CONTINUING MEDICAL EDUCATION

The Differential Diagnosis of Dyspnea

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SUMMARY

Background: Dyspnea is a common symptom affecting as many as 25% of patients seen in the ambulatory setting. It can arise from many different underlying conditions and is sometimes a manifestation of a life-threatening disease.

Methods: This review is based on pertinent articles retrieved by a selective search in PubMed, and on pertinent guidelines.

Results: The term dyspnea refers to a wide variety of subjective perceptions, some of which can be influenced by the patient's emotional state. A distinction is drawn between dyspnea of acute onset and chronic dyspnea: the latter, by definition, has been present for more than four weeks. The history, physical examination, and observation of the patient's breathing pattern often lead to the correct diagnosis, yet, in 30–50% of cases, more diagnostic studies are needed, including biomarker measurements and other ancillary tests. The diagnosis can be more difficult to establish when more than one underlying disease is present simultaneously. The causes of dyspnea include cardiac and pulmonary disease (congestive heart failure, acute coronary syndrome; pneumonia, chronic obstructive pulmonary disease) and many other conditions (anemia, mental disorders).

Conclusion: The many causes of dyspnea make it a diagnostic challenge. Its rapid evaluation and diagnosis are crucial for reducing mortality and the burden of disease.

▶ Cite this as:
Berliner D, Schneider N, Welte T, Bauersachs J: The differential diagnosis of dyspnoea. Dtsch Arztebl Int 2016; 113: 834–45. DOI: 10.3238/arztebl.2016.0834

Dyspnea (shortness of breath) is a common symptom affecting as many as 25% of patients seen in the ambulatory setting. It can be caused by many different underlying conditions, some of which arise acutely and can be life-threatening (e.g., pulmonary embolism, acute myocardial infarction). Thus, rapid evaluation and targeted diagnostic studies are of central importance. Overlapping clinical presentations and comorbid diseases, e.g., congestive heart failure and chronic obstructive pulmonary disease (COPD), can make the diagnostic evaluation of dyspnea a clinical challenge, all the more so as the term "dyspnea" covers a wide variety of subjective experiences. The presence of this symptom is already a predictor of increased mortality.

Learning goals

This article should enable the reader to:

- be familiar with the problems that lead adult patients to complain of shortness of breath (dyspnea),
- name the main steps in the diagnostic evaluation of dyspnea, and
- identify the main elements in the differential diagnosis of dyspnea of non-traumatic origin.

Methods

This review is based on pertinent articles retrieved by a selective search in PubMed, on the current guidelines of the European Society of Cardiology (ESC), the German Society of Cardiology (*Deutsche Gesellschaft für Kardiologie,* DGK), and the German Society for Pneumonology and Respiratory Medicine (*Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin,* DGP), and on information contained in textbooks of general and internal medicine. The search terms included the following, among others: "dyspnea"; "dyspnea, epidemiology"; "dyspnea, primary care, prevalence";

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Prevalence

Dyspnea (shortness of breath) is a common symptom affecting as many as 25% of patients seen in the ambulatory setting.

"dyspnea, prevalence"; "dyspnea, guidelines"; "dyspnea, pathophysiology"; "dyspnea, causes"; "dyspnea, general practitioner"; "dyspnea, primary care"; "dyspnea, acute coronary syndrome"; "PLATO trial"; "dyspnea, side effect"; "EMS, dyspnea"; "ED, dyspnea."

Illustrative case study

A 64-year-old woman presents to her family doctor complaining of progressive shortness of breath on exertion. She can climb no more than two flights of stairs without stopping; recently, she has been able to walk no longer than 5 minutes on flat ground without becoming "exhausted." She has, in fact, been experiencing shortness of breath for some time now, but has noticed a marked worsening in the last few days.

The definition of dyspnea

In a consensus paper (1), the American Thoracic Society defines dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. . . . [it] derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses."

Dyspnea is an umbrella term for a number of distinguishable subjective experiences including effortful respiration, a feeling of choking or asphyxiation, and hunger for air. The subjectivity of dyspnea is one of the main difficulties confronting the clinician whose task it is to determine the diagnosis and judge the severity of the underlying condition. The pathogenesis of dyspnea is still not fully clear and is now under investigation. Current explanatory hypotheses are based on the concept of a regulatory circuit that consists of afferent information relayed centrally (from chemoreceptors for pH, CO_2, and O_2 , as well as from mechanoreceptors in the musculature and the lungs [C fibers in the parenchyma, J fibers in the bronchi and pulmonary vessels]) and a corresponding ventilatory response (2).

Various instruments are used to assess dyspnea, ranging from simple descriptions of intensity (visual analog scale, Borg scale) to multidimensional questionnaires (e.g., the Multidimensional Dyspnea Profile). These instruments have been validated and are useful for communication. There are other, disease-specific classifications, including the New York Heart Association (NYHA) classification of chronic congestive heart failure (2, 3).

Epidemiology

Dyspnea is a common symptom both in general practice and in hospital emergency rooms. It has been reported that 7.4% of patients presenting to emergency rooms complain of dyspnea (4); among patients in general practice, 10% complain of dyspnea when walking on flat ground and 25% complain of dyspnea on more intense exertion, e.g., climbing stairs (5). For 1–4% of patients, dyspnea is their main reason for consulting a doctor (6, 7). In specialty practice, patients with chronic dyspnea account for 15–50% of those seen by cardiologists and just under 60% of those seen by pneumonologists (2). 12% of patients seen by emergency medical rescue teams have dyspnea, and half of them need to be hospitalized; those who are hospitalized have an in-hospital mortality of ca. 10% (8). The distribution of underlying diagnoses varies from one care situation to another, as shown in *Table 1*.

A more precise classification of the patient's symptoms is helpful in the differential diagnosis. There are multiple criteria to be considered (3):

- temporal
  - acute onset, vs. chronic (present for more than four weeks), vs. acute worsening of preexisting symptoms
  - intermittent vs. permanent
  - episodic (attacks)
- situational
  - at rest
  - on exertion
  - accompanying emotional stress
  - depending on body position
  - depending on special exposure(s)
- pathogenetic
  - problems relating to the respiratory system (central control of breathing, airways, gas exchange)
  - problems relating to the cardiovascular system
  - mixed cardiac and pulmonary causes
  - other causes, e.g., anemia, thyroid disease, poor physical condition (i.e., muscle deconditioning)
  - mental causes

The diagnosis and treatment of dyspnea are sometimes made more difficult by the simultaneous presence of more than one underlying disease, particularly in elderly, multimorbid patients.

Diagnostic evaluation

The diagnostic assessment of dyspnea is a challenge in routine practice, particularly because the term "dyspnea"/"shortness of breath" covers a variety of subjective experiences.

Dyspnea

Dyspnea is a common symptom: 7% of patients in hospital emergency rooms and as many as 60% of those in ambulatory pulmonological practice complain of dyspnea.

TABLE 1

The more common causes of dyspnea in emergency medical rescue situations, in hospital emergency rooms, and in general medical practice*

Rescue service	Emergency room	General practice
Heart failure (15–16%)	COPD (16.5%)	Acute bronchitis (24.7%)
Pneumonia (10–18%)	Heart failure (16.1%)	Acute upper respiratory infection (9.7%)
COPD (13%)	Pneumonia (8.8%)	Other airway infection (6.5%)
Bronchial asthma (5–6%)	Myocard. infarction (5.3%)	Bronchial asthma (5.4%)
Acute coronary syndrome (3–4%)	Atrial fibrillation or flutter (4.9%)	COPD (5.4%)
Pulmonary embolism (2%)	Malignant tumor (3.3%)	Heart failure (5.4%)
Lung cancer (1–2%)	Pulmonary embolism (3.3%)	Hypertension (4.3%)

*modified from (6, 8, e3); COPD, chronic obstructive pulmonary disease

Illustrative case study—continuation I

This patient is suffering from an acute exacerbation of chronic dyspnea. She relates that she has high blood pressure that is stably controlled with drugs, with systolic blood pressure between 135 and 150 mmHg when measured at home. She is overweight: she weighs 85 kg and is 168 cm tall (body-mass index 30.1 kg/m²). She is also a smoker (ca. 35 pack-years) but has no other known cardiovascular risk factors. She states that she has no productive cough or sputum production.

In addition to the history and physical examination, the initial diagnostic evaluation in ambulatory general medical practice (9) includes laboratory tests (including a complete blood count, thyroid function tests, D-dimers), an ECG to detect possible arrhythmias, right-heart strain, and other abnormalities, and ultrasonography if indicated (e.g., to rule out a pleural effusion). If a lung disease is suspected, pulmonary function tests should be performed. The further disposition of the patient (referral to a specialist, admission to the hospital) depends on the suspected diagnosis and the severity of the problem.

Acute dyspnea

Dyspnea of acute onset may be a manifestation of a life-threatening condition. Alarm signs include confusion, marked cyanosis (as a new finding), dyspnea while speaking, and insufficient respiratory effort or respiratory exhaustion. The potential threat to life should be assessed at once. Measurement of the vital signs (heart reate, blood pressure, oxygen saturation of the blood) is obligatory for timely decision-making about what to do next, in particular whether the patient acutely needs to be treated in an intensive care unit or to receive invasive assisted ventilation. The respiratory rate is a further important criterion for the acuity and severity of the condition. An elevated respiratory rate on admission to the hospital indicates a worse outcome (higher likelihood of treatment in an intensive care unit, higher mortality) (10, 11) and is an independent parameter in many score systems in emergency medicine and intensive care (e.g., the Emergency Severity Index and the APACHE II).

Initial misdiagnoses lead to prolonged hospitalization and are associated with higher mortality (12). Most persons who suddenly develop dyspnea feel themselves to be in grave danger. Often, emotional factors such as panic, anxiety, and frustration additionally worsen the patient's subjective distress.

Further clues to the underlying disease can be derived from the patient's past medical history (including diagnoses, interventions, and operations) and from symptoms and signs other than dyspnea that point toward particular diagnoses *(Table 2, eTable 1)*. The possible causes of acute dyspnea are listed in e*Table 2*.

The role of biomarkers

An acute myocardial infarction or cardiac arrhythmia can be detected with an ECG. A plain chest x-ray can reveal pulmonary congestion, pneumothorax, or pneumonia. Specific blood tests called biomarkers also play an important role in the differential diagnosis of acute dyspnea.

Natriuretic peptides

The natriuretic peptides, brain natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP), are useful for the exclusion of clinically relevant congestive heart failure (13–16). In its guidelines, the European Society of Cardiology (ESC) recommends threshold values of <100 pg/mL for BNP and <300 pg/mL for NT-proBNP to rule out

Differential diagnosis

The criteria that can be used in the differential diagnosis of dyspnea are of three kinds:

- temporal course
- situational aspects
- causative factors

A potentially life-threatening problem

Dyspnea of acute onset may be a manifestation of a life-threatening condition and therefore calls for rapid diagnostic evaluation.

acute congestive heart failure (17). Note that the thresholds for patients with symptomatic chronic congestive heart failure are markedly lower (<35 pg/mL and <125 pg/mL, respectively). The negative predictive value of the natriuretic peptides for the exclusion of congestive heart failure is reportedly 94% to 98% (17).

Troponins

If the clinical evidence points to an acute coronary syndrome as the cause of dyspnea, serial determination of cardiac troponin (troponin I or troponin T) is helpful. This can be used to rule out acute myocardial ischemia with a high degree of certainty (18); the threshold value (or threshold rise in values) for a positive test result depends on the particular test used. The positive predictive value of repeated troponin measurement for acute myocardial ischemia is 75% to 80% (18).

D-dimers

D-dimers are fibrin degradation products generated by fibrinolysis; they are found in higher concentrations after thrombotic events. They have a high negative predictive value in the diagnostic evaluation of pulmonary embolism but are not useful as a screening test for it, as an elevated D-dimer concentration is not specific. In routine practice, before D-dimers are measured, the probability of an acute pulmonary embolism should be assessed by other means first, e.g., with risk scores such as the Geneva Score or the somewhat more commonly used Wells Score *(eTable 3)*. If the likelihood of pulmonary embolism is low (or, in some cases, intermediate), a normal D-dimer concentration rules out pulmonary embolism with high probability. On the other hand, if the Wells Score is high, indicating that pulmonary embolism is very likely, the next step in the diagnostic evaluation is an imaging study. Moreover, it is emphasized in the current guidelines for the diagnosis and treatment of pulmonary embolism that the use of age-adjusted threshold values (age × 10 µg/L for patients over age 50) markedly improves the specificity of the D-dimer test, while keeping its sensitivity above 97% (19, 20).

Cardiac troponins and natriuretic peptides can also be elevated in patients with an acute pulmonary embolism leading to clinically relevant right-heart strain (19). Troponin can, in fact, be elevated in any acute pulmonary disease. If there is any evidence of

TABLE 2

Symptoms and signs accompanying dyspnea that may be of differential diagnostic significance*

Additional symptoms and signs	Differential diagnostic considerations
Diminished or absent breathing sounds	COPD, severe asthma, (tension) pneumothorax, pleural effusion, hematothorax
Distention of the neck veins	
with rales in the lungs	ADHF, ARDS
with normal auscultatory findings	pericardial tamponade, acute pulmonary arterial embolism
Dizziness, syncope	valvular heart disease (e.g., aortic valvular stenosis), hypertrophic or dilated cardiomyopathy, marked anemia, anxiety disorder, hyperventilation
Hemodynamic dysfunction:	
hypertensive	hypertensive crisis, panic attack, acute coronary syndrome
hypotensive	forward heart failure, metabolic disturbance, sepsis, pulmonary arterial embolism
Hemoptysis	lung cancer, pulmonary embolism, bronchiectasis, chronic bronchitis, tuberculosis
Hyperventilation	acidosis, sepsis, salicylate poisoning, psychogenic (incl. anxiety)
Impairment of consciousness	psychogenic hyperventilation, cerebral or metabolic disturbance, pneumonia
Orthopnea	acute congestive heart failure, toxic pulmonary edema
Pain	
on respiration	pneumothorax, pleuritis/pleuropneumonia, pulmonary embolism
independent of respiration	myocardial infarction, aortic aneurysm, Roemheld syndrome, renal or biliary colic, acute gastritis
Pallor	marked anemia
Paradoxical pulse	right-heart failure, pulmonary arterial embolism, cardiogenic shock, pericardial tamponade, exacerbation of bronchial asthma
Peripheral edema	congestive heart failure
Rales	ADHF, ARDS, pneumonia
Use of auxiliary muscles of respiration	respiratory failure/ARDS, severe COPD, severe asthma
Wheezes	(exacerbation of) bronchial asthma, COPD, ADHF, foreign body

*modified from (3, e4–e6), ARDS, acute respiratory distress syndrom; ADHF, acutely decompensated heart failure; COPD, chronic obstructive pulmonary disease

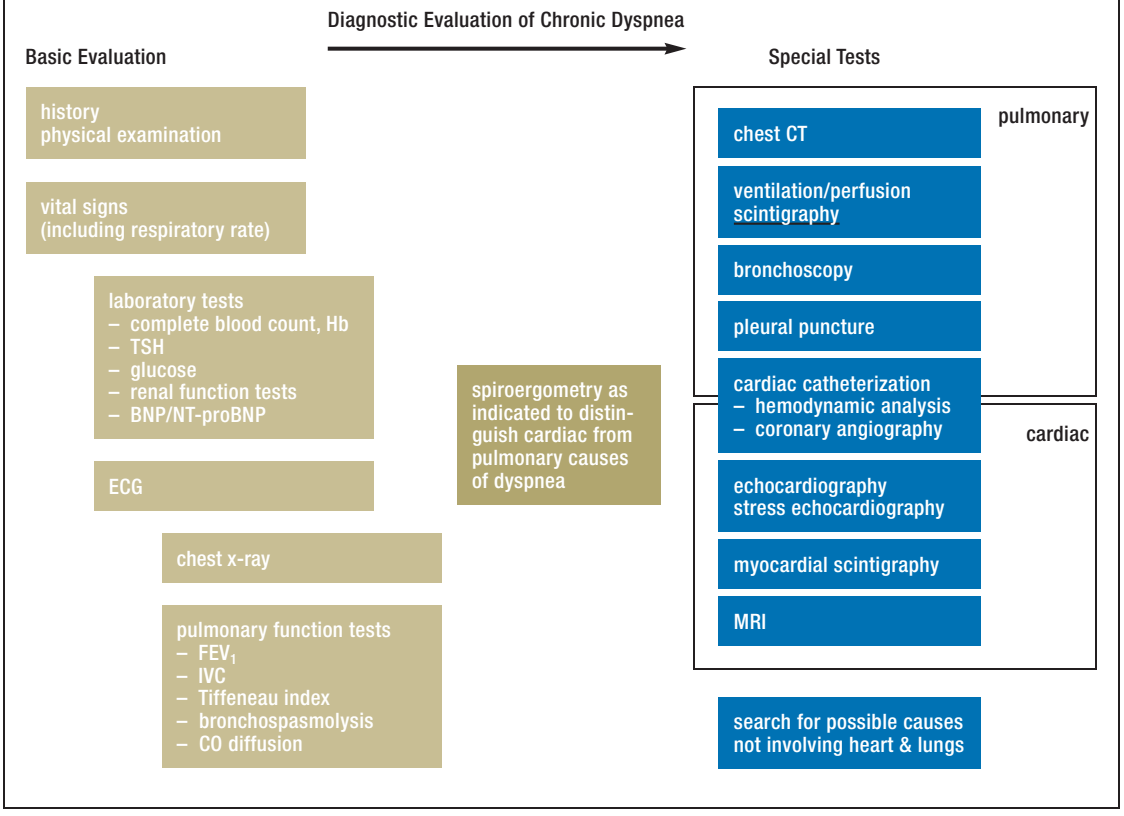
The importance of emotional factors

Emotional factors may worsen the symptoms.

Biomarkers

The natriuretic peptides, brain natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP), are useful for the exclusion of clinically relevant congestive heart failure.

FIGURE 1



The diagnostic evaluation of chronic dyspnea, modified from (3, 9, 22, 24) BNP: brain natriuretic peptide CT: computed tomography ECG: electrocardiography FEV_1: forced expiratory volume in 1 second Hb: Hemoglobin IVC: inspiratory vital capacity MRI: magnetic resonance imaging NT-proBNP: N-terminal prohormone brain natriuretic peptide TSH: thyroid-stimulating hormone

clinically relevant right-heart strain, the patient should be evaluated in a timely fashion by transthoracic echocardiography.

Chronic dyspnea

Chronic dyspnea is usually due to one of a small number of causes: bronchial asthma, COPD, congestive heart failure, interstitial lung disease, pneumonia, and mental disorders (e.g., anxiety disorders, panic disorders, somatization disorders) (3, 12). Further causes are given in *eTable 2*. In older, multimorbid patients, however, it is often difficult to ascribe dyspnea to a single cause.

Here, too, the clinical history (including risk factors, exposures, and prior illnesses *[Table 2, eTable 1]*) often points toward the correct diagnosis or at least narrows down the differential diagnosis. However, a correct diagnosis is made on the basis of the history alone in only one-half to two-thirds of cases (21–23). Along with auscultation (revealing, e.g., evidence of pulmonary congestion, or absent or enhanced breathing sounds), observation of the patient's breathing pattern often yields further clues to the probable underlying illness. Rapid, shallow breathing reflects the diminished pulmonary compliance of interstitial lung disease, while deep, slow breathing is typical of COPD (24).

Illustrative case study—continuation II

Auscultation reveals diminished respiratory sounds at the bases and diffuse, mild rales. A 2/6 systolic heart

The more common causes of chronic dyspnea

Bronchial asthma, COPD, congestive heart failure, interstitial lung disease, pneumonia, and mental disorders

Difficulties

A correct diagnosis is made on the basis of the history alone in only one-half to two-thirds of cases.

murmur is also audible over the mitral area. There is minimal ankle edema. The ECG reveals sinus rhythm with a heart rate of 84/min and a positive Sokolow index, which is a sign of left ventricular hypertrophy.

Further diagnostic testing is chosen on an individual basis; a proposed diagnostic algorithm for general use has undergone clinical testing (22). Some authors recommend performing diagnostic testing in multiple steps, with increasing specificity at each step, so that the result of each test leads to the appropriate choice of the next one.

Often, a specific diagnosis can be suspected on the basis of the history and physical examination alone, but, if this is not possible, a small number of basic tests can be performed as a fast and easy way to narrow down the differential diagnosis and keep the need for further testing to a minimum *(Figure 1)*. Spiroergometry can help identify the main cause by distinguishing between cardiac and pulmonary disturbances.

Depending on these initial findings, the appropriate type of ancillary diagnostic testing can be chosen for the next step, e.g., echocardiography, computerized tomography, or invasive right- and left-heart catheterization for hemodynamic assessment *(Figure 1)*. The choice of initial test, in particular, should depend on the probable diagnosis as determined on clinical grounds. The advantage of this selective testing principle over more comprehensive testing is that excessive testing is avoided; its disadvantages, clearly, are potential diagnostic delay and a possible failure to note pathological findings in patients whose dyspnea is multifactorial.

In some cases, the cause of dyspnea can be clarified only through the use of multiple tests in combination. In a study of 1969 dyspneic patients with no known heart or lung disease, an attempt was made to determine what parameter(s) would be of the greatest help in determining the appropriate type of further diagnostic testing (25). The following parameters were studied:

- measured values of the 12-lead ECG, ECG abnormalities
- CT for determination of the calcium score of the coronary arteries
- left and right ventricular volume and ejection fraction
- spirometric parameters
- percentage of lung volume with emphysematous change (pulmonary CT)
- percentage of lung volume with interstitial change (pulmonary CT)
- laboratory values including fibrinogen, creatinine, CRP, NT-proBNP
- body-mass index
- smoking status
- blood pressure
- diabetes mellitus
- manifestations such as orthopnea, respiratory infections, or seasonal allergies.

The only independent predictors of the diagnosis in patients with dyspnea were the FEV_1, the NT-proBNP concentration, and the percentage of lung volume with emphysematous change on CT.

Specific diseases

Dyspnea due to diseases of the respiratory system

Bronchial asthma – The cause is chronic inflammation of the airways leading to variable airway obstruction. The patients complain of frequent attacks of shortness of breath, often at night as well. Multiple allergies may be present. The precipitating factors can include respiratory irritation, allergen exposure, exercise, weather changes, and (respiratory tract) infections. Auscultation reveals expiratory wheezes due to obstruction. Spirometry shows a decrease in both the forced expiratory volume at one second (FEV_1) and the peak expiratory flow (PEF) (26), both of which may be normal in the asymptomatic interval between episodes. The obstruction, and the symptoms, improve markedly after the inhalation of a bronchodilator drug (β_2-agonist or anticholinergic drug). Episodes of acute dyspnea in a patient with asthma are called exacerbations. Tachypnea, wheezes, and a prolonged expiratory phase are typical clinical findings (27).

Chronic obstructive pulmonary disease (COPD) – Chronic bronchitis is present, according to the definition of the World Health Organization, when cough and discharge have been present for at least three months in at least two consecutive years. In COPD, chronic inflammation leads to destruction of lung parenchyma and thereby to overinflation of the lungs and a decline in elastic restorative forces. COPD is usually characterized by a fixed obstruction of the lower airways. The affected patients are usually over age 40, and nearly all are smokers or past smokers (28–30). Pulmonary function tests and body plethysmography afford further diagnostic

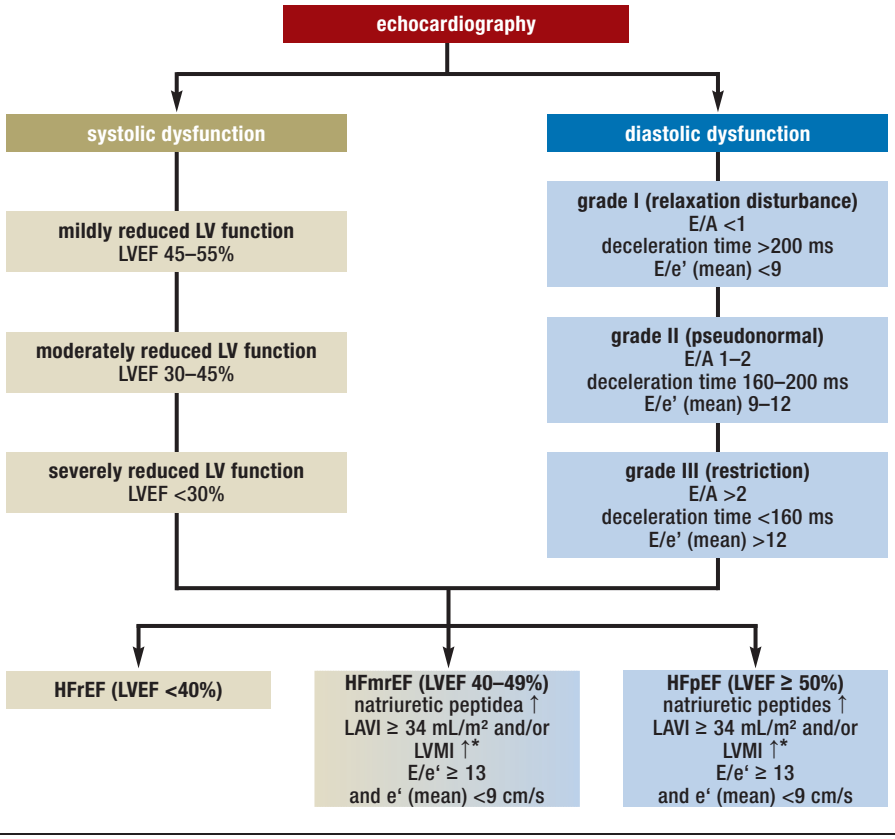
Spiroergometry

Spiroergometry is a suitable means of distinguishing cardiac from pulmonary causes of dyspnea.

COPD

COPD is generally characterized by a fixed obstruction of the lower airways. The patients are usually over 40 years old and are nearly always current or former smokers.

FIGURE 2



Echocardiographic criteria for congestive heart failure with reduced or preserved left ventricular ejection fraction (HFrEF and HFpEF, respectively) and the new category with so-called mid-range ejection fraction (HFmrEF); modified from (17, 38).
LV: left ventricular
LVEF: left ventricular ejection fraction
LAVI: left atrial volume index
LVMI: left ventricular mass index
(↑*: ≥ 115 g/m² for men, ≥ 95 g/m² for women)
E: maximal speed of E-wave in inflow profile over the mitral valve
A: maximal speed of A-wave in inflow profile over the mitral valve
e'(mean): mean maximal (early) diastolic speed of the septal and lateral mitral valve annulus (tissue Doppler)

help. The Tiffeneau index (FEV_1/IVC, where IVC is the inspiratory vital capacity) is typically under 0.7, and the residual volume may be elevated as an expression of overinflation of the lungs. Abnormally low CO diffusion indicates emphysema. A plain chest x-ray reveals flattened diaphragm shadows and often rarefaction of the pulmonary vasculature. The occurrence of exacerbations that necessitate hospitalization is associated with a worse outcome. COPD shares risk factors with left heart failure and is often found together with it (28, 29).

Many current or past smokers suffer from symptoms resembling those of COPD without meeting the classic definition for it. It was shown, in a recently published study, that these patients have exacerbations, diminished activity in everyday life, and anatomical evidence of airway changes (thickened airway walls) just as COPD patients do. They are often treated with drugs against airway obstruction, although evidence for this practice is lacking (31).

Pneumonia—Dyspnea is the main symptom of pneumonia primarily in patients over age 65 (ca. 80%) (29). Pleuritic pain, fever, and cough are typical accompanying symptoms. Examination reveals tachypnea, inspiratory rales, and sometimes

Assessment of severity

The severity of pneumonia can be assessed with the CRB-65 score.

Pneumonia

Pleuritic pain, fever, and cough are typical symptoms of pneumonia. The physical findings include tachypnea, inspiratory rales, and sometimes bronchial breathing.

bronchial breathing. Laboratory testing (inflammatory parameters; hypoxemia in arterial blood gas analysis, in severe cases), chest x-ray, and in some cases chest CT are diagnostically helpful.

The CRB-65 score is used to assess the severity of pneumonia. One point is awarded for each item present: C stands for confusion of new onset, R for respiratory rate ≥ 30/min, B for systolic blood pressure <90 mmHg, diastolic blood pressure ≤ 60 mmHg, and 65 for age ≥ 65). This score can serve as a guide to the need for hospitalization. Patients with a score of 0 can generally be treated outside the hospital; those with a score of 1 should be hospitalized if they have hypoxemia and comorbidities; and those with a score of 2 or more should always be admitted to the hospital (32, 33).

Interstitial lung diseases—Patients report chronic shortness of breath and nonproductive cough, and they are often smokers (34). Examination reveals crackling rales at the bases, and sometimes also digital clubbing and hourglass nails.

Pulmonary function testing reveals low vital capacity (VC) and total lung capacity (TLC), a high normal Tiffeneau index, and reduced CO diffusion. The differential diagnosis of interstitial lung diseases is complex, and the prognosis and treatment differ from one type of interstitial lung disease to another. Consultation with a pneumonologist is advisable (29, 35).

Pulmonary embolism—The clinical picture of acute pulmonary embolism is often characterized by dyspnea of acute onset. Patients often report pleuritic pain and sometimes have hemoptysis. Examination reveals shallow breathing and tachycardia. There is often evidence of a deep venous thrombosis of the lower limb as the source of the pulmonary embolism (19).

Dyspnea due to diseases of the cardiovascular system

Congestive heart failure—Along with dyspnea, there are other symptoms including fatigue, diminished exercise tolerance, and fluid retention (17). The common causes are advanced coronary heart disease, primary cardiomyopathy, hypertension, and valvular heart disease. There is an important clinical distinction between heart failure with reduced ejection fraction (HFrEF), in which the left ventricular ejection fraction (LVEF) is less than 40%, and the almost equally common heart failure with preserved ejection fraction (HFpEF), with elevated cardiac filling pressure (*Figure 2*). There is also a newly described entity called heart failure with mid-range ejection fraction (HFmrEF, in which signs of diastolic dysfunction are combined with an LVEF between 40% and 49%) (17). In all types of congestive heart failure, the stroke volume and cardiac output are diminished.

Echocardiography is the principal diagnostic test. It enables the assessment of diminished systolic and/or diastolic function with the aid of surrogate parameters *(Figure 2)* (36).

Illustrative case study—continuation III

The findings presented above suggest a cardiac cause of dyspnea. Because the patient is a smoker, pulmonary function tests are performed; these reveal mild obstruction (not reversible with a bronchospasmolytic agent). Echocardiography reveals normal systolic function and grade 2 impairment of diastolic function, with left ventricular hypertrophy. Mild mitral insufficiency is found, corresponding to the heart murmur. The NT-proBNP is markedly elevated, at 546 ng/mL with normal renal function. These findings enable the diagnosis of heart failure with preserved ejection fraction (HFpEF) as the main cause of dyspnea, certainly further worsened by the patient's overweight habitus (BMI 30.1) kg/m²) and smoking, with mild resulting airway obstruction. As a differential diagnostic consideration, the mild obstruction seen on pulmonary function testing might also be due to chronic pulmonary congestion. Once the patient's congestion has been dealt with adequately with medication, the pulmonary function tests should be repeated.

Coronary heart disease—Dyspnea can also be a symptom of coronary stenosis, even if it is not a "classic" symptom (37). It can be present simultaneously with angina pectoris, or as the predominant or sole symptom of coronary heart disease, e.g., in a patient with diabetes mellitus.

The history, particularly the timing and setting of the onset of dyspnea (stress, cold, etc.), often suggests coronary heart disease as a potential cause. Patients with dyspnea of unclear origin should be evaluated for possible coronary heart disease. The assessment includes conventional ergometry as well as stress tests in combination with imaging studies,

Congestive heart failure as a cause of dyspnea

Aside from dyspnea, patients also have other symptoms including fatigue, lessened physical performance, and fluid retention. Both HFrEF and HFpEF are associated with low stroke volume.

Coronary heart disease

Exertional dyspnea may be an atypical sign of coronary heart disease.

such as stress echocardiography, myocardial perfusion scintigraphy, and stress magnetic resonance tomography. Suggestive findings should be followed up by cardiac catheterization (37).

Dyspnea more typically arises as part of the constellation of symptoms in an acute coronary syndrome or myocardial infarction, as well as in cardiogenic shock as a consequence of low cardiac output (18, 39).

Valvular heart disease – Among elderly patients in particular, valvular heart disease is a further possible cause of dyspnea. The most common valvular diseases are aortic valvular stenosis and mitral insufficiency (40). Typical findings of aortic valvular stenosis include diminished physical performance, episodes of collapse, syncope, and dizziness, and, sometimes, chest pain resembling angina pectoris. Auscultation often points to the diagnosis (a rough systolic heart murmur heard loudest parasternally over second intercostal space, with projection into the carotid arteries). Patients with mitral insufficiency present with signs of heart failure. The ECG often reveals atrial fibrillation due to volume overload of the left atrium. Here, too, auscultation points to the diagnosis (a holosystolic murmur over the cardiac apex, sometimes projected into the axilla). Echocardiography is the definitive diagnostic study.

A fundamental consideration in the evaluation of dyspnea

Heart and lung diseases are often present in the same patient at the same time. If a cause for dyspnea is found in one of these two organ systems, the search must continue for a possible additional cause in the other organ system, as comorbidity is very common.

Dyspnea due to diseases outside the respiratory and cardiovascular systems

The World Health Organization (WHO) defines anemia as a hemoglobin (Hb) value below 8.06 mmoL/L (13 g/dL) in men or 7.44 mmoL/L (12 g/dL) in women. There is no sharp threshold value of Hb below which anemic patients become dyspneic. Anemia calls for further diagnostic evaluation in all cases, particularly if the Hb concentration is below 11 g/dL or has fallen for unclear reasons.

Diseases of the ears, nose, and throat that affect the airways can also cause dyspnea. In disturbances of the upper airways, the main symptom other than dyspnea is stridor (expiratory in bronchopulmonary airway compromise, inspiratory in supraglottic airway compromise, biphasic in airway compromise at or just below the glottis). A rule of thumb states that dyspnea arises when the tidal volume is reduced by 30% (e1). Possible causes include congenital malformations, infections, trauma, neoplasia, and neurogenic disturbances.

Neuromuscular diseases that can cause dyspnea include muscle diseases such as Duchenne muscular dystrophy, myasthenia, motor neuron diseases such as amyotrophic lateral sclerosis, and neuropathies such as Guillain-Barré syndrome (e1). In most cases, these diseases have other neurological manifestations aside from dyspnea.

Mental illnesses such as anxiety disorders, panic disorders, somatization disorders, or "functional complaints" should be regarded as diagnoses of exclusion after an extensive somatic work-up has been performed. Improvement of dyspnea with distraction or physical exercise may be a clue to a disturbance of this type.

Finally, iatrogenic (pharmacological) causes of dyspnea deserve mention as well. Non-selective beta-blockers can cause bronchospasm via their β_2-blocking effect and thereby precipitate attacks of dyspnea. Nonsteroidal anti-inflammatory drugs that inhibit cyclo-oxygenase 1 lead to increased conversion of arachidonic acid to leukotrienes through the activity of lipo-oxygenases; leukotrienes, in turn, can cause bronchoconstriction. Moreover, acetylsalicylic acid (a member of this group of drugs), if given in high doses, can also induce dyspnea via central receptors. Dyspnea due to the platelet aggregation inhibitor ticagrelor is surely a rare event in routine practice, although the initial PLATO study (e2) revealed that it arose in 13.8% of patients. The effect is probably mediated by adenosine receptors.

Conflict of interest statement
The authors state that they have no conflicts of interest.

Manuscript submitted on 30 May 2016, revised version accepted on 25 August 2016

Translated from the original German by Ethan Taub, M.D.

Valvular heart disease

Aortic valvular stenosis and mitral insufficiency are the most common valvular diseases causing dyspnea.

Drugs that can cause dyspnea

- nonselective beta-blockers
- nonsteroidal anti-inflammatory drugs
- platelet aggregation inhibitors

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Cite this as:
Berliner D, Schneider N, Welte T, Bauersachs J:
The differential diagnosis of dyspnea.
Dtsch Arztebl Int 2016; 113: 834–45. DOI: 10.3238/arztebl.2016.0834

The English version of this article is available online:
www.aerzteblatt-international.de

Supplementary material:
eReferences:
www.aerzteblatt-international.de/ref4916

eTables:
www.aerzteblatt-international.de/16m0834

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Question 1
What ist the commonest cause of dyspnea in general medical practice?
a) acute bronchitis
b) pneumonia
c)bronchial carcinoma
d) COPD
e) pulmonary embolism

Question 2
What percentage of patients in general medical practice complain of dyspnea on marked exertion?
a) about 5%
b) about 12%
c) about 25%
d) about 37%
e) about 50%

Question 3
What biomarker is now well-established for the exclusion of clinically relevant congestive heart failure?
a) D-dimers
b) NT-proBNP
c) troponin T
d) copeptin
e) CA125

Question 4
A patient with dyspnea has had an acute myocardial infarction ruled out. She has a high Wells score. What is the most likely diagnosis?
a) angioedema
b) pneumothorax
c) pulmonary embolism
d) toxic pulmonary edema
e) pericardial tamponade

Question 5
What are the typical manifestations of pneumonia?
a) flatulence, sensory disturbances, hyperventilation
b) anxiety, shaking chills, agitation
c) wheezing, neuropathy, colic
d) snoring, hyperactivity, hot flashes
e) fever, cough, pleuritic pain

Question 6
A low Tiffeneau index points toward what diagnosis?
a) pulmonary embolism
b) COPD
c) aortic valvular stenosis
d) coronary heart disease
e) interstitial lung disease

Question 7
What test should always be performed if lung disease is suspected as the cause of dyspnea?
a) right-heart catheterization
b) stress echocardiography
c) spiroergometry
d) pulmonary function test
e) bronchoscopy

Question 8
What diagnostic test is most suitable for distinguishing betwen cardiac and pulmonary causes of dyspnea?
a) spiroergometry
b) chest CT
c) myocardial scintigraphy
d) pleural puncture
e) stress echocardiography

Question 9
What blood tests should be obtained initially in the basic diagnostic evaluation of chronic dyspnea of unknown cause?
a) troponin und D-dimers
b) aspartate aminotransferase and alanin aminotransferase
c) ferritin and transferrin saturation
d) surfactant protein D and lactate dehydrogenase
e) hemoglobin and TSH

Question 10
Stridor accompanying dyspnea points to what differential diagnosis?
a) pneumothorax
b) acidosis
c) tracheal stenosis
d) mitral insufficiency
e) COPD

Supplementary material to:

The Differential Diagnosis of Dyspnea

by Dominik Berliner, Nils Schneider, Tobias Welte, and Johann Bauersachs

Dtsch Arztebl Int 2016; 113: 834–45. DOI: 10.3238/arztebl.2016.0834

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eTABLE 1

Symptoms and signs accompanying dyspnea that may be of differential diagnostic significance (modified from [3, e4–e6])

Additional symptoms and signs	Differential diagnostic considerations
Bradycardia	SA or AV block, overdose of drugs that slow the heart rate
Brainstem signs, neurologic deficits	brain tumor, cerebral hemorrhage, cerebral vasculitis, encephalitis
Cough	nonspecific; mainly reflects diseases affecting the airways and the lung parenchyma
Cyanosis	respiratory failure (acute) heart defect with right-to-left shunt, Eisenmenger syndrome (chronic)
Diminished or absent breathing sounds	COPD, severe asthma, (tension) pneumothorax, pleural effusion, hematothorax
Distention of the neck veins	
with rales in the lungs	acutely decompensated congestive heart failure, acute respiratory failure
with normal auscultatory findings	pericardial tamponade, acute pulmonary arterial embolism
Dizziness, syncope	valvular heart disease (e.g., aortic valvular stenosis), hypertrophic or dilated cardiomyopathy, marked anemia, anxiety disorder, hyperventilation
Exhaustion, generalized weakness, exercise intolerance, muscle weakness	anemia, collagenoses, malignant disease (e.g., lung cancer), neuromuscular disease
Fever	pulmonary infection, e.g., pneumonia or acute bronchitis, exogenous allergic alveolitis, thyrotoxicosis
Heart murmur	cardiac valvular disease
Hemodynamic dysfunction:	
hypertensive	hypertensive crisis, panic attack, acute coronary syndrome
hypotensive	forward heart failure, metabolic disturbance, sepsis, pulmonary arterial embolism
Hemoptysis	lung cancer, pulmonary embolism, bronchiectasis, chronic bronchitis, tuberculosis
Hepatojugular reflux	acutely decompensated congestive heart failure
Hoarseness	disease of the glottis or trachea, recurrent laryngeal nerve palsy
Hyperventilation	acidosis, sepsis, salicylate poisoning, psychogenic (incl. anxiety)
Impairment of consciousness	psychogenic hyperventilation, brain disease, metabolic disturbance, pneumonia
Orthopnea	acute congestive heart failure, toxic pulmonary edema
Pain	
on respiration	pneumothorax, pleuritis/pleuropneumonia, pulmonary embolism
independent of respiration	myocardial infarction, aortic aneurysm, Roemheld syndrome, renal or biliary colic, acute gastritis
Pallor	marked anemia
Paradoxical pulse	right-heart failure, pulmonary arterial embolism,cardiogenic shock, pericardial tamponade, exacerbation of bronchial asthma
Peripheral edema	congestive heart failure
Platypnea	hepatopulmonary syndrome, intrapulmonary shunting
Rales	pneumonia, acutely decompensated congestive heart failure, acute respiratory failure
Stridor	
inspiratory	croup, foreign body, bacterial tracheitis
expiratory/combined	foreign body, epiglottitis, angioedema
Urticaria	Angioedema
Use of auxiliary muscles of respiration	(acute) respiratory failure, severe COPD, severe asthma
Vegetative symptoms (trembling, cold sweat, etc.)	respiratory failure, anxiety disorder, acute myocardial infarction
Wheezes	(exacerbation of) bronchial asthma, COPD, acutely decompensated congestive heart failure, foreign body

eTABLE 2

Causes of acute and chronic dyspnea (modified from [24])

Acute dyspnea		Chronic dyspnea
• angioedema • anaphylaxis • infection of the pharynx • vocal cord dysfunction • foreign body • trauma	Head and neck region, upper airways	• laryngeal tumor • vocal cord paralysis • vocal cord dysfunction • tumor compressing the upper airways • tracheal stenosis • goiter
• rib fractures • flail chest • pneumomediastinum • COPD exacerbation • asthma attack • pulmonary embolism • pneumothorax • pleural effusion • pneumonia • acute respiratory failure • lung contusion/trauma • hemorrhage • lung cancer • exogenous allergic alveolitis	Chest wall, pleura, lungs	• bronchial asthma • bronchiectasis • bronchiolitis • COPD • pulmonary emphysema • chronic thromboembolic pulmonary hypertension • interstitial lung disease • sarcoidosis • exogenous allergic alveolitis • bronchiolitis obliterans • cystic fibrosis • lung tumor narrowing or compressing the airways • pleural effusion • pulmonary right-to-left shunt • pulmonary hypertension • carcinomatous pleuritis • elevated hemidiaphragm, phrenic nerve palsy
• acute coronary syndrome/myocardial infarction • acutely decompensated congestive heart failure • pulmonary edema • high-output failure • cardiomyopathy • (tachy-)arrhythmia • valvular heart disease • pericardial tamponade	Heart	• arrhythmia • constrictive pericarditis • pericardial effusion • coronary heart disease • physical deconditioning • congestive heart failure (HFrEF, HFpEF) • intracardiac shunt • restrictive cardiomyopathy • valvular heart disease
• stroke • neuromuscular disease	CNS/ neuromuscular	• amyotrophic lateral sclerosis • enzyme defect, glycogen storage disease (e.g., McArdle) • mitochondrial disease • polymyositis/dermatomyositis
• organophosphate poisoning • salicylate poisoning • carbon monoxide poisoning • ingestion of other toxic substances • (diabetic) ketoacidosis	Toxic/ metabolic	• metabolic acidosis (e.g., in diabetes mellitus or chronic renal failure) • renal failure • thyroid disease
• sepsis • fever • anemia • encephalitis • traumatic brain injury • acute renal failure • drugs (e.g., beta-blockers, ticagrelor) • hyperventilation • anxiety • intra-abdominal process • ascites • pregnancy • obesity	Other	• anemia • anxiety disorder, panic attacks, somatoform disorder, depression • ascites • chronic renal failure • kyphoscoliosis • late pregnancy • obesity • abdominal wall hernia • early pregnancy (progesterone effect) • physical deconditioning

COPD, chronic obstructive pulmonary disease; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; CNS, central nervous system

eTABLE 3

The Wells score for estimating the probability that pulmonary embolism is present (modified from [19, e7])

	Original version	Simplified version
Prior pulmonary embolism or deep venous thrombosis	1.5	1
Heart rate > 100/min	1.5	1
Surgery or immobilization in the last 4 weeks	1.5	1
Hemoptysis	1	1
Active malignant disease	1	1
Clinical evidence of deep venous thrombosis	3	1
Alternative diagnosis less likely than pulmonary embolism	3	1
3-level classification	∑	
low probability (3.6% [2.0–5.9%])	0–1	–
intermediate probability (20.5% [17.0–24.1%])	2–6	–
high probability (66.7% [54.3–77.6%]	≥ 7	–
2-level classification	∑	∑
pulmonary embolism unlikely	0–4	0–1
pulmonary embolism likely	≥ 5	≥ 2