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

VENERA CRISTINA DINESCU1, ILEANA PUIU2, SORIN NICOLAE DINESCU3, DIANA RODICA TUDORASCU4, ELENA CATALINA BICA5, RAMONA CONSTANTINA VASILE1, MARIUS GABRIEL BUNESCU1, FLORIN MARIUS ROMANESCU2, NICOLETIA CIOATERA6, LUCIANA TEODORA ROTARU4, ROXANA EDME MUSTAFA8, CRISTINA FLORESCU5

1University of Medicine and Pharmacy of Craiova, Health Promotion and Occupational Medicine Department, 2 Petru Rares Str., 200349 Craiova, Romania
2University of Medicine and Pharmacy of Craiova, Pediatrics Department, 2 Petru Rares Str., 200349 Craiova, Romania
3University of Medicine and Pharmacy of Craiova, Epidemiology and Primary Health Care Department, 2 Petru Rares Str., 200349 Craiova, Romania
4University of Medicine and Pharmacy of Craiova, Internal Medicine Department, 2 Petru Rares Str., 200349 Craiova, Romania
5University of Medicine and Pharmacy of Craiova, Department of Physiology, 2 Petru Rares Str., 200349, Craiova, Romania
6University of Craiova, Chemistry Department, 107i Calea Bucuresti Str., Craiova, Romania
7University of Medicine and Pharmacy of Craiova, Emergency & First Aid Department, Emergency Department, Emergency County Hospital Craiova, 2-4 Petru Rares Str., 200349, Craiova, Romania
8University of Medicine and Pharmacy of Craiova, Cardiology Department, 2 Petru Rares Str., 200349 Craiova, Romania

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. 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 FEV1), 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 as cor 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
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 echocardiographically 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 correlation test.
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 on the degree of ventilatory dysfunction.](image)

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 moderate 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.](image)

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...
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).

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).

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 disease in 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 explored by 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.

References

1. Fernandez Alvarez, R., Martinez Gonzalez, C., Quero Martinez, A., Blanco Perez, J.J., Carazo Fernandez, L., Prieto Fernandez, A. Guidelines for the diagnosis and monitoring of silicosis. Arch Bronconeumol. 2015 Feb;51(2):86-93.

2. Leung, C.C., Yu, I.T., Chen, W. Silicosis. Lancet. 2012 May 26;379(9830):2008-18.

3. Rushton, L. Chronic obstructive pulmonary disease and occupational exposure to silica. Rev Environ Health. 2007 Oct-Dec;22(4):255-72.

4. Roncati, L., Barbolini, G.State-of-the-art nanopathological diagnostics.UltrastructPathol. 2017 Sep-Oct;41(5):309-311.

5. Gheonеa, D.I., Sandulescu, S.M., Fiureлescu, S., Tudorascu, M.R., Ciobanu, M.O., Badea, O., Gheonea, D.I., Sandulescu, D.L. A rare case of ovarian splenosis. Rom J Morphol Embryol. 2016;57(2 Suppl):811-816.

6. Calborean, V., Miscoci, S.A., Istratoaeia, O., Galceava, O., Alexander, D.O., Guta, M.M., Gheонеа, D.M., Padureanu,V., Fortofoiu, C.M., Dij Marsесu, A.L., Gheonea, D.I. Correlation Between Liver Cirrhosis and Risk of Cardiac Arrhythmias, Rev. Chim. (Bucharest), 69, no 6, 2018, p. 1527-1532.

7. Mesina, C., Stoean, L.C., Stoean, R., Sandita, V.A., Gruia, C.L., Foarfa, M.C., Rotaru, L.T., Ciobanu, A.E., Mesina, M., Calborean, V., Gheonеа, D.M., Ciобаnu, D. Immunohistochemical Expression of CDB, CDX2, PS2, D2-40 and K67 in Colorectal Adenocarcinoma, Conventional and Malignant Colorectal Polyps.Rev. Chim. (Bucharest), 69 no. 2, 2018, p. 419-428.

8. Florescu, C., Rogoveanu, I., Vere, C.C., Tarteа, G.C., Tarteа, E.A., Mогoanta, L. From molecular mechanism to morphological changes in cardiomyopathy. Rom J Morphol Embryol, 2016, 57(4):1207–1214.

9. Tarteа, G.C., Florescu, C., Pirici, D., Caragea, D., Tarteа, E.A., Vere, C.C. The substrate of the biopsychosocial influences in the carcinogenesis of the digestive tract. J Mind Med Sci, 2016, 3(2):108-117.

10. Donoiu, I., Tarteа, G.C., Chavez-Gonzalez, E. Is there a utility for QRS dispersion in clinical practice? J Mind Med Sci, 2017, 4(2):132-141.

11. Mihailovicu, A.R., Padureanu, V., Albu, C.V., Dinescu V.C., Pirilog, M.C., Dinescu S.N., Malin, R.D., Calboreanu, V. Myocardial Noncompaction. Rev. Chim. (Bucharest), 69, no 8, 2018, p.2209-2012.

12. Gheonеа, V., Militaru, C., Calboreanu, V., Gheonеа, L.M., Chирita, A.L., Mita, A., Galceava, O., Gheonеа, V., Stanca, D., Udristoiu, I., Clinical and biochemical considerations regarding stress and arrhythmic risk in patients with chronic viral liver diseases. Rev. Chim. (Bucharest), 69, no. 4, 2018, p.881-885.

13. Gheonеа, V., Chирita, A.L., Dumitrescu, E.M., Rogoveanu, I., Istratoaeia, O., Gheonеа, V., Pana, R.C. Particularities of associating viral hepatitis with pregnancy and mental disorders, Rom J Morphol Embryol 2016, 57(1): 45-50.

14. Ciurea, R.N., Rogoveanu, I., Pirici, D., Tarteа, G.C., Strebа, C.T., Florescu, C., Catalin, B., Puiu, I., Tarteа, E.A., Vere, C.C. B2 adrenergic receptors and morphological changes of the enteric nervous system in colorectal adenocarcinoma. World J Gastroenterol, 2017, 23(7):1250-1261.

15. Puiu, I., Albu, C.V, Tarteа, E.A., Calboreanu, V., Gheonеа, V., Dinescu, S.N., Vasile, R.C., Dinescu, V.C., Bica, E.C., Romanescu, F.M., Tudorascu, D.R. Relationships Between Giaл Enteric Cells, Beta-cell Signaling and Tumor Proliferative Activity in Patients with Colorectal Neoplasia. Rev. Chim. (Bucharest), no.10, 2018, p.2461-2464.

16. Tarteа, E.A., Florescu, C., Donoiu, I., Pirici, D., Mihailovicu, A.R., Albu, V.C., Balсеаnu, T.A., Ianсau, M., Badea, C.D., Vere, C.C., Sfredeл, V. Implications of inflammation and remodeling of the enteric glial cells in colorectal adenocarcinoma. Rom J Morphol Embryol, 2017, 58(2):473-480.

17. Tudorascu, D.R., Pirici, D., Tarteа, E.A., Mustafa, E.R., Florescu, C., Vere, C.C., Balea, A.M., Puiu, I., Tarteа, G.C., Albu, V.C. Synaptophysin expression as prognostic factor for survival in colorectal carcinomas. Rom J Morphol Embryol, 2017, 58(4):1409-1415.

18. Mihailovicu, V., Gheonеа, V., Octavian, I., Mustafa, R.E., Cococarу, P.A., Alexander, D.O., Galceava, O., Mita, A., Miscoci, S.A., Al Namаt, R., Gheонеа, D.I. QT interval analysis in patients with chronic liver disease, Rev. Chim. (Bucharest), 69, no. 5, 2018, p.1134-1138.

19. Mihailovicu, A.R., Deliu, R., Margaritescu, C., Simionescu, C.E., Donoiu, I., Istratoaeia, O., Tudorascu, D.R., Tarteа, E.A., Gheonеа, D.I. Collagen I and III and TIMP-1, MMP-1 and TIMP-1 expression in diffused cardiomyopathy, Romanian Journal of Morphology and embryology, 2017, vol.58 (3): 777-781.

20. Puiu, I., Stanca, P., Bulea, D., Niculescu, C., Niculescu, V.E., Stoian, F. Diagnosis of tuberculosis lymphadenitis in children. Pediatrics 2008; 121 (Suppl 2): S130-1.

21. Puiu, I., Dan, A.O., Tarteа, E.A., Rogoveanu, O.C., Bica, E.A., Dinescu, S.N., Vasile, R.C., Dinescu, V.C., Romanescu, F.M., Tudorascu, D.R. Assessing Factors that Influence the Level of Glycated Hemoglobin in Children and Adolescents with Type 1 Diabetes. Rev. Chim. (Bucharest), 69, no. 11, 2018, p.4233-4236.

22. Florescu, C., Istratoaeia, O., Tarteа, G.C., Pirici, D., Strebа, C.T., Catalin, B., Puiu, I., Tarteа, E.A., Caragea, D.C., Ghiлusi, M.C., Romanescu, M.V., Rogoveanu, I., Vere, C.C. Neuro-neoplasic interrelationships in colorectal level - immunohistochemical aspect in three cases and review of the literature. Rom J Morphol Embryol, 2016, 57(2 Suppl):639–650.

23. Calborean, V., Ciобаnu, D., Mireа, S.C., Galceava, O., Gheonеа, V., Padureanu, V., Fortofoiu, C.M., Fortofoiu, M., Mita, A., Dinescu, S.N., Miscoci, S.A., Dinescu, V.C. Benefit of Cardiac Resynchronization Therapy in Patients with Heart Failure. Rev. Chim. (Bucharest), 69, no. 9, 2018, p.2744-2748.

24. Calborean, V., Gheonеа, V., Dinescu, N.S., Stanca, D., Galceava,O., Fortofoiu, M., Mita, A., Mihailovicu, A.R., Miscoci, S.A., Balea, V.D., Dinescu, V.C. Arrhythmia risk in patients with chronic hepatic disease. Rev. Chim. (Bucharest), 69, no. 11, 2018, p.3337-3340.
25. CALBOREAN, V., GHEORMAN, V., CONSTANTIN, C., ISTRATOAE, O. Venous Thromboembolism Secondary to Adult-Onset Still’s Disease: a Case Report. Journal of Cardiovascular Emergencies 2018;4(2):101-105.

26. MISCOCI, A., PIRVU, C.D., CALBOREAN, V., STREBA, C.T., ROGOVEANU, O.C., PADUREANU, V., VERE, C.V. The importance of circulating tumor products as liquid biopsies in colorectal cancer. Journal of Mind and Medical Sciences. 2018; 5(1): 39-45

27. HADDAD, F., HUNT, S., ROSTENTHAL, D., MURPHY, D. Right ventricular function in cardiovascular disease Part I. Circulation, 2008; 117: 1436-1448.

28. HADDAD, F., DOYLE, R., MURPHY, D., HUNT, S. Right ventricular function in cardiovascular disease Part II. Circulation, 2008; 117: 1717-1731.

29. KAWUT, S.M., POOR, H.D., PARikh, M.A., HUEPER, K., SMITH, B.M., BLUEMKE, D.A., LIMA, J.A., PRINCE, M.R., HOFFMAN, E.A., AUSTIN, J.H., VOGEL-CLAUSSEN, J., BARR, R.G. Corpulmonaleparvus in chronic obstructive pulmonary disease and emphysema: the MESA COPD study. J Am Coll Cardiol. 2014 Nov 11;64(19):2000-9.

Manuscript received: 23.09.2018