EPIDEMIOLOGIC DATA, PROGNOSIS AND ETIOPATOGENY IN CHRONIC COR PULMONALE COPD RELATED

MARIA-ELENA SCRIDON¹

Pneumophtysiology Hospital, Sibiu

Keywords: COPD-Abstract: Cor pulmonale represents an important complication of chronic obstructive pulmonary Pulmonary Arterial disease (COPD), because it is responsabile for a large number of hospitalizations for heart faillure. The Hypertension-Chronic development of pulmonary arterial hYpertension (PAH) influences the prognosis of persons with COPD. Cor Pulmonale PAH is the primary cardiovascular complication encountered in chronic obstructive pulmonary disease. The prevalence of PAH increases as COPD worsens, and the development of PAH and cor pulmonale appears to affect survival of patients with COPD. Potential causes proposed to explain the development of PAH in COPD include gas exchange abnormalities, destruction of the pulmonary vascular bed, alterations in respiratory mechanics, changes in intrinsic pulmonary vessel tone, and increased blood viscosity. The goal is the early detection of PAH which complicate COPD and so proper therapy can be established.

Cuvinte cheie: BPOC – hipertensiune pulmonară-cord pulmonar cronic **Rezumat:** Cordul plmonar cronic reprezintă o complicație importantă a bronhopneumopatie cronică obstructivă (BPOC) fiind responsabil de un număr mare de spitalizări pentru insuficiență cardiacă. Dezvoltarea hipertensiunii pulmonare (HTP) influențează prognosticul pacienților cu BPOC. Prevalența HTP crește în stadiile avansate ale BPOC, iar dezvoltarea HTP și a cordului pulmonar afectează supraviețuirea pacienților cu BPOC. Posibilele cauze responsabile de dezvoltarea HTP în BPOC sunt anomaliile schimburilor gazoase, distrucția patului vascular pulmonar, alterarea mecanicii respiratorii, modificări ale tonusului vascular pulmonar intrinsec și creșterea vâscozității sanguine. Scopul este de a depista timpuriu HTP care complică BPOC pentru a se putea lua măsuri terapeutice adecvate.

The term cor pulmonale was introduced in 1913 by Dr. Paul D. White. It is used very often, but its definition varies, presently there is no consent regarding it. In 1963 a OMS committee defined cor pulmonale as the "hypertrophy of the right ventricle secondary to diseases which affect the pulmonary function and structure".

In 1970 Behnke & co (1) suggested the replacement of the term "hypertrophy" with "the alteration of the structure and function of the right ventricle". Also, the clinical definition of cor pulmonale through the presence of edema at patients with respiratory insufficiency was suggested. Nevertheless, because pulmonary hypertension is "sine qua non" (7) in the cor pulmonale, it has been decided that the most adequate definition is the following: the hypertrophy or the dilatation of the right ventricle as a consequence of pulmonary hypertension resulting from diseases that affect the structure and function of the lung; the pulmonary arterial hypertension leads to chronic cor pulmonale and can lead in time to insufficiency of the right ventricle.(2)

Cor pulmonale is the term used for the pulmonary hypertension secondary to the pulmonary parenchymal pathology, the thoracic cavity, excluding the congenital cord diseases and the dysfunctions of the left ventricle. (2)

Epidemiologic data

The chronic cor pulmonale represents a disease with an increasing distribution, most frequently detected late because of the long evolution of the disease. Most of the times, the patients visit the doctor when the right ventricle insufficiency phenomena have appeared and they present a reserved progrnosis.

The incidence of the cor pulmonale varies in different countries dependig on the prevalence of smoking, pollution and other factors.

Cor pulmonale is a regular type of cardiac disease, a result of the tight association with BPOC, which alarmed in the last years through the increase of morbidity and mortality. BPOC is the major cause involved in the appearance of respiratory insufficiency, being probably responsible for the appearance of 80-90% of the cor pulmonale cases. Poor statistic data regarding the incidence and prevalence of the chronic cor pulmonale exist, because of the very decreased availability of the cardiac catheterization at patients with increased risk. An alternative method is represented by the non-invasive methods, mostly by the Doppler echocardiography, which makes the evaluation of a large number of patients with respiratory diseases possible.

A study in the UK tried to determine the patients with an increased risk of developing pulmonary hypertension and cronical cor pulmonale among the patients with hypoxemic pulmonary diseases. This population study evaluated adults over 45 years old and determined that 0,3 % had values of the PaO2<55 mmHg as well as FEV1<50%. For England, these values represent 60.000 subjects with risk of pulmonary hypertension eligible for oxygen therapy. The mortality in cor pulmonale is also difficult to evaluate.

In the USA, cor pulmonale represents approximately 6-7% of all types of cardiac diseases of adults, and COPD is the

¹Author Corresponding: Maria-Elena Scridon, 11, Record street, Sibiu, Romania; e-mail: olariumariaelena@yahoo.com; tel +40-0745300455 Article received on 11.03.2010 and accepted for publication on 18.03.2010 ACTA MEDICA TRANSILVANICA June 2010; 2(2)192-194

most frequent cause. Although the prevalence of the COPD in the USA is of approximately 15 million, the exact prevalence of cor pulmonale cannot be approximated because this disease does not appear in all COPD cases, and the clinical examination as well as the paraclinic routine examinations have a decreased sensitivity in determining the pulmonary hypertension.

In Delhi, India, where the air pollution is high, the incidence was estimated at approximately 16%. In Sheffield, England, where the air pollution is very high, the cronical cor pulmonale is registered at approximately 30-40% of the patients with cardiac insufficiency.(8)

Generally, cor pulmonale reaches high levels in the areas with intense pollution, where smoking is a widely spread habit, and as a cosequence the chronic bronchitis and pulmonary emphysema are widely spread. In a constant manner, the statstics have proven a higher incidence of these affections at the masculine gender, as a consequence of a more intense exposure to vicious air.

It is estimated that chronic cor pulmonale is responsible of 10-30% of the internments for cardiac decompensation. The autopsic studies at patients with chronic respiratory diseases have established the presence of cor pulmonale at over 40%. It is estimated that the pulmonary hypertension is present at over 40% of the patients with FEV1<1 L. Stewens & co evaluated 500 patients with COPD and cor pulmonale, of which only 6 patients presented increased values of the medium pulmonary arterial pressure (>50 mmHg). The authors have concluded that the seriousness of the pulmonary hypertension is not entirely the consequence of the pulmonary hypertension must be also examined for determining another cause for its increase. (13,15)

Prognosis

Although pulmonary hypertension develops slowly in COPD, its appearance is a poor factor of prognosis. Weizenblum & co revealed a survival of 72 % at 4 years in the case of patients with COPD without pulmonary hypertension and of only 49% in the case of those with PAPm > 20 mmHg. The patients with COPD who developed cor pulmonale have 30% chances of survival in 5 years. It is not clear yet to what extent the chronic cor pulmonale has an independent prognosis value or the prognosis is given by the presence of COPD or other chronic pulmonary diseases. (7,19)

The appearance of the right cardiac insufficiency is in a classical manner a sign of reserved prognosis at patients with chronic respiratory diseases. The PAP level is a good prognosis indicator of the COPD evolution, but also in other categories of chronic respiratory diseases such as the idiopathic pulmonary fibrosis and the sequelae of pulmonary tuberculosis.

At patients with BPOC and slight pulmonary hypertension (20-35 mmHg) the survival rate is of 50% in 5 years. The prognosis is particularly reserved at patients with more severe pulmonary hypertension, the oxygen therapy performed over a long period of time being a therapeutic possibility that can ameliorate it. PAP still remains a excellent indicator of the prognosis for patients with COPD and long-time oxygen therapy, because it is a good marker of the duration and severity of the alveolar hypoxia at these patients. (1)

In the USA, the mortality rate due to chronic pulmonary diseases is of 100.000/ year, but the percentage of pulmonary hypertension cannot be determined. The pulmonary hypertension is a complication of the advanced COPD and the separation of the two clinical entities is not possible. (2)

The mortality due to secondary cor pulmonale COPD is of 30- 35% in one year. Very few data regarding the survival of patients with pulmonary fibrosis +/- COPD exist, as a cause of cor pulmonale. The death rate in one year was of 38%, the premature death prediction factors being the inferior recurrent pulmonary infections, the persistent dyspnea, although the adequate therapy for bronchial dilatation was performed, the masculine gender, the central cyanosis and the co-existance of COPD.

In a prospective study which included 74 patients with COPD, it measured the pulmonary arterial pressure, the pulmonary vascular resistance and the cardiac debit in 1 and 2 years. Although the survivors presented only minor modifications of these parameters, at those who did not survive a sustained growth of the PAP and pulmonary vascular rezistence (PVR) values was determined. (6)

Pathogeny

The development of the pulmonary hypertension in COPD is due to more factors.

1. Hypoxemia and hypercapnia – A negative correlation exists between PAP and the oxygen saturation at persons with CPOD. More than that, the hypoxic vasoconstriction and arterial hypoxemia at patients with COPD may lead to severe modifications of the pulmonary vessels including the growth of the flat muscular cells, medial thickening of the muscular arterioles and the fibrinoid necrosis of the vascular walls. The structural changes of the pulmonary vessels, more than the vasoconstriction alone, is apparently responsible of the sustained growth of the pulmonary arterial pressure. The vasoconstriction induced by the hypoxemia is accentuated by the acidosis. Hypercapnia is also responsible for the growth of the pulmonary arterial pressure through the augmentation of the hypoxemic vasoconstrictor response or through the hyporventilation start. (10)

2. The destruction of the pulmonary vascular bed – PAH from COPD is believed to appear through the injury of the capillary endothelial cells. The destruction of the pulmonary vascular bed is apparently particularly responsible of the pulmonary arterial pressure growth at effort.

3. Intrinsic modifications of the pulmonary vasodilatation substances – the mediators implied in the regulation of the pulmonary vascular tonus include nitric oxide (NO), a relaxation factor derived from endotelin and endotelin 1. The release of NO, a relaxation factor derived from the intima of the pulmonary vessels, is believed to inhibit the cellular proliferation from the pulmonary vessels. The hypoxemy blocks the production and release of NO, being responsible of the growth of the pulmonary vascular tonus and the pulmonary vascular remodelation. The pulmonary hypertension in COPD is followed by the reduction of exhaled NO.(3,4,5,14)

4. The growth of the sanguine viscosity – the policitemia secondary to chronic hypoxemia is responsible for the growth of the sanguine viscosity, with accentuation of the pulmonary arterial pressure. It has been demonstrated that phlebotomy produces a slight decreasing of the pulmonary arterial pressure and of the pulmonary vascular resistance at persons with COPD and policitemia. (16)

5. The alteraion of the respiration mechanics – the pulmonary vascular resistance may be altered by the growth of the airways resistance. At patients with severe COPD, the hyperventilation during the exacerbation episodes rises the alveolar pressure, having as a consequence the growth of PAP. (19)

Particular aspects of the HTP in BPOC

The main characteristic of the pulmonary hypertension in the chronic pulmonary diseases is its slight-moderate degree, with PAP values of repose in the periods of stability of the disease of 20-35 mmHg. These modest values of the pulmonary pressure are well known in COPD, and they are different from the values of the left cardiac pathology, congenital cardiac diseases, pulmonary thromboembolism and primary pulmonary hypertension, where the values are frequently over 40-50 mmHg. PAP over 40 mmHg is unusual at patients with COPD, excepting those who are investigated during exacerbations or when they present another cardiopulmonary disease.

The consequence of this modest level of the pulmonary hypertension is the late appearance of the right cardiac insufficiency and the frequent incapacity of the non-invasive methods to diagnose the pulmonary hypertension. Nevertheless, the pulmonary hypertension, even if it reaches modest values in repose, is accentuated at effort, during sleep and during the acutizations of the infections.

During the late stages, PAP grows intensely at effort in the case of patients with COPD and repose pulmonary hypertension. This growth is explained by the fact that the pulmonary vascular resistance does not decrease during effort at these patients, the cardiac debit is increasing and the pulmonary arterial pressure is increasing accordingly.

The acute increases of PAP during sleep were observed at patients with COPD and respiratory insufficiency. These events were observed mainly during rapid eis movements (REM) sleep, when severe desaturations appear. These desaturation episodes during sleep are not caused by apnea, excepting the cases of sleep apnea sysndrom associated with COPD, but by the alveolar hypoventilation and/or the alteration of the ventilation/perfusion relation. The more the desaturation is more severe, the more accentuated is the pulmonary pressure, being able to grow by over 10 mmHg in relation to the base line. (9)

The respiratory insufficiency episodes are followed by the aggravation of the hypoxemia and hypercapnia, and at the same time by a pronounced PAP growth, sometimes by over 20 mmHg, returning to the base values after the remission of this episode.

The progression of the pulmonary hypertension is slow at patients with COPD, and the pulmonary arterial pressure can remain stable on a period of 3 to 10 years. At a lot of 93 patients with COPD, who were monitored during 90 months, the average of the PAP modifications was of only +0,5 mmHg in a year. This means that the majority of the patients with COPD, whose pulmonary arterial pressure is initially normal < 20 mmHg, will not exceed the value of 25 mmHg in the next 5 years. A percentage of 30% of the patients with advanced COPD will develop a notable aggravation of PAP during the monitoring. These patients are not different from the others at the beginning, but are characterized by a severe deterioration of PaO2 and PaCO2 during the evolution, which justifies the necessity of measuring the sanguine gasometry regularly at patients with advanced COPD.(18)

The clinical suspicion and the early detection of the pulmonary hypertension in COPD, of the cor pulmonale as their complication, must represent a target of the clinician, for instituting the adequate therapy on time and for the purpose of appreciating the evolution and prognosis objectively.

BIBLIOGRAPHY

- 1. Behnke RH, Blount SG, Bristow *J*, Carrieri V, Pierce JA, Sasahara A, et al. Primary prevention of pulmonary heart disease. J Am Osteopath Assoc 1970;(69):1139-1146.
- Budev MM, Arroliga AC, Wiedemann HP, Matthay AR. Cor pulmonale. Semin Respir Crit Care Med. 2003 ;24(3):233-44.
- 3. Cargill RI, Kiely DG, Clark RA, Lipworth BJ. Hypoxaemia and release of endothelin-1. Thorax 1995;(50):1308-1310.
- 4. Clini E, Cremona G, Campana M, Scotti C, Pagani M,

Bianchi Aet al. Production of endogenous nitric oxide in chronic obstructive pulmonary disease and patients with cor pulmonale. Correlates with echo-Doppler assessment. Am J Respir Crit Care Med 2000;(162):446-450.

- Dinh-Xuan AT, Higenbottam TW, Wallwork J. Relationship between chronic hypoxia and in vitro pulmonary relaxation mediated by endothelium-derived relaxing factors in human chronic obstructive lung disease. Angiology 1992;(43):350-356.
- Finlay M, Middleton HC, Peake MD, Howard P. Cardiac output pulmonary hypertension, hypoxaemia and survival in patients with chronic obstructive airways disease. Eur J Respir Dis 1983;(64):252-263.
- 7. Fishman AP. Chronic cor pulmonale. Am Rev Respir Dis 1978;114:775–94.
- Fishman PA. Pulmonary Hypertension and Cor Pulmonale. In *Fishman S. Pulmonary Diseases* Ed. McGraw-Hill 1998; Chapter 83; pp: 1261-1297.
- Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease: the effect of short and long-term oxygen. Chest 1984;(85):6–14.
- Harris P, Heath D. The pulmonary vasculature in emphysema. In: Harris P, Heath D, eds. The human pulmonary circulation. Edinburgh: Churchill Livingstone; 1986:507-521.
- Harris P, Segel N, Green J, Housley E. The influence of the airways resistance and alveolar pressure on the pulmonary resistance in chronic bronchitis. Cardiovasc Res 1968;(2):84-94.
- Klinger JR, Hill NS. Right ventricular dysfunction in chronic obstructive pulmonary disease. Evaluation and management. Chest 1991;(99):715-723.
- MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;(150):833-852.
- Moncada S, Palmer RMJ, Higgs EA. Prostacyclin and endothelial-derived relaxing factor: biological interactions and significance. In: Verstraete M, Verrmylen J, Lijnen RH, eds. Thrombosis and Haemostasis. Belgium: University Press Leuven, 1987:597-618.
- Rigolin VH, Robiolio P, Wilson JS, Harrison JK, Bashore TM. The forgotten chamber. Cathet Cardiovasc Diagn 1995;(35):18-28.
- 16. Segel N, Bishop JM. The circulation in patients with chronic bronchitis and emphysema at rest and during exercise with special reference to the influence of change in blood viscosity and blood volume on the pulmonary circulation. J Clin Invest 1966;(45):1555-1568.
- Teofilo L, Lee-Chiong Jr., Matthay RA. Pulmonary Hypertension and Cor Pulmonale in COPD. Semin Respir Crit Care Med 2003; 24(3): 263-272.
- Weitzenblum E, Hirth C, Ducolone A, et al. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. Thorax 1981;(36):752-758.
- 19. Weitzenblum E. Chronic cor pulmonale. Heart 2003;(89):225-230.
- World Health organization. Chronic cor pulmonale. A report of the expert committee. Circulation 1963;(2):594-598.