Early Predictive Biochemical, Electrocardiographic and Echocardiographic Markers for Cardiac Damage in Patients with Pulmonic Silicosis

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The aim of this study was to identify correlations between electrocardiographic and echocardiographic changes in patients with silicosis prior to the occurrence of chronic pulmonary heart disease. We conducted a prospective, descriptive, analytical study, in which we included a group of 67 patients consecutively admitted to the Health Promotion and Occupational Medicine Clinic between December 2016 and January 2018, aged 47 to 78 years.There was a biochemical and electrocardiographic evaluation for each patient as well as a right ventricle echocardiographic evaluation (diameters, volumes, function). A control group, including 25 patients with benign minor diseases that required a cardiologist consultation, was also used. From the electrocardiographic point of view, slight changes were observed regarding the waves of electrical activity of the right ventricle. Taking into account the degree of ventilatory dysfunction (depending on FEV_1), changes in right heart echocardiographic parameters were identified. Thus, in what the most important right ventricular parameters, including the tricuspid annular plane systolic excursion (TAPSE) or the RV index of myocardial performance (RVMPI) were concerned, values at the upper limit of normality were recorded in most patients with moderate and severe ventilatory dysfunction. Values of echocardiographic parameters of the right heart at the upper limit of normality, correlated with the degree of ventilatory dysfunction, are early markers for cardiovascular damage in patients with pulmonary silicosis prior to the occurrence of chronic pulmonary heart disease also known ascor pulmonale.

Keywords: silicosis, pneumoconiosis, pulmonary heart disease

Silicosis is a collagen pneumoconiosis, irreversible, a potentially fatal, progressive and untreatable fibrotic lung disease caused by long-term inhalation and deposition of powders respirable crystalline silica [1].

Silicosis is caused by prolonged inhalation and deposition of pulp with high concentration of free crystalline silicon dioxide in the pulmonary tissue. It has been widely spread in the past, a rise in incidence being observed in the years following the Second World War [1-3]. However, silicosis continues to remain a public health issue in both developed and developing countries.

The etiological agent of silicosis is crystalline silicon dioxide or free silica which is a broad-spread mineral in the earth's crust structure. It is formed from silicon and oxygen under elevated pressure and temperature conditions and is presented in two forms: crystalline form and amorphous form [4].

Although there is no curative treatment for silicosis, management strategies for patients with this disease can improve quality of life and can prevent damage for both respiratory and cardiac function.

Experimental part

The aim of the study

The aim of this study was to identify correlations between biochemical, electrocardiographic and echocardiographic changes in patients with silicosis prior to the occurrence of chronic pulmonary heart disease.

Material and methods

We conducted a prospective, descriptive, analytical study, in which we included a group of 67 patients consecutively admitted to the Health Promotion and Occupational Medicine Clinic of Emergency County Hospital of Craiova, Romania, between December 2016 and January 2018, aged 47 to 78 years. A single group of patients diagnosed with pulmonary silicosis was established, which was then subdivided into subgroups, depending on the different clinical and pathological characteristics of the patients included in the study, subgroups that were considered when performing the statistical tests. In some cases it was necessary to have a reference group, so for this, we have established the

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control group in which we included 25 patients with benign minor diseases (especially in the ocular sphere or conditions requiring small surgical interventions), or patients who presented themselves in the Polyclinic of the Emergency County Hospital of Craiova, who required a routine cardiological consultation, before surgery, they were clinically electrocardiographically and echocardiographically evaluated.

The study was conducted in accordance with the rules and principles of the Ethics Committee of the University of Medicine and Pharmacy of Craiova and complied with all the provisions of the international forums governing scientific research and the Helsinki Declaration issued by the International Medical Association (WMA - World Medical Association), Code of Good Medical Practice, and others. Each patient enrolled in the study gave his consent by signing the informed consent and the acceptance form for the use of clinical and biochemical data from the Medical Observation Sheet for the study.

As mentioned above, in addition to the information obtained from the electrocardiographic and echocardiographic analysis, we also used the clinical and biochemical information from the Medical Observatory Sheets, everything was included in an electronic file for each patient, excluding all the information that could lead to patients identification, such as detailed name or other personal identification data.

For inclusion in the study, we used the following criteria: age 18+ for both genders, absence of pathological personal history of primary pulmonary hypertension or other pathological history that could alter systolic and diastolic function of the right ventricle, the diagnosis of silicosis was objectively based on the criteria established by the legislation in force, the agreement to participate in the study, materialized by signing the informed consent. To exclude patients from the study, we used the following criteria: age less than 18 years, presence of primary pulmonary arterial hypertension, presence of other pathological personal history that could alter systolic and diastolic function of the right ventricle, lack of informed consent by patients.

Electrocardiographic analysis is a non-invasive method that integrates the electrical activity of the heart. In our study we focused on the duration and amplitude of the P wave in DII lead, representing atrial depolarization, but also on measuring the amplitude and duration of right ventricular depolarization waves (R wave in V1 or V2 and S wave in V5 or V6), knowing that overloading of the right cord may cause one or more electrocardiographic changes in patients with pulmonary silicosis. For these recordings we used a portable electrocardiograph type MAC 2000 (GE Healthcare, USA). Also, echocardiographic analysis was performed at the cardiology clinic using a TOSHIBA APPLIO 400 ultrasound machine, using a probe with a frequency range of 3.5-7.5 MHz. Parameters determined ecocardiographically in our study focused primarily on the right heart (diameters, volumes, function), as it can be seen in figure 1 and 2.

The main parameters were analyzed by using the Microsoft Office Excel 2010 software (Microsoft Corporation, Redmond, Washington, USA) and, after graphics were exported to the GraphPad software (version 7, GraphPad Software, La Jolla, CA, USA) where after the mean and standard deviation for each group were calculated, then the statistical analysis continued. We used the *t Student* test to assess statistical differences between the averages of two data groups and the ANOVA variance test to analyze the statistical differences between the averages of more than two data groups. To establish correlations between different data, we used the Pearson

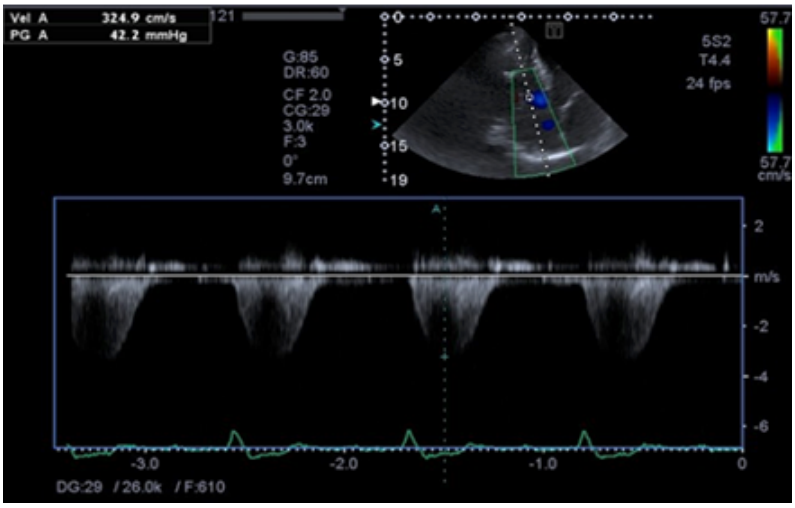

Fig. 1. Continuous Doppler (CW). Apical 4 chambers section with the Doppler CW volume sample placed on the tricuspid valves. Record of the tricuspid transvalvular flow with a view of a velocity of 3.24 m / s (high velocity unlike PW), with the possibility of calculating the maximum gradient between RV and RA (in this image with a value of 42.2 mmHg) used in estimating systolic pulmonary arterial pressure

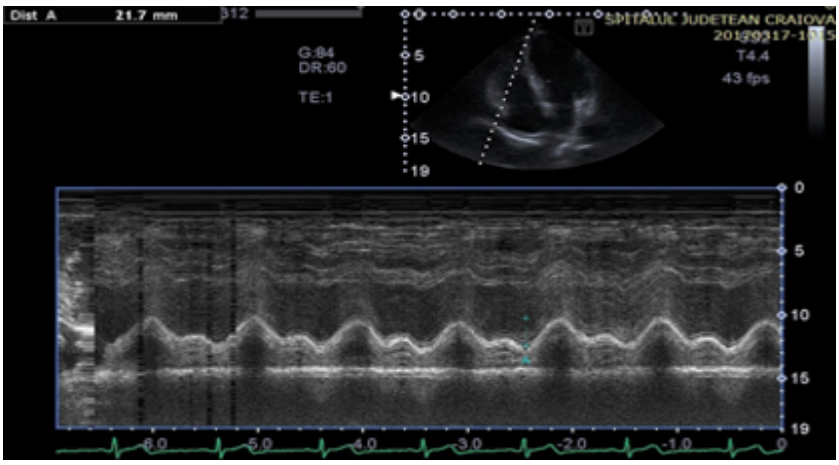

Fig. 2. The tricuspid annular plane systolic excursion (TAPSE) through M mode

correlation test. In all cases where we had p <0.05 we considered a statistically significant difference between the average of the groups.

Results and discussions

Biochemical changes in patients with pulmonary silicosis

By analyzing alanine aminotransferase (ALAT) for the patients included in the study and referring to the degree of ventilatory dysfunction, we noticed that there was no statistically significant difference between the different groups included in the study (p> 0.05), as it can be seen in figure 3.

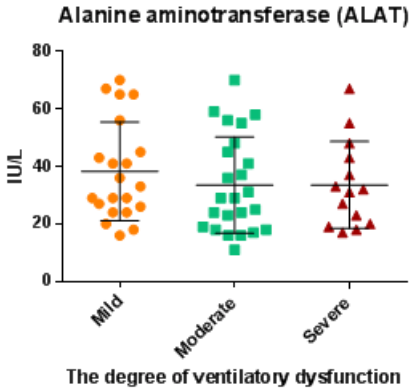

Fig. 3. Alanine aminotransferase (ALAT) depending the degree of ventilatory dysfunction.

As expected, the mean erythrocyte count was higher in patients with severe ventilatory dysfunction than in patients with moderate or mild dysfunction (fig. 4), with a statistically significant difference between the group of patients with mild ventilatory dysfunction and the group of patients with severe ventilatory dysfunction (p = 0.018). Also, hemoglobin concentration was higher in patients with severe ventilatory dysfunction compared to patients with moderate ventilatory dysfunction (p = 0.044) or in patients with mild ventilatory dysfunction (p = 0.022) as it can be seen in figure 5.

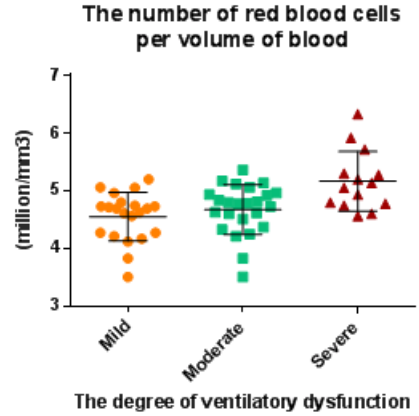

Fig. 4. The number of red blood cells per volume of blood Depending on the degree of ventilatory dysfunction

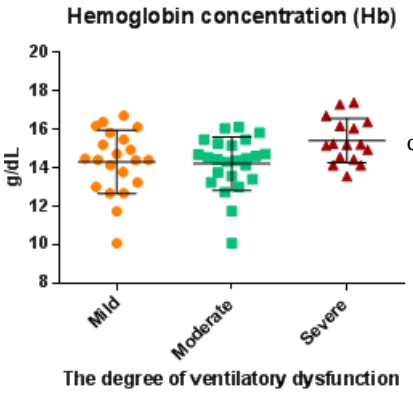

Fig. 5. Hemoglobin concentration depending on the degree of ventilatory dysfunction

By evaluating the amplitude of the P wave in the DII lead depending on the degree of ventilatory dysfunction, we observed that in the control group the amplitude of the P wave in DII lead was between 0.06 - 0.18 mV, in the group with mild ventilatory dysfunction between 0.1 - 0.18 mV, in the group with moderate ventilatory dysfunction between 0.08 - 0.26 mV and in the group with severe ventilatory dysfunction between 0.14 - 0.26 mV (fig. 6). We, therefore, observed a gradual increase in P-wave amplitude in the DII lead to the degree of ventilatory dysfunction, there being a very significant difference between the normality group and the group of patients with moderate or severe ventilatory dysfunction (p<0.001). Also, the same level of significance is noted between the group of patients with mild ventilatory dysfunction vs. group of patients with severe ventilatory dysfunction (p<0.001). We also noticed an increase in the amplitude of the R wave in V1 or V2 and the S wave of V5 or V6 along with the degree of ventilatory dysfunction, as it can be seen in figure 7 and 8.

Assessing the basal diameter of the right ventricle in relation to the degree of ventilatory dysfunction, we observed that in the control group the basal diameter of

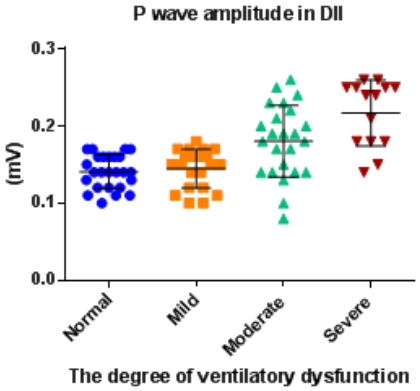

Fig. 6. P wave amplitude in DII lead depending on the degree of ventilatory dysfunction.

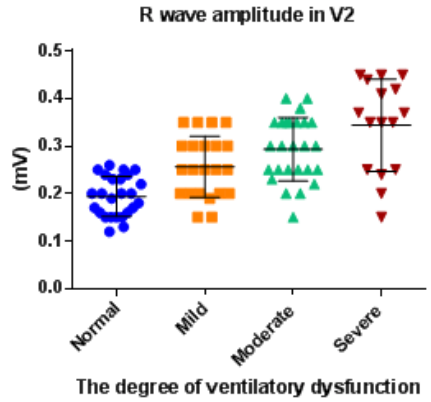

Fig. 7. R wave amplitude in V1/V2 depending on the degree of ventilatory dysfunction.

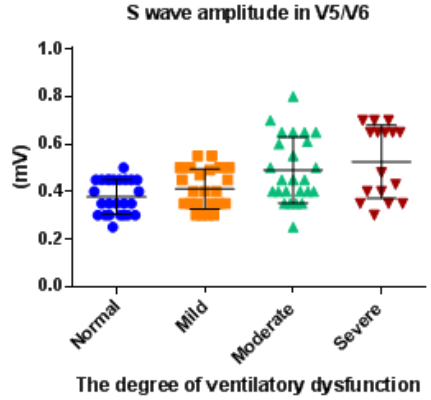

Fig. 8. S wave amplitude in V5/V6 depending on the degree of ventilatory dysfunction

the right ventricle was between 27-36 mm, in the group with mild ventilatory dysfunction between 28-37 mm, in the group with moderate ventilatory dysfunction between 31 - 40 mm and in the group with severe ventilatory dysfunction between 35 - 44 mm (fig. 9). We observed a gradual increase in the basal diameter of the right ventricle related to the degree of ventilatory dysfunction, there being a very significant difference between the control group and the group of patients with moderate or severe ventilatory dysfunction ($p<0.001$), unlike the control group vs. group of patients with mild ventilatory dysfunction ($p > 0.05$).

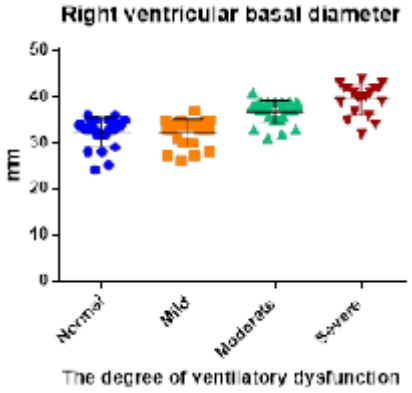

Fig. 9. Right ventricular basal diameter depending on the degree of ventilatory dysfunction

Analyzing the transverse diameter of the right atrium as compared to the degree of ventilatory dysfunction, we observed that in the control group the transverse diameter was ranged between 27-36 mm, in the group with mild ventilatory dysfunction it was between 29-37 mm, in the group with moderate ventilatory dysfunction it was between 31 - 45 mm and in the group with severe ventilatory dysfunction between 32 - 42 mm (fig. 10). We, therefore, noticed a gradual increase in the transverse diameter of the right atrium versus the degree of ventilatory dysfunction, there being a very significant difference between the control group and the group of patients with moderate or severe ventilatory dysfunction ($p<0.001$). There is also the same level of significance among the group of patients with mild ventilatory dysfunction vs. the group of patients with severe ventilatory dysfunction ($p<0.001$). Additionally, there is a significant difference between the group of patients with mild ventilatory dysfunction vs. the group of patients with moderate ventilatory dysfunction ($p<0.01$) and an insignificant one among the group of patients with moderate ventilatory dysfunction and the group of patients with severe ventilatory dysfunction ($p = 0.56$), unlike the normality vs. the group of patients with mild ventilatory dysfunction, where it is insignificant ($p = 0.86$).

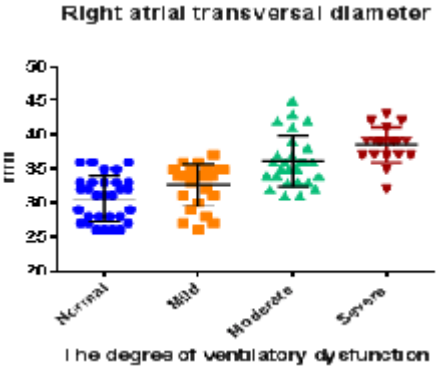

Fig. 10. Right atrial transversal diameter depending on the degree of ventilatory dysfunction.

Analyzing the tricuspid annular plane systolic excursion (TAPSE) in relation to the degree of ventilatory dysfunction, we noticed that TAPSE was between 18.4 - 23 mm in the control group, in the group with mild ventilatory dysfunction between 17.3 - 23 mm, in the group whit moderate ventilatorydysfunction between 15 - 22 mm and in the group with severe ventilatory dysfunction between 15.5 - 21.7 mm (fig. 11). We therefore observed a gradual decrease in the TAPSE dependingon the degree of ventilatory dysfunction, with a very significant difference between the control group and the group of patients with moderate or severe ventilatory dysfunction ($p<0.001$), but also between the group patients with mild ventilatory dysfunction and the group of patients with severe ventilatory dysfunction.

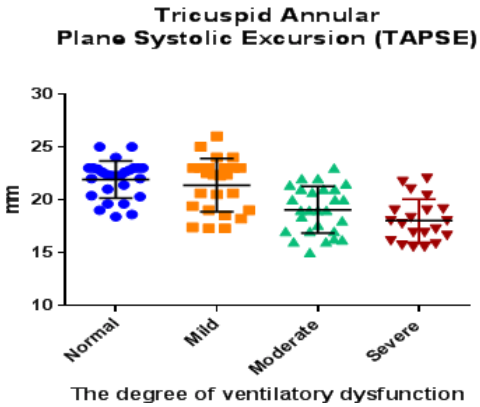

Fig. 11. Tricuspid Annular Plane Systolic Excursion (TAPSE) depending on the degree of ventilatory dysfunction

We also noticed anincrease in systolic pulmonary artery pressure (SPAP) and right ventricular myocardial performance index (MPI) by pulsed Doppler, depending on the ventilatory dysfunction caused by silicosis and manifested by a decrease of FEV_1 (fig. 12 and 13).

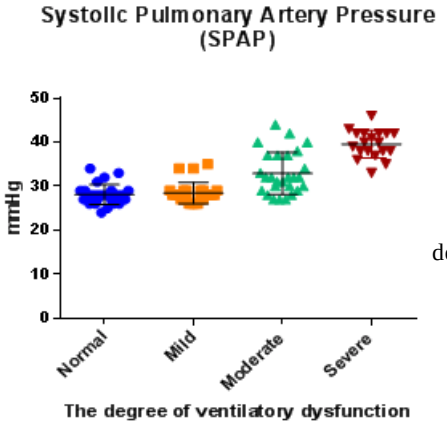

Fig. 12. Systolic Pulmonary Artery Pressure (SPAP) depending on the degree of ventilatory dysfunction

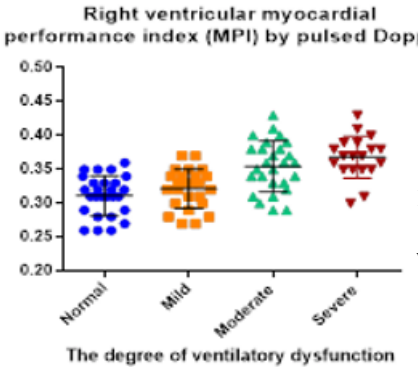

Fig. 13. Right ventricular myocardial performance index (MPI) by pulsed Doppler depending on the degree of ventilatory dysfunction

Any disease that affects the structure and function of the respiratory system may lead to cardiac damage, ultimately resulting in the occurrence of chronic pulmonary heart disease [5-26]. In our study we evaluated the impact of pulmonary damage (silicosis) on the function and structure of the right cord prior to the onset of the chronic pulmonary heart diseasein order to establish early markers

of cardiovascular damage in pulmonary silicosis [27]. The right heart echocardiographic evaluation (diameters, volumes, function) has always been a challenge in practice due to the complex shape, it is unobtrusive to any known geometric form, and which for this reason does not fit into simple models of volume calculation [27]. Therefore, the right ventricle function is difficult to be exploredby classical two-dimensional ultrasound, requiring three-year data. 2D ultrasound can offer qualitative data on right ventricle function, which is extremely useful in practice [28].

The right ventricle, due to its structural features (asymmetric geometry, thin wall), adapts well to preload (volume) and with difficulty to overload and pulmonary hypertension. VD will reshape as structure (hypertrophy, dilation) and function (RV hypertrophy is associated with alteration of myocyte microtubules, changes in calcium uptake, decreased sarcomer contraction) [26]. In addition, hyperventilation syndrome which is present in pulmonary diseases with hypoxia, hypercapnia, acidosis and increased blood viscosity, secondary increased erythrocyte count, accentuates RV suffering [27-29].

Conclusions

Values of the right heart echocardiographic parameters at the upper limit of normality, correlated with the degree of ventilatory dysfunction, are early markers for cardiovascular damage in patients with pulmonary silicosis prior to the occurrence of chronic pulmonary cord.

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