Role of biomarkers in patients with dyspnea

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Abstract. – Background: The use of biomarkers has been demonstrated useful in many acute diseases both for diagnosis, prognosis and risk stratification.

Objectives: The purpose of this review is to analyze several biomarkers of potential use in patients referring to Emergency Department with acute dyspnea.

State of the Art: The role of natriuretic peptides has a proven utility in the diagnosis, risk stratification, patient management and prediction of outcome in acute and chronic heart failure (HF). New immunoassays are available for the detection of mid-region prohormones in patients with acute dyspnea such as Mid-region pro-adrenomedullin (MR-proADM) and Mid-region pro-atrial natriuretic peptide (MR-proANP). Also procalcitonin, copeptin and D-dimer, which are markers of inflammation, bacterial infections and sepsis, seem to be useful in the differential diagnosis of dyspnea. Conventional and high-sensitivity troponins are fundamental, not only in the diagnosis of acute coronary syndromes, but also as indicators of mortality in patients with acute decompensated heart failure.

Perspectives: Further studies with randomized controlled clinical trials will be needed to prove the theoretical clinical advantages offered by a shortness of breath biomarkers in terms of diagnostic, prognostic, cost effective work-up and management of patients with acute dyspnea.

Conclusions: A multimarker pannel approach performed by rapid and accurate assays could be useful for emergency physicians to promptly identify different causes of dyspnea thus managing to improve diagnosis, treatment and risk stratification.

Key Words:
Dyspnea, Biomarkers, Emergency department, Natriuretic peptides, MR-proADM, MR-proANP, Procalcitonin, Troponins, Copeptin and D-dimer.

Introduction

In the past years many definitions of dyspnea have been given such as “sensation of breathlessness”, “shortness of breath”, “awareness of respiratory distress”, “difficult, labored or uncomfortable breathing”. Sometimes these definitions confuse the real symptom reported by patient with the clinical sign observed by physicians. Therefore, dyspnea can be defined as an unpleasant or uncomfortable sensation of difficult breathing experienced by an individual not only due to pathophysiological but also social, psychological and environmental factors. This subjective experience is not always consistent with the clinical and instrumental findings. Frequently, in Emergency Department (ED) many patients with dyspnea have other associated symptoms such as fever, cough, chest pain or palpitations. These accompanying symptoms or signs are important clues about the etiology of dyspnea. In acute settings it is important to promptly recognize the causes of shortness of breath thus managing to start early treatment and improve patients’ outcome. Many causes of dyspnea can expose patient to life threatening events if the correct diagnosis is not established. The differential diagnosis of dyspnea is very broad but acute heart failure (AHF), acute coronary syndrome (ACS) and pulmonary embolism (PE) are the main diseases to be excluded for their potential severity and mortality. Patients referring to ED for dyspnea may have more than one underlying etiology from different organs and systems (Table I). The differential diagnosis of dyspnea could be even more challenging in case of ED overcrowding. Current literature reveals important diagnostic, prognostic and therapeutic implications of several biomarkers used in many acute diseases.

The aim of this work the usefulness of several biomarkers not only in the diagnosis but also in the etiology, severity, treatment and risk assessment in patient presenting in ED with dyspnea.

Clinical Approach to Acute Dyspnoeic Patient

The main purpose of emergency physician is to identify rapidly acute and serious life threatening causes of dyspnea such as Acute Coronary
Syndromes (ACS), Acute Heart Failure (AHF) and Pulmonary Embolism (PE), Pneumonia and acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD). Although several and innovative techniques can be used in the differential diagnosis, clinical history and physical examination remain the cornerstones of this approach. A rapid clinical history should be useful to evaluate the onset, duration and intensity of acute dyspnea, any accompanying symptoms, current drug therapy and any concomitant diseases. Although many patients may have more than one underlying etiology for their shortness of breath, a detailed medical history can often identify the primary process resulting in dyspnea.

After a general initial observation, an accurate physical examination should start with patients’ vital signs measurement including pulse oxime-
try and a systematic evaluation should be conducted in order to identify any signs of the most common underlying diseases (Table II).

Medical history and physical examination are essential tools in the differential diagnosis of dyspnea, but instrumental and laboratory investigations are needed to confirm clinical suspicions. In ED an electrocardiogram should be performed in all patients with shortness of breath, thus managing to exclude heart diseases as principal determinants of dyspnea. It is important to remind that silent electrocardiographic findings in ACS may lie in the location of the lesion, since up to 50% of infarctions in the left circumflex distribution may be silent9-11. Chest radiography is a quick, available and non expensive screening tool when a pulmonary or cardiac cause of dyspnea is suspected. It is useful to look for cardiomegaly, pleural effusions, interstitial and vascular edema, pneumothorax and lung consolidations. Echocardiography is a non invasive, rapid and safe extension of the clinical examination providing essential information not only on cardiac anatomy but also on systolic and diastolic function. The use of this technique in the vital early minutes after the arrival of critically ill patients should improve the diagnosis and treatment of a variety of conditions such as breathlessness, undifferentiated shock, chest pain and cardiac arrest12.

A routine diagnostic evaluation of patients with dyspnea includes a complete blood count serum electrolytes, serum creatinine, estimated glomerular filtration rate (GFR), glucose, liver function tests, and urinalysis. The measurement of serum digoxin level is important in patients taking this drug because of the occurrence of adverse drug reactions is common, owing to its narrow therapeutic index. Arterial blood gas analysis is a diagnostic and rapid tool used to evaluate acute changes of blood pH including modifications of normal partial pressures of oxygen and carbon dioxide. Many blood gas analyzers will also report concentrations of lactate, hemoglobin, several electrolytes, oxyhemoglobin, carboxyhemoglobin and methemoglobin13.

While pulmonary angiography is a reliable but invasive test used when the results of non-invasive imaging are equivocal, the multi detector computed tomography (MDCT) has become the method of choice to diagnose suspected PE in routine clinical practice. It allows adequate visualization of the pulmonary arteries up to at least the segmental level with a sensitivity of 83%, a specificity of 96% and a positive predictive value of 86%14.

Pulmonary function tests (PFTs), if available in ED, may be useful in the assessment of dyspneic patient. These tests can contribute to distinguish an obstructive from a restrictive pulmonary disease pattern9.

**Table II. Clinical findings in patient with dyspnea.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute decompensated heart failure and acute coronary syndrome</td>
<td>Tachypnea, peripheral edema, jugular venous distension, hepatojugular reflux, rales, wheezing, crackles, decreased tactile fremitus, S3 or S4, hyper or hypotension, arrhythmias, diaphoresis</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Tachypnea, tachycardia, hypoxia, hypotension, fever, increased pulmonic component of second heart sound, concomitant deep venous thrombosis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Fever, tachypnea, inspiratory crackles, increased tactile fremitus, bronchial breath sounds</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary diseases</td>
<td>Tachypnea, tachycardia, prolonged expiratory phase, wheezing, decreased breath sounds, cyanosis agitation or letargy, accessory muscle use, supraclavicular retractions, halting speech, diaphoresis</td>
</tr>
</tbody>
</table>

*B-Type Natriuretic Peptide (BNP) and N-terminal fragment (NT-proBNP)*

B-Type Natriuretic Peptide (BNP) is a 32-amino-acid polypeptide secreted by cardiac ventricles in response to excessive stretching of cardiomyocytes due to ventricular volume expansion and pressure overload15. BNP is co-secreted along with a 76 amino acid N-terminal fragment (NT-proBNP) which is biologically inactive. BNP binds to and activates the atrial natriuretic factor receptors NPRA, and to a lesser extent NPRB, in a fashion similar to atrial natriuretic peptide (ANP) but with 10-fold lower affinity. NPRA and NPRB are atrial natriuretic peptide receptors linked to guanylyl cyclases to convert GTP to cGMP. cGMP will then stimulate cGMP-depen-
dent protein kinase (PKG) which induces vascular smooth muscle relaxation with a consequent decrease of total peripheral resistance and venous return (preload) to the heart. The biological half-life of BNP, however, is twice as long as that of ANP, and that of NT-proBNP is even longer, making these peptides better targets than ANP for diagnostic blood testing BNP accurately reflects current ventricular status. The half-life of NT-ProBNP is 1 to 2 hours vs. 20 minutes for BNP.

Due to the relatively long half-lives of natriuretic peptides, abrupt changes in left ventricular filling pressures may not be reflected by rapid changes in peptides. Conditions other than heart failure associated with elevated natriuretic peptide levels include: LV hypertrophy, tachycardia, right ventricular overload, myocardial ischemia, hypoxemia, renal dysfunction, advanced age, liver cirrhosis, sepsis, and infection. Natriuretic peptide levels may be relatively low in patients with obesity and flash pulmonary oedema.

Both BNP and NT-proBNP levels in the blood are currently used not only to diagnose acute congestive heart failure (CHF) but also to correlate with the severity of symptoms and prognosis.

Diagnosis of heart failure is considered unlikely when B-type natriuretic peptide level is below 100 pg per millilitre (pg/ml). In this case alternative causes of dyspnea had to be investigated. If B-type natriuretic peptide level is more than 500 pg/ml, heart failure has to be considered the main diagnosis thus initiating appropriate therapy. For patients with B-type natriuretic peptide levels between 100 and 500 pg per millilitre, it is important to evaluate both heart failure and many other causes of dyspnea. When using NT-proBNP, a cut point of 300 pg/ml is proposed to “rule out” a diagnosis of HF, while higher age-dependent cut points are suggested to “rule in” HF. Patients with NT-proBNP levels >450 pg/ml (<50 years), >900 pg/ml (50-75 years), and >1800 pg/ml (>75 years) all have a high likelihood of heart failure as the diagnosis (Figure 1). In acute conditions rapid B-type natriuretic peptide assay may be useful in differentiating cardiac from pulmonary causes of shortness of breath making a differential diagnosis in patient referring to ED with acute dyspnea in conjunction with other clinical and instrumental information such as clinical history, physical examination, blood tests, electrocardiography, chest X ray and echocardiography. In acute setting this biomarker could also reduce time to the initiation

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**Figure 1. BNP Consensus Algorithm**

Patients presenting with dyspnea

Physical examination, chest x-ray, ECG, BNP level

- **BNP < 100 pg/ml**
  - HF very improbable (2%)

- **BNP 100-400 pg/ml**
  - Clinical suspicion of HF or past history of HF
  - HF probable (75%)

- **BNP > 400 pg/mL**
  - HF very probable (95%)
of the most appropriate therapy, time to discharge and total cost of treatment thus improving the management of patient referring to ED with acute dyspnea\textsuperscript{15}.

**Adrenomedullin (ADM) and Mid-region pro-Adrenomedullin molecule (MR-proADM)**

Adrenomedullin (ADM) is a 52-amino acid ringed-structure peptide with C-terminal amidation, originally isolated from human pheochromocytoma. ADM mediates vasodilatory and natriuretic properties through the second messenger cyclic adenosine 3’,5’-monophosphate (cAMP), nitric oxide and the renal prostaglandin system. ADM immunoreactivity and its gene are widely distributed in cardiovascular, pulmonary, renal, gastrointestinal, cerebral and endocrine tissues. ADM is also synthesized and secreted from vascular endothelial and smooth muscle cells\textsuperscript{21}. It is a potent vasodilator with hypotensive, inotropic and natriuretic effects stimulated by cardiac pressure and volume overload. It can be considered a vasodilatory peptide with potent hypotensive effects. Recent studies suggest that ADM plasma concentration is increased in several diseases such as hypertension, congestive heart failure, chronic renal failure and septic shock\textsuperscript{22-24}. ADM plasma measurement is limited because of its biologic instability and short half-life of 22 minutes.

The Mid-region fragment of pro-Adrenomedullin (MR-proADM) is a peptide consisting in 24 to 71 amino acids, secreted in equimolar amounts than ADM but more stable in plasma and easier to measure. As described elsewhere mean MR-proADM in healthy individuals is 0.33 ± 0.07 nmol/L (range 0.10-0.64 nmol/L)\textsuperscript{23}. ADM gene transcription and the subsequent MR-proADM release in acutely dyspnoeic patients is due to three possible mechanism: volume overload, bacterial endotoxins, proinflammatory cytokines and impaired removal of circulating biomarker during lung injury and kidney dysfunction\textsuperscript{26}.

According to the current literature MR-proADM assessment is used not only in the diagnosis and risk stratification of patients with sepsis and community-acquired pneumonia\textsuperscript{27,28}, but also as a prognostic marker in those with COPD and acute myocardial infarction\textsuperscript{29,30}.

The combination of MR-proADM with NT-proBNP, BNP and other biomarkers can be useful in the risk stratification for all-cause mortality in patients with acute destabilized heart failure\textsuperscript{31,32}. Recent studies demonstrated that MR-proANP is as useful as BNP for AHF diagnosis in dyspneic patients and may provide additional clinical utility when BNP is difficult to interpret. Moreover, MR-proADM identifies both patients with high 90-day mortality risk and adds prognostic value to BNP\textsuperscript{32}.

**Atrial Natriuretic Peptide (ANP), ProANP and Mid-region Pro-Atrial Natriuretic Peptide (MR-proANP)**

Atrial Natriuretic Peptide (ANP) is a 28-amino acid peptide produced, stored and released by cardiac atrial and ventricular myocytes in response to many signals such as hypervolemia, hypernatremia, angiotensin-II, sympathetic stimulation of β-adrenoceptors and endothelin. The hormone is constitutively expressed in the ventricle in response to stress induced by increased afterload as in case of aortic stenosis or ischemic insult. ANP can bind to three different receptors with intrinsic guanylate cyclase activity: natriuretic peptide receptor A (NPRA), natriuretic peptide receptor B (NPRB) and natriuretic peptide receptor C (NPRC). ANP mediates body water homeostasis by inhibiting renin and aldosterone secretion. As a result of this inhibition there is an increased glomerular filtration rate (GFR) due to a greater sodium and water excretion. ANP is also a potent vasodilator that relaxes vascular smooth muscle in arterioles and venules, thereby reducing blood pressure\textsuperscript{33}.

The classical endocrine effects of natriuretic peptides to modulate fluid and electrolyte balance and vascular smooth muscle tone are complemented by autocrine and paracrine actions that include regulation of coronary blood flow and, therefore, myocardial perfusion; modulation of proliferative responses during myocardial and vascular remodeling; and cytoprotective anti-ischemic effects\textsuperscript{34}.

There are evidences that ANP increases in patients with acute coronary artery disease and heart failure. This concept might be the basis for the development of new therapeutic strategies in such diseases\textsuperscript{35}.

The amino-terminal portion of proANP (termed NT-pro-ANP, or proANP) is secreted at the same molar ratio as ANP. Because it has a much longer half-life than has ANP, it has been suggested that proANP is a more reliable analyte\textsuperscript{36}. However, results from various competitive
immunoassays and high-performance liquid chromatography analyses indicate that pro-ANP may be subject to further fragmentation. Consequently, sandwich immunoassays for proANP might underestimate actual levels of proANP and immunoassays for measurement of mid-regional pro-ANP (MR-proANP) may have an advantage due to its blood sample stability. The trigger for MR-proANP release is cardiac overload and increased cardiac wall stretch, both being specific pathophysiological conditions in patients with acute destabilized HF. Recent literature suggests that MR-proANP can be considered a valid natriuretic peptide marker for patients with HF. It is equivalent to BNP or NT-proBNP in the diagnosis of acute HF in patients presenting with shortness of breath to ED. The MR-proANP cut-off point to make diagnosis of HF is 120-130 pmol/L. MR-proANP seems to be superior to BNP and NT-proBNP for predicting 90-day mortality in patients with dyspnea due to AHF. The role of MR-proANP has been evaluated in other diseases. MR-proANP levels not only are increased in LRTI, especially in community acquired pneumonia, but its measurement might be useful in risk stratification and correlation with severity of pneumonia. Moreover, MR-proANP levels increase progressively with the severity of sepsis and are independent predictors of mortality in ventilator-associated pneumonia. In critically ill patients increased circulating natriuretic peptides have been shown to correlate with the myocardial depression occurring in septic shock and to be a valuable tool for risk assessment in septic patients. MR-proANP levels are increased also in patients with stroke, particularly in those with cardioembolic strokes where this biomarker seems to predict 90-day mortality and functional outcome accurately. In view of these potential applications, MR-proANP measurement can be a useful complementary tool to make a differential diagnosis in patients referring to ED for dyspnea, in order to improve decisions regarding therapy and site of care.

**Troponins**

People with acute dyspnea are one of the most common cohort of patients referring to ED. Thus it is important to distinguish patients with potential life-threatening diseases and to differentiate those with ACS from those with noncardiac etiology early in the evaluation. In ED biomarkers elevations are fundamental for the diagnosis of myocardial infarction because both symptoms and electrocardiogram changes may be absent or non-specific.

The preferred biomarker for myocardial necrosis is cardiac troponin (I or T), which has nearly absolute myocardial tissue specificity as well as high clinical sensitivity, thereby reflecting even microscopic zones of myocardial necrosis. The 3-unit troponin complex (troponin I, T and C) is located on the actin filament and regulates skeletal and cardiac muscle contraction. There are tissue-specific isoforms of troponin I, T and C, but there is just one cardiac troponin I (cTnI) isoform in myocardial tissue. Elevated troponin levels then persist in the blood owing to the slow release and degradation of the structural pool, since the half life of troponin and its complex is about 2 hours. The prolonged window during which troponin levels are elevated allows for increased clinical detection of cardiac events and greater clinical sensitivity. Cardiac troponin concentrations begin to rise 4-6 hours with a maximum peak 18-24 ours after the onset of symptoms. There is huge variability in the sensitivity of assays. The appropriate cut-off value for each assay is unique and cannot be compared with any other. An increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population. Detection of a rise and/or fall of the measurements is essential to the diagnosis of acute myocardial infarction. The discriminatory percentile must be determined for each specific assay. It is important to underline that troponin elevations reflect myocardial damage without indicating its mechanism. Measurement of total CK is not recommended for the diagnosis of myocardial infarction, because of the large skeletal muscle distribution and the lack of specificity of this enzyme. Elevation of CK-MB can occur in trauma, rhabdomyolysis, myopathies or during the peripartum period. The specificity of CK-MB can be enhanced by calculating CK-MB/CK ratio which can be reduced in patients with concomitant heart and skeletal muscle injury. A TnI cut-off corresponding to the 10% coefficient of variation (0.1 microg/L) demonstrates a cumulative sensitivity of 93% with a corresponding specificity of 81% at 2 hours. The sensitivity is considerably higher compared to CK-MB and myoglobin.

In critically ill patients troponin elevations can be due to occult coronary artery diseases, toxic substances or direct damage secondary to me-
Mechanical or electrical energy such as cardiac trauma, cardioversion and direct-current shock. A variety of toxic insults may exacerbate underlying ischemic heart disease as occurs in sepsis or cardiotoxicity of high dose chemotherapy. In septic shock, clinically unrecognized myocardial cell injury is a marker of left ventricular dysfunction. The latter condition tends to occur more often in severely ill older patients with underlying cardiovascular disease.

During pulmonary embolism, acute right ventricular strain or infarction due to increased pulmonary arterial resistance can be a possible cause of troponin elevation which usually resolves in 40 hours or less.

Moreover, spontaneous progression of severe congestive heart failure is structurally characterized by cellular degeneration and multiple foci of myocardial cell death. Cardiac troponin I can be then considered a sensitive and specific molecular marker of congestive heart failure in patients with severely reduced left ventricular performance. Recent evidences suggest that a positive cardiac troponin test is associated also with higher in-hospital mortality.

Recently, new sensitive troponin assays have been introduced thanks to the continuous improvement of technology. These troponins have a higher sensitivity than the previous assays and an improved precision at the lower limit of detection that is below the 99th percentile in a normal reference population. These new sensitive troponins can substantially improve not only the early diagnosis of acute myocardial infarction but also its prompt evidence-based treatment. Moreover, recent evidences suggest that these assays may remain of limited value for the diagnosis of unstable angina.

**Procalcitonin (PCT) and Copeptin**

In ED the use of biomarkers can contribute not only to distinguish cardiac from non-cardiac dyspneic patients but also to recognize more than one underlying etiology. One of the most common causes of acute exacerbation of COPD is due to respiratory tract infections by bacteria or viruses both presenting with similar clinical features. Procalcitonin (PCT) is the prehormon of calcitonin which is normally secreted by the C cell of the thyroid in response to hypercalcemia. Currently it is believed that other cells such as adipocytes, hepatocytes, lung epithelial cells, muscle cell and peripheral blood mononuclear cells are able to release PCT in response to microbial, inflammatory and sepsis-related cytokines (bacterial toxins, lypopolysaccharides, Tumor Necrosis Factor α, IL-1b, IL-2 and IL-6). In contrast with the short half-life of calcitonin of 10 minutes, PCT has a half-life of 22-35 h and it is stable in samples. The production of PCT is not attenuated by non-steroidal and steroidal anti-inflammatory drugs. Currently PCT is described as a marker of bacterial infection but it has also a proven utility to predict the risk for mortality in patients with community-acquired pneumonia, in critically ill patients with sepsis and in those with ventilator-associated pneumonia. As previously reported elsewhere, a PCT level <0.1 µg/L indicates a low probability of bacterial infection, a level > 0.1 and < 0.25 µg/L indicates a possible bacterial infection and a PCT level > 0.25 µg/L indicates a high probability of bacterial infection.

PCT serum concentrations increase up to several thousand-fold in microbial infections and this increase correlates with infection’s severity or inadequate response to antibiotic therapy. Recent literature suggests that repeated PCT measurements can be useful not only to start an earlier antibiotic guided therapy but also to avoid or reduce drug administration if unnecessary. The rational use of a PCT antibiotic guided therapy could contribute to reduce or avoid the emergence of antibiotic related side effects and multidrug resistance bacteria especially in patient with non-pneumonic acute exacerbation of COPD. While PCT assessment has been extensively studied in sepsis, its role in cardiovascular disease is poorly understood. Recent studies suggest PCT association with major adverse cardiac events, left ventricular dysfunction and remodelling following acute myocardial infarction.

In acute conditions PCT measurements in combination with other biomarkers could help physicians in discriminating the most frequent causes of dyspnea and the real need for an antibiotic therapy.

Copeptin, also known as the arginine vasopressin (AVP) associated glycopeptides is a 39 amino acids derived from a 169 amino acids precursor termed preprovasopressin. Due to its stability in plasma and serum samples, copeptin can be measured using a remarkably sensitive sandwich immunoluminometric assay. When measured in healthy individuals, median copeptin plasma levels are 4.2 pmol/L, with a range of 1 – 13.8 pmol/L. This biomarker can be used as a diagnostic and prognostic tool in...
different clinical conditions. Its plasma levels are increased in patients with CHF, acute myocardial infarction, lower respiratory tract infection, acute exacerbation of COPD and in those with sepsis or septic shock. Moreover, combined measurement of plasma copeptin with other biomarkers such as BNP and NT-proBNP could provide prognostic value in terms of prediction of outcome in patients with CHF and risk stratification at an early stage after AMI. Copeptin is also a good prognostic marker to assess poor short- and long-term prognosis in acute exacerbation of COPD requiring hospitalization.

D-dimer

Acute pulmonary embolism (PE) is a common, serious and potentially lethal condition that a good emergency physician should consider if any suspicion exists, because a prompt diagnosis and treatment can dramatically reduce the high morbidity and mortality of the disease. The variability of presentation sets the patient and clinician up for potentially missing the diagnosis. The classic presentation with abrupt onset of pleuritic chest pain, shortness of breath, and hypoxia is rarely the case. Other associated symptoms are back pain, shoulder pain, upper abdominal pain, syncope, hemoptysis, new onset of wheezing, or a new cardiac arrhythmia. The diagnosis of pulmonary embolism is difficult because the clinical diagnosis is nonspecific and all of the objective tests have limitations. It is well known that more than half of all patients with pulmonary embolism remain undiagnosed.

D-dimer assay can be considered as a first-line standard test used in the evaluation of patients with suspected pulmonary embolism. The fibrin fragment D-dimer is produced by degradation of crosslinked fibrin by plasmin. D-dimer levels are elevated in plasma in the presence of an acute clot because of simultaneous activation of coagulation and fibrinolysis. Currently there is a number of available assays with different characteristics. Modern ELISA test kits and ELISA-derived assays have a sensitivity of >95% and a specificity of about 40%. Hence, a normal D-dimer level renders acute PE or deep venous thrombosis unlikely, with a high negative predictive value (NPV) of D-dimer. In the Emergency Department, a negative ELISA D-dimer test can exclude PE without further testing in approximately 30% of patients. A positive result, however, only indicates the necessity of further diagnostics such as CT angiography which is the main thoracic imaging test for investigating suspected PE. Age, pregnancy and a range of pathological conditions often lead to fibrin formation such as cancer, inflammation, infection, necrosis, aortic dissection and postoperative patients. In these pathological conditions the positive predictive value (PPV) of D-dimer is low.

Recent literature investigated the use of combined biomarkers in patients with suspected pulmonary embolism. The measurement of amino-terminal pro-B-type natriuretic peptide in addition to D-dimer improves specificity for acute pulmonary embolism without sacrificing negative predictive value.

Conclusions

We considered several biomarkers that are already used in many Emergency Departments thanks to their reliability, reproducibility and rapid execution in patients arriving with acute dyspnea in ED. These biomarkers, such as natriuretic peptides (BNP and NT-proBNP), PCT, MR-proADM, MR-proANP and Troponins, can help emergency physicians in making a differential diagnosis in dyspnoeic patients thus excluding the most severe and life-threatening diseases. Currently many other biomarkers have been studied but they are still not used routinely in acute conditions cause of their poor reproducibility, high costs and the lack of standardization. Among these it is important to mention the soluble isofrom of a interleukin-1 receptor family member ST2 (sST2), adiponectin, chromogranin A and the C-terminal endothelin-1 precursor fragment (CT-proET-1) that are important predictors of one-year mortality in patients with diagnosed ADHF. However, each emerging biomarker will probably offer some additional informations concerning the pathophysiology of acute dyspnea and suggest the most appropriate treatments.

A multimarker pannel approach performed by rapid and accurate assays could be useful for emergency physicians to promptly identify different causes of dyspnea thus managing to improve diagnosis, treatment and risk stratification. The increasing research experience will facilitate more efficient assessments of new biomarkers but clinical history and physical examination
remain the cornerstones of ED physicians for patients with acute dyspnea.

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Role of Biomarkers in patients with dyspnea


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