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# Features of Spectral Estimates of the Photoplethysmographic Waveform Variability in Patients with Aortic Stenosis

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**A well-known method for assessing the autonomic status of patients in clinical practice is the use of spectral estimates of finger's photoplethysmographic waveform variability (PPGV). However, these estimates have not been studied in patients with aortic stenosis. Therefore, this study aimed to identify in the PPGV spectrum the markers of autonomic dysfunction specific for patients with aortic stenosis. The study included 34 patients with aortic stenosis at the age of 54 (43, 67) years and 30 healthy subjects at the age of 34 (31, 36) years (data presented as median with lower and upper quartiles). The following spectral estimates of PPGV were evaluated: LF% (low-frequency band, 0.04–0.15 Hz, in the percentage of total spectral power, 0–0.4 Hz), HF% (high-frequency band, 0.15–0.4 Hz, in the percentage of total spectral power, 0–0.4 Hz), and LF/HF ratio. The study revealed the statistically significant ($p<0.05$) differences in HF% and LF% values in patients with aortic valve disease compared with healthy people. LF% was increased by 2-4 times in group of patients with aortic stenosis, while HF% was increased by 1.2-7 times. The difference between the groups at LF/HF ratio was statistically insignificant. Patients with aortic stenosis are characterized by higher LF% and HF% values, relative to healthy people of comparable age.**

**Keywords:** Aortic Stenosis; Photoplethysmogram; Spectral Analysis.

Currently, aortic valve failure makes 43% of all cases of lesions of the heart valve apparatus[1], with almost half of them being aortic stenosis[2]. The issue of early diagnosis of the disease in asymptomatic patients is quite acute due to the widespread prevalence of aortic valve pathology, prolonged asymptomatic course, high disability, and mortality[2, 3].

Earlier it was shown that destruction of autonomic control of the cardiovascular system is observed with the development of aortic valve failure (stenosis and/or cardiac decompensation)[4]. To date, there exist and are actively used methods for assessing the functioning of autonomic regulation, such as the analysis of heart rate variability (HRV) and the assessment of spectral parameters of photoplethysmographic waveform variability (PPGV)[5, 6]. Clinical practice includes the use of HRV estimates for assessing the risks of developing cardiovascular pathology[5, 7], sudden cardiac death[8], assessing the quality of patient treatment (including cardiac surgery)[9, 10], as well as predicting the risk of developing cardiovascular complications in patients with previous cardiac diseases[11-14]. We have previously described the features of autonomic regulation in men with arterial hypertension and ischemic heart disease using spectral analysis of PPGV in these groups of patients in comparison with healthy people[15]. In the course of the study, significant differences were revealed in the frequency components of the PPGV spectrum, which characterize the autonomic imbalance. Nevertheless, approaches to the diagnosis of autonomic dysfunction in patients with aortic valve defects, in particular, aortic stenosis, have not been adequately studied.

This study aimed to identify autonomic dysfunction markers in the PPGV spectrum that are specific for patients with aortic stenosis.

## MATERIAL AND METHODS

**Patients**

The study was of a cohort nature. The study group included 34 patients with stenosis of the aortic valve, who were planned for surgical intervention – prosthetics of this valve. The inclusion criteria were male sex (to exclude gender differences) and age over 18 years. The exclusion criteria were coronary heart disease, heart rate abnormalities (atrial fibrillation, frequent extrasystole, etc.) impeding the analysis of PPGV, endocrine disorders, peripheral microcirculation disorders, chronic gastrointestinal diseases (hepatitis, gastric ulcer, duodenum disease, and cholecystitis), chronic renal diseases and exacerbations of other chronic diseases, and obesity (body mass index more than 30 kg/m$^2$). Adherence to inclusion and exclusion criteria was evaluated during clinical investigation.

The study derives from the clinical practice of the Bakulev Scientific Center for Cardiovascular Surgery (Moscow, Russia).

The control group included 30 healthy volunteers.

Detailed clinical characteristics of the groups are presented in Table 1.

**Ethical approval**

Design of this study was approved by the Ethics Committee of the Saratov State Medical University (Saratov, Russia) in 2019. Informed consent was obtained from all participants. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Signal recording**

The variability of blood filling in the distal blood stream was recorded using a photoplethysmographic sensor from the distal phalanx of the left first finger. Signal data registration for all subjects was carried out using a multichannel polyrecorder (electroencephalograph analyzer EEGA-21/26 "Encephalan-131-03", model 10 with a set of standard sensors, NPKF "Medicom MTD", Russia). All signals were sampled at 250 samples per second and digitized at 14 bits. The time of the signal recording was always the same – morning hours (8.00-11.00), which excluded the influence of daily fluctuations in the autonomic regulation of the cardiovascular system. The recording was performed in a horizontal position of the subject. The duration of each recording was 5 minutes. Before the recording, the subjects were in a horizontal position, at rest for 10 minutes.

**Signal processing**

The power spectra of PPGV were calculated directly from the photoplethysmographic signal based on a technique similar to our previous work (see "Signal processing" section in [15]). We calculated for these spectra the following spectral estimates of PPGV: LF% (low-frequency band, 0.04–0.15 Hz, in the percentage of total spectral power, 0–0.4 Hz), HF% (high-frequency band, 0.15– 0.4 Hz, in the percentage of total spectral power, 0–0.4 Hz), and LF/HF ratio.

**Statistical analysis**

Continuous variables are reported as medians with lower and upper quartiles – Me (LQ, UQ). Binary variables are presented as frequencies and percentages – n (%). We applied the Shapiro–Wilk test to check whether the values were normally distributed. Since most variables were not normally distributed, further analysis was carried out using non-parametric statistical methods. We used the Mann–Whitney test to compare the values of continuous variables between the subjects' groups. We applied the Chi-square (÷2) test to compare the binary variables and to compute the significance level for the difference between two proportions. The results were considered statistically significant if the p-value was less than 0.05.

## RESULTS

The study revealed the statistically significant ($p<0.05$) differences in values among two parameters (HF% and LF%) in patients with aortic valve disease compared with healthy people. The relative values (LF%) of low-frequency oscillations were increased by 2-4 times in group of patients with aortic stenosis, while the contribution

**Table 1.** Clinical characteristics of the groups

| Estimate | Patients with aortic stenosis (n=34) | Healthy subjects (n=30) | P-level |
|---|---|---|---|
| Age | 54 (43, 67) | 49 (43, 56) | 0.656 |
| Body mass index, kg/m$^2$ | 28.0 (25.5, 30.4) | 24.2 (22.8, 25.5) | <0.001 |
| BSA, m$^2$ | 2.02 (1.95, 2.13) | 1.92 (1.87, 2.16) | 0.341 |
| Prior myocardial infarction | 0 | 0 | — |
| Angina pectoris | 0 | 0 | — |
| Prior stroke | 2 (5.9) | 0 | 0.181 |
| Prior atrial fibrillation | 2 (5.9) | 0 | 0.181 |
| Hypertension | 16 (47.1) | 0 | <0.001 |
| Smoking | 5 (14.7) | 3 (10.0) | 0.573 |
| Diabetes | 0 | 0 | — |
| COPD | 1 (2.9) | 0 | 0.351 |
| Creatinine, mg/dL | 1.01 (0.89, 1.13) | 0.78 (0.74, 0.81) | 0.002 |
| Prior PCI | 0 | 0 | — |
| Systolic blood pressure, mmHg | 125 (120, 130) | 120 (110, 125) | 0.741 |
| Diastolic blood pressure, mmHg | 74 (70, 80) | 75 (70, 80) | 0.922 |
| Blood glucose, mmol/L | 5.3 (4.9, 5.7) | 5.2 (4.8, 5.5) | 0.425 |
| White blood cells, 10*9/L | 6.9 (5.7, 7.7) | 6.8 (5.8, 7.9) | 0.488 |
| Hematocrit, % | 42 (40, 44) | 43 (41, 44) | 0.812 |
| EDV, ml | 141 (112, 187) | 123 (98, 133) | <0.001 |
| EDV / BSA, ml/m$^2$ | 70.3 (58.0, 91.7) | 67.8 (55.3, 77.6) | 0.272 |
| End-systolic volume, ml | 47 (36, 62) | 42 (34, 55) | 0.214 |
| End-systolic diameter, cm | 3.5 (3.1, 3.9) | 3.3 (2.8, 3.5) | 0.021 |
| EDD, cm | 5.4 (5.0, 6.0) | 4.6 (4.1, 5.0) | <0.001 |
| EDD / BSA, cm/m$^2$ | 2.7 (2.4, 3.0) | 2.5 (2.3, 3.1) | 0.874 |
| LVEF, % | 63 (59, 68) | 65 (61, 69) | 0.612 |
| ACE inhibitors | 25 (73.5) | 0 | <0.001 |
| Beta-blockers | 22 (64.7) | 0 | <0.001 |
| Statins | 8 (23.5) | 0 | 0.006 |
| Diuretics | 27 (79.4) | 0 | <0.001 |
| Calcium antagonists | 3 (8.8) | 0 | 0.101 |

Continuous variables are presented as median with lower and upper quartiles – Me (LQ, UQ). Binary variables are presented as frequencies and percentages – n (%).

BSA, body surface area; PCI, percutaneous coronary intervention; COPD, cronic obstructive pulmonary disease; EDV, end-diastolic volume; EDD, end-diastolic diameter; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme.

of relative high-frequency (HF%) oscillations increased by 1.2-7 times. The interquartile range of the values of the LF/HF index was larger in healthy group, but the differences between the groups were statistically insignificant (Table 2).

## DISCUSSION

According to our study, in patients with stenosis of the aortic valve requiring surgical correction, the contribution of low-frequency oscillations (to a greater extent characterizing sympathetic effects on peripheral vascular resistance[16]) and high-frequency oscillations (associated to a greater extent with respiratory effects[17]) in the distribution of the relative values of spectral components of PPGV is increased. These changes accordingly affect the LF/HF index.

It is known that the dynamics of heart damage in case of aortic valve stenosis include several stages. The stage 1 includes an increase in the mass of the left ventricular myocardium, an increase in the filling pressure of the left ventricle, and systolic dysfunction, defined as a decrease in ejection fraction <50%[18]. Further, the pathological process is aggravated by damage to the left atrium and mitral valve (stage 2)[19], the involvement of the pulmonary vascular system and tricuspid valve (stage 3)[20], and damage to the right ventricle (stage 4)[21]. In other words, the forced intensified mechanical work of the heart leads to the formation and growth of concentric hypertrophy of the left ventricular myocardium[22], as a result of which the effective operation of the Frank-Starling mechanism supporting systemic hemodynamics is possible. Nevertheless, there is evidence that in patients with aortic stenosis and severe compensatory myocardial hypertrophy, the left ventricular ejection fraction is significantly reduced[23]. As a result, the reflex regulation of the heart's activity changes, the sympathoadrenal system is activated and catecholamines are released leading to an increase in the heart rate. Because of this, the period of diastolic filling of the left ventricle is significantly decreased, increasing the already reduced cardiac output, the total peripheral vascular resistance rises even more, and tissue perfusion decreases[24, 25].

According to the literature, the work of the respiratory and vasomotor centres is closely related to each other. Fundamental experimental studies show that respiratory and autonomic nerve rhythms originate in the same region of the brain stem or are controlled by a common centre[26, 27]. This is evidenced by data on the dynamic relationship between the phases of breathing and the activity of the autonomic nervous system: an increase in the activity of the muscular sympathetic nerve at the end of expiration and a decrease at the end of inspiration[28], with a simultaneous increase in diastolic pressure in this phase[29].

As noted earlier, a decrease in the left ventricular ejection fraction with a compensatory increase in the activity of the sympathetic part of the nervous system is observed with aortic valve stenosis. Taken together, it leads to circulatory failure in the systemic circulation and a decrease in tissue perfusion[22]. In turn, hypoxia leads to an increase in the concentration in the blood of lipid peroxidation products, hydrogen ions, etc. This creates the prerequisites for the formation of metabolic acidosis and irritation of chemoreceptors. Along with this, the progression of aortic valve defect leads to the fact that the right heart is also involved in the pathological process (stages 3 and 4). It leads to an increase in pressure in the pulmonary circulation and overstretching of the mechanoreceptors of the right atrium and

**Table 2.** Comparison of spectral estimates of photoplethysmographic waveform variability between the groups

| Estimates | Patients with aortic stenosis (n=34) | Healthy subjects (n=30) | p-level |
|---|---|---|---|
| HF% | 52 (30, 66) | 22 (4, 61) | 0.019 |
| LF% | 38 (22, 53) | 13 (5, 29) | <0.001 |
| LF/HF% | 0.7 (0.4, 1.8) | 0.6 (0.2, 4.8) | 0.639 |

Data are presented as median with lower and upper quartiles – Me (LQ, UQ).

pulmonary arteries[30]. Afferentation from both chemo- and mechanoreceptors initiates the work of the respiratory centre aimed at maintaining homeostasis[31].

We assume that a significant increase in the relative values of the contribution of low-frequency oscillations (estimated as LF%) supports the known fact of an increase in sympathetic influences on peripheral vascular resistance in aortic stenosis. Along with this, a significant increase in the relative values of the contribution of high-frequency (respiratory) oscillations (estimated as HF%) is possible due to an increase in the functional activity of the respiratory centre.

In our previous work[15], we studied two groups of patients with other cardiovascular disease (hypertensive patients, and patients with stable coronary artery disease) of the same age as the group of patients with aortic stenosis. Patients with stenosis from current study gave higher LF% values from both groups of these patients. Also, the HF% values in the patients of this study are comparable to the values of patients with hypertension from our previous work.

A limitation of our study is the stable drug therapy in all patients with aortic stenosis at the time of testing (see Table 1). It was part of the preoperative preparation and could influence the results of the study of autonomic regulation of blood circulation.

## CONCLUSION

Patients with aortic stenosis are characterized by higher LF% and HF% values, relative to healthy people of comparable age. We consider that the use of PPGV spectral estimates has prospects for the development of new diagnostic methods in cardiology.

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