Dyspnoea: diagnostic challenge

T. Saaresranta[1,2]
U. Anttalainen[1,2]
J. Toikka[3]
O. Polo[4]

[1]Dept of Pulmonary Diseases, Turku University Central Hospital, [2]Sleep Research Unit, University of Turku, Turku, and [3]Dept of Clinical Physiology and [4]Dept of Pulmonary Diseases, Tampere University Hospital, Tampere, Finland

Correspondence:
T. Saaresranta
University of Turku
Sleep Research Unit
Lemminkäisenkatu 2
20520 Turku
Finland
E-mail: tasaare@utu.fi

Competing interests
None declared

Provenance
Commissioned article, peer-reviewed

Introduction

Dyspnoea continues to pose a diagnostic challenge for physicians. The reasons resulting in the sensation of shortness of breath range from the innocent to the life-threatening (table 1). A detailed history and appropriate investigations combined with clinical skills are needed to achieve the correct diagnosis.

Case 1

Case history

A 28-year-old woman consulted a chest physician having suffered continuous dyspnoea for the previous 2 weeks. She had had mild asthmatic symptoms for several years, and had been using only dry powder inhaled salbutamol (0.2 mg) less than once per week. During

Table 1 Differential diagnosis of dyspnoea

Respiratory		
	Airways disease	Asthma
		Chronic obstructive pulmonary disease (COPD)
		Chronic bronchiolitis and emphysema
		Bronchiectasis
		Cystic fibrosis
		Laryngeal or pharyngeal tumour
		Bilateral cord palsy
		Cricoarytenoid rheumatoid
		Tracheal obstruction
		Tracheomalacia
		Amyloid of airways
	Parenchymal disease	Allergic alveolitis
		Sarcoidosis
		Fibroses and diffuse alveolitis
		Obliterative bronchiolitis
		Pneumonia
		Diffuse infections
		Respiratory distress syndrome
		Infiltrative and metastatic tumour
		Pneumothorax
	Pulmonary circulation	Pulmonary embolism
		Pulmonary hypertension
		Pulmonary arteritis
		Pulmonary thrombosis
	Chest wall and pleura	Effusion
		Pleural tumour
		Fractured ribs
		Ankylosing spondylitis
		Kyphoscoliosis
		Neuromuscular diseases
		Bilateral diaphragmatic paralysis
	Increased respiratory stimulation	Pregnancy
		Progestins and other respiratory stimulants
Cardiac		Left ventricular failure
		Mitral valve disease
		Cardiomyopathy
		Pericardial effusion or constriction
Non-cardiorespiratory		Psychogenic
		Anaemia
		Haemorrhage
		Acidosis
		Hypothalamic lesions

pregnancy, she had suffered dyspnoea without increased diurnal variability in peak expiratory flow (PEF). She had no history of panic or other psychiatric disorders. Otherwise her history was unremarkable.

Before presentation, the patient had taken a 1-week holiday in the Canary Islands. Dyspnoeic symptoms started within the first 2 days of the holiday and continued throughout the holiday as well as after arrival back in Finland. She consulted the emergency department of her local hospital after arrival in Finland. Owing to the history of air travel, pulmonary embolism was suspected. However, haemoglobin, full blood count, C-reactive protein, electrocardiogram, chest spiral computed tomography (CT), plasma D-dimer concentration and pulse oximetry did not suggest pulmonary embolism or any other pathological condition, and the patient was sent home.

On the fourth day after arrival back in Finland, the patient contacted her chest physician. She told her doctor that she was continuously short of breath. The sensation of dyspnoea had neither reduced nor worsened since its onset. She also told her doctor that: "Salbutamol does not work as it usually does" and that the drug did not relieve her symptoms at all. On examination, the patient was not anxious, and heart and lung auscultation were normal. She was not cyanotic or short of breath at rest, and could complete sentences. She had performed peak flow measurements during the previous 4 days. Her values were within normal range, did not increase significantly after salbutamol, and the diurnal variation was ≤8%. She had no symptoms of respiratory infection.

Task 1

Which of the following options best describes your next step?

a) Ask the nursing staff to administer high-flow oxygen immediately.

b) Refer the patient to the emergency department to assess the patient fully and initiate treatment.

c) Start inhaled corticosteroids to treat a suspected exacerbation of asthma.

d) Consult a psychiatrist.

e) Review the patient's history for further details and take arterial blood gases.

Answer 1

a) This answer is incorrect. Investigations at the emergency department 3 days previously were unremarkable, and the patient's condition has not deteriorated since. Pulse oximetry in the emergency department while breathing room air did not indicate hypoxia. She was not short of breath at rest.

b) This answer is incorrect. The patient underwent quite thorough investigations in the emergency department 3 days previously. Ventilation–perfusion scan is unlikely to give any additional information in this particular patient, who has obviously normal lung function. Other further investigations could be scheduled within a wider time-frame.

c) This answer is incorrect. Lung auscultation and PEF values were unremarkable, and the patient had no symptoms suggesting respiratory tract infection.

d) This answer is incorrect. The patient has no previous history of panic disorder or other psychiatric disorder, and was not anxious on examination.

e) This is the correct answer. The chest physician reviewed the patient's history in more detail. The patient was not able to tell of any history of atopic symptoms. She had a loving husband and a 2-year-old daughter. During pregnancy, she had suffered remarkable dyspnoea even during the first trimester. Thorough examinations had excluded exacerbations of asthma and pulmonary embolism. The doctor enquired about the use of oral contraceptives. She denied using them, but told the doctor that she had started with noretisterone 15 mg per day (a progestin derivative) on the first day of her holiday in order to postpone her periods. Arterial blood gases confirmed hyperventilation induced by the progestin therapy. Within about 1 week after discontinuation of the progestin treatment, the patient was no longer short of breath.

Progesterone is a powerful respiratory stimulant [1, 2]. Progesterone levels increase markedly during pregnancy, and 15% of women are already short of breath during the first trimester, before the enlarged uterus compromises breathing [3]. Some people are sensitive to progestin-induced dyspnoea and hyperventilation, and normal therapeutic doses may cause hyperventilation.

Case 2

Case history

A primary care physician referred a 77-year-old female lifelong nonsmoker to the pulmonary clinic with pulmonary hypertension. She had type 2 diabetes, hypercholesterolaemia, hypertension and juvenile rheumatoid arthritis. Coronary heart disease and heart insufficiency had been suspected but the diagnoses had not been confirmed. Asthma had been diagnosed 7 years previously by a chest physician. At the time of asthma diagnosis, skin-prick tests were positive for cat and dog. During the previous 2 years, the patient had exhibited asthma symptoms during the pollen season with decreased PEF. Her medication included glimepiride 3 mg *b.i.d.*, rosiglitazone 8 mg once daily, furosemide 40 mg every second day, triamteren 50 mg combined with trichlormethiazide 1 mg daily, combination of inhaled salmeterol 50 µg plus fluticasone 500 µg *b.i.d.*, rosuvastatin 10 mg daily, sodium aurothiomalate injections once a month, and inhaled salbutamol when needed.

The patient had suffered exercise-induced dyspnoea for years, but during the previous few months this had worsened. Now she had dyspnoea even when walking on flat ground. Twice she had suffered chest pains, which were alleviated after taking sublingual glyceryl nitrate. Two months prior to her visit to the pulmonary clinic, the patient consulted a cardiologist. Echocardiography showed increased pulmonary artery pressure (50 mmHg), but otherwise findings were unremarkable. The cardiologist suggested that a pulmonary disease was responsible for the pulmonary hypertension. Cardiac frequency was 92 beats per minute, but otherwise heart auscultation was normal. Lung auscultation revealed basal inspiratory crackles, but no expiratory wheeze. Physical examination was otherwise unremarkable. Home measurements of PEF showed basal values 190–310 L per min, with a diurnal variability of >20% twice during the previous week. After β_2-agonist administration, values increased to 220–340 L per min. Five years earlier, peak PEF level had been clearly higher (250–370 L per min). Haemoglobin was 117 g per L, full blood count otherwise normal. Sedimentation rate was 23 mm per h and C-reactive protein 6 mg per L. Plasma sodium and potassium, serum alanine aminotransferase, fasting glucose, lipids and creatinine were unremarkable.

Task 2

Which of the following options best describes your next step?

a) The patient has airflow obstruction and symptoms suggesting exacerbation of asthma. Add a leukotriene receptor antagonist, ask nursing staff to carry out spirometry and see the patient again within 3 months at your office.

b) As above, but also consult a cardiologist due to suspected coronary artery disease.

c) Ask for spirometry, diffusion capacity of the lung ($D_{L,CO}$) testing, high-resolution CT, spiroergometry and blood tests.

Answer 2

a) This answer is incorrect. The clinical picture is not typical for an asthma exacerbation and the patient already has quite a high dose of inhaled fluticasone combined with a long-acting β_2-agonist. She also has increased pulmonary pressure and inspiratory crackles on auscultation. Further investigations are needed.

b) This answer is incorrect. The patient has recently consulted a cardiologist, who has suggested further investigations due to a suspected pulmonary background to the patient's symptoms.

c) This is the correct answer. Aggravated dyspnoea, inspiratory crackles and increased pulmonary pressure could suggest parenchymal lung diseases. High-resolution CT revealed some bronchiectasis, but otherwise findings were unremarkable. Spiroergometry showed decreased exercise capacity (49–56% predicted). Exercise capacity was not restricted by pulmonary causes and exercise-induced hypoxia was not detected. FEV_1 improved from 2.08 L per s (105% pred) to 2.25 L per s (114% pred). $D_{L,CO}$ was 68% (74% pred). Serum antinuclear antibodies, myeloperoxidose antibodies, proteinase-3 antibodies and anti-neutrophil cytoplasmic antibodies (both coarse granular and perinuclear patterns) were unremarkable. Arterial blood gas analysis revealed pH 7.46, carbon dioxide tension 5.2 kPa, oxygen tension 8.5 kPa, HCO_3^- 27.7 mmol per L, base excess 3.7 mmol per L. New PEF shows remarkable variability (figure 1). Patient has mild irritative cough but no sputum.

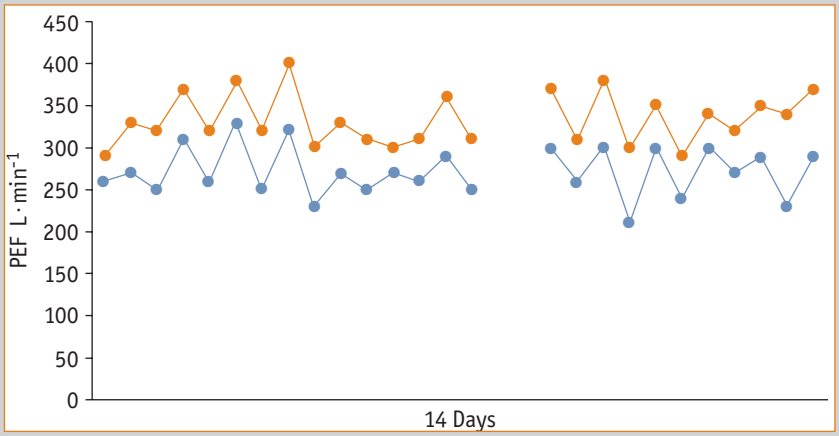

Figure 1
Peak flow chart showing diurnal variability and bronchodilator response.

An oral course of high-dose prednisolone was prescribed for 2 weeks. However, it did not significantly alleviate the patient's symptoms, nor did it improve PEF.

Task 3
Which of the following options best describes your next step?
a) Prescribe antibiotics due to bronchiectasis.
b) Prescribe a leukotriene receptor antagonist.
c) Ask for a ventilation–perfusion scan.

Answer 2

a) This is an incorrect answer. The patient has no sputum and the clinical picture is not typical.
b) This is an incorrect answer. A high-dose oral steroid course has had little if any effect. It is not likely that a leukotriene receptor antagonist would have a remarkable effect.
c) This is the correct answer. The ventilation–perfusion scan revealed a slightly uneven distribution of ventilation and perfusion (figure 2). In the right lung, there were strong ventilation–perfusion mismatches in the anterior segment of the upper lobe and the superior segment of the lower lobe, suggesting lung emboli.

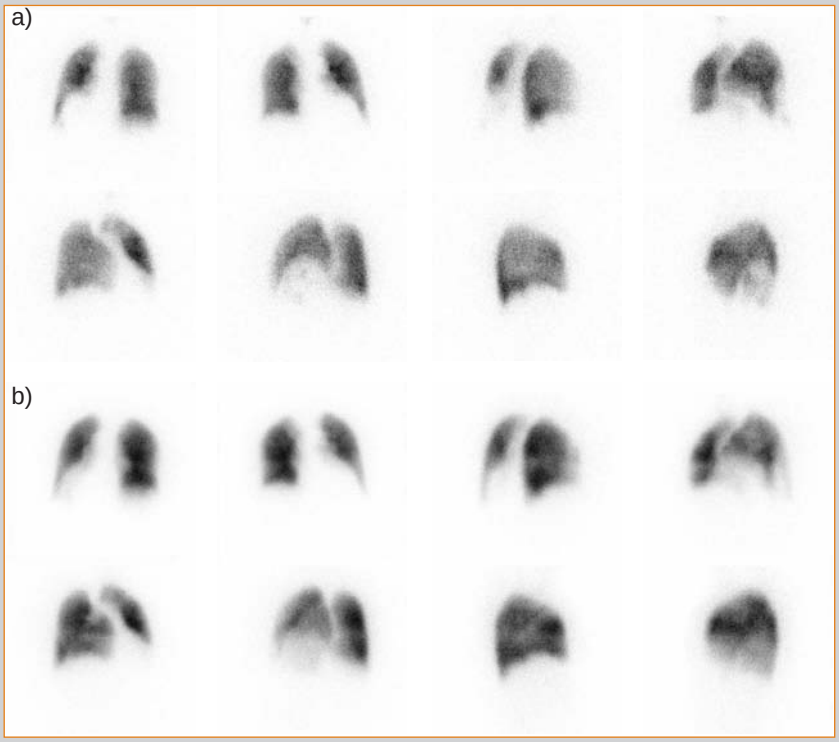

Figure 2
Ventilation–perfusion scan.

Anticoagulation therapy (warfarin) was initiated. After 6 months on warfarin, exercise tolerance was normalised and PEF improved to a basal level of 330 L per min, and after β_2-agonist to 420 L per min.

The high mortality rate and nonspecific symptoms of pulmonary embolism lead clinicians into the undesirable position of simultaneously overtesting [4, 5] and underdiagnosing [6] the disease. Several authors have developed clinical prediction rules to categorise patients according to pre-test probability for pulmonary embolism. However, these clinical prediction rules have not been shown to perform better than subjective clinical *gestalt* [7–9]. Therefore, the detailed review of patient history and clinical examination still form the basis for appropriate investigations and diagnosis.

It has also been suggested that there might be an association between asthma and thromboembolism due to "cross-talk" between the amplification of the coagulation and inflammatory cascades [10]. This might be the reason for pulmonary embolism in the current patient, but this remains unconfirmed.

Referances

1. *Skatrud JB, Dempsey JA, Kaiser DG. Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanism. J Appl Physiol 1978; 44: 393–344.*
2. *Saaresranta T, Polo-Kantola P, Irjala K, Helenius H, Polo O. Respiratory insufficiency in postmenopausal women: sustained improvement of gas exchange with short-term medroxyprogesterone acetate. Chest 1999; 115: 1581–1587.*
3. *Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. Br J Obstet Gynaecol. 1978; 85: 260–263.*
4. *Trowbridge RL, Araoz PA, Gotway MB, Bailey RA, Auerbach AD. The effect of helical computed tomography on diagnostic and treatment strategies in patients with suspected pulmonary embolism. Am J Med 2004; 116: 84–90.*
5. *Verschuren F, Hainaut P, Thys F, et al. ELISA D-dimer measurement for the clinical suspicion of pulmonary embolism in the emergency department: one-year observational study of the safety profile and physician's prescription. Acta Clin Belg 2003; 58: 233–240.*
6. *Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. BMJ 1991; 302: 709–711.*
7. *Perrier A, Bounameaux H, Morabia A, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. Arch Intern Med 1996; 156: 531–536.*
8. *Chunilal SD, Eikelboom JW, Attia J, et al. Does this patient have pulmonary embolism? JAMA 2003; 290: 2849–2858.*
9. *Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet 2002; 360: 1914–1920.*
10. *Divac A, Djordjevic V, Jovanovic D, et al. Recurrent pulmonary embolism in a patient with asthma. Respiration 2004; 71: 428.*