Evaluation and management of the acutely dyspneic patient: the role of biomarkers

Alex Harrison MD\textsuperscript{a,*,1}, Stanley Amundson MD\textsuperscript{a,b,c}

\textsuperscript{a}Division of Medical Education and General Internal Medicine, Scripps Mercy Hospital, San Diego, CA 92103, USA
\textsuperscript{b}Internal Medicine Residency Program, Scripps Mercy Hospital, San Diego, CA 92103, USA
\textsuperscript{c}School of Medicine, University of California, San Diego, CA 92103, USA

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Abstract The etiology of dyspnea can often be difficult to rapidly and accurately determine and can delay timely and appropriate therapies. The current literature reveals important diagnostic, prognostic, and therapeutic implications of several currently used biomarkers: sensitive D-dimer, myoglobin, creatine kinase–MB, cardiac troponins, and b-type natriuretic peptide. These biomarkers were found to have a high sensitivity and negative predictive value for rapidly ruling out potential serious etiologies of dyspnea, namely, pulmonary embolism (PE), acute myocardial infarction (AMI), and congestive heart failure (CHF). In the setting of a low to moderate pretest probability of PE, a negative sensitive D-dimer can rule out a PE with 97% accuracy. After 10 hours from the onset of symptoms, normal levels of myoglobin, creatine kinase–MB, and cardiac troponin I can rule out an AMI with greater than 96% accuracy. A b-type natriuretic peptide level less than 80 pg/mL can confidently rule out decompensated CHF with greater than 99% accuracy. However, no literature was found analyzing the use of these biomarkers in combination. A dyspnea biomarker panel could rapidly and accurately assist a clinician to rule out PE, AMI, and CHF. If a PE, AMI, or CHF is determined to be the cause of dyspnea, a biomarker panel could help risk stratify and help determine initial therapies. Subsequent clinical research is needed to corroborate this postulation.

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1. Introduction

Dyspnea, or breathing discomfort, is a common symptom that afflicts millions of patients and can result from a variety of underlying conditions, primarily involving abnormalities of the respiratory and or cardiovascular system [1]. Precisely identifying the problem and implementing appropriate treatment in a timely fashion can be very challenging, and if delayed, can result in poor outcomes. The vast majority of causes for acute to subacute dyspnea involves cardiogenic (acute myocardial infarction [AMI], congestive heart failure [CHF], and tachydysrhythmias) and respiratory (bronchospasm secondary to asthma or chronic obstructive pulmonary disease [COPD] exacerbations, pulmonary embolus, pneumothorax, pulmonary infection from bronchitis or pneumonia, upper airway obstruction secondary to aspiration or anaphylaxis) pathology. Some of these entities can be reliably diagnosed by physical examination such as [2]
2. Background

Biomarkers are used widely to assist in diagnosis, risk stratification, treatment, and surveillance of recurrence in various disease processes. Beta-human chorionic gonadotropin (beta-hCG) to determine pregnancy, thyroid-stimulating hormone to assess thyroid function, prostate-specific antigen for prostate cancer screening, and thyroglobulin and carcinoembryonic antigen to monitor treatment response and survey disease recurrence are just a few examples. More recent discoveries and clinical investigations have resulted in the development of new biomarkers, and efforts are underway to test their utility. Through metaanalysis, Sabatine et al [12] showed that a multimarker approach to risk stratification in non–ST elevation acute coronary syndromes by simultaneously assessing serum cardiac troponin I (cTnI), C-reactive protein, and b-type natriuretic peptide (BNP) provides unique prognostic information.

This manuscript will review the potentially powerful clinical information offered by a rapid shortness of breath panel measuring the following 5 biomarkers: sensitive D-dimer, myoglobin, creatine kinase–MB (CK-MB), serum cTnI, and BNP. Theoretically, each of the 5 biomarkers selected for analysis in the postulated shortness of breath panel should add important information about the etiology, severity, treatment, and risk profile to the assessment of the patient with dyspnea. The diagnostic and prognostic value of these biomarkers is detailed below.

3. Shortness of breath biomarker panel

3.1. Pulmonary embolism

In the United States, more that 500,000 cases of pulmonary emboli are diagnosed each year of which approximately 200,000 are fatal [13]. The clinical presentation of acute pulmonary embolism (PE) is notoriously variable; it is estimated that more than half of all patients with pulmonary emboli remain undiagnosed [14,15]. Untreated PE’s are associated with a mortality rate of approximately 30%, primarily because of recurrent embolism, whereas timely effective therapy results in a mortality of only 2% to 8% [15,16-20]. A rapid and accurate diagnosis is imperative for prompt administration of anticoagulation and assessment regarding need for thrombolysis. Sensitive D-dimer, BNP, and troponin-I are biomarkers that offer significant clinical insight regarding the initial diagnosis and or severity of pulmonary emboli.

The utility of measuring D-dimer, a degradation product of cross-linked fibrin, has been extensively studied for the diagnosis of both deep venous thrombosis (DVT) and PE. D-dimer is detectable at levels greater than 500 ng/mL in nearly all patients with PE [21]. However, an elevated D-dimer concentration is insufficient to establish the diagnosis of PE because such values are both nonspecific and commonly present in hospitalized patients, particularly those with malignancy or recent surgery [21,22]. Despite this low specificity, the sensitivity and negative predictive value of the sensitive D-dimer assay in patients with suspected venous thromboembolism (VTE) is extremely high. The sensitive D-dimer assay using radioimmunoassay or enzyme-linked immunosorbent assay has a negative predictive value of 97% to 100% [23-26]. If a D-dimer concentration could be accurately and rapidly determined to be less than 500 ng/mL at the time of presentation, a large number of patients with a low pretest probability of PE could be spared further testing, including lung scanning [27-30]. Approximately 75% of all patients in whom a DVT or PE is suspected clinically undergo confirmatory investigations ultimately revealing the absence of a VTE. With a moderate or low pretest probability of PE (Table 1), a negative sensitive D-dimer can possibly eliminate unnecessary and potentially risky invasive procedures in these patients [31]. However, if the pretest probability is high, further testing may be indicated—that is, venous Doppler ultrasound, ventilation perfusion scans, or computed tomography (CT) angiograms.

Helical CT angiograms have rapidly become the test of choice to evaluate a patient’s pulmonary artery anatomy because they are noninvasive, easily obtainable, and provide additional extravascular information about the lungs. How-
ever, this procedure is impractical in evaluating all cases of suspected VTE because of considerable contrast injection and requisite of an experienced radiologist. It is also very costly. Finally, a CT angiogram is hardly the ideal first diagnostic test because approximately 3 quarters of patients suspected of possible VTE will ultimately have alternative diagnoses. A screening test with a high sensitivity and negative predictive value such as sensitive D-dimer is more cost effective and practical for initial evaluation. Positive screening evaluations with sensitive D-dimer should then be followed with more advanced investigations such as helical CT angiography or ventilation perfusion scans. If the pretest probability of VTE is high, however, a negative sensitive D-dimer is not sufficient to rule out a DVT or PE without a second test [31].

Although the sensitive D-dimer biomarker would serve as the primary marker to rule out a VTE, cTnI and BNP could be useful by offering important risk stratification information if the D-dimer is elevated secondary to PE. Serum troponins are elevated in 30% to 50% of patients with a moderate to large PE [32-36]. The presumed mechanism is acute right side of the heart overload [32,37]. Although not useful for diagnosis of PE, elevated troponins are predictive of an adverse prognosis as they are associated with marked increases in the incidence of prolonged hypotension and in-hospital mortality [33,35,37,38]. Similarly, the prognostic value of BNP is potentially significant [39-42]. n-Type natriuretic peptide is elevated in the setting of heart failure, as ventricular cells are recruited to secrete both atrial natriuretic peptide and BNP in response to the high ventricular filling pressures [43]. Pulmonary embolism can result in an elevation of serum BNP levels, and the magnitude of this elevation has been shown to correlate with the risk of subsequent complications and prolonged hospitalization [40-42]. Thus, an elevated D-dimer with an elevated cTnI and BNP in the setting of a PE suggests not only PE but also acute right side of the heart strain and failure. However, whereas elevations in BNP in the setting of a large PE are clinically useful, these elevations are not always seen as they may require time to become elevated; thus, a low BNP level may not always confer a benign clinical course [43]. Thrombolysis of submassive and massive PE’s has shown dramatic improvement in both short and long-term outcomes [44-48]. Therefore, an elevated cTnI and BNP in the setting of an acute PE may help prompt consideration for thrombolysis. The role of myoglobin and CK-MB in PE appear limited as elevations in these biomarkers are generally not observed in this setting [49,50].

### 3.2. Acute myocardial infarction

The use of biomarkers for detecting myocardial infarction (MI) is the standard of care. Although serum troponins and CK-MB detect myocardial cell death, other less specific but highly sensitive markers detect myocardial cell injury sooner. Serum myoglobin, although currently underused, has tremendous potential for early detection of MI.

Myoglobin is a ubiquitous heme protein with a molecular weight of 17800 kDa, and because of its small size, is rapidly released from damaged tissues. Its half-life in the plasma is only 8.9 ± 1.5 minutes [51,52]. Among patients with an AMI, the serum myoglobin concentration is elevated in roughly similar proportions as CK-MB and troponins [53]. The delayed release of the cTnI and CK-MB decreases their sensitivity until 4 to 6 hours after the onset of symptoms (Fig. 1); some patients do not show an enzyme elevation for as long as 12 hours. Serum myoglobin rises within 1 to 4 hours and is more sensitive during this early period than the other markers [54]. The CHECKMATE study showed that an approach using rapid multimarker analysis identifies patients with an AMI earlier, and provided better risk stratification for mortality than a local laboratory-based single-marker approach [55].

It should be noted that there are a number of limitations to the use of serum myoglobin for the diagnosis of AMI. The rapid release and metabolism of myoglobin can result in an undulating or “staccato” pattern characterized by increases and decreases in the plasma myoglobin concentration that can lead to clinical confusion [56]. Also, like lactate dehydrogenase, myoglobin lacks specificity for the heart, and its use alone for diagnosing an AMI is fairly poor. Serum concentrations are elevated after injury to a variety of tissues (especially skeletal muscle) or recent cocaine use and in patients with impaired renal function due to decreased clearance [57,58]. However, the early sensitivity of myoglobin and its ability to detect an AMI more rapidly than other biomarkers render its use in combination and serial

![Cardiac Marker Temporal Patterns](image)

**Fig. 1.** Time course of serum markers in AMI. Figure 1 shows the temporal pattern of cardiac biomarker release after the onset of an acute myocardial infarction (AMI). The three markers illustrated are myoglobin, CK-MB, and cardiac troponin I (cTnI). The y-axis shows the relative elevation above the upper limit of reference range of each biomarker. The x-axis demonstrates the time after AMI measured in hours. The figure illustrates that serum myoglobin is elevated most rapidly after the onset of an AMI and that cTnI remains elevated for the greatest duration of time post AMI.
analyses with cTnI and CK-MB a valuable addition to the panel analysis.

Cardiac troponin concentrations usually begin to rise 4 to 6 hours after MI (Fig. 1). However, with cTnI and CK-MB, at least 12 hours is required to detect elevations in all patients. As a result, serial testing is performed after 4 or more hours if the initial values are indeterminate, the electrocardiogram (ECG) is not diagnostic, and the clinical suspicion of an MI remains high. Elevations in serum cTnI levels after an AMI persist for at least 10 days and even longer in patients with very large infarctions, thereby permitting late diagnosis [59].

Creatine kinase–MB has high specificity for cardiac tissue and is still commonly used for detecting AMI. As with total CK, CK-MB typically begins to rise 4 to 6 hours after the onset of infarction but is not elevated in all patients until about 12 hours (Fig. 1). An elevated serum CK-MB is relatively specific for myocardial injury, particularly in patients with ischemic symptoms when skeletal muscle damage is not present. These elevations return to baseline within 36 to 48 hours compared to duration as long as 10 days seen with troponins. Thus, CK-MB cannot be used for late diagnosis, but new elevations can help detect reinfarction.

An elevation in the serum concentration of one or more of the above markers (myoglobin, CK-MB, cTnI) is seen in virtually all patients with an AMI [58,60]. The Diagnostic Marker Cooperative Study, a large, prospective, double-blind study of patients who presented to the emergency department (ED) with chest pain showed that CK-MB subforms (91 and 89%) and myoglobin (78 and 89%) were most sensitive and specific within 6 hours of symptom onset, whereas CK-MB (96 and 98%) and troponins (96 and 93% for cTnI) were most sensitive and specific at 10 hours [58]. To date, serial analysis of these 3 biomarkers to assess cardiac myocyte necrosis is the most sensitive and specific method to detect an AMI.

Recent evidence supports the use of BNP in contributing to the diagnosis as well as offering important prognostic information in patients with an AMI [12,61-64]. b-Type natriuretic peptide is synthesized on demand in response to myocardial wall stress. Increased BNP gene transcription has been demonstrated in both infarcted tissue and surrounding viable myocytes that are often ischemic and under increased wall stress during an AMI [65]. However, the magnitude of BNP elevation seen in patients with AMI is lower than that associated with heart failure and falls within the range seen in many other common conditions, such as left ventricular hypertrophy, asymptomatic left ventricular dysfunction, PE, and cor pulmonale. Therefore, an elevated BNP can suggest ischemia or infarction, but its sensitivity and specificity are not sufficient for diagnosis in AMI [61].

Importantly, BNP does appear to possess significant prognostic value in the perinfarct period. In patients with an ST elevation MI, higher BNP levels predict a greater likelihood of death, independent of other prognostic variables, including left ventricular ejection fraction [66,67]. Subsequent studies verify the prognostic value of BNP in non–ST elevation MIs as well. The OPUS-TIMI 16 investigators found that the rate of death at 10 months increased from less than 1% among patients with BNP levels in the lowest quartile to greater than 10% in those with BNP in the highest quartile [68]. This finding has prompted speculation that those individuals with low BNP levels (<43 pg/mL in this study) in the setting of an AMI may require less aggressive management strategies [69]. This association between BNP and mortality was present in all patients including those subsets without prior history or current evidence of heart failure. Multivariate analyses adjusting for age, diabetes, renal insufficiency, heart failure, ST segment changes on ECG, levels of troponins, and C-reactive protein showed an independent association between BNP and mortality [68]. Levels of BNP were also associated with the development or progression of heart failure [68]. Ongoing studies of elevated BNP in patients with an AMI are evaluating early aggressive treatments targeting early heart failure. The prognostic information offered by BNP levels in the setting of an AMI creates a very valuable asset in a biomarker panel. Although BNP values can help differentiate those at increased risk for developing heart failure and increased mortality risk, it should be noted that a low BNP value does not ensure a benign clinical course and cannot detect those patients at high risk for reinfarction.

Sensitive D-dimer assays may detect small elevations of D-dimer in the setting of an AMI because thrombus formation and degradation occur within the coronary artery; however, this small elevation in D-dimer is not reliable for aiding in the diagnosis of an AMI [70,71].

3.3. Congestive heart failure

Establishing heart failure as a cause of dyspnea in patients presenting to the emergency room is extremely important, but symptoms and physical findings may not be sufficiently sensitive to make an accurate diagnosis. With chronic and more advanced heart failure, ventricular cells are recruited to secrete BNP in response to the high ventricular filling pressures [72]. The plasma concentration of BNP is increased in patients with asymptomatic and symptomatic left ventricular dysfunction. The value of rapid measurement of plasma BNP for distinguishing between heart failure and a pulmonary cause of dyspnea was best evaluated in the Breathing Not Properly study of 1586 patients presenting to the emergency room or urgent care setting with a major complaint of acute dyspnea [73]. A BNP value greater than 100 pg/mL diagnosed heart failure with a sensitivity, specificity, and predictive accuracy of 90%, 76%, and 83%, respectively. The predictive accuracy of plasma BNP for heart failure was determined as the best univariate parameter when compared to cardiomegaly on chest x-ray, history of heart failure, or rales on physical
examination; similarly, BNP was superior to the widely used NHANES and Framingham criteria for the diagnosis of heart failure (83% vs 67% and 73%, respectively) [73].

Several other studies evaluating the predictive value of plasma BNP found a high positive and negative predictive value for the diagnosis of heart failure [74-76]. Based upon these data, BNP was approved by the Food and Drug Administration as an aid in the diagnosis of heart failure in late 2000. b-Type natriuretic peptide values above 400 pg/mL have a high positive predictive value, whereas values below 100 pg/mL have a very high negative predictive value for dyspnea caused by heart failure [77,78]. Therefore, a normal BNP level has tremendous clinical utility in rapidly determining whether or not a patient’s dyspnea is due to underlying heart failure. In Europe, because a BNP level less than 80 pg/mL has a negative predictive value of greater than 98% [78], it is recommended as one means of ruling out heart failure [79].

The diagnoses of dyspnea in the patient with both longstanding COPD and CHF can prove particularly troublesome. Underlying emphysema can mask cardiomegaly and pulmonary edema on chest x-ray, whereas pulmonary edema can cause wheezing similar to that seen in a flare of the patient’s COPD. In this setting, the utility of BNP is invaluable, especially when a baseline BNP level is known [73]. Baseline and historical laboratories are extremely helpful when evaluating a patient who is decompensating. A baseline BNP providing information about a patient’s steady-state ventricular filling pressure and wall tension is equally as useful as a baseline creatinine providing information about a patient’s steady-state renal function regarding a patient who presents with renal failure.

The BNP values determined in the acutely dyspneic patient have tremendous prognostic value for future cardiac events. Greater than half of patients with elevated BNP levels above 400 pg/mL had an adverse cardiac event—defined by a repeat visit to the ED with CHF, hospital admission for CHF, or all cause cardiac mortality—over the subsequent 6 months in a study published in 2002 [80].

b-Type natriuretic peptide is the first biomarker that was found valuable in monitoring patients, in tailoring management and titrating therapy, in providing objectivity in assessing discharge and admission criteria, and both predicting adverse cardiac events and readmissions in CHF inpatients [80-84].

The cost effectiveness of rapid BNP testing in dyspneic patients proved impressive in the recently published BASEL study. It was a randomized controlled trial that demonstrated obtaining BNP levels on all patients who present with shortness of breath decreased the number of patients requiring admission by 10%, decreased the number of patients requiring monitoring in the intensive care unit, improved the time to accurate and appropriate treatment, decreased the average number of hospital days by 3, and drastically reduced the cost of each hospital visit by saving nearly $2000 per patient, without changing outcomes in morbidity and mortality [84]. This cost effectiveness and healthcare savings could prove more pronounced in the setting of a biomarker panel, as fewer diagnostic tests may be needed to establish the appropriate diagnosis. Although the value of BNP in diagnosing heart failure has been known for several years, the wealth of additional clinical information it provides is still accumulating. Determining BNP values in dyspneic patients presenting to the ED has been widely adopted and would be an essential component of a biomarker profile for shortness of breath.

Like atrial natriuretic peptide (ANP), BNP is cleaved from the C-terminal end of its prohormone, proBNP; and the N-terminal fragment (NT-proBNP) is also released into the circulation. NT-proBNP is the inactive amino terminus of proBNP, and like BNP, can be measured in the serum. NT-proBNP has been shown in studies to correlate clinically in a similar fashion to BNP, and whereas not as thoroughly studied, could potentially offer similar clinical information as BNP in biomarker panel [85-88].

4. Discussion

The evidence detailed above supports the use of biomarkers in diagnosing, determining appropriate treatment, and risk stratifying patients who present with dyspnea. Is there an advantage to obtaining all of these markers via a shortness of breath panel as opposed to ordering each individually? Actually, the advantages are multiple. Obtaining a rapid biomarker panel is crucial. Often, specific laboratory tests are run in different areas of the hospital laboratory with varying turnaround times for results. As well, logically, it would behoove the clinician to receive the biomarker results simultaneously to maximize the panel’s diagnostic utility. As demonstrated above, an elevated BNP in the setting of a PE, an AMI, and in heart failure has significantly different clinical implications and offers different management strategies. If the biomarkers were ordered individually and an elevated BNP value were available before the D-dimer or cardiac marker analysis, the clinician would know that there is evidence of increased ventricular filling pressure but might not understand the underlying cause, that is, secondary to a massive PE, myocardial necrosis in an AMI, or solely due to CHF.

It is hoped that the cost of ordering the biomarkers in panel form would be much less than ordering each marker individually, as the panel would require fewer blood samples and less technical laboratory work. The panel could be initiated early in the triage process and may help discover a diagnosis not previously entertained, such as PE (because greater than half of PE’s go unrecognized). The advantages of a shortness of breath biomarker profile in the acutely dyspneic patient are numerous and could prove very cost effective in quickly offering diagnostic, therapeutic, and risk stratification information.
In addition to aiding in diagnosis, the biomarker panel can offer tremendous value and clinical support by rapidly ruling out particularly worrisome diagnoses such as PE, AMI, and CHF in the acutely dyspneic patient. In the differential diagnosis, a high negative predictive value of a low sensitive d-dimer confidently lowers the chance of PE; a normal serum myoglobin, CK-MB, and cTnI hours after the onset of symptoms renders active myocardial necrosis unlikely; and a normal BNP value nearly rules out the possibility of decompensated CHF. A rapid biomarker panel offering this important clinical information in the emergency room in a timely fashion can prove tremendously valuable.

A clinical algorithm in the near future using a shortness of breath panel could demonstrate a scenario in which a patient presents with acute dyspnea, then undergoes a detailed targeted history and physical examination along with an immediate chest x-ray, ECG, and shortness of breath panel. The clinical picture combined with the results of these studies would then trigger further targeted workup and initial therapeutic strategies.

5. Limitations

There are many limitations to the proposed shortness of breath biomarker panel as is the case currently with each individual marker. In medicine, no test is flawless and can stand alone to provide information with 100% accuracy. Many of the markers in this proposed panel are selected for their high sensitivity and negative predictive value but have relatively low specificity and positive predictive value. Elevations in sensitive D-dimer can be seen in a number of clinical settings outside a PE, namely, immobilized individuals and those with an underlying malignancy or who have undergone recent surgery. These elevations require careful clinical interpretation because an elevated sensitive D-dimer in a low-risk clinical setting does not signify a PE. Similarly, myoglobin can be elevated in a number of clinical settings outside an AMI. It is commonly elevated in individuals with skeletal muscle damage or renal failure. The positive predictive value for elevations in myoglobin alone is quite poor for diagnosing an AMI and needs to be placed in the clinical context, compared to other necrosis markers (CK-MB and cTnI), and measured serially over time.

The purpose of such a panel is meant to rapidly help provide a clinician further clinical information about a dyspneic patient and potentially indicate diagnoses that are less likely when sensitive markers with high negative predictive values are normal or negative. Abnormal values or elevations in these biomarkers do not diagnose these conditions and require careful clinical interpretation. Various scenarios such as sepsis in a patient with baseline left ventricular dysfunction or renal failure could potentially cause elevations of all these markers and not indicate a massive PE or AMI. The advent of new and highly sensitive and specific tests is intended to add to the clinician’s armamentarium, not to supplant the role of a thorough history and physical examination.

6. Summary

Biomarker profiles can offer tremendous clinical information. In the evaluation of the acutely dyspneic patient, a rapid biomarker panel can aid in diagnosis, help determine prompt appropriate treatment, help risk stratify patients, and rule out PE, AMI, and CHF. Use of such profiles should prove time efficient, prevent unnecessary costly and potentially harmful testing, determine appropriate patients for aggressive therapies, and guide cost effective workup and management of patients.

The clinical information offered by a shortness of breath biomarker panel can be illustrated in Table 2.

### Table 2: Predicted results of a shortness of breath panel in various disease states

<table>
<thead>
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<th>D-Dimer</th>
<th>Myoglobin</th>
<th>CK-MB</th>
<th>cTnI</th>
<th>BNP</th>
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<tr>
<td>PE</td>
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<td>AMI</td>
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<tr>
<td>CHF</td>
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<tr>
<td>No PE, AMI, or CHF</td>
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</table>

This table illustrates the predicted pattern of biomarker elevation expected in various disease states. If a PE is present, then the sensitive D-dimer would be elevated, and depending upon whether or not the PE is massive, resulting in right heart strain, then cTnI and BNP could be elevated as well. In the setting of an AMI, the cardiac biomarkers of myoglobin, CK-MB, and cTnI would be elevated indicating myocardial necrosis. An elevated BNP and possibly sensitive D-dimer could be seen as well in the setting of an AMI. An isolated elevation of BNP would be appreciated in the setting of CHF. If none of these disease states were present, then there would not be an elevation of any of the measured biomarkers if measured several hours after the onset of symptoms or serially over time.

7. The future

Because biotechnology advances and proteomics help make rapid and accurate assays clinically available, biomarker profiles such as the one outlined in this article will become clinically available. Subsequent randomized controlled clinical trials will be needed to prove the theoretical clinical advantages of such biomarker panels.

References


The role of biomarkers in the dyspneic patient


