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Modern Diagnostics of Pulmonary Arterial Hypertension

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Diagnosticul modern al hipertensiunii pulmonare arteriale

Lucrarea reprezintă o sinteză a cercetărilor actuale din domeniul diagnosticului modern al hipertensiunii pulmonare arteriale. Datele analizate provin dintr-o bibliografie bogată din literatura de specialitate. La etapa actuală, diagnosticarea sindromului de hipertensiune pulmonară arterială se realizează cu utilizarea diferitelor metode: electrocardiografia, ecocardiografia Doppler, radiografia toracică, scintigrafia pulmonară prin perfuzie şi prin ventilaţie, tomografia computerizată, testele funcţiei pulmonare şi cateterizmul cardiac. De asemenea, articolul conţine informaţii practice referitoare la rolul diferitelor metode imagistice în aprecierea patologiei.

Cuvinte-cheie: hipertensiunea pulmonară arterială, metode de diagnostic.

Современная диагностика легочной артериальной гипертензии

Представленная работа является синтезом актуальных методов диагностики легочной артериальной гипертензии. Анализируемые данные селектированы из множества литературных источников данного профиля. В настоящее время диагностика синдрома легочной артериальной гипертензии осуществляется с использованием различных методов: электрокардиография, эхокардиография Допплер, рентгенография грудной клетки, перфузионная и вентиляционная сцинтиграфия легких, компьютерная томография, методы функциональной диагностики, катетеризация сердца. Статья также содержит практическую информацию о роли различных методов лучевой диагностики в определении соответствующей патологии.

Ключевые слова: легочная артериальная гипертензия, методы диагностики.

Introduction

Pulmonary hypertension is a serious disease with a poor prognosis. Pulmonary hypertension is defined by a mean pulmonary arterial pressure of over 25 mm Hg at rest and of over 30 mm Hg during activity. According to the recent 2003 WHO classification, pulmonary hypertension can be categorized as pulmonary arterial hypertension, pulmonary venous hypertension, hypoxic pulmonary hypertension, chronic thromboembolic pulmonary hypertension, or pulmonary hypertension from other causes. Pulmonary arterial hypertension is characterized histopathologically by vasoconstriction, vascular proliferation, in situ thrombosis and the remodeling of all 3 levels of the vascular walls. These pathologic changes result in progressive increases in the mean pulmonary artery pressure and in pulmonary vascular resistance, which, if left untreated, leads to right-ventricular failure and death. Early on in the disease progress, the signs and symptoms of PAH are often nonspecific, making diagnosis a challenge. Patients often show signs of progressively worsening dyspnea and fatigue. Patients with severe pulmonary arterial hypertension die of right heart failure.

Diagnostic procedures include clinical history and physical examination, a standard chest radiography, electrocardiography, transthoracic Doppler echocardiography, pulmonary function tests, arterial blood gas analysis, ventilation and perfusion lung scan, high-resolution computed tomography of the lungs, contrast-enhanced spiral computed tomography of the lungs and pulmonary angiography, blood tests and immunology, abdominal ultrasound scan, exercise capacity assessment, and hemodynamic evaluation. Invasive and non-invasive markers of the severity of the disease, either biomarkers or physiological parameter, and tests that can be widely applied, have been proposed to reliably monitor the clinical course. Pulmonary biopsy is rarely indicated. Transthoracic echocardiography is a key screening tool in the diagnostic algorithm. Because transthoracic echocardiography is an inexpensive, easy, and reproducible method, it is the most commonly used noninvasive diagnostic tool to determine pulmonary arterial pressure. It not only provides an estimate of pulmonary pressure at rest and during exercise, but may also help to exclude any secondary causes of pulmonary hypertension, predict the prognosis, monitor the efficacy of specific therapeutic interventions, and detect the preclinical stage of the disease. In addition, the measurement of serum markers, such as brain natriuretic peptide (BNP) are diagnostically useful and of prognostic significance.

Once the diagnosis and etiology of pulmonary hypertension have been established, several parameters can predict its outcome in patients: functional class, right ventricular function, pulmonary hemodynamics, and certain laboratory parameters. Also, exercise parameters such as distance walking, peak oxygen uptake, or peak systolic blood pressure, can predict a reliable prognosis in patients.

Classification of Pulmonary Hypertension

Pulmonary hypertension was previously divided into primary and secondary categories; primary pulmonary

hypertension described an idiopathic hypertensive vasculopathy, exclusively affecting pulmonary circulation, whereas secondary pulmonary hypertension was associated with a causal underlying disease process (2, 3). The diagnosis of primary pulmonary was one of exclusion after ruling out all causes of pulmonary hypertension (4). The recent identification of a gene responsible for the inherited forms of this disease, along with the development of specific medical treatments and the refinement of surgical techniques, has prompted a revised classification of pulmonary hypertension (5). In 2003, the Third World Symposium on pulmonary arterial hypertension held in Venice, Italy decided to maintain the general architecture and philosophy of the Evian – France classification (1998) and to propose some modifications. The aim of the modifications was to make the "Venice clinical classification" more comprehensive, easier to follow, and more widespread as a tool of classification (1).

Clinical classification of Pulmonary Hypertension (PH) – Venice 2003.

1. Pulmonary arterial hypertension (PAH)

1.1. Idiopathic (IPAH)
1.2. Familial (FPAH)
1.3. Associated with (APAH):
1.3.1. Connective tissue disease
1.3.2. Congenital systemic to pulmonary shunts
1.3.3. Portal hypertension
1.3.4. HIV infection
1.3.5. Drugs and toxins
1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
1.4. Associated with significant venous or capillary involvement
1.4.1. Pulmonary veno-occlusive disease (PVOD)
1.4.2. Pulmonary capillary haemangiomatosis (PCH)
1.5. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension associated with left heart diseases

2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia

3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Sleep-disordered breathing
3.4. Alveolar hypoventilation disorders
3.5. Chronic exposure to high altitudes
3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

4.1. Thromboembolic obstruction of proximal pulmonary arteries
4.2. Thromboembolic obstruction of distal pulmonary arteries
4.3. Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)

5. Miscellaneous

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

Definition and clinical symptoms

In its early stages, pulmonary arterial hypertension may be asymptomatic. Pulmonary hypertension often presents itself with nonspecific symptoms. The most common symptoms – exertional dyspnea, fatique, and syncope – reflect an inability to increase cardiac output during activity. The leading symptom of pulmonary arterial hypertension is exertional dyspnea. A minority of patients may report typical angina despite normal coronary arteries. The symptoms of pulmonary hypertension can also include weakness and abdominal distension (7). Hemoptysis resulting from the rupture of distended pulmonary vessels is a rare but potentially devastating event. Raynaud`s phenomenon occurs in approximately 2% of patients with primary pulmonary hypertension, but it is more common in patients with pulmonary hypertension related to connective tissue disease. More specific symptoms may reflect the underlying cause of pulmonary hypertension (8). Symptoms at rest are reported only in very advanced cases.

Diagnostics

The clinical cardinal symptom of pulmonary hypertension is dyspnea. The diagnostic process of pulmonary hypertension requires a series of investigations that are intended to make the diagnosis, to clarify the clinical class of pulmonary hypertension and the type of pulmonary arterial hypertension, and to evaluate functional and hemodynamic impairment (Table 1).

Table 1

Diagnosis of pulmonary hypertension

NON-INVASIVE
Echocardiography transthoracic
Walking distance of 6 minutes: for severity code, therapy control and prognosis
Laboratory tests
Pulmonary function: spirometry
Spiroergometry
Ventilation-perfusion lung scan
Computer tomography of the lung: interstitial tissue visualization
INVASIVE
Right cardiac catheterization
Pharmacological tests

Non-invasive diagnostics

Physical examination. Physical examination can reveal increased jugular venous distention, a tricuspid regurgitant holosystolic murmur, and a loud P2; all suggestive of elevated right-sided pressure. Lung sounds are usually normal. Hepa-

tomegaly, peripheral oedema, ascites and cool extremities, characterize patients at a more advanced stage of the disease with right ventricular failure at rest.

Electrocardiography. Electrocardiographic signs of the right heart include right axis deviation, right ventricular hypertrophy, and peaked P waves. However, electrocardiography lacks sufficient diagnostic accuracy to serve as a screening tool for the detection of pulmonary arterial hypertension. Right ventricular hypertrophy on ECG is present in 87% of patients and right axis deviation in 79% of patients (7). ECG has inadequate sensitivity (55%) and specifity (70%) (10). A normal ECG does not exclude the presence of severe pulmonary hypertension.

Chest radiography. The chest radiograph is inferior to ECG in detecting pulmonary hypertension, but it may show evidence of underlying lung disease (3). In 90% of pulmonary arterial hypertension patients, the chest radiograph is abnormal at the time of diagnosis (7). The findings include central pulmonary arterial dilatation which contrasts with "pruning" of the peripheral blood vessels. A hilar-to-thoracic ratio greater than 0.44, a right descending pulmonary artery diameter of greater than 18 mm, and right atrial and ventricular enlargement may be seen, which progresses in more advanced cases. However, a normal chest radiograph does not exclude mild pulmonary hypertension, including left-heart disease or pulmonary veno-occlusive disease.

Echocardiography. Transthoracic echocardiography is an excellent non-invasive screening test for patients with suspected pulmonary hypertension. Transthoracic echocardiography estimates pulmonary artery systolic pressure and can provide additional information about the causes and consequences of pulmonary hypertension.

Pulmonary artery systolic pressure is equivalent to right ventricular systolic pressure in the absence of pulmonary outflow obstruction. With CW-Doppler-echocardiography, right ventricular systolic pressure (RVSP) can be obtained by adding the estimated right atrial pressure (RAP) to the pressure gradient derived from systolic regurgitant tricuspid flow velocity v, according to the formula: RVSP = 4 v2 + RAP. Echocardiographic estimation of the right atrial pressure can be attained by measuring the diameter of the inferior vena cava and the respiratory motion of the inferior vena cava (Table 2). According to the normal ranges of Doppler-derived values of pulmonary artery pressures, mild pulmonary hypertension can be defined as pulmonary artery systolic pressures of approximately 36-50 mmHg or resting tricuspid regurgitant velocity of 2.8-3.4 m/sec, assuming a normal right atrial pressure of 5 mmHg. The right ventricular systolic pressure may be underestimated in some cases because of suboptimal tracings of the regurgitation jet, of decreased tricuspid regurgitant jet velocity due to high right atrial pressures, and poor estimation of right atrial pressures. However, in order to estimate a right ventricular systolic pressure by echocardiography, tricuspid regurgitation must be present.

Table 2

Echocardiographic estimation of the right atrial pressure (RAP) by measuring the diameter of the inferior vena cava and the respiratory motion of the vena cava inferior (VCI)

VCI-diameter (cm)	Respiratory motion (%)	RAP (mmHg)
<1,5	100	<5
1,5-2,5	>50	5-10
1,5-2,5	<50	10-15
>2,5	>50	15-20
>2,5 + dilated	0	>20
Hepatic vein	–	–

Indirect signs of pulmonary hypertension are: paradoxical septal motion (septal bowling or flattering), decreased or missing collapse of the vena cava inferior, pericardial effusion, right ventricular hypertrophy and reduced right ventricular ejection time. Additional examination to the routine echocardiography is the estimation of right ventricular Tei-index (isovolumetric contraction time and relaxation time/ejection time) (4) and the "tricuspid annular plane systolic excursion" (TASPE). The peak early diastolic pulmonary regurgitation velocity is useful in estimating mean pulmonary artery pressure (mean PAP). Together with the dimension of the right atrium and pericardial effusion, Tei-index and TASPE are important prognostic parameters in patients with pulmonary hypertension, while the right ventricular systolic pressure does not correlate with survival (10). Echocardiography is the most useful imaging modality for detecting pulmonary hypertension and excluding underlying cardiac disease.

Ventilation/Perfusion Scanning. Ventilation/perfusion scans are often used to rule out other causes of dyspnea. Fortunately, ventilation-perfusion lung scanning is a reliable method for differentiating chronic thromboembolism from primary pulmonary hypertension (9). Normal ventilation and quantification scans rule out chronic thromboembolic disease (10). The finding of one or more segmental or larger perfusion defects is a sensitive marker of embolic obstruction.

Computer Tomography. Computerized tomographic (CT) scanning of the chest with high-resolution images is useful in excluding occult interstitial lung disease and mediastinal fibrosis. It also is helpful in the diagnosis of pulmonary embolism. Magnetic resonance imaging can be used to assess the size and function of the right ventricle, myocardial thickness, the presence of chronic thromboembolic disease with a mosaic pattern of the lung parenchyma, and cardiac and pulmonary pressures (6, 7).

Pulmonary Function Testing. The role of pulmonary function testing is to rule out parenchymal or obstructive lung disease as a cause of the patient`s symptoms. Unless hypoxia is present, pulmonary hypertension cannot be attributed to these disorders until pulmonary function is severely reduced. Some patients with pulmonary artery hypertension can suffer a mild decline in their total lung capacity and diffusing capacity for carbon monoxide, but the severity of these declines does not correlate with dis-

ease severity. With pulmonary function testing, neither an accurate diagnosis nor adequate follow-up examinations are possible.

Six-minute Walk Test. Submaximal testing with a 6-minute walk test is recommended at the time of diagnosis to establish baseline functional impairment and at the follow-up to assess response to therapy and prognosis (8). The mortality risk is increased 2.4-fold in patients with pulmonary arterial hypertension who are able to walk less than 300 m in 6 minutes and 2.9-fold in those with a greater than 10% decline in arterial oxygen saturation (14). The 6-minute walk distance correlates with severity by NYHA functional class in patients with pulmonary hypertension. Patients who walk less than 332 m have a significantly lower survival rate than those who walk farther (10).

Cardiopulmonary Exercise Testing. Cardiopulmonary exercise testing (CPET) allows the measurement of ventilation and pulmonary gas exchange during exercise testing, providing additional "pathophysiologic" information to that derived from standard exercise testing. Cardiopulmonary exercise testing has no added value in the initial diagnostic testing of pulmonary hypertension. The most important parameters are the maximal oxygen uptake (peak VO2) and the relation from ventilation to CO2-relief (VE/VCO2). Pulmonary hypertension patients show reduced peak O2, reduced peak work rate, reduced ratio of VO2 increase to work rate increase, reduced anaerobic threshold and reduced peak oxygen pulse; they show also increased VE and VCO2 slope representative of ventilatory inefficiency (13).

Invasive diagnostics

Right Heart Catheterization. Right heart catheterization remains the gold standard for the diagnosis of pulmonary hypertension. All patients suspected of having significant pulmonary hypertension after clinical and transthoracic echocardiographic evaluation should undergo right heart catheterization, particularly if they are candidates for treatment (6).

The goals of right heart catheterization, in addition to making a diagnosis, are to measure right atrial and ventricular pressures, to detect pulmonary artery pressure (PAP systolic, PAP diastolic, PAP mean) and pulmonary artery capillary wedge pressure (PCWP), to measure pulmonary vascular and systemic vascular resistance (PVR, SVR), to calculate cardiac output/index (end organ function) by Fick principle or thermodilution, to evaluate pulmonary artery O2-saturation, and to look for the presence of left-to-right shunts and right-to-left shunt (the latter makes left heart cardiac catheterization necessary). The significance of right heart catheterization is to assess the severity of the hemodynamic impairment, to predict the prognosis, to identify other causes of pulmonary hypertension, to monitor the etiopathology, to evaluate the right ventricular function, and to test the vasoreactivity of the pulmonary circulation.

Vasodilator testing during right-heart cardiac catheterization should only be done by using short-acting vasodilators such as adenosine/epoprostenol intravenously or by administering prostacyclin, nitric oxide or iloprost by inhalation. According to the European Society of Cardiology, a response to acute vasodilator testing includes a decrease of more than 10 mmHg in the mean pulmonary artery pressure and/or a decrease of the mean pulmonary artery pressure under 40 mmHg. Responders to acute vasodilator testing have a favorable clinical response and course when treated with calcium channel blockers, but calcium channel blockers should be strictly avoided in non-responders. There are no absolute contraindications to right heart catheterization and complications are rare, though may happen.

Disease monitoring

While echocardiography is the screening method for acquisition of pulmonary hypertension (high sensitivity), the right heart cardiac catheterization has a higher specificity and is a required method to confirm the diagnosis definitely. Some patients with mild and moderate pulmonary hypertension can be managed without right heart catheterization. Those with mild to moderate pulmonary hypertension due to chronic hypoxemia (resting, exertional or noctural) can be followed with serial echocardiography for evidence of progression on appropriate oxygen and/or noctural ventilatory support. For patients with mild to moderate pulmonary hypertension by echocardiography who do not have NYHA class III symptoms, right heart cardiac catheterization can be reserved as a future option if pulmonary hypertension progresses on serial echocardiography every 3 to 6 months.

Right heart function and ejection fraction are of great importance in patients with pulmonary hypertension: clinical severity and mortality rate do increase in concert with the degree of limitation of the right ventricular function and ejection fraction. The higher the mean pulmonary arterial pressure and the pulmonary wedge pressure and the worse the right ventricular function, the higher the mortality with left heart insufficiency will be. Patients with a low ejection fraction and high pulmonary artery pressure show a particularly bad prognosis, independent of the degree of restricted left ventricular function (11, 12).

Conclusion

Pulmonary hypertension is defined as an elevation in pulmonary arterial pressures and is characterized by symptoms of dyspnea, chest pain and syncope. If left untreated, pulmonary arterial hypertension has a high mortality rate, typically from decompensated right-sided heart failure. Estimated median survival is approximately 2.8 years.

The past decade has seen major advances in our understanding of the pathophysiological mechanisms underlying the development of pulmonary arterial hypertension. The diagnosis is now more clearly defined according to a new clinical classification, and clear algorithms have been devised for the investigation. Imaging methods are very important for the diagnosis of pulmonary arterial hypertension. However, the prognosis of pulmonary arterial hypertension remains guarded despite recent advances and new therapeutic options.

References

1. Guidelines on diagnostic and treatment of arterial pulmonary hypertension. European heart Journal 2004; 25: 2243-2278.
2. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One. Am J Respir Crit Care Med 1994; 150:833-852.
3. Hatano S, Strasser T. World Health organization 1975 primary pulmonary hypertension. Geneva. WHO; 1975.
4. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997; 336:111-117.
5. Galie N, Torbicki A, Barst R et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The task force on diagnosis and treatment of pulmonary arterial hypertension of the European society of cardiology. Eur Heart 2004; 25:2243-2278.
6. Fox DJ, Khattar RS. Pulmonary arterial hypertension: classification, diagnosis and contemporary management. Postgrad Med J 2006; 82:717-722.
7. Simonneau G, Galie N, Rubin L et al. Clinical classification of pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43:S5-S12.
8. Rich S, Dantzker DR, Ayres SM et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987; 107:216-223.
9. Gurubhavatula I, Palevsky HI. Pulmonary hypertension in systemic autoimmune disease. Rheum Dis Clin North Am 1997; 23:365-394.
10. Nauser TD, Stites St. Diagnosis and treatment of pulmonary hypertension. Am Fam Physician 2001; 63:1789-1798.
11. Palevsky HI, Fishman AP. Chronic cor pulmonale. Etiolology and management. JAMA 1990; 263:2347-2353.
12. Olsclewski H., Seeger W. Pulmonary hypertension. Pathology, diagnosis, treatment and development of a pulmonary-selective therapy. Ed. Uni-Med, 2002.
13. Bromberg C., Gatzoulis M. Recent advances in the treatment of pulmonary hypertension. Hell J Cardiol 2005; 46: 165-173.
14. Peacock A, Rubin L. J. Pulmonary Circulation diseases and their treatment. Second ed., Ed. Arnold, 2004.

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Terapia antiinflamatoare la bolnavii cu bronhopneumopatie obstructivă cronică

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Anti-Inflammatory Therapy in the Treatment of Patients with Obstructive Pulmonary Disease

The aim of the study was to investigate the effects of Eurespal (Fenspirid) on the clinical manifestations and parameters of inflammation in patients with chronic obstructive pulmonary disease (COPD). The two stages of the study included a 3-week treatment during exacerbation periods and a 3-month outpatient follow-up during clinical remission periods. During exacerbation periods of COPD the researchers observed earlier and more noticeable antitussive and mucolytic action of Eurespal which were associated with the lessening of bronchial obstruction and inflammation, a significant drop of the C-reactive protein level and an increase of total oxidant serum level. Long-term (3 months) treatment with Eurespal led to further positive dynamics of clinical and laboratory indices of inflammation. The results of the study demonstrate that inclusion of Eurespal in complex therapy of COPD increases efficacy of treatment through its anti-inflammatory action during the periods of exacerbation and relative remission.

Key words: Eurespal, chronic obstructive pulmonary disease, inflammation.

Противовоспалительная терапия в лечении больных хронической обструктивной болезнью легких

Было изучено влияние эреспала (фенспирид) на клиническое течение и показатели воспаления у больных хронической обструктивной болезнью легких (ХОБЛ). Исследование проводили в 2 этапа: в течение 3 нед терапии при обострении заболевания и на протяжении 3 мес амбулаторного лечения в периоде клинической ремиссии. При обострении ХОБЛ терапия эреспалом оказывала более ранний и отчетливый противокашлевой, муколитический эффекты, сопровождаясь уменьшением обструкции, интенсивности воспаления в бронхах, достоверным снижением содержания С-реактивного белка и увеличением содержания общих антиоксидантов в сыворотке крови. Длительное (в течение 3 мес) лечение эреспалом обеспечивало у больных ХОБЛ дальнейшую положительную динамику клинико-лабораторных показателей воспаления. Результаты исследования позволяют считать, что включение эреспала в комплексную терапию ХОБЛ повышает эффективность лечения как при обострении, так и ремиссии заболевания, оказывая выраженное противовоспалительное действие.

Ключевые слова: Эреспал, хроническая обструктивная болезнь легких, воспаление.

Introducere

Boala pulmonară bronhopneumopatia obstructivă cronică (BPOC) este o problemă actuală a ocrotirii sănătăţii şi una dintre cauzele de bază în mortalitatea cauzată de bolile pulmonare. BPOC exercită o influenţă semnificativă asupra calităţii vieţii şi longevităţii pacienţilor şi cauzează pierderi