

ACUTE DYSPNEA: FROM PATHOPHYSIOLOGY, EVALUATION TO DIAGNOSIS

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REZUMAT

Pacienții cu boli cardiace și pulmonare acuză frecvent tulburări respiratorii, simptom specificat în termeni medicali ca dispnee. Dispnea este răspunzătoare pentru o dizabilitate semnificativă a pacienților, cât și pentru milioanele de consultații ce se adresează serviciilor de urgență cu acest simptom. Dispneea acută este o provocare diagnostică pentru orice medic. Este necesară evaluarea corectă și în funcție de caz aplicarea unei terapii de urgență. În majoritatea pacienților etiologia dispneei acute este o boală cardiacă sau pulmonară, astfel că un diagnostic exact este necesar pentru a trata boala producătoare a simptomatologiei pentru care se adresează pacientul.

Cuvinte cheie: dispnee acută, fiziopatologia dispneei, evaluarea clinică a dispneei

ABSTRACT

Patients with cardiopulmonary disease often have respiratory distress, in medical terms referred as dyspnea. Dyspnea is responsible for substantial disability and for millions of patient visit to the hospital each year. Acute dyspnea represents a diagnostic challenge, for any physician. There is the need to assess dyspnea and if it's necessary to apply life supporting measures. In most patients, the common etiology of dyspnea consists of cardiac or pulmonary disease. An accurate diagnosis of the underlying disease that caused dyspnea is imposed to treat correctly the patient.

Key Words: acute dyspnea, pathophysiology of dyspnea, evaluation of dyspnea

Learning objectives: After studying this article, the practitioner should be able to: 1. understand the definition, pathogenesis and pathophysiology of acute dyspnea; 2. have knowledge about the etiology and most common causes of acute dyspnea; 3. make a correct diagnosis through history, clinical as well as laboratory examination of a patient with acute dyspnea.

BACKGROUND

Acute dyspnea represents a diagnostic challenge, for any physician. There are no prospective diagnostic algorithms for this problem in the recent literature. The general practitioner has to assess the emergency and to apply life supporting measures. Patients with cardiopulmonary disease often have respiratory

distress, in medical terms referred as dyspnea. In most patients, the common etiology of dyspnea consists of cardiac or pulmonary disease. Dyspnea is responsible for substantial disability and for millions of patient visits to the hospital each year.¹

DEFINITION

Dyspnea, can be defined as an uncomfortable awareness of breathing. Dyspnea has been classified as acute or chronic on the basis of the tempo. Acute dyspnea is defined as dyspnea arising in the previous 24 to 48 hours. It is a frequent, badly tolerated symptom, but not a sign. It is a subjective sensation, with various intensities, for which there is no accurate objective measurement.² The patients do not use the word itself so that the physician has to interpret the

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patients' symptoms and decide what is dyspnea and what not.

ETIOLOGY

Acute dyspnea has multiple causes. Dyspnea can be the first manifestation of a life threatening disease or it can have a functional cause. The most common causes of acute dyspnea are pulmonary and cardiac diseases, as well as acute blood loss, metabolic acidosis, anxiety, poor physical condition. (Table 1)

Table 1. Most common causes of acute dyspnea.

Cardiac disease
Pulmonary disease
Acute blood loss
Metabolic acidosis
Anxiety
Poor physical condition

Mostly the common causes of acute dyspnea consists of a cardiac or a pulmonary disease. Fedullo and co. examined the causes of dyspnea in a study population of 162 consecutive pts of the emergency room and found out that frequently, 25.9 % presented heart failure, asthma 25.3%, acute exacerbation of chronic obstructive pulmonary disease in 14.3%, pneumonia in 7.4%, functional causes 4.3%, in comparison with pulmonary thrombo-embolism which was present in less than 2%.³

The cause of dyspnea can be a manifestation of an acute disease or an exacerbation of a chronic previous disease.⁴

The most frequent etiologies are asthma, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), pneumonia, ischemic coronary disease (ICD), and psychogenic.⁵

In the presence of a pulmonary or cardiac disease, the recurrence or the exacerbation of the underlying process are more frequent. Acute dyspnea in a patient with underlying COPD indicates also an acute exacerbation, so that any information about the onset, timing, severity, and presence of exacerbating factors are very important. Recent upper respiratory infection, cough, sputum production, wheezing, haemoptysis, or a history of smoking may suggest a pulmonary cause for dyspnea.

Physicians should ask details about symptoms that may indicate the presence of an underlying heart disease. An important cause of acute dyspnea is acute

myocardial infarction. Horne et al. showed that 47% of 88 patients from a study group with acute MI, reported shortness of breath, while 64% had chest pain.⁶

In angina pectoris, defined as chest pain of cardiac origin due to an imbalance between myocardial oxygen supply and demand, patients frequently describe a heavy pressure or squeezing triggered by exercise. Patients usually describe supplementary symptoms such as dyspnea, nausea, vomiting, diaphoresis, and weakness.

A detailed medication history should be always taken because there are some drugs, such as penicillin, dapsone, sulfonamides, quinidine, amiodarone, nitrofurantoin or aspirin, which can be implied in the etiology of acute dyspnea. (Table 2)

Table 2. Drugs inducing dyspnea related diseases.

Drug	Related Disease
Penicillin and quinidine	Hemolytic anemia
Sulfonamides and dapsone	Sulfhemoglobinemia
Amiodarone and nitrofurantoin	Acute or chronic fibrosis
Aspirin sensitivity	Asthma

Anemia is frequently an important etiologic cofactor and not the only cause of an acute dyspnea.

A more detailed list of specific etiologies of acute dyspnea, some of them rare, includes gastrointestinal disease as well as pain. (Table 3)

In up to one third of cases, acute dyspnea has multifactorial causes so that additional medical history findings such as the presence of fever, night sweats, chills, weight loss, chest pain, recent trauma, history of a recent proximal deep venous thrombosis or symptoms of gastro-esophageal reflux disease can help the practitioner to make the right diagnosis.

PATHOPHYSIOLOGY

The pathophysiology of dyspnea is complex, and not well understood.^{6,7} Although dyspnea is a sensation, no specialized dyspnea receptors, nor a specific cortical area processing this information related to dyspnea, have been identified.

Dyspnea occurs whenever the work of breathing is excessive, but it can be described by patients under the terms of „air hunger”, „increase effort or work of breathing”. „feeling of suffocation”, “breath stops”, “air hunger”, “chest tightness” or ”constriction”. This can be explained because it includes distinctive

Table 3. Etiology of acute dyspnea.

Pulmonary	Upper airway obstruction <ul style="list-style-type: none">• Epiglottitis, glottis edema (bee stick or ACE inhibitors), laryngospasm, vocal cords dysfunction, foreign body aspiration, benign or malign tumor of the upper airways Lower airway obstruction <ul style="list-style-type: none">• <u>Frequent</u>: acute exacerbation of chronic obstructive pulmonary disease, asthma bronchial• <u>Rare</u>: bronchiolitis Pulmonary vascular disease <ul style="list-style-type: none">• <u>Frequent</u>: thromboembolus/tumor embolus/fat embolus• <u>Rare</u>: pulmonary hypertension, high altitude pulmonary edema Pleural disease <ul style="list-style-type: none">• <u>Frequent</u>: pneumothorax, pleural effusion Other <ul style="list-style-type: none">• Respiratory muscles/thoracic cage, systemic neuromuscular disease, phrenic nerve dysfunction, giant ascites
Cardiac (Heart failure)	<ul style="list-style-type: none">• Ischemic coronary heart disease• Hypertensive heart disease• Valvular disease, septal defects• Cardiomyopathy• Arrhythmias• Myxoma• Pericardial disease:<ul style="list-style-type: none">○ Pleural effusion○ Pericarditis
Metabolic, endocrinologic	<ul style="list-style-type: none">• Diabetic ketoacidosis, lactic acidosis• Fever, sepsis• Hyperthyroidism• Drugs: aspirin intoxication, progesterone therapy
Other	<ul style="list-style-type: none">• Anemia/hemoglobinopathy• Decreased/abnormal hemoglobin/carboxyhemoglobin• Gastro esophageal reflux disease• Anxiety/depression/psychogenic• Intense pain

sensation, generated through different patho-physiologic mechanisms such as an increase in the respiratory drive and the stimulation of the irritant receptors in the lungs.⁸

Moreover, the intensity of dyspnea can be influenced by the relative match between the respiratory motor command located in the central nervous system and the afferent feedback from receptors located in the respiratory system.

Dyspnea results from a complex interaction between multiple receptors, the autonomous nervous system, and the cerebral cortex. At least three different factors are implied into the development of dyspnea:¹

- The amount of work that must be performed by the respiratory muscles to provide adequate ventilation;

- The abnormality of the respiratory gases in the the body fluids;

- The state of the mind.

When the lungs and the chest wall are less compliant or when the resistance to airflow is increased, an exceeding force generation in the respiratory muscles is required, in order to produce a given volume change.¹

Increased work of breathing occurs also when the ventilation is excessive for the level of activity, but there are no perceptual differences between a deep

breath with a normal mechanical load and a normal breath with an increased mechanical load. Only the one with the increased mechanical load is associated with discomfort.⁹

The sense of respiratory effort arises from a signal transmitted from the motor cortex to the sensory cortex simultaneously with the outgoing motor command to the ventilatory muscles. The sense of respiratory effort plays an important part, mainly when the respiratory muscles are fatigued and weakened or when their loading is increased. It has been postulated that dyspnea occurs whenever the respiratory muscular force generated during breathing approaches their maximal force-generating ability, due to the transduction of mechanical to neural stimuli.

Different stimulation of the receptors of the upper respiratory tract, lungs, respiratory muscles or chest wall produces an excessive or abnormal activation of the respiratory centers in the brainstem. There has not been identified an uniform trigger for dyspnea.

The activation of the respiratory centers comes from stimuli transmitted through and from a variety of structures and pathways, including:

- Intrathoracic receptors via vagal nerves;
- Afferent somatic nerves particularly from the respiratory muscles and joints;
- Chemoreceptors in the brain, aortic and carotid bodies (for carbon dioxide and oxygen concentration in blood);
- Cortical centers;
- Afferent fibers in the phrenic nerves (probably).

There are several different mechanisms that operate to different degrees, in the various clinical situation in which dyspnea occurs.

Dyspnea is the result of a complex interaction of efferent signals from the cortical centers (motor centers and brainstem automatic centers) and of afferent signals from various mechanoreceptors, located in the upper airways, lungs and chest wall.^{1,8}

There are clinical observations that suggest that the facial and upper respiratory tract receptors can modify the sensation of dyspnea and that receptors in the trigeminal nerve distribution can modulate the intensity of dyspnea.

In the lung there are several receptors: irritant receptors in the respiratory epithelium that mediate bronchoconstriction in response to chemical or mechanical stimuli, stretch receptors responding to lung inflation implied in the ending of inspiration and unmyelinated nerve endings, known as C fibers that respond to interstitial congestion and are located in the blood vessel walls and interalveolar septa. Afferent

information from these receptors reaches the central nervous centers via the vagus nerve. Recent studies demonstrated that vagal information from different lung receptors can alter the quality and the intensity of dyspnea.^{10,11}

Hypercapnia is an important cause for dyspnea, exerting pH changes at the level of central chemo receptors. Recent works established that hypercapnia can cause dyspnea independently of any associated reflex increase in the respiratory muscle activity.

Hypoxia has not a clearly described role in the generation of dyspnea; and in recent literature there are few studies that formally examine the relationship between hypoxia and dyspnea. The mechanoreceptors located in the face, upper airway, lung, and chest wall are able to affect the individual perception of dyspnea.¹

The sense of air hunger arises, in part from increased respiratory activity within the brainstem, and the sensation of chest tightness probably results from stimulation of vagal irritant receptors. While afferent information from the mechanoreceptors probably passes through the brainstem before reaching the sensory cortex, it is not certain that some afferents project directly to the sensory cortex, bypassing the brainstem.¹

In most conditions multiple mechanisms cohabit, while different conditions can share a common mechanism.

DIAGNOSIS

Evaluation of the patient with acute dyspnea

Evaluation of acute dyspnea begins with a complete and thorough history and physical examination. Studies have shown that a medical history and clinical examination alone predicts the final diagnosis in 70% to 80% cases.^{1,12}

The most common etiologies are asthma, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), pneumonia, cardiac ischemia, and psychogenic. There is the rule of 10 P's. (Table 4)

Causes of hospitalisation

Patients who are hemodynamically unstable (eg, hypotensive and tachycardic), who have hypoxia (e.g. oxygen saturations below 90%), or who will require rapid diagnostic procedures or aggressive therapeutic regimens to control their symptoms should be hospitalized. History taking should be tailored to include information pertinent to evaluating potential etiologies for dyspnea.

Table 4. Rule of 10 P's.

Acute Dyspnea - 10 P's

- Pneumonia
- Pneumothorax
- Pulmonary constriction/asthma
- Peanut (or other foreign body)
- Pulmonary embolus
- Pericardial tamponade
- Pump failure (heart failure)
- Peak seekers (high altitudes)
- Psychogenic
- Poisons

Table 5. Differentiating history and physical examination for cardiac and pulmonary causes of dyspnea.

	Cardiac Disease	Pulmonary Disease
History	Dyspnea on exertion Paroxysmal nocturnal dyspnea Orthopnea Associated chest pain	Dyspnea with rest and exertion Tobacco use Cough Sputum production Wheezing Pleuritic chest pain
Physical examination	Jugular venous distention Peripheral edema Ascites Pleural effusions Pulmonary edema Cardiomegaly S3 gallop	Expiratory wheezes Decreased air movement Resonance to percussion Barrel-chested physique

History

History taking should be tailored to include information pertinent to evaluating potential etiologies for dyspnea. Pulmonary and cardiac diseases are responsible for the vast majority of cases; therefore, special attention should be given to these possibilities. Table 5 outlines the differentiating history and physical examination findings for cardiac and pulmonary disease. Table 1 lists the major causes of acute dyspnea.

Pre-existing pulmonary or cardiac disease should be noted because the presence of either makes recurrence or exacerbation of the underlying process more likely. Acute dyspnea in a patient with underlying COPD is likely to indicate an acute exacerbation of COPD. Information about the onset, timing, associated symptoms, severity, and exacerbating and relieving

factors obviously are important. Physicians should specifically ask about the presence of pedal edema, paroxysmal nocturnal dyspnea, orthopnea, angina, or palpitations; these symptoms may indicate occult heart disease. Wheezing, cough, sputum production, hemoptysis, recent upper respiratory infection, or a history of smoking may suggest a pulmonary etiology for the dyspnea. In addition, the occupational history may point to a pulmonary cause (eg, sandblasting and silicosis or pipefitting and asbestosis).

Additional medical history findings that may be helpful include the presence of fever, chills, night sweats, weight loss, change in appetite, chest pain/pleurisy, recent trauma, or symptoms of gastroesophageal reflux disease. A detailed medication history always should be taken. Drugs may cause hemolytic anemia (quinidine and penicillin); methemoglobinemia (nitrites and nitrates); sulfhemoglobinemia (dapsone and sulfonamides); and acute or chronic fibrosis

(nitrofurantoin or amiodarone). Aspirin sensitivity is a cause of asthma in a significant number of patients. Acute myocardial infarction (MI) is an important cause of acute dyspnea. A study evaluating the frequency of symptoms among 88 patients who presented with acute MI found that 47% reported shortness of breath.⁷ The most common symptoms of acute MI in this study were chest pain and diaphoresis, occurring in 64% and 78% of patients, respectively.⁶

Angina pectoris is defined as chest pain of cardiac origin due to an imbalance between myocardial oxygen supply and demand. Patients frequently describe the discomfort as a heavy pressure or squeezing that usually is brought on by exertion. Associated symptoms include dyspnea, diaphoresis, nausea, vomiting, and weakness.

Details in the past medical history may be useful for establishing a diagnosis. History of proximal deep venous thrombosis should prompt a search for pulmonary thromboembolism or pulmonary hypertension. Previous history of cancer, particularly breast or bronchogenic, should raise the suspicion of a malignant pleural effusion. Although usually associated with chronic dyspnea, previous thoracic radiation and chemotherapy with busulfan or other agents are known to be associated with pulmonary fibrosis, which may present with acute dyspnea.

Physical examination

Results of the physical examination can direct the physician toward a specific diagnosis. General assessment of the patient may yield such information as severity of dyspnea, presence of tachypnea, central or peripheral cyanosis, presence of pursed lip breathing (indicative of severe obstructive lung disease), central obesity consistent with obstructive sleep apnea, or extreme cachexia (suggestive of malignancy). Pallor raises anemia as a consideration. The pharynx should be examined for signs of obstruction or enlarged tonsils, which may predispose to obstructive sleep apnea. Stridor, indicative of an upper airway obstruction from laryngospasm, tumor, or vocal cord dysfunction, should be sought. Auscultation of the lung fields can elicit further evidence of a pulmonary etiology. A localized wheeze may be evidence of foreign body or tumor. Decreased or absent breath sounds unilaterally may represent pneumothorax (when accompanied by hyper resonance to percussion) or pleural effusion (when accompanied by dullness to percussion). Crackles or rhonchi are indicative of pneumonia, pulmonary fibrosis, or pulmonary edema. Wheezing, a prolonged expiratory phase of respiration, increased lung fields by percussion, or palpable liver without hepatomegaly is indicative of obstructive airway disease. Pleural friction rubs may be a sign of pleurisy or pulmonary infarction. CHF is suggested by the presence of an S3 gallop, bibasilar crackles, elevated jugular venous pressure, a laterally displaced point of maximal cardiac impulse, and/or peripheral edema. S3 gallop, a sign of left ventricular failure, can be heard in conditions resulting in rapid ventricular filling and volume overloading, such as mitral or aortic insufficiency. An S3 gallop is low pitched and is heard best at the apex with the bell of the stethoscope. An increased pulmonic S2, right ventricular heave, and elevated jugular venous pressure are indicative of pulmonary hypertension. S4 (atrial gallop) in a patient presenting with acute dyspnea is suggestive of decreased left ventricular compliance.

S4 is a presystolic, low-pitched sound that occurs just before S1 and is heard best at the apex with the bell of the stethoscope. S4 is encountered in conditions that cause decreased ventricular compliance such as hypertension, aortic stenosis, coronary artery disease, acute MI, and hypertrophic cardiomyopathy. These conditions cause increased resistance to ventricular filling following atrial contraction. Evidence of deep venous thrombosis may indicate the presence of a pulmonary thromboembolism. Most pulmonary embolisms arise from venous thromboembolisms of the lower extremity. The possibility of pulmonary embolism is suggested by the acute onset of dyspnea, pleuritic chest pain, severe hypoxia, and risk factors such as recent surgery, underlying malignancy, and a bedridden or sedentary state. One study found that the most common symptoms of pulmonary embolism include dyspnea (73%), pleuritic pain (66%), cough (37%), lower extremity edema (28%), and hemoptysis (13%).¹³ Physical signs included crackles on lung auscultation (51%), and tachycardia (30%).

Laboratory examination

The laboratory work-up of dyspnea is directed by the results of the history and physical examination. Chest radiograph, oxygen saturation, arterial blood gas (ABG) analysis, electrocardiogram (ECG), echocardiogram, and cardiac enzyme levels may help differentiate between an acute pulmonary versus an acute cardiac etiology. A ventilation-perfusion scan and/or a lower extremity Doppler study should be performed if pulmonary thromboembolism is suspected. In patients presenting with an exacerbation of COPD or asthma, measurement of oxygen saturation is essential. Pulse oximetry is an effective screening tool for detecting hypoxia, and it has the advantage of lower cost and discomfort to the patient compared with ABG sampling. Pulse oximetry also is easy to use, and it provides immediate results and continuous assessment. However, an ABG analysis may be needed in the initial assessment of a chronic smoker with acute dyspnea because of elevated carboxyhemoglobin levels caused by smoking. Carbon monoxide causes the pulse oximeter to overestimate the arterial oxygen saturation, especially when carboxyhemoglobin levels exceed 2%.¹⁴ For patients presenting with acute chest pain, the ECG is the most important initial laboratory examination. A prospective study of 247 patients who presented to an emergency department with acute chest pain found that the initial history, physical examination, and ECG are the most important predictors of cardiac events, with a 96%

sensitivity of predicting a cardiac event.¹⁵ The addition of cardiac marker data, including serum troponin I levels, did not improve the positive predictive value in this patient population beyond that of the history, physical examination, and ECG.¹⁶

B-type natriuretic peptide (BNP), a cardiac neurohormone, recently has been identified to have diagnostic potential in patients with left ventricular dysfunction.¹⁷ BNP is released by the ventricles in response to increased end-diastolic pressure or volume expansion. A BNP level of 100 pg/mL is highly indicative of decompensate heart failure.¹⁷

Differentiation between cardiac and pulmonary dyspnea is possible in most patients by clinical evidence, but is difficult when there is a coexistence of cardiac and lung disease.¹⁸ Among elderly patients, heart failure is often misdiagnosed in an urgent care setting because of the lack of specific symptoms.

B-type natriuretic peptide, also known as BNP, is a cardiac neurohormone, specifically secreted from the cardiac ventricles as a response to ventricular myocardial stretch (due to volume expansion or pressure overload) and resultant increased wall tension.

Because BNP levels are elevated in patients with cardiac dysfunction, and correlates with the NYHA class, BNP measurement is a valuable tool in the early diagnosis and treatment of patients with heart failure. In most studies, the cutoff concentration for the CHF diagnosis is 100 pg/mL, although in other studies, lower BNP levels have been used.¹⁹

BNP levels are also useful in the differentiation of dyspnea secondary to cardiac dysfunction and its precursor conditions, from dyspnea due to pulmonary conditions. (Table 6)

Table 6. Significance of BNP levels.

BNP levels	Meaning
Below 100 pg/mL	Indicate no heart failure
Between 100-300 pg/mL	Suggest that heart failure is present
Above 300 pg/mL	Indicate mild heart failure
Above 600 pg/mL	Indicate moderate heart failure
Above 900 pg/mL	Indicate severe heart failure

In dyspneic patients, serum levels of BNP < 50 pg/ml can exclude HF with a good probability. In patients with acute dyspnea secondary to pulmonary conditions BNP levels are below 100 µg/mL.

Patients with acute dyspnea secondary to CHF have BNP levels above 500 pg/ml. If the BNP concentration lies between 100-500 pg/ml, and the patient has a normal renal function, one must not

ignore (has to think at a differential diagnosis with) an underlying thromboembolic disease, a pulmonary hypertension or a left ventricular dysfunction without an acute decompensation.^{20,21}

Recent studies have demonstrated the accuracy of BNP for CHF diagnosis, severity staging and for prediction of prognosis and treatment.²² Patients with higher BNP levels have a poorer prognosis and should receive a more aggressive therapy.

D-dimers are a degradation product of cross linked fibrin, whose level becomes elevated following clot formation. The presence of D-dimer fragments suggests that a coagulation-fibrinolytic process is taking place. A low or normal level excludes the presence of a fresh thromboembolic material undergoing dissolution in the deep veins or in the pulmonary arterial tree.

Elevated D-dimers fragments persist for 7 to 12 days and indicate recent or ongoing fibrinolysis. A high level is not specific for diagnosis of venous thromboembolism, being present in a wide variety of conditions. D-dimers can be measured either by an ELISA technique or latex agglutination assay. With negative predictive values close to 100%, certain D-dimer assays like quantitative ELISA tests, have the potential to be the only screening test necessary to exclude DVT and PE.⁷

CONCLUSION

Difficult and labored breathing with shortness of breath is one of the most common and distressing symptoms experienced by patients. Various pathophysiological mechanisms underlie the symptom of dyspnea. Multiple mechanisms may be present in a patient. The evaluation of the dyspneic patient must begin with a thorough history and physical examination, the key characteristics of the symptom, including quality, intensity, duration, frequency, and distress. The words utilized by patients to describe their breathing discomfort may provide insights into the underlying pathophysiology of their disease.

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