

# Cardiopulmonary laboratory biomarkers in the evaluation of acute dyspnea

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**Abstract:** Dyspnea is a common chief complaint in the emergency department, with over 4 million visits annually in the US. Establishing the correct diagnosis can be challenging, because the subjective sensation of dyspnea can result from a wide array of underlying pathology, including pulmonary, cardiac, neurologic, psychiatric, toxic, and metabolic disorders. Further, the presence of dyspnea is linked with increased mortality in a variety of conditions, and misdiagnosis of the cause of dyspnea leads to poor patient-level outcomes. In combination with the history and physical, efficient, and focused use of laboratory studies, the various cardiopulmonary biomarkers can be useful in establishing the correct diagnosis and guiding treatment decisions in a timely manner. Use and interpretation of such tests must be guided by the clinical context, as well as an understanding of the current evidence supporting their use. This review discusses current standards and research regarding the use of established and emerging cardiopulmonary laboratory markers in the evaluation of acute dyspnea, focusing on recent evidence assessing the diagnostic and prognostic utility of various tests. These markers include brain natriuretic peptide (BNP) and N-terminal prohormone (NT-proBNP), mid-regional peptides proatrial NP and proadrenomedullin, cardiac troponins, D-dimer, soluble ST2, and galectin 3, and included is a discussion on the use of arterial and venous blood gases.

**Keywords:** cardiopulmonary, emergency, heart failure, troponin, BNP, galectin 3, MR-proANP, MR-proADM

## Introduction

Dyspnea is defined as the “subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” by the American Thoracic Society.<sup>1</sup> A normal physiologic response to intense exertion, dyspnea becomes pathological when experienced outside of this context. It is the chief complaint for approximately 4 million emergency department (ED) visits annually in the US, comprising 3.5% of all ED visits.<sup>2,3</sup> Despite being a subjective symptom, dyspnea has been strongly tied to illness severity, morbidity, and mortality. Dyspnea has been found to be more closely associated with cardiac mortality than angina,<sup>4</sup> and the most potent predictor of mortality in patients with chronic lung disease.<sup>5</sup>

A wide variety of distinctive mechanisms can result in the common sensation of dyspnea. The presentation of acute dyspnea requires a quick and focused workup to establish the appropriate diagnosis. Misdiagnosis has been shown to increase morbidity, cost, and time to discharge.<sup>6</sup> Various laboratory studies can be used in the evaluation of acute dyspnea, and many new markers are being examined for their utility in this capacity. Appropriate use of studies can help to decrease time to diagnosis,

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make treatment decisions, properly assess risk, and reduce overall costs. The following is a review of current standards and research regarding the use of laboratory markers in the evaluation of acute dyspnea.

## Brain natriuretic peptide

Brain natriuretic peptide (BNP) was first isolated in 1988,<sup>7</sup> and quickly garnered excitement in the field of heart failure (HF). In the mid-1990s, the introduction of an inexpensive assay allowed for the use of natriuretic peptide (NP) levels as a diagnostic tool for HF in clinical practice, approved by the US Food and Drug Administration in 2000 as an adjunct for HF diagnosis.<sup>8</sup> BNP and the N-terminal prohormone of BNP (NT-proBNP) are currently the gold standard for diagnosis of HF in patients presenting with acute-onset dyspnea.

BNP is one of three major NPs, with atrial NP (ANP) and C-type NP. Each functions to maintain circulatory homeostasis. BNP is primarily synthesized and secreted from the ventricular myocardium, although in pathologic states it can be synthesized in both the atrial and ventricular chambers. Both ANP and BNP induce vasodilation, natriuresis, and diuresis in an effort to oppose the renin–angiotensin–aldosterone system and ameliorate stress from increased volume on the heart. ANP is stored in granules and readily released, whereas BNP undergoes transcription and synthesis in response to stressors, requiring more intense and prolonged stress to elevate circulating levels.<sup>9</sup> BNP thus serves as an excellent marker of pathologic ventricular wall distention and cardiac pressures.<sup>10</sup>

Increased wall stress in the ventricles results in the synthesis of pre-proBNP, which undergoes two cleavages to form biologically active BNP<sub>1–32</sub> and the inactive amino-terminal fragment NT-proBNP. Both BNP and NT-proBNP are used clinically, with similar outcomes; however, they are not interchangeable assays. NT-proBNP has a longer half-life (1–2 hours) compared with BNP (20 minutes), resulting in less fluctuation and higher overall NT-proBNP levels in the blood. The primary mechanism of clearance for BNP is neutral endopeptidase, with additional clearance conducted by NP receptors and the renal system, while NT-proBNP is primarily cleared renally.<sup>11</sup> Despite this difference, data demonstrate that both BNP and NT-proBNP are cleared equally by the kidneys.<sup>12</sup> The role of neutral endopeptidase in metabolizing BNP, but not NT-proBNP, can have a different impact on the levels of circulating biomarkers. Importantly, neutral endopeptidase inhibitors provide a promising therapy for HF patients and are being increasingly used in clinical practice.<sup>12</sup> Patients enrolled in this study taking the neutral

endopeptidase inhibitors were found to have reduced levels of NT-proBNP in correlation with clinical improvement; BNP levels, however, did not reduce, due to the decreased metabolism by neutral endopeptidase. As the use of neutral endopeptidase inhibitors increases, it will become difficult to interpret BNP levels, and this should be taken into consideration.

Both levels can be measured on a point-of-care testing device that allows for results within 20 minutes (Alerie Triage; Hoffman-La Roche Ltd, Basel, Switzerland). Results from point-of-care testing have been shown to correlate with standard laboratory assays, and all available assays have proved significantly and independently predictive of HF.<sup>11</sup> Availability of assays is institution-dependent.

Studies showing the validity and efficacy of BNP and NT-proBNP have been incorporated into common practice over the past decade. Early trials suggested that BNP testing was both sensitive and specific in an urgent-care setting.<sup>13,14</sup> In 2002, the landmark Breathing Not Properly study found that using a cutoff of 100 pg/mL, BNP values were significantly sensitive and specific, with strong negative and positive predictive values: at 90%, 73%, 90%, and 75%, respectively. Importantly, the number of patients in the ED for whom the clinician was uncertain of diagnosis was reduced from 43% with clinical assessment alone to 11% with the inclusion of BNP.<sup>15,16</sup> The 2005 PRIDE study confirmed similar efficacy for NT-proBNP.<sup>17</sup> Many large-scale trials have provided further support of the diagnostic validity of the NPs, including the ICON, HFinCH, BASEL, and IMPROVE-CHF studies.<sup>17–20</sup>

Investigations into the impact of the use of NPs as biomarkers for evaluation of dyspnea have shown significant cost reduction. The IMPROVE-CHF study demonstrated that NP testing for management of patients presenting to the ED with dyspnea improved cost savings (average of 15%), time to diagnosis, and selected outcomes.<sup>18</sup> The cost savings of NP use in the ED have been validated;<sup>21</sup> however, whether NP testing has any impact on outcomes is debated. Meta-analyses of outcomes of NP testing for patients with dyspnea of suspected cardiac origin have found moderate reduction in length of hospital stay and time to discharge, but no significant impact on admission rates, secondary admission, or mortality.<sup>21,22</sup>

Further investigations have focused on the prognostic value of NP levels.<sup>18,19</sup> Patients with BNP levels  $\geq 1,730$  pg/mL had in-hospital mortality three times greater than those with BNP levels  $< 430$  pg/mL. Harrison et al found that 54% of patients with a BNP  $\geq 480$  pg/mL at time of pre-

sensation had subsequent HF exacerbations within 6 months; likewise, patients with a BNP  $\geq 230$  pg/mL or greater had a relative risk of 7.0 for future HF events.<sup>23</sup> There is ongoing study into the use of NPs for therapeutic management. The PROTECT study found therapy guided by targets for reduction of NT-proBNP by 30% or to  $< 1,000$  pg/mL was superior to standard-of-care HF management.<sup>24</sup>

The 2015 European Society of Cardiology/European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension recommend the use of BNP and NT-proBNP to assess risk for patients with pulmonary arterial hypertension. While these biomarkers are nonspecific and thus less useful for diagnosing pulmonary arterial hypertension, they are helpful for prognostication in their capacity as markers of myocardial stretch.<sup>25,26</sup>

The variety of factors that can alter BNP makes a discrete cutoff value difficult to determine, and highlights the continued importance of clinical acumen in ordering and interpreting NP results. For unclear reasons, NP levels increase with age,<sup>27,28</sup> independently of age-related diastolic dysfunction.<sup>29</sup> NT-proBNP is more significantly impacted by age than BNP, and thus recommended cutoff values for NT-proBNP are age-adjusted. Female sex is also associated with higher levels of circulating NPs. Studies have suggested there is a potential association with estrogen<sup>28</sup> and an inverse relationship between testosterone and NP levels,<sup>30</sup> although this remains unconfirmed.

Renal disease can result in elevated systemic pressures and decreased filtration and excretion.<sup>31</sup> BNP levels elevate with an approximate glomerular filtration rate  $< 60$  mL/min/m<sup>2</sup>. Despite increases with renal dysfunction, both BNP and NT-proBNP maintain their diagnostic utility.<sup>16,17</sup> Higher cutoff points for these patients have been suggested.<sup>16,17,32</sup> Of note, hemodialysis decreases but does not completely clear BNP or NT-proBNP levels.<sup>33</sup>

Diabetes has been associated with higher NP levels,<sup>34,35</sup> and elevated NT-proBNP may be predictive of cardiovascular events and death.<sup>36–38</sup> Patients with chronic HF have elevated baseline BNPs. NP levels remain useful for ruling out an acute HF decomposition in this subset of patients.<sup>11,17,39</sup> Likewise, the diagnostic and negative predictive values of the tests are maintained with all cardiac comorbidities.

There is a great deal of interest in the potential use of NPs as markers of coronary artery disease, as some have suggested that NPs are produced with ischemia independently of ventricular wall stress. The extent of coronary artery disease has been correlated with increased NPs, and increased levels at presentation with acute coronary syndrome (ACS) have been associated with increased morbidity.<sup>40,41</sup>

Pulmonary disease can elevate NP levels to a lesser extent.<sup>15</sup> In the Breathing Not Properly study, patients with both HF and pulmonary disease had markedly higher BNP levels than those with pulmonary disease alone (587 pg/mL vs 109 pg/mL).<sup>16</sup> High-output states, such as cirrhosis, sepsis, and severe hyperthyroidism, similarly place strain on the heart via hyperdynamic stress. Elevation of BNP levels in the setting of sepsis is a reliable indicator of development of sepsis-induced cardiac depression.<sup>42</sup> Investigations into the prognostic value of NPs in the setting of sepsis and cirrhosis are ongoing.

Factors that depress NP levels include obesity, flash pulmonary edema, and pericardial constriction. Increased body mass index has an inverse relationship with BNP and NT-proBNP in patients both with and without HF, and has been reproduced across different cultural settings.<sup>27,43–45</sup> Using a threshold of 100 pg/mL, Daniels et al showed that 20% of obese patients with HF obtained false-negative BNP results. This group suggested a cutoff value of 54 pg/mL for BNP for patients with body mass index  $\geq 35$  kg/m<sup>2</sup>. Interestingly, they also found that a higher lean mass was more strongly correlated with increased NP levels than body mass index. Therefore, they suggest using a cutoff of 170 pg/mL in patients with high lean body mass to increase specificity.<sup>45,46</sup>

In the setting of acute cardiogenic flash pulmonary edema (particularly when onset of symptoms is less than 1 hour), the transcription and release of BNP has not had time to establish an appropriate response to the sudden increased stressor. For these patients, clinical suspicion of HF should supersede NP levels. Pericardial constriction, likewise, can cause significant symptoms in the setting of normal BNP levels, due to the absence of myocardial stretch.

Lastly, patient medications should be considered when interpreting NP levels. The chronic use of  $\beta$ -blockers and angiotensin-receptor blockers may reduce levels of NPs in patients with HF.<sup>47,48</sup>

Current recommendations for use of NPs in the acute setting for patients presenting with dyspnea emphasize that for both BNP and NT-proBNP assays the sensitivity is greater than the specificity. Therefore, it is most useful for ruling out HF in patients with low-to-intermediate pretest probability.<sup>49,50</sup> Both the American Heart Association and American College of Cardiology endorse a class IIA recommendation for the use of NPs. To date, there has not been an easily identifiable optimum cutoff value for ruling HF in or out. Current recommendations from the American College of Emergency Physicians, as well as suggestions for different cutoff points for specific patient populations, are listed

**Table 1** Suggested natriuretic peptide cutoff values for acute decompensated heart failure

	ACEP recommendation	CKD	BMI >35kg/m <sup>2</sup>
<b>Exclude</b>			
BNP	<100	<200 <sup>5</sup>	54
NTproBNP	<300	<300 <sup>21</sup>	NA
<b>Identify</b>			
BNP	>500		NA
NTproBNP			
<50 years	>450	>1,200 <sup>6</sup>	NA
50–75 years	>900	>4,502 <sup>6</sup>	NA
>75 years	>1,800		NA

**Note:** ACEP recommendations.<sup>110</sup>

**Abbreviations:** ACEP, American College of Emergency Physicians; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NA, not applicable; BNP, brain natriuretic peptide; CKD, chronic kidney disease; BMI, body mass index.

in Table 1. BNP levels have been shown to correlate with severity of disease, which is helpful for risk stratification. Serial testing of patients, however, has not been shown to impact clinical practice, and is not suggested.<sup>51</sup> Likewise, routine testing of BNP in the ED does not improve diagnosis, costs, or outcomes in patients with dyspnea, and thus a clinical indication for testing is vital. The utility of NPs in diagnosis of HF is well founded; however, its function with respect to other clinical conditions is still under investigation, with no clear recommendations at this time. Due to the many factors that can influence NP levels, it is important to interpret results cautiously.

## Mid-regional peptides: MR-proANP and MR-proADM

ANP is released from the atria in response to increased atrial stretch, and has diuretic, natriuretic, and vasodilatory effects.<sup>52</sup> Adrenomedullin (ADM), released from a multitude of tissues, also has potent vasodilatory, hypotensive, and natriuretic effects. Clinical use has been limited by a lack of stability in vitro. Measurement of the stable, mid-regional (MR) prohormones of these peptides (MR-proANP and MR-proADM) is now possible, and studies have investigated their ability to provide diagnostic and prognostic information for patients presenting with acute dyspnea to the ED.<sup>53</sup>

A large, multicenter prospective study demonstrated noninferiority of MR-proANP (cutoff point  $\geq 120$  pmol/L, sensitivity 97%, specificity 59.9%, accuracy 73.6%) to BNP (cutoff point  $\geq 100$  pg/mL, sensitivity 95.6%, specificity 61.9%, accuracy 72.7%) for the diagnosis or exclusion of acute HF in patients presenting to the ED with dyspnea (Table 1). This study also found that MR-proADM was

superior to BNP or NT-proBNP in identifying dyspneic patients with acute decompensated HF (ADHF) at high risk of 90-day mortality.<sup>54</sup> MR-proANP levels have been shown to predict ADHF independently from BNP, and may therefore provide additional diagnostic value. Those with elevated MR-proANP or MR-proADM levels have markedly reduced survival.<sup>55</sup> While the diagnostic and prognostic potential for MR-proANP, MR-proADM, and NPs are promising, at this current time, their clinical utility remains unclear, and further studies are necessary before they should be used routinely.<sup>56</sup>

## Galectin 3

Gal-3 is a member of the  $\beta$ -galactoside-binding lectin family of protein biomarkers found in a variety of tissues. It plays an established role in the pathophysiology of many cancers; its role in HF has recently garnered more attention. Expression of Gal-3 is associated with adverse remodeling via activated cardiac fibroblasts and macrophages.<sup>57</sup> Blood levels of Gal-3 are independently predictive of recurrent decompensations and death in patients with HF. The prognostic value of Gal-3 is additive with NP levels.<sup>58</sup> Current American Heart Association/American College of Cardiology Foundation HF guidelines give a class IIB indication for the use of a Gal-3 assay for additive risk stratification in patients with established HF.<sup>59</sup> Recent studies, however, have not replicated the significance of the prognostic power of Gal-3.<sup>60</sup>

NT-pro-BNP is superior to Gal-3 for identifying HF, as elevated Gal-3 is not specific for cardiac pathology. Gal-3 levels are directly associated with relative wall thickness, and inversely related to peak oxygen consumption and 6-minute walking distance.<sup>61</sup> Gal-3 is also common to systemic inflammatory processes, including pneumonia and sepsis,<sup>62</sup> and is upregulated in fibrosis of the liver, lung, and kidney. Elevations of Gal-3 have been used as a diagnostic marker for a variety of cancers, as well as idiopathic pulmonary fibrosis. Additionally, Gal-3 levels do not correlate with the severity of dyspnea classified by the New York Heart Association functional classification, which further limits its diagnostic value.<sup>58</sup>

Gal-3 has been under investigation for use as a marker for increased HF risk in the general population. In a population-based study of 8,000 patients over 10 years, Gal-3 was predictive of all-cause mortality, but was not specifically correlated with cardiovascular death.<sup>57</sup> Ho et al established an increased risk of HF in the general population with high levels of Gal-3. The investigators did not recommend routine

screening of Gal-3, however, as testing did not significantly improve overall discrimination of risk in the general population.<sup>63</sup> A recent study found elevations in Gal-3 to be correlated with increased risk of HF and cardiovascular death in patients after ACS.<sup>64</sup> This indicates a potential role for Gal-3 monitoring in patients after ACS. Studies do not support the use of routine screening with Gal-3 at this time.

## Biomarkers suggesting myocardial injury

Acute myocardial infarction (MI) is a life-threatening cause of acute dyspnea. Approximately a third of patients with acute MI – more significantly women, diabetics, and the elderly – present without chest pain. These patients may have dyspnea as the sole presenting symptom, and are at risk for higher in-hospital mortality.<sup>65</sup> The use of cardiac biomarkers, particularly cardiac troponins, is critical in the diagnosis of acute MI.

Cardiac troponins I and T (cTnI and cTnT) are tissue-specific isoforms of regulatory proteins involved in the actin–myosin interaction of cardiac muscle,<sup>66</sup> and they are both sensitive and specific biomarkers for detection of myocardial injury.<sup>67,68</sup> Elevation of cardiac biomarkers >99th percentile for a reference population is part of the third universal definition of MI.<sup>68</sup>

Advances in troponin assays have resulted in the development of highly sensitive assays (hs-cTn) which can detect cardiac troponin levels even in the majority of healthy individuals. The higher sensitivity of these assays has the potential advantage of allowing faster ruling in or out of acute MI, reducing the time to diagnosis.<sup>69</sup> These tests appear to increase the accuracy of MI diagnosis, especially at 1 hour.<sup>70</sup> While highly sensitive assays are widely used in Europe, many centers in the US continue to utilize conventional cardiac troponin assays. The 2015 European Society of Cardiology guideline algorithm for ruling out acute MI without ST elevations now requires the use of hs-cTn testing at presentation and at 3 hours, and allows for an alternative rule-out algorithm with testing at presentation and at 1 hour using hs-cTn assays with validated, assay-specific cutoff values, demonstrating the potential of these assays to reduce the time to diagnosis in the ED.<sup>71</sup>

Despite the specificity of troponins for myocardial tissue, the differential diagnosis for troponin elevation is extensive, and includes renal failure, HF, pulmonary embolism, myocarditis, arrhythmias, severe acute neurological disease, acute respiratory failure, chronic obstructive pulmonary disease (COPD), sepsis, pulmonary hypertension, and infiltrative

diseases, among other disorders (Table 2).<sup>72</sup> It is important to distinguish acute from chronic causes of troponin elevation. The current recommendation of the third universal definition of MI is to draw cardiac troponin on first assessment of patients with suspected MI, with a repeat measurement in 3–6 hours. Further measurements should be performed for additional episodes of suspected ischemia or uncertain timing of symptom onset. A rising or falling pattern with at least one value over the 99th percentile, along with strong clinical suspicion, is generally required for diagnosis of MI.<sup>68</sup> Supporting data for the diagnosis of ACS as the cause of troponin elevation include ST-segment or T-wave changes, development of pathological Q waves, and symptoms of cardiac ischemia.

Cardiac troponins may be elevated in a number of cardiopulmonary conditions that can present with dyspnea. Over a third of patients with acute pulmonary embolism have elevated troponin I, likely due to right ventricular strain.<sup>73</sup> Though these markers are not sensitive or specific for diagnosis, elevations of troponins have been associated with a higher risk of short-term mortality.<sup>74</sup> Undetectable levels of hs-cTn have been shown to have excellent negative predictive value for in-hospital adverse events,<sup>75</sup> though the positive predictive value of troponin assays is quite low.<sup>75</sup>

Acute exacerbations of COPD have been linked to a four-fold elevation in troponin T, though the mechanism underlying this elevation remains uncertain.<sup>77</sup> The pattern of elevation is typically modest and flat, as opposed to the rising or falling pattern seen in MI. Elevation in cardiac troponin for patients with COPD exacerbations, acute respiratory distress syndrome (ARDS), and chronic pulmonary hypertension is predictive of

**Table 2** Causes of elevated troponin

Myocardial infarction
Heart failure
End-stage renal disease
Pulmonary embolism
COPD
Sepsis and other critical illness
Acute cerebrovascular event
Intense exercise
Cardiac contusion
Acute pericarditis and myocarditis
Tachyarrhythmias
Cardioversion
Cardiopulmonary resuscitation
Coronary vasospasm
Cardiac surgery, percutaneous coronary intervention
False-positive test

**Note:** Information from Inbar R, Shoenfeld Y.<sup>76</sup>

**Abbreviation:** COPD, chronic obstructive pulmonary disease.

higher all-cause mortality.<sup>78–80</sup> Many patients with acute HF will have troponin elevations above the 99th percentile even in the absence of acute MI. These elevations are also associated with increased risk of mortality, especially when a rising pattern is seen. Additionally, stably elevated troponin in patients with chronic HF is also associated with increased all-cause mortality.<sup>81</sup> In chronic renal failure, troponins are commonly elevated. They are still the preferred biomarker for diagnosis of acute MI; however, there exists a wide range of estimates for their sensitivity and specificity in this setting.<sup>82</sup>

In summary, a number of life-threatening causes of acute dyspnea, including acute MI, ADHF, pulmonary embolism (PE), COPD exacerbation, and ARDS, among others, may have significantly elevated troponins on presentation. Many of these conditions are frequently comorbid with ischemic cardiovascular disease. Even in the absence of acute MI, troponins are markers of myocardial injury and portend a worse prognosis. The clinical context, comorbidities, baseline troponin levels, and pattern and degree of troponin rise must be taken into account in diagnosing MI as a cause of acute dyspnea.

## D-dimer

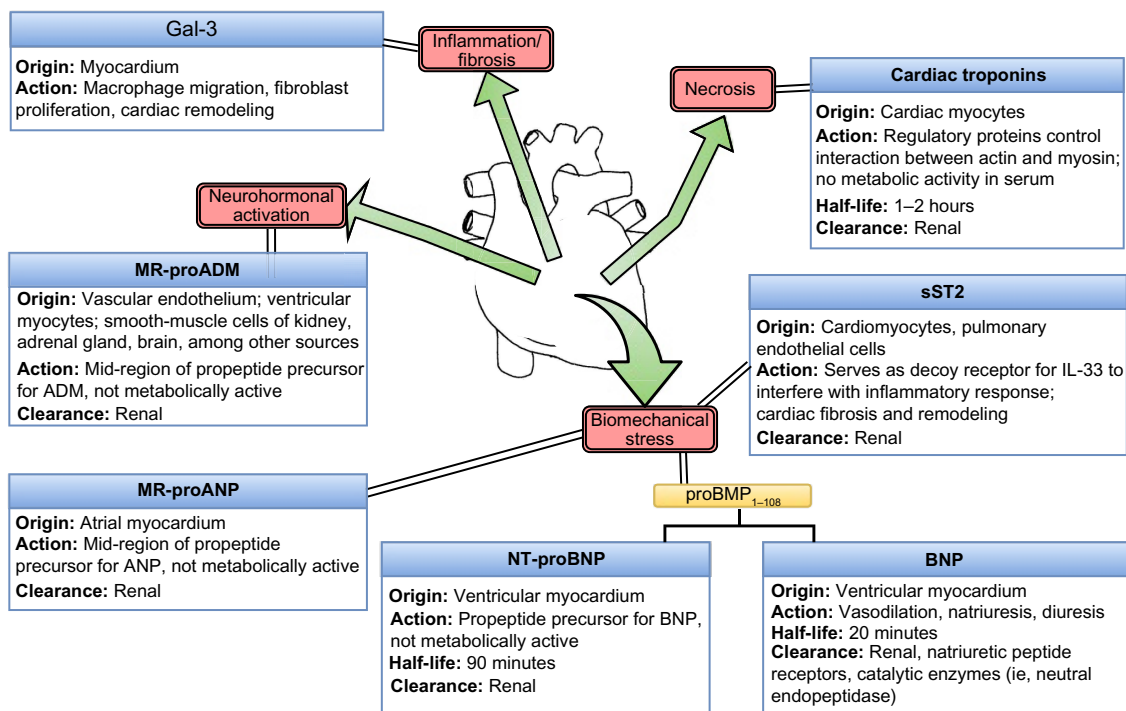
Patients presenting with acute-onset dyspnea should be ruled out for PE, as it is a potentially life-threatening cause of

dyspnea. Dyspnea is the most common presenting symptom of PE, and may suggest the presence of a hemodynamically significant clot.

D-dimer is a degradation product of fibrin. When normal, D-dimer is highly sensitive for excluding PE,<sup>83</sup> but the specificity of the test is poor. Multiple trials have confirmed the safety of using a clinical decision rule to determine a pretest probability of PE in combination with D-dimer assay to rule out PE.<sup>84–86</sup>

Pretest probability can be assessed using the Wells criteria or Geneva score, with or without the PE rule-out criteria (PERC). Both the Wells criteria and Geneva score have been simplified to enhance clinical utility. The Wells criteria have been validated using both a three-tiered grouping system (low, moderate, or high likelihood of PE), as well as a dichotomized categorization (unlikely vs likely to have PE). Similarly, the Geneva score separates patients into low-, intermediate-, and high-likelihood categories. Those patients falling into the low or intermediate categories, using the initial Wells criteria or Geneva score, or the unlikely category, using the updated Wells criteria, should be considered for a D-dimer test.<sup>76,87</sup>

For patients with low (<15%) pretest probability of PE, clinicians can consider using the PERC to exclude the diagnosis (level B recommendation). A patient must meet all



**Figure 1** Basic pathophysiology of cardiac biomarker production.

**Abbreviations:** MR-proADM, mid-region prohormone adrenomedullin; ANP, atrial natriuretic peptide; sST2, soluble ST2; NT-proBNP, N-terminal prohormone brain natriuretic peptide; BNP, brain natriuretic peptide; ADM, adrenomedullin.

eight of the PERC criteria to be ruled out for PE. D-dimer assay and PERC have not been compared systematically; D-dimer testing for ruling out PE has been more thoroughly analyzed, and is thus recommended.

Normal D-dimer levels in low-risk patients are helpful to exclude acute but not chronic PE, or incomplete resolution of prior PE(s). Likewise, D-dimer testing has been shown to have low sensitivity for small segmental PEs.<sup>88</sup>

Patients for whom the pre-test probability of PE is high should not have a D-dimer assay sent. In these patients, a normal D-dimer is not sufficient to exclude PE, and may provide false reassurance. The current diagnostic approach for patients with elevated D-dimer results is inefficient and costly,<sup>89</sup> and honing the algorithm for diagnosis in this population is a priority.

Heterogeneity in the use of different assays is a problem for standardization and interpretation of D-dimer measurement.<sup>90,91</sup> The most sensitive methods for measuring serum D-dimer levels are the enzyme-linked immunosorbent assay (ELISA) and turbidimetric testing. ELISAs are the reference standard, but are expensive and labor- and time-intensive, and thus impractical in an acute setting. Whole-blood assays and latex agglutination provide rapid results, and are used widely in clinical settings. Although not as sensitive as ELISA, these methods have been confirmed to be reliable when using the clinical decision rule with D-dimer testing for ruling out PE.<sup>92</sup>

Baseline D-dimer levels tend to be higher in older patients and in African-Americans.<sup>93</sup> Additionally, acute illness, malignancy, chronic kidney disease, and rheumatoid factor can elevate D-dimer. There is a continuous increase in D-dimer throughout normal pregnancy for all gestations. There is no official consensus for how to approach D-dimer testing in these populations. The American Thoracic Society does not recommend the use of D-dimer to rule out PE in pregnant woman, with a small body of evidence indicating that a negative D-dimer assay is inadequate to rule out PE for these patients; however, further research is encouraged to hone these guidelines.<sup>94</sup> For patients in each of the aforementioned populations, clinicians must incorporate consideration of these factors into assay interpretation.

For patients presenting with acute dyspnea, D-dimer is useful only for ruling out PE in patients who are unlikely to have PE by clinical decision. Suggestions of D-dimer for use in treatment monitoring are currently under investigation.

## Blood gases

Blood gas (BG) analysis provides valuable insight into a patient's respiratory and metabolic status, including assess-

ment of oxygenation, gas exchange, the need for supportive ventilation, and acid–base disorders.<sup>95,96</sup> Guidelines for diagnosis and management of several common causes of acute dyspnea require use of the arterial BG (ABG). In COPD exacerbations requiring inpatient treatment, ABGs are useful in the initial assessment, as worsening hypoxia or hypercapnia are indications for inpatient treatment. Monitoring PO<sub>2</sub>, PCO<sub>2</sub>, and pH via ABG is a critical part of managing COPD exacerbations and determining the need for adjustments in oxygen therapy or initiating mechanical ventilation.<sup>97</sup> Use of the ABG is also recommended in all patients presenting with presumed severe HF and severe cardiopulmonary disease, including ARDS.<sup>1,98</sup>

In unselected patients presenting to the ED with a chief complaint of dyspnea, ABGs drawn upon presentation provide only limited diagnostic value. With the exception of diagnosing anxiety-induced hyperventilation, ABGs are not particularly helpful in distinguishing between cardiac and pulmonary etiologies of dyspnea. However, ABGs may be helpful for prognostication, eg, pH independently predicts intensive care-unit admission and 12-month mortality.<sup>99</sup>

Venous BG (VBG) measurement can also be used to assess respiratory and acid–base status in the evaluation of the patient with acute dyspnea. The arterial pH is typically 0.03 higher than the venous (95% prediction interval 0.029–0.038), while there is less acceptable agreement for PCO<sub>2</sub> (95% prediction interval –10.7 to 2.4 mmHg).<sup>100</sup> PO<sub>2</sub> is obviously quite different.<sup>82</sup> Some have suggested that when used in the correct clinical context, a venous PCO<sub>2</sub> cutoff of 45 mmHg may be used to screen for clinically significant hypercarbia.<sup>101</sup> Notably, the difference in arterial and venous measurements increases substantially in patients with circulatory compromise.<sup>102</sup> At this time, further outcome-based research is needed before recommending routine use of VBG over the ABG.

In summary, while the ABG remains an important aspect of the diagnosis and management of several cardiopulmonary disorders that present with acute dyspnea, its utility in distinguishing causes of acute dyspnea is limited.

## ST2

Soluble ST2 (sST2), a member of the IL-1 receptor family, is secreted into the circulation by cardiomyocytes and pulmonary endothelial cells in response to inflammatory and cardiac diseases.<sup>103–105</sup> Upon release, sST2 inhibits IL-33/ST2 signaling by functioning as a decoy IL-33 receptor, thus downregulating the inflammatory response.<sup>106</sup> While sST2 levels were significantly higher in patients with acute HF than

in those without, NT-proBNP has been shown to be superior in diagnosis of HF.<sup>104</sup> High levels of sST2 correlate with disease severity and increased morbidity in patients with ADHF and ACS.<sup>106</sup>

Elevated levels have also been found in patients with pathologic pulmonary disease, including COPD, pulmonary hypertension, asthma, and pneumonia.<sup>107–109</sup> In one study, sST2 concentration  $\geq 0.20$  ng/mL strongly predicted 1-year mortality in patients with dyspnea (hazard ratio 5.6), and this was even more pronounced in patients with acute HF (hazard ratio 9.3). Elevated levels of sST2 in the setting of noncardiac dyspnea have been associated with poor outcomes.<sup>105</sup>

Due to its poor specificity, ST2 has limited utility in distinguishing the etiology of dyspnea. However, it does provide prognostic value for patients with HF, ACS, and potentially other cardiopulmonary processes. Further research is needed to establish the utility of ST2 use in clinical practice.

## Conclusion

The laboratory assays described serve various purposes in helping to hone the diagnosis of dyspnea (Figure 1). A summary of recommendations is as follows:

The use of any laboratory assay should be based on clinical suspicion of underlying etiology based on thorough history, physical examination, and preliminary hemodynamic evaluation.

Both BNP and NT-proBNP are helpful biomarkers for identifying ADHF as the cause of acute dyspnea, and Gal-3 has shown limited diagnostic utility.

NPs, ABG, MR peptides, sST2, and Gal-3 have all demonstrated prognostic power for patients presenting with acute-onset dyspnea. Further investigation is needed to establish the most effective way to use these tests diagnostically.

Use of troponins for diagnosis of MI requires recognition of the pattern and degree of elevation. Even in the absence of acute MI, troponins are markers of myocardial injury and portend worse prognosis.

D-dimer should only be used to rule out PE in patients unlikely to have PE based on the clinical decision rule.

BGs do not have diagnostic utility in distinguishing cardiac from pulmonary causes of dyspnea in undifferentiated patients; however, ABG remains an important aspect of the diagnosis and management of severe cardiopulmonary disorders that present with acute dyspnea. VBG results can also be useful in assessing respiratory and acid–base status, but should be interpreted with caution, especially in patients with circulatory compromise.

Concomitant clinical considerations, including patient characteristics, medical history, medications, and possible mixed diagnoses, should always be incorporated into assay interpretation.

## Disclosure

The authors report no conflicts of interest in this work.

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