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Prognosis, screening, early detection and differentiation of arterial pulmonary hypertension

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Summary

Pulmonary hypertension (PH) has been partially reclassified during the 2003 Third World Symposium on Pulmonary Arterial Hypertension held in Venice. PH is a common disorder that may complicate a variety of cardiopulmonary diseases, including severe COPD, left ventricular failure and chronic thromboembolic obstruction of the pulmonary arteries. Pulmonary arterial hypertension (PAH) is an increase in pulmonary arterial pressure which is not due to classical coexistent cardiopulmonary disease. PAH usually occurs in the absence of an evident cause (idiopathic or familial) or it may be associated with connective tissue disease, HIV infection, chronic liver disease, congenital systemic-to-pulmonary shunts, venous or capillary involvement, thyroid or myeloproliferative disorders as well as a result of the use of toxic agents and anorexigens. The actuality of developed disease-specific treatments over the past decade, emphasises the importance of an early screening and detection of PH which, even optimally treated in advanced stages, still remains a progressive lethal disease in most of its forms. Early identification represents a real challenge for the clinician: in fact, it is believed that an early recognition and, thus, an early treatment, might be associated with improved survival. In this review, after a short introduction on disease prognosis, we will focus on screening and early recognition of some categories of PH, based on a sequential approach that includes clinical suspicion, detection and differentiation of pulmonary hypertension. This strategy should consent to reach an assessment of severity, ultimately providing the best selective use of therapies.

Key words: pulmonary hypertension; pulmonary arterial hypertension; early detection, screening

Introduction

Pulmonary arterial hypertension (PAH), the most serious chronic disorder of the pulmonary circulation, is a syndrome based on diverse aetiologies and pathogenesis, potentially leading to right heart failure and death [1]. Untreated pulmonary hypertension (PH) goes through a sequence of haemodynamic and clinical deteriorations, illustrated in figure 1, but pathophysiological changes still emerge in the presymptomatic phase of the disease: in the model represented on the figure it becomes apparent that patients presenting early in the course of the disease still have elevations in PAP but they are minimally asymptomatic or even asymptomatic, given the stability of cardiac output. Dyspnoea may become apparent only during

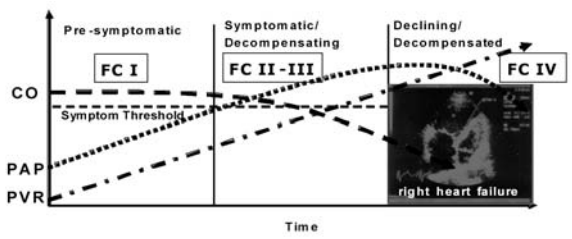

Figure 1

Matching of haemodynamic (cardiac output, CO, mean pulmonary arterial pressure, PAP, and pulmonary vascular resistances, PVR) and clinical (functional NYHA classes, FC) deterioration in untreated arterial pulmonary hypertension. See the Introduction section for the additional description.

List of abbreviations

PH	Pulmonary hypertension
PAH	Pulmonary arterial hypertension
iPAH	Idiopathic pulmonary arterial hypertension
CTEPH	Chronic thromboembolic pulmonary hypertension
TTE	Transthoracic Doppler echocardiography
PASP	Pulmonary arterial systolic pressure

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exercise. This presymptomatic disease phase characterises the real diagnostic challenge for the clinician. In fact, it is believed that an early recognition and, consequently, an early treatment might be associated with improved survival. Unfortunately, the great majority of the randomised clinical studies investigating the effects of the new drugs over time, have focused on a selection of patients with the functional class (II) – III – IV while pre-symptomatic NYHA-class I patients have been almost ignored due to unspecific symptoms and diagnostic complexities. Indeed, very few data are available and the best strategy for this category remains undetermined.

Prognosis

Before the availability of the new targeted-specific treatments, conventionally treated idiopathic PAH patients had a very poor survival. Through the mid-1980s, the median life expectancy was 2.8 years from the time of diagnosis as demonstrated in the historical American prospective registry of the NIH [1] and further corroborated in a more recent French historical group of untreated patients with idiopathic pulmonary hypertension (iPAH; 2]. As pointed out by D'Alonzo et al. [1], the haemodynamic profile at baseline has a great prognostic value in PAH: patients with the worst prognosis may be identified at baseline by elevated mean right atrial and pulmonary arterial pressures, associated with a reduced cardiac index (CI) and a decreased central venous oxygen saturation. As an example, a given conventionally treated patient with a baseline right atrial pressure of more than 20 mm Hg and a CI of less than 2 L/min/m^2 at rest is characterised as a subject with bad prognosis, the median survival time being approximately 6 months. Finally, it must be pointed out that, compared to responders, non-responders to the acute vasoreactivity test with the traditional drugs (nitric oxide, adenosine, PGI_2), had the worst prognosis [3, 4].

In recent years, the first significant improvement in survival for patients with iPAH has been achieved with the intravenously infused synthetic prostacyclin epoprostenol. Its efficacy has been tested in controlled clinical trials in iPAH and in PAH associated to scleroderma and it represents today the only treatment to improve survival in idiopathic PAH-patients [5, 6]. In the study of McLaughlin and co-workers [6], data showed that survival was strongly dependent on the severity of the disease at baseline, namely the NYHA functional class at the moment of diagnosis. First of all, this statement underlines the importance of the functional class in addition to the exercise capacity at baseline as prognostic factors for survival in PAH [7]. Moreover, it underlines the importance of an early screening in the outcome impact of the disease.

The importance of a national registry for analysing disease awareness

Results classified in national registries are important to provide estimates for the prevalence of patients diagnosed with PAH according to standardised definitions. Clinical and haemodynamic descriptions contained in these registries may identify the current treatment practice and the disease course detection. For instance, in the Swiss retrospective registry published in 2001, we collected 106 patients with PAH; the median age was 43 years but 79% were in NYHA class III or IV at the moment of diagnosis [8]. Recently, the results of the national French registry have also been published [9]: this registry showed that, despite advances in understanding and treating PAH and presumably better awareness, patients were still initially diagnosed with a severe clinical impairment. Indeed, 75% of patients were identified and classified in NYHA functional class III or IV. In the whole cohort of patients, there was a delay of 27 months between the onset of symptoms and diagnosis, and the majority of patients had severe symptoms at presentation. Together, it appears that awareness is still largely unsatisfactory in the field of diagnosing PAH. Reasons for failure to attain a timely and definitive diagnosis may be multiple, the most cited ones being the insidious early-stage symptoms, the failure to consider PAH as a cause of breathlessness, the confusion with other more common conditions, the similarity with other cardiopulmonary disorders and the fact that idiopathic pulmonary arterial hypertension is a diagnosis of exclusion. In conclusion, increased awareness is needed for attaining an early and accurate diagnosis of PAH, because a timely identification may lead to improved outcomes. For practical purposes, we suggest to adopt a systematic diagnostic approach, such as the one proposed by the "Task force" of the European Society of Cardiology [10].

Diagnostic approach of pulmonary hypertension

To detect PAH in the latent phase, the clinician must maintain a high index of clinical suspicion in the presence of even small signs and symptoms. Then, by employing a systematic diagnostic approach based on the new clinical classification ("The Venice classification"; [11]), he will be able to exclude or confirm PH, to establish a cause and severity of the disease and, finally, to monitor its progression.

Clinical suspicion of PH

Exertional dyspnoea in a patient without evident signs of specific heart and lung diseases should arise the suspicion of PH. Other unspecific *symptoms* can include angina and/or syncope during exercise, palpitations, cyanosis and Raynaud's phenomenon. Physical *signs* include distended jugular veins, a loud pulmonary second sound, a systolic murmur of tricuspid regurgitation, right ventricular extra sounds, hepatomegaly, peripheral oedema and ascites (table 1). Unfortunately, many signs are present only in advanced stages of the disease. Moreover, the non-specific nature of these complaints may lead to a misdiagnosis by delaying an accurate assessment. In particular, it is important to develop a rapid detection approach when signs and symptoms are present in high risk populations for PAH such as in patients with connective tissue diseases, previous pulmonary embolism or deep vein thrombosis, congenital heart diseases, portal hypertension, present or previous use of appetite suppressants and HIV. There is a rationale for periodic *screening* in patients with these predisposing diseases as well as in the family members of patients with the familial PAH-form, so that asymptomatic patients are recognised in their early stage of pulmonary hypertension (table 2). Occasionally, PH can be suspected in patients undergoing diagnostic procedures (ECG, chest X-ray and echocardiography) for other clinical reasons, including exertional dyspnoea, chest pain and syncope. While early detection of pulmonary hypertension is of paramount importance for disease management, it is central to emphasise that the prognostic value of this concept has not been established. Indeed, very few data are available and the best therapeutic strategy for this category remains undetermined.

Table 1
Physical signs and symptoms of pulmonary arterial hypertension.

Symptoms	Exertional dyspnoea
	Palpitations / arrhythmias
	Exertional syncope / angina
	Cyanosis
	Raynaud's phenomenon
Physical signs	Congested jugular veins
	Peripheral oedema / ascites / hepatomegaly
	Systolic murmur of tricuspid regurgitation
	Right ventricular extra sounds
	Loud pulmonary second sound

Table 2
Screening of patients at risk for pulmonary hypertension.

Patients with:	– Familial history of iPAH
	– Connective tissue diseases
	– Previous pulmonary embolism or deep vein thrombosis
	– Congenital heart disease
	– Portal hypertension
	– Previous or present use of appetite suppressants
	– HIV
are at risk for developing pulmonary hypertension.	

Detection of PH

When PH is suspected, investigations able to confirm the diagnosis are crucial. The first and most simple step is symbolised by the combination of techniques such as *ECG*, *chest X-ray* and, most importantly *transthoracic Doppler-echocardiography*. A normal *ECG* does not exclude even a severe form of PH. Although the lack of sufficient sensitivity and specificity can prevent the ECG to serve as an effective screening or detection method for PAH [12], the presence of signs of right atrial enlargement or signs of right ventricular hypertrophy and overload detected by this technique, could inspire further evaluation in a patient suspected to have pulmonary hypertension. In patients with a suspicion of PH, a *chest X-ray* should be obtained to reveal possible features of PH and to reasonably exclude left heart and lung parenchymal diseases. Indeed, the chest radiograph is mostly useful to show co-morbidities or particular causal conditions of PH such as interstitial lung disease, chronic obstructive pulmonary disease and left heart failure of various origins. In the historical American prospective registry of the NIH [1], the chest X-ray was abnormal in most of the patients with iPAH. However, the patients included were mostly classified as functional classes III and IV at the moment of diagnosis, explaining the high prevalence of pathological radiographs (ie dilatation of central pulmonary arteries, "pruning" of the peripheral vessels, right atrial-ventricular enlargement, as shown in figure 2). *Transthoracic Doppler- echocardiography* (TTE) is the most recommended non-invasive screening test for patients with suspected PH, because it can also provide information about the causes and the consequences of PH. As a screening, TTE is considered today the most reliable tool allowing a differential diagnosis between pre- and post-capillary pulmonary hypertension. Sensitivity and specificity of the technique may range from 0.79 to 1 and from 0.6 to 0.98 respectively [13]. Tricuspid regurgitant jets can be assessed by the TEE in the majority (74%) of patients with PH [14] and there is a fairly good [0.57–0.93] correlation between TTE and right

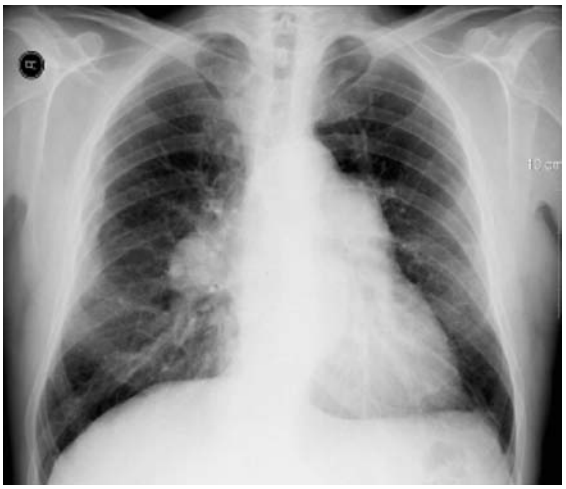

Figure 2

Chest radiograph in a patient with severe chronic thromboembolic pulmonary hypertension (mean PAP: 52 mm Hg) showing a dilatation of the central pulmonary arteries, a sudden reduction of the vessel calibres (right), a bulging of the middle left arch and a scarcity of peripheral vessels ("pruning").

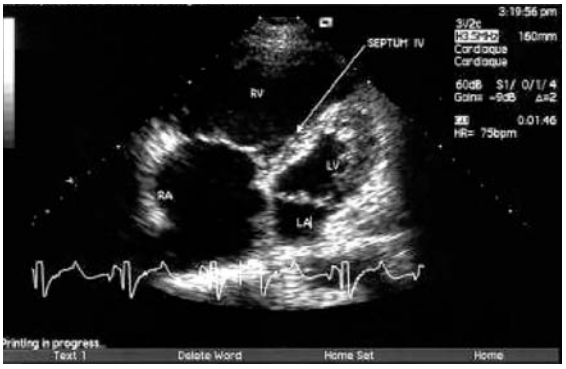

Figure 3

Qualitative echocardiographic approach: four chamber transthoracic Doppler echocardiography view in a patient with severe idiopathic pulmonary hypertension, showing an enlarged right ventricle and right atrium, the compression of the left ventricle and the flattening of the interventricular septum during diastole (courtesy of: G. Fiori, MD, Regional Hospital, Locarno).

heart catheterisation values of pulmonary artery systolic pressure (PASP) [12]. The *qualitative* TTE approach may assess the severity of PH by detecting enlarged right ventricle and right atrium, compression of the left ventricle and flattening of the septum during diastole (figure 3). *Quantitatively*, echocardiography allows to estimate PASP, which is equivalent to right ventricular systolic pressure in absence of pulmonary outflow obstruction. This is obtained by measuring the systolic regurgitant tricuspid jet-velocity *v* and by estimating right atrial pressure from characteristics of the inferior vena cava (figure 4). An important question arising at this point is represented by the definition of the normal value range for PASP among a healthy population. The most cited study exploring this important feature has been published in 2001 by McQuillan and co-workers [15]. According to these authors, a normal PASP range was reported to vary between 15 and 57 mm Hg (with a mean value of 28±5 mm Hg). Right ventricular systolic pressure (or PASP) increased with age and/or body mass index of the population studied, highlighting the problem of potential false positive echocardiographic diagnoses of PH in aged and/or obese patients. Thus, a confirmation of PH with a right heart catheter is required in doubtful cases especially those exhibiting an advanced exertional dyspnoea. Following the data of McQuillan and coworkers, the recent guidelines of the European Society of Cardiology on diagnosis and treatment of pulmonary hypertension suggest that a mild form of PH may be defined as a PASP of approximately 36–50 mm Hg, assuming a normal right atrial pressure of 5 mm Hg [10]. Concerning false negative echocardiographic results, Mukerjee and co-workers reported a weak correlation between Doppler-echo measurements and the right heart catheter haemodynamic pressure profile in a group of 137 systemic sclerosis – associated PH patients with or without pulmonary fibrosis [16]. In this study, echocardiography was performed adequately (good specificity) only in advanced cases of PH, while low tricuspid gradients (≤40 mm Hg) were unable to discriminate between normal or pathological pulmonary arterial pressure.

Grünig and co-workers demonstrated for the first time that *stress Doppler echocardiography* is a useful methodology to detect an abnormal PASP response in asymptomatic carriers of a familial pulmonary hypertension gene (BMPR-2 mutations). Therefore, stress Doppler echocardiography may also be an extremely useful tool to identify persons at risk for PH even before pulmonary arterial pressures at rest are elevated, for example patients with connective tissue diseases, liver pathologies or previous pulmonary embolism [17]. In another study, Alkotob and co-workers have recently determined the incidence of stress-induced PH along with the relationship between stress-induced PH and exercise capacity in a referral at risk population of patients with scleroderma [18]. Sixty-five patients underwent exercise Doppler echo: in 46% of the population studied, there was an increase of PASP above 35 mm Hg with the peak PASP linearly related to exercise time. The authors concluded that stress-induced PH was common in scleroderma patients, even when resting pulmonary pressure was normal. They also concluded that PASP measurement during exercise may prove to be useful for the detection of future resting pulmonary hypertension. Taken together, these results emphasise the importance to perform study protocols investigating exercise Doppler echo in subgroups of patients at risk for PAH.

Differentiation of PH

After the PH detection is accomplished, the disease needs to be differentiated according to the new clinical classification of Venice [11]. Essential tests, according to the clinical opinion achieved at that point of the algorithm, are pulmonary function tests (complete spirometry, DL_{CO}), arterial blood gas analysis, night oxymetry or polygraphy, ventilation/perfusion lung scan, high resolution CT of the lung, contrast enhanced spiral CT of the lung, traditional pulmonary angiography, abdominal ultrasound scan, various blood tests and HIV test. *Pulmonary function tests* are useful to confirm or exclude parenchymal or airflow disorders. In idiopathic PAH, they may be completely normal or show a slight restrictive abnormality, while DL_{CO} may characteristically show a moderate decrease [19]. A decreased DL_{CO} may obviously indicate the presence of an interstitial parenchymal lung disease but in this case, a high resolution CT will easily transfer the functional disturbance into the

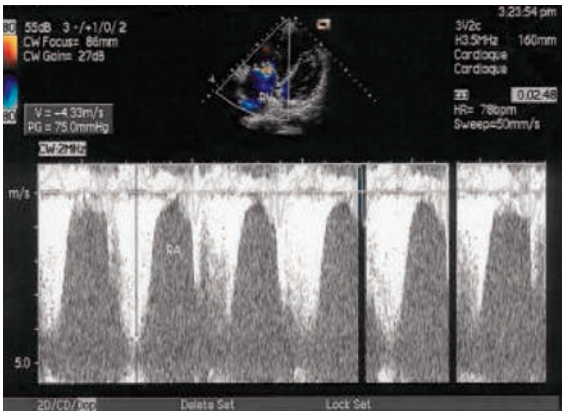

Figure 4

Quantitative echocardiographic approach in the same patient as in figure 3: estimation of pulmonary arterial systolic pressure (PASP) by measuring the end-systolic regurgitant tricuspid jet velocity *v* and by estimating the right atrial pressure. In this example, a measured jet velocity of –4.33 m/sec corresponds to a pressure gradient of 75 mm Hg. By adding an estimated right atrial pressure of 12 mm Hg, PASP resulted in a value of 87 mm Hg (courtesy of: G. Fiori, MD, Regional Hospital, Locarno).

right diagnostic box. Patients with systemic sclerosis may have an isolated reduction of DL_{CO} without parenchymal lung involvement and this may indicate the presence or the development of a pulmonary hypertension [20]. *The arterial blood gas analysis* typically shows the presence of a moderate respiratory alkalosis coupled with hypoxaemia secondary to V/Q mismatch or right-to-left shunt [21]. *Overnight oxymetry* will rule out an arterial desaturation during the night as a manifestation of a sleep disordered breathing, sufficient to explain an increase of pulmonary arterial pressure. However, one must remember that a nocturnal hypoxaemia is a frequent finding even in patients with iPAH in absence of sleep apnoea [22]. *Ventilation-perfusion lung scan* is the best test to evaluate the presence of chronic thromboembolic pulmonary hypertension (CTEPH) [23]. Segmental defects larger than ventilation anomalies represent a typical result (figure 5) but even less specific patchy non-segmental abnormalities may be found [24]. *Contrast-enhanced helical CT* can demonstrate centrally located chronic pulmonary thromboemboli (figure 6) and show obstruction or a reduction in the diameter of the arterial lumen when compared to the external diameter of the pulmonary artery. Very proximal lesions in the right or left pulmonary arterial trunks are well characterised (figure 6), whereas the distal lesions downstream from the first branches may be rarely visible. Consequently, a normal contrast-enhanced CT scan does not exclude the diagnosis of CTEPH and does not preclude the possibility of pulmonary endarterectomy. In CTEPH, a mosaic pattern of lung attenuation as a characteristic of regional perfusion disturbances has also been described with the high resolution CT [25]. Third generation CT scanners are much better at delineating obstruction of segmental branches and may show increased bronchial artery collateral flow which is indicative of the obstructive aetiology seen in CTEPH [26]. The classical *high resolution CT of the lung*, which is essential to rule out interstitial lung diseases and confirm emphysema, may sometime be very useful in suggesting pulmonary veno-occlusive disease by showing a ground-glass, mosaic-attenuation pattern located predominantly centrally or in the lower lobes [27, 28]. *Pulmonary angiography* still remains the gold standard for the precise diagnosis of CTEPH and, by far the best exam for the assessment of operability (thromboendarterectomy) [24]. In patients with a predominant distal disease, the combination of ventilation-perfusion scanning and angiography allows to exclude other forms of PH, particularly iPAH [29]. *Magnetic resonance imaging* is a growing imaging technique in the assessment of patients with PH. It may allow to better clarify the relationship between pathological – functional abnormalities of the pulmonary circulation and the heart function. Functional analysis may include calculation of left and right ventricular ejection fractions and peak velocities, net forward volumes per heartbeat, and blood volume per minute in the left and right pulmonary arteries and ascending aorta [30]. *An abdominal ultrasound scan* is used to exclude liver cirrhosis and true portal hypertension, since this may be significantly correlated with PAH. On the other hand, one should be

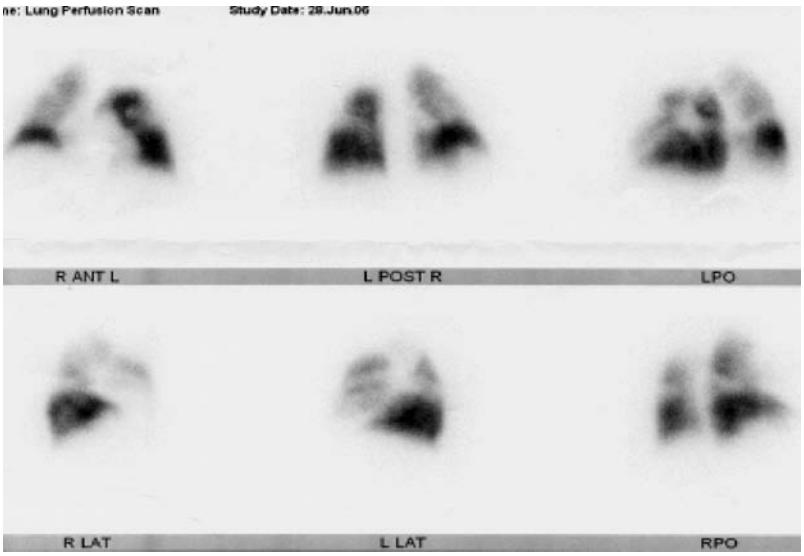

Figure 5

Scintigraphy in a patient with thromboembolic pulmonary hypertension. The lung perfusion scan reveals segmental, large and bilateral defects. The ventilation phase (not shown) was normal.

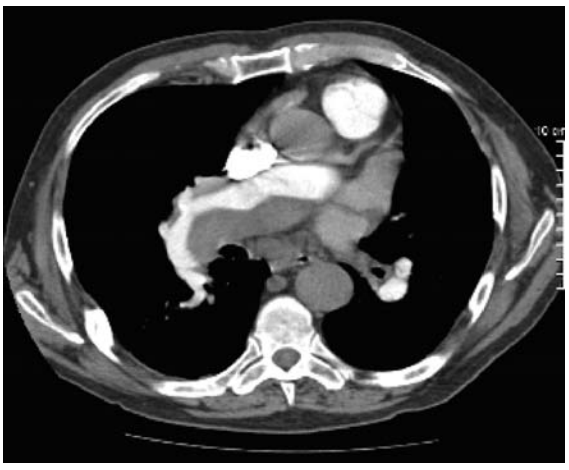

Figure 6

Contrast-enhanced helical CT demonstrating widespread centrally located chronic pulmonary thromboemboli (arrow) and ensuing obstruction in the diameter of the arterial lumen when compared to the external diameter of the pulmonary artery, in a patient with a severe form of proximal and distal chronic thromboembolic pulmonary hypertension (same patient as in figure 2).

conscious that the prevalence of PAH in patients undergoing liver transplantation has been reported to vary between 3.5% and 4% [31]. Finally, *biochemical markers and immunology tests* are part of the general differentiation of PH. Connective tissue diseases, thyroid diseases, myeloproliferative diseases and blood coagulation disorders are mainly confirmed or diagnosed by laboratory criteria. In addition to these tests, a HIV serological analysis is proposed for all patients with PAH [9].

Conclusion

Pulmonary hypertension is still recognised late in the course of the disease. A timely and accurate diagnosis remains an unresolved mission, because early-stage symptoms are insidious. Failing to consider PAH as a cause of breathlessness is a frequent condition and the association between a disease and the pulmonary vascular pathology is commonly misplaced. Attaining an accurate diagnosis of PAH implies the use of simple but concise decision trees in order to propose a logical sequence of investigations. These may allow to suspect, detect and differentiate pulmonary arterial hypertension earlier than in the past.

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