# Increased Concentrations of Serotonin and 5-Hydroxyindoleacetic Acid in Blood Plasma from Patients with Pulmonary Hypertension due to Mitral Valve Disease

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Serotonin content in the plasma and platelets and 5-hydroxyindoleacetic acid concentration in the plasma were shown to increase in patients with pulmonary arterial hypertension due to mitral valve disease. A positive correlation was found between the severity of pulmonary arterial hypertension and concentrations of serotonin ($r$=0.48) and 5-hydroxyindoleacetic acid in the plasma ($r$=0.9).

**Key Words:** *pulmonary arterial hypertension; serotonin; 5-hydroxyindoleacetic acid; blood; high-performance liquid chromatography*

Pulmonary arterial hypertension (PAH) is classified into idiopathic PAH and pulmonary hypertension in various diseases [6]. PAH due to mitral valve disease is accompanied by an increase in the load on the right heart, which contributes to the development of right ventricular failure and decrease in the quality of life and lifespan of patients.

Pathological changes during PAH are characterized by thrombosis *in situ* [3], which results from endothelial dysfunction, hypertrophy, and proliferation of vascular smooth muscle cells [12]. Much attention is paid to the role of serotonin (5-HT) in the development and progression of PAH. A correlation was found between the increase in 5-HT concentration and pulmonary vascular resistance in patients with platelet disorders [8]. Similar relationships were revealed in more than 80% patients with primary pulmonary hypertension (PH) [9]. In the 1990s, an epidemic of primary PH occurred in European patients receiving derivatives of fenfluramine (anorexic drug, 5-HT reuptake inhibitor). These data confirm the fact that 5-HT plays a role in the pathogenesis of PH [13].

5-HT is a biogenic amine. More than 95 percent of 5-HT are synthesized by enterochromaffin cells of the intestine. The remaining five percent of 5-HT are produced in the brain and neuroendothelial cells of the lungs [1,4]. Plasma 5-HT concentration is low. The concentration of 5-HT is highest in platelets (99% 5-HT in platelet granules). 5-HT uptake by platelets is realized by the transmembrane transporter [14]. 5-HT is mainly metabolized in the lung. Monoamine oxidase catalyzes the conversion of 5-HT to a final metabolite 5-hydroxyindoleacetic acid (5-HIAA) in vascular endothelial cells of the lungs. 5-HIAA is excreted with urine [7].

Functional activity of the serotoninergic system is not taken into account during the therapy of PAH patients. However, this system plays an im-

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portant role in the development of PAH in animals. Previous studies showed that treatment with 5-$HT_2$ receptor antagonists prevents the development of primary PAH.

The role of serotonin in PAH due to mitral valve disease remains unknown. Here we evaluated the relationship between the severity of PAH due to mitral valve disease and concentrations of 5-HT (plasma and platelets) and its metabolite 5-HIAA (plasma) in patients.

## MATERIALS AND METHODS

We examined 12 patients with PAH as a complication of rheumatic mitral valve disease (3 men and 9 women, 43-70 years old, average age 56 years). The control group was composed of 7 volunteers (6 men and 1 woman, 39-61 years old, average age 45 years) without a history or echocardiographic signs of cardiovascular diseases. The severity of PAH was determined from pulmonary artery systolic pressure (PAP) according to the results of echocardiography. It was calculated as the ratio of systolic PAP to systemic systolic arterial pressure (in %). PAP in PAH patients and healthy volunteers was 31-76% (mean 51%) and 16-24% (mean 20%) of systolic arterial pressure, respectively.

The venous blood was taken from the cubital vein via a catheter. Blood sampling was performed with patients in the prone position immediately after sleep (7.00-7.30). The blood (10 ml) was collected into an ice-cooled plastic tube with 50 ml heparin "for injections". Platelets were counted in 10 ml blood using a Goryaev chamber. The blood was centrifuged at 1000 rpm and 4°C for 10 min. Platelets were pelleted by centrifugation of the supernatant (platelet-rich plasma) at 2700 rpm for 15 min. The plasma and platelets in some tubes were frozen at -80°C until further study. The concentrations of 5-HT and its metabolite (5-HIAA) in the plasma and platelets were measured by high-performance liquid chromatography with electrochemical detection [2].

The results were analyzed by means of Statistica 6.0 software. The significance of differences between the mean values was estimated by Student's *t* test. The differences were statistically significant at $p<0.05$. The data were also analyzed by Pearson correlation test.

Written consent for the trial was obtained from all subjects. This study was approved by the Ethics Committee of the Ministry of Health of the Republic of Tatarstan.

## RESULTS

Plasma 5-HT concentration in PAH patients was 4-fold higher than in the control (Fig. 1). Plasma 5-HT concentration in 3 of 12 patients with PAH did not differ from the control. These data were not taken into account in a further analysis. A positive correlation was found between plasma 5-HT concentration and severity of PAH ($r=0.48$). The greater was the severity of PAH, the higher was the concentration of 5-HT in blood plasma. The increase in plasma 5-HT concentration may result in thrombosis and vasoconstriction, which is realized via 5-$HT_2$ and 5-$HT_{1B/1D}$ receptors [10].

Platelet 5-HT concentration in PAH patients was 3-fold higher than in the control (Table 1). The elevated level of 5-HT in blood plasma probably results in activation of the 5-HT transporter, which is followed by increase in platelet 5-HT concentration.

No correlation was revealed between platelet 5-HT concentration and severity of PAH ($r=0.17$). The elevation of platelet 5-HT concentration is followed by an increase in 5-TH release upon stimulation of platelets with thromboxane $A_2$, ADP, thrombin, tissue factor, platelet factor 4, and 5-HT [15]. 5-HT activates other platelets in the pulmonary vascular bed [5], which is realized via the platelet membrane 5-$HT_{2A}$ receptor. Chronic aggregation of platelets and accumulation of 5-HT in the site of vascular damage are accompanied by hyperproliferation of the endothelium and smooth mus-

**TABLE 1.** Concentrations of 5-HT and 5-HIAA in PAH Patients

| Group | Concentration | | |
|---|---|---|---|
| | 5-HT | | plasma 5-HIAA, nmol/liter plasma |
| | plasma, nmol/liter plasma | platelets, nmol/$10^9$ platelets | |
| Control | 12.36±1.88 | 422.75±120.99 | 24.33±4.45 |
| PAH | 55.60±10.56*** | 1102.66±264.11* | 158.98±51.79** |

**Note.** *$p<0.05$, **$p<0.01$, and ***$p<0.001$ compared to the control.

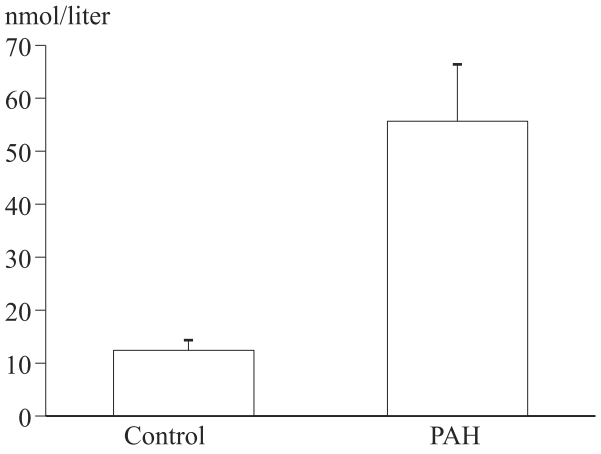


**Fig. 1.** Plasma 5-HT concentration in blood plasma of PAH patients.

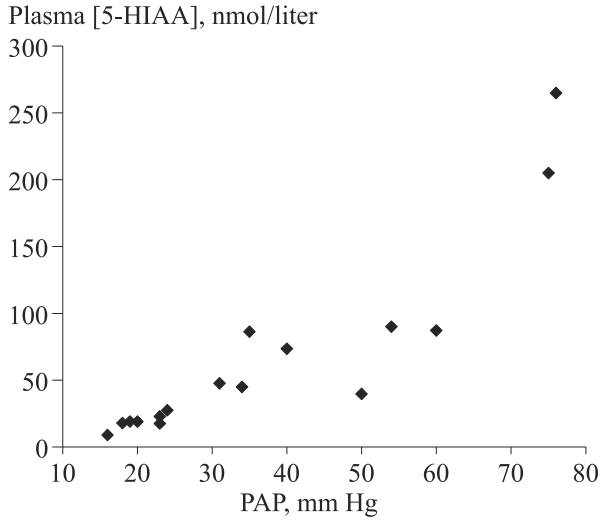


**Fig. 2.** Correlation between 5-HIAA concentration and systolic PAP (% of systemic systolic arterial pressure).

cle cells. These changes serve as a pathogenetic component of PH [11].

Plasma 5-HIAA concentration in PAH patients was 6.5-fold higher than in the control (Table 1). A strong positive correlation was found between 5-HIAA concentration and severity of PH ($r$=0.9). The greater was the severity of PAH, the higher was the rate of 5-HT metabolism. The observed changes were probably associated with increased activity of monoamine oxidase A, which plays a role in the conversion of 5-HT into its final metabolite. A weak correlation was found between the concentrations of 5-HT and 5-HIAA in blood plasma ($r$=0.32, Fig. 2).

Our results confirm the notion that the development of PAH is mediated by similar pathophysiological mechanisms and does not depend on the etiological factor. The development of PAH during mitral valve disease is associated with hemodynamic disturbances in the valve and left atrium. It should be emphasized that PH, idiopathic PH, and hypoxia-induced PH are mediated by the same pathophysiological mechanisms. Activity of the 5-HT system is elevated in patients with PAH due to mitral valve disease. Our findings should be taken into account in a study of the pathogenesis and therapy of patients with this disease. The surgery for mitral valve disease does not necessarily improve PAP. Neurohormonal and structural changes in the vascular wall probably persist in these patients. Pathogenetic therapy is required to decrease or prevent proliferation and remodeling of pulmonary vessel walls.

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