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LETTER TO THE EDITOR

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Structured evaluation of unclear dyspnea–An attempt to shorten the diagnostic delay in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

To the Editor,

Pulmonary hypertension (PH) is a common condition, present in up to 10% in individuals aged >65 years.[1] Whitin this entity, pulmonary arterial hypertension (PAH; group I PH) and chronic thromboembolic pulmonary hypertension (CTEPH; group 4 PH) comprise two rare, but detrimental conditions characterized by pulmonary vasculopathies and remodeling of pulmonary arteries, leading ultimately to right heart failure and death.[2] These conditions are accompanied by high morbidity and mortality, for which early diagnosis and treatment initiation are paramount to improve outcome.[3]

Although considerable efforts made into management, treatment, prognostic risk stratification, and increased public awareness during the past decades, with positive impact on outcomes, regrettably, the diagnostic delay in PAH, with a median of 1.2 years, has not improved significantly since the 1980s.[2,4] A corresponding diagnostic delay has also been observed in CTEPH.[5] This highlights the importance of an early and structured evaluation of unclear dyspnea and the possibility of fast-track referral to specialists for earlier diagnosis and treatment initiation to improve survival.[4]

The recent 2022 ESC/ERS PH guidelines emphasize the importance of a pragmatic-, multimodal-, and multistep approach in the diagnosis of PH, leading to the proposal of a new algorithm, aiming at earlier detection of PAH and CTEPH in the communities.[2] While the algorithm is of great value to potentially minimize the diagnostic delay in PAH and CTEPH,[2] primary care doctors may benefit more from a broader approach, due to the rarity of PAH and CTEPH, as well as the nonspecific and multidimensional nature of dyspnea.[3] Additionally, the algorithm is focused on cardiac- and pulmonary diseases,[2] encouraging a broader evaluation approach. We propose herein a complementary approach to the 2022 ESC/ERS PH guidelines algorithm for how a structured evaluation of unclear dyspnea can be performed, as an attempt to optimize proper referrals to PH centers and minimize the diagnostic delay in PAH and CTEPH.[2,3,6] Unless high suspicion of PAH or CTPEH is present, warranting a fast-track referral as proposed in the 2022 ESC/ERS PH guidelines algorithm,[2] we suggest that physicians should shift from initially suspecting PH to specifically evaluating dyspnea, gradually narrowing down the wide spectrum of differential diagnoses to potentially find PAH and CTEPH. The present manuscript refer to our recent review in Swedish, in which the evaluation, pathophysiology, and the differential diagnoses of dyspnea in relation to PAH and CTEPH have been extensively discussed.[3]

STRUCTURED EVALUATION OF DYSPNEA

We propose a three-step approach for the evaluation of dyspnea, which in relation to available resources, should be initiated independently of where the patient is in the health care system.[3]

STEP 1–BASELINE EVALUATION

A comprehensive medical history with a thorough physical examination including assessment of vital parameters are imperative in guiding and further directing the evaluation of dyspnea. The aim should be directed towards finding and ruling out common causes of dyspnea, primarily cardiopulmonary aetiologies, but also other causes such as anemia and thyroid disease. This can be initiated through analysis of biochemical markers, a 12-lead electrocardiogram, a chest radiogram, and a simple spirometry with reversibility test, all of which should be readily available in a primary care

setting, as suggested by Figure 1 **(step 1)**.[3] Unless fast-track referral is performed, the **Step 1** tests should be conducted, and depending on the findings, more targeted tests can then be done as proposed in **Step 2**.

STEP 2–TARGETED EVALUATION

Based on the overall clinical suspicion related to the history and findings in **Step 1** (Figure 1), further targeted evaluation using more advanced diagnostic modalities may be necessary, including further biochemical testing, and echocardiography to enhance the clinical suspicion and confirm ventricular dysfunction, valvular disease, or PH. Computed tomography (CT) of the chest with high-resolution technique should be used to clarify the presence of parenchymal changes in the lungs, such as emphysema and fibrosis. Defining ventilation/perfusion mismatch including acute and/or chronic pulmonary embolism using pulmonary scintigraphy is necessary to exclude CTEPH, whereas conventional CT pulmonary angiography is often considered in the acute stages of pulmonary embolism.

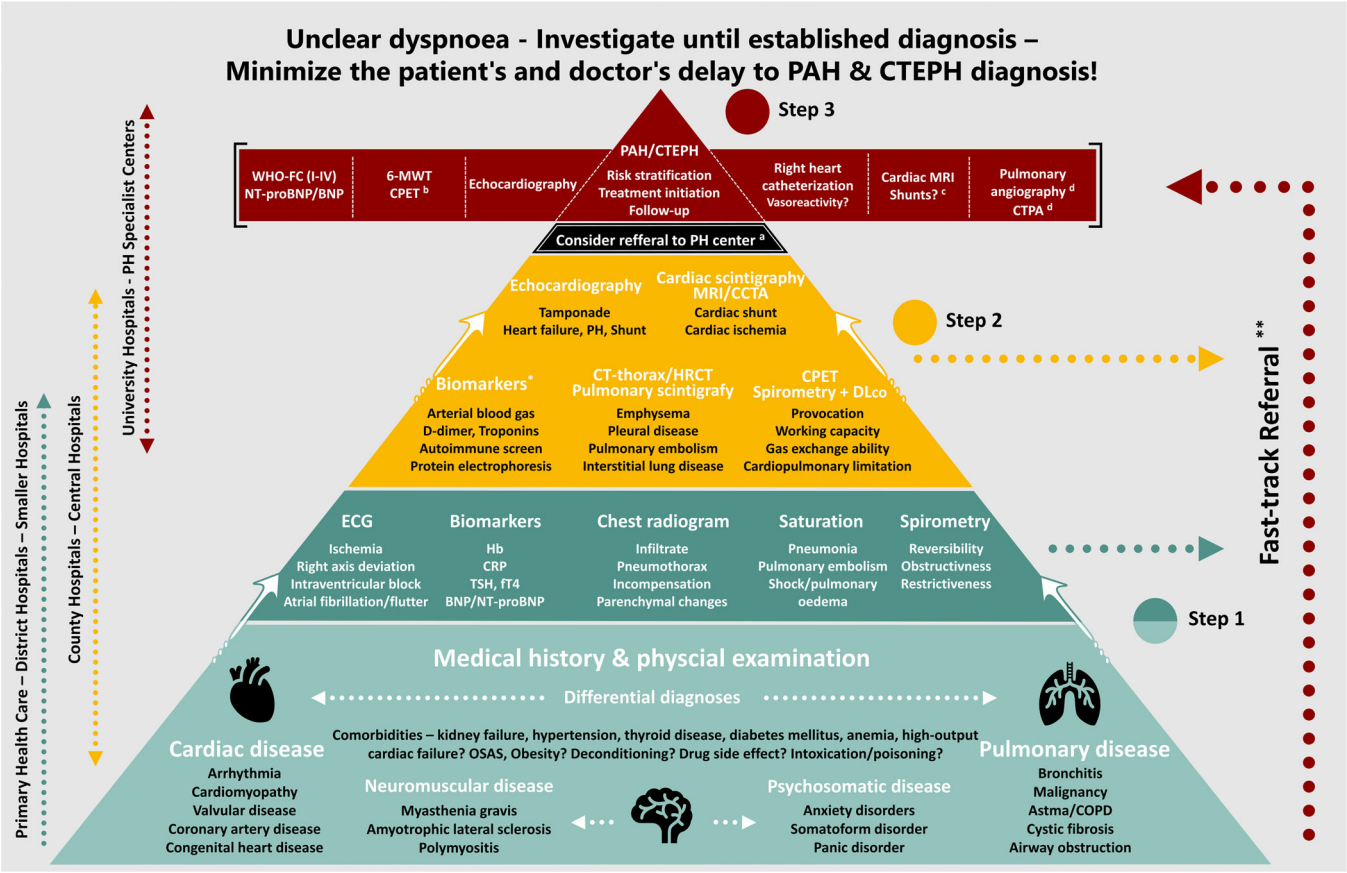

FIGURE 1 Structured algorithm for evaluation of patients with unclear dyspnea with focus on early identification of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). Unclear dyspnea should be investigated with a multistep approach (Step 1–3), initially aiming at narrowing down the large number of differential diagnoses. In case of unclear diagnosis after an adequate evaluation according to Step 1 and 2, and in suspicion of high pressure in the pulmonary circulation, contact/referral to a pulmonary hypertension center should be considered. Exertional-dyspnea, fatigue, presyncope or syncope may be the initial symptoms of PAH and should, especially in younger adults, warrant investigation according to the algorithm.[7] [a]In case of suspicion of PAH/CTEPH or unclear etiology after evaluation according to step 1 and 2. [b]Cardiopulmonary exercise testing (CPET) is not performed routinely but provides added prognostic information to the 6-min walking test (6-MWT). [c]Cardiac magnetic resonance imaging (MRI) – and stepwise measurement of O_2 saturation. [d]Is performed in pre-capillary pulmonary hypertension (PH) with indices of pulmonary thrombotic embolisms in imaging modalities. *Disease specific diagnostic biomarkers, including sweat testing for cystic fibrosis, genetic testing, tissue biopsies, and the potential use of emerging and validated cardiopulmonary biomarkers of dyspnea. **Fast-track referral as suggested by the 2022 ESC/ERS PH guidelines algorithm in case of high suspicion/likelihood of PAH or CTEPH.[2] BNP, b-type natriuretic peptide; CCTA, coronary computed tomography angiography; COPD, chronic obstructive pulmonary disease; CTPA, computed tomography pulmonary angiography; DLco, pulmonary diffusing capacity of carbon monoxide; NT-proBNP, N-terminal pro b-type natriuretic peptide; OSAS, obstructive sleep apnea syndrome.

Furthermore, characterization of the lung function may prompt further investigation with spirometry with diffusion capacity with carbon monoxide, especially in suspicion of PAH or CTEPH to exclude pulmonary functional diseases. In relation to available resources, cardiopulmonary exercise testing may be considered to characterize the limitation of exercise capacity, and the dominant origin of dyspnea.[2] Moreover, in suspicion of coronary artery disease, further testing including coronary CT angiography or noninvasive functional imaging studies with cardiac magnetic resonance imaging, stress-echocardiography, or myocardial scintigraphy may be indicated, according to prevailing guidelines.[3,8]

REFERRAL TO SPECIALIST CENTER

If the diagnosis has not been established after an adequate investigation according to **Step 1** and **2** (Figure 1), early contact with/referral to a PH specialist center should be performed. In case of high suspicion of PAH or CTEPH, to avoid diagnostic delay, immediate referral/contact (fast-track referral, Table 1) should be considered to a PH center for consultation and further investigation.[3]

STEP 3

In this step, referral to a PH center has been done after excluding common causes of dyspnea and no diagnosis has been established along with a suspicion of PAH or CTEPH. Herein, invasive haemodynamic assessment using right heart catheterization constitutes the cornerstone in the PH evaluation. Moreover, further targeted assessment are made anew, including an echocardiography, electrocardiogram, and biochemical marker testing. Cardiac magnetic resonance imaging may also be performed to detect vascular anomalies, cardiac shunts and for prognostication as well as risk stratification. When CTEPH is suspected after pulmonary scintigraphy, further imaging using pulmonary angiography, and CT pulmonary angiography should be done to assess operability and further treatment possibilities. When the PAH diagnosis is established, treatment initiation, follow-ups, and risk stratification to guide treatment are conducted at the PH center, in which the work is based on a

TABLE 1 Important assessments to consider when referring to, or contacting a pulmonary hypertension center.

Purpose of referral, medical history, and physcial exam	Weight and body mass index
	Comorbidities
	Heredity
	Drugs
	Fast-track referral? Presence of warning signs[a]
Biochemical markers	BNP/NT-proBNP
	Autoimmune screening[b]
Echocardiography	Pericardial effusion
	Left ventricular function
	Atrial enlargement
	Valvular disease, peak tricuspid regurgitation velocity
Other imaging modalities	Chest radiogram
	High-resolution computed tomography
	Pulmonary scintigraphy or computed tomography Pulmonary angiography
Pulmonary function	Spirometry with or without DLco

Abbreviations: BNP, b-type natriuretic peptide; DLco, pulmonary diffusing capacity of carbon monoxide; NT-proBNP, N-terminal pro b-type natriuretic peptide.

[a]To not delay diagnosis, **fast-track referral** as suggested by the 2022 ESC/ERS PH guidelines algorithm should be conducted in case of high suspicion/likelihood of PAH or CTEPH, or in the presence of warning signs ("rapid progression of symptoms, severely reduced exercise capacity, presyncope or syncope on mild exertion, signs of right heart failure"),[2] particularly in the presence of familial PAH.

[b]Including the analysis of antinuclear antibody (ANA) and extractable nuclear antigen (ENA) upon suspicion of connective tissue disease, such as systemic sclerosis.

holistic and multidisciplinary collaboration between diverse health care professions to ensure and maintain high quality care.[3] It is also paramount to have a close and a dynamic collaboration between expert centers and primary care physicians to optimize prompt referrals, in relation to expertise and capacity.[3]

AUTHOR CONTRIBUTIONS

Salaheldin Ahmed, Abdulla Ahmed, and Göran Rådegran stood for the concept. Salaheldin Ahmed drafted the letter. Salaheldin Ahmed, Abdulla Ahmed, and Göran Rådegran revised the manuscript critically and approved the final version for publication.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study

ETHICS STATEMENT

The present letter is based on data from published literature, and hence no specific ethical approval was required.

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