table 3. *Characteristics of groups of patients with chronic obstructive pulmonary disease and different severity of bronchial obstruction*

Parameter	Group 1 (FEV_1<43.10%) n = 20	Group 2 (FEV_1 = 43.10–56.37%) n = 20	Group 3 (FEV_1>56.37%) n = 20	H	p-value
Age, years	69 [62.3; 71]	61.5 [58; 67.3]	63.5 [61; 70]	5.11	0.0777
Height, cm	170.5 [168.8; 175]	170.5 [165.5; 178]	172 [169.3; 175]	0.21	0.8994
Weight, kg	62 [57.8; 76]	72 [66.5; 92.3]	75 [63; 84.3]	4.41	0.1105
BMI, kg/m^2	21.8 [20.3; 24.5]	24.6 [21.7; 30]	25.1 [21.9; 26.1]	4.77	0.0922
Tobacco exposure, packs/years	54 [33.8; 67.1]	47.5 [33.8; 51.3]	45 [41.5; 55.3]	1.75	0.4167
$SatO_2$, %	93 [92; 94.3]	95 [94.8; 96.3]	95 [95; 96]	9.71*	0.0078

* — difference is significant between groups 1 and 2, 1 and 3 at p<0.05

Table 4. *Applanation tonometry parameters in patients with chronic obstructive pulmonary disease and different severity of bronchial obstruction*

Parameter	Group 1 (FEV_1<43.10%) n = 20	Group 2 (FEV_1 = 43.10–56.37%) n = 20	Group 3 (FEV_1 >56.37%) n = 20	H	p-value
		Peripheral hemodynamic parameters			
SBP, mm Hg	138 [120; 147.8]	135 [120.8; 145.5]	132 [121.8; 137.8]	0.70	0.7032
DBP, mm Hg	79 [70; 85.8]	86 [80; 91.8]	85 [77.3; 92.3]	5.04	0.0804
PBP, mm Hg	60 [47.5; 70.5]	44.5 [40.8; 54.3]	44.5 [40; 51.8]	7.37	0.0251
HR, bpm	90 [76; 95.3]	71 [68.3; 78]	70 [67.8; 76.8]	19.69*	0.0001
P_MAX_DPDT, mm Hg/s	996 [674.8; 1,188]	641 [578.5; 769.5]	702.5 [620.3; 837.5]	8.73**	0.0127
		Central hemodynamic parameters			
SBP_c, mm Hg	118.5 [108; 132]	123.5 [114.8; 137.5]	120 [112.8; 126.3]	0.67	0.7168
DBP_c, mm Hg	80 [71; 87.3]	87.5 [81; 92.8]	86 [78.3; 93.3]	4.19	0.1232
PBP_c, mm Hg	42 [34.8; 50]	33.5 [30.8; 42.3]	33.5 [29.5; 40]	4.84	0.0890
C_MPS, mm Hg	108 [97.5; 120.5]	114.5 [106; 124.3]	111.5 [102.8; 116.3]	0.99	0.6098
C_MPD, mm Hg	92 [82.3; 99.3]	97.5 [89.8; 103.5]	96.5 [86.5; 102.5]	2.56	0.2787
C_P_{T1h}, mm Hg	33.5 [25.5; 37.8]	25 [22.8; 31.3]	25.5 [22; 29.5]	6.41	0.0406
C_AP_{75}, mm Hg	11.5 [9.8; 16]	8 [6; 11]	8.5 [4.8; 11]	7.90***	0.0193
Aix_{75}, %	28 [23.8; 32]	22 [19; 29.3]	24 [17; 30.3]	2.31	0.3143
ED, ms	273.5 [250.8; 291.8]	290.5 [277.5; 304.3]	272 [259.5; 287]	3.36	0.1865
DD, ms	392.5 [371.5; 502.5]	554 [482; 593.3]	571 [514.8; 609]	21.95*	<0.0001
$DD_{\%}$, %	60 [57; 63.3]	65.5 [63.8; 67.3]	67 [64; 69.3]	26.65*	<0.0001
C_TTI, mm Hg*s/min	2,472 [2,272; 2,934]	2,372 [2,005; 2,660]	2,168 [1,976; 2,428]	7.54***	0.0231
C_DPTI, mm Hg*s/min	3,267 [3,020; 3,726]	3,793 [3,625; 4,063]	3,778 [3,494; 4,130]	11.16*	0.0038
C_SEVR, %	135 [111.5; 142.8]	165 [147; 180.5]	175 [162.3; 190.5]	29.71*	<0.0001

Note: * — difference is significant between groups 1 and 2, 1 and 3 at p<0.05; ** — difference is significant between groups 1 and 2 at p<0.05; *** — difference is significant between groups 1 and 3 at p<0.05

Patients with the most severe bronchial obstruction (group 1) showed the lowest coronary blood flow efficiency value (C_SEVR) among all three groups due to both a decreased parameter (C_DPTI) characterizing the level of pressure in coronary arteries throughout the diastole and the duration of coronary blood flow, and an increased myocardial load (C_TTI). Decrease in coronary blood flow in group 1 was determined mainly by absolute (DD) and relative ($DD_{\%}$) decrease in diastole duration due to increased HR. In addition, the decreased area of the diastolic part of the central pulse wave and an increased area of the systolic part of the pulse wave occurred due to the earlier return of reflected waves generated at the periphery to the heart, as a result of increased rigidity of main arteries. This is evidenced by an increase in augmentation pressure of central systolic pressure corrected to HR of 75 beats per minute in patients with a more significant impairment of bronchial obstruction. However, no statistically significant differences in the levels of central blood pressure were found. In case of more severe bronchial obstruction, an increased rate of maximum rise of the peripheral pulse wave (P_MAX_DPDT) and of the pressure at the point of maximum rise of the central pulse wave (C_P_{T1h}) was observed. An increase in these parameters and in the peripheral pulse pressure indicates the impaired damping function of the aorta as a result of its increased stiffness in the group of patients with the most severe bronchial obstruction.

Moderate correlation was found between FEV_1 and C_SEVR, FEV_1 and diastole duration, between FEV_1 and HR, between FEV_1 and saturation, between saturation and HR.

Graphical representation of the relationships found is shown in Figures 1-5.

Discussion

Analysis of the relationship between parameters of applanation tonometry and severity of obstructive ventilation disorders indicates increasing discrepancy between actual myocardial blood supply and myocardial load in patients with COPD with disease progression. Pathophysiological processes that develop in the presence of bronchial obstruction can explain deterioration of myocardial blood supply as FEV1 decreases. There is evidence of decreased myocardial contractility in patients with severe and extremely severe COPD, as well as the negative effect of hypoxia and persistent inflammation on myocardial contractility [9]. Decrease in myocardial blood supply seems to be based on HR increase, which rises with the decrease in FEV_1; it is indirectly confirmed by finding correlation between these parameters. On the one hand, HR increase is a compensatory mechanism for supporting tissue perfusion, and is adaptive and protective in case of systolic myocardial dysfunction. On the other hand, specific myocardial blood supply in diastole leads to the fact that, as HR increases, the time for blood perfusion through the coronary arteries is reduced, thereby negatively affecting blood supply to myocardium [10, 11]. However, other mechanisms of the mutual influence of these parameters on the reduction of coronary blood flow cannot be excluded. For example, M. A. Makarova, et al. (2013) demonstrated the effect of hypoxia on the development of endothelial dysfunction in patients with COPD [12]. Impaired endothelial function leads to an increased risk of blood clots in the arterial bed, and to an imbalance of vasoconstrictor and vasodilation mechanisms [13]. In addition, there is evidence of a relationship between persistent inflammation and increased heart rate [14]. Taking into account the age of patients, we can assume an increase in the frequency of cardiac catastrophes in patients with COPD as the ventilation function of lungs decreases; it compares favorably to the results obtained by Canadian researchers (Sin D., et al., 2005), which showed a higher risk of coronary events in patients with COPD with underlying progression of bronchial obstruction [15].

Higher values of C_AP_{75} and pulse pressure in the group of patients with significant bronchial obstruction indicate a higher degree of arterial stiffness. High values of P_MAX_DPDT in this group of patients are probably determined not by increased cardiac output, but by the impaired damping function of rigid aortic wall. In this case, there is no decrease in cardiac output due to the expansion of the aorta in systole; all energy reaches the periphery and leads to a rapid rise of the pulse wave. Impaired damping of the pulse wave is also confirmed by the increased height of the central pulse at the point of maximum rise of the direct pulse wave (C_P_{T1h}).

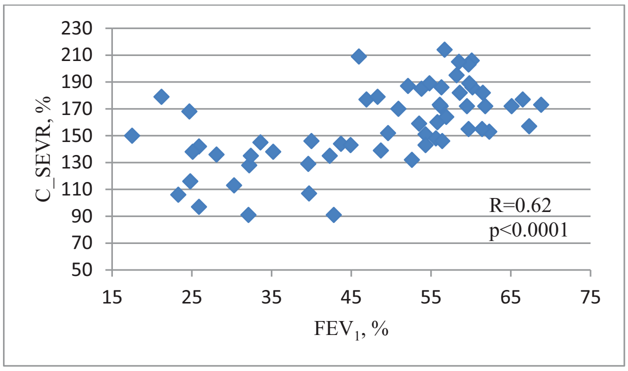

Figure 1. *Scatter plot of C_SEVR relative to FEV_1*

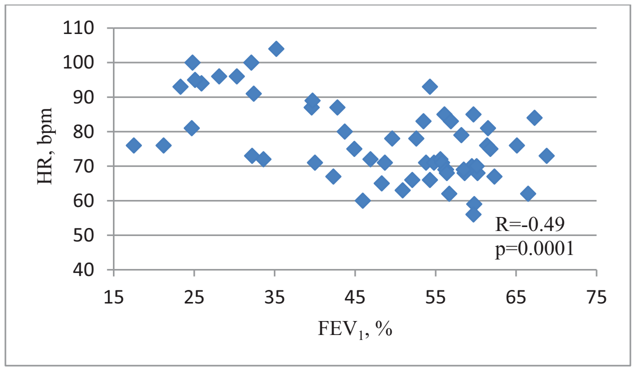

Figure 2. *Scatter plot of HR relative to FEV_1*

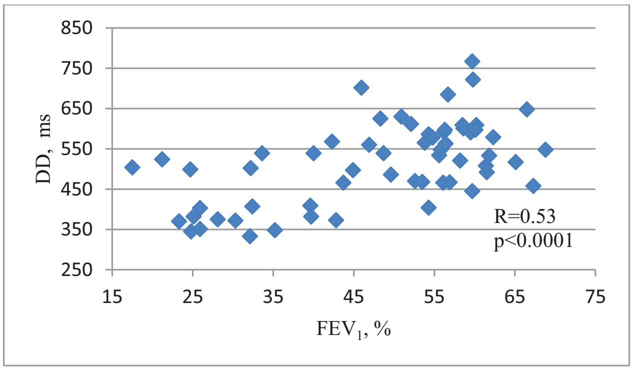

Figure 3. *Scatter plot of DD relative to FEV_1*

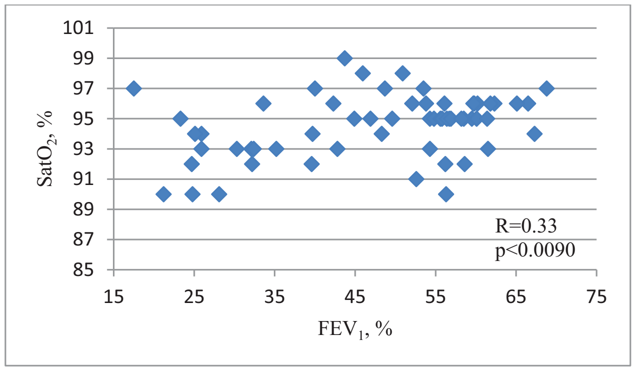

Figure 4. *Scatter plot of $SatO_2$ relative to FEV_1*

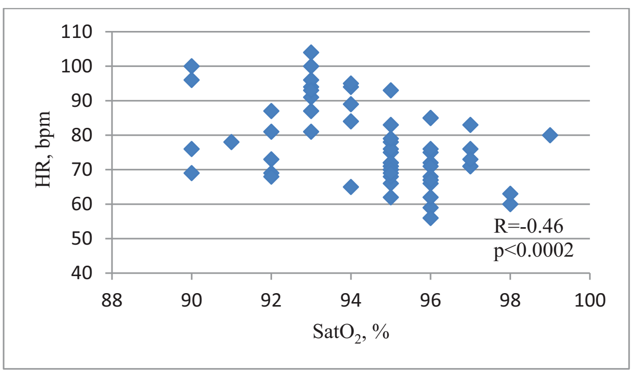

Figure 5. *Scatter plot of HR relative to $SatO_2$*

It was proven that increased vascular rigidity that led to an increase in cardiac output energy has a damaging effect on target organs and is a recognized risk factor for the development of cardiovascular events [4]; it can partly explain the high prevalence of cardiovascular diseases in patients with COPD.

Conclusions

In patients with severe obstruction, increased arterial stiffness with impaired aortic damping function is observed; it results in impaired transfer of systole energy to diastole, which leads to an increase in the pressure of augmentation of the central pulse wave (C_AP_{75}), the height of central pulse at the point of maximum rise of the antegrade pulse wave (C_P_{T1h}), the maximum rise rate of the peripheral pulse wave (P_MAX_DPDT).

In patients with COPD, as bronchial obstruction increases, an imbalance in the ratio between myocardial load and actual blood supply increases, which can also contribute to the development of cardiovascular pathology in patients with COPD.

Author Contribution

D. A. Punin (ORCID ID: https://orcid.org/0000-0003-3424-4540): study design development, conducting research (spirometry, applanation tonometry), statistical processing, analysis and interpretation of the data, making up the conclusions, manuscript preparation

V. A. Milyagin (ORCID ID: https://orcid.org/0000-0003-0383-1072): a systematic review of the problem and the choice of research direction, study design development, data analysis, making up the conclusions

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