BIOMARKERS OF ACUTE CARDIOVASCULAR AND PULMONARY DISEASES

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ABBREVIATION LIST

AAD	= acute aortic dissection
ACS	= acute coronary syndrome
AE	= acute exacerbation
ARDS	= acute respiratory distress syndrome
BNP	= B-type natriuretic peptide
CMR	= cardiac magnetic resonance
COPD	= chronic obstructive pulmonary disease
C(P)K	= creatine (phospho-) kinase
CRP	= C-reactive protein
CT	= computed tomography
ESC	= European Society of Cardiology
HF	= heart failure
GDF-15	= growth differentiation factor-15
IL	= interleukin
LDL	= low-density lipoprotein
miR	= microRNA
MPO	= myeloperoxidase
NLR	= negative likelihood ratio
NT-proBNP	= N-terminal pro-type B natriuretic peptide
PE	= pulmonary embolism
PLR	= positive likelihood ratio
POC	= point-of-care
PTX3	= pentraxin 3
sLOX-1	= soluble lectin-like oxidized LDL receptor-1
SP-D	= surfactant protein D
STEMI	= ST-elevation myocardial infarction
TEFP	= troponin-ejection fraction product
TGFβ	= transforming growth factor beta
TTS	= Takotsubo syndrome

ABSTRACT

Acute cardiothoracic and respiratory diseases frequently remain a challenge to diagnose and differentiate in the emergency setting. The main diseases that manifest with chest pain include ischemic heart disease, myocarditis, acute pericarditis, aortic dissection/rupture and pulmonary embolism (PE). Diseases that primarily present with dyspnea include heart failure (HF), acute respiratory distress syndrome (ARDS), pneumonia, asthma exacerbations and chronic obstructive pulmonary disease. Pre-test probabilities of clinical findings play a vital part in diagnostic decisions, and the use of a Bayesian approach to these greatly improves the ability to stratify patients more accurately. However, blood tests (biomarkers) are increasingly used to assist in rapid decision-making in the emergency setting in combination with imaging methods such as chest radiograph, ultrasound and increasingly computed tomography, as well as physiological tests such as the electrocardiogram in addition to physical examination. Specific tests for ischemic heart disease and myocarditis (cardiac troponins), HF (B-type natriuretic peptide [BNP] and NT-proBNP), aortic dissection (smooth muscle markers) and PE (D-dimer) have been developed. Surfactant protein-D and interleukin-8 have been developed for ARDS. Additionally, circulating microRNAs have emerged as promising biomarker candidates in cardiovascular disease. With this increasing array of biochemical markers to aid in the diagnosis of chest diseases presenting with chest pain and dyspnea, we herein review the clinical usefulness of these markers, in particular in differentiating cardiac from pulmonary diseases. A symptom-oriented assessment as necessary for use in the critical setting is described in addition to discussion of individual biomarkers.

Keywords: biomarkers; chest disease; critical care.

BIOMARKERS OF ACUTE CARDIOVASCULAR DISEASES

Acute coronary syndromes

Acute coronary syndromes (ACS), including acute myocardial infarction and unstable angina, remain the most common pathological entity that has been investigated for biomarker use and development because of their high prevalence worldwide, being the leading cause of mortality in western countries.[1-3]

Most studies in this field have been consistently aimed at early and specific detection of myocardial ischemia/necrosis. While creatine (phospho-)kinase [C(P)K], myoglobin and fatty acid-binding protein have been used historically,[4-6] the emergence of troponin assays has revolutionized our approach to the biochemical diagnosis of acute myocardial ischemia/necrosis. Troponin is an actin-binding protein consisting of T-, I- and C-isoforms with the T- and I-isoforms being more widely applied to clinical use with the primary reason for differing use lying in proprietary licensing. While earlier troponin assays showed a bi-modal peak,[4] recent development of high-sensitivity troponin assays and their clinical application may provide a new approach to the assessment of myocardial ischemia/necrosis.[5] Assays from multiple vendors are under clinical testing, but generally, they are sensitive enough to measure levels from clinically asymptomatic patients that may have been undetectable previously. Whether elevations in high-sensitivity troponin levels in asymptomatic patients warrant treatment and how to approach such patients are issues yet to be addressed. At present, the European Society of Cardiology (ESC) guidelines suggest that temporal measurements showing increased (i.e., 1.5-fold) or sustained rises (i.e., 1.2-fold) in troponin levels after three hours (as compared to normal upper limit/99th percentile) should be considered as diagnostic criteria.[5,6] Measurements at one hour from onset have also been suggested to be sufficient for diagnosis,[7] but in either case, careful interpretation is recommended. It is worth noting that troponin levels can be elevated in the setting of demand ischemia (including effort angina, left ventricular hypertrophy and decompensated heart failure [HF]) aside from ACS (Table 1).

Biomarkers that reflect plaque vulnerability of the coronary arteries to assess early precursory conditions of subsequent plaque rupture/ACS have also been a topic of interest. Markers of plaque formation (e.g., oxidized low-density lipoproteins [LDL]) and inflammation (e.g., interleukin [IL]-6, C-reactive protein [CRP], pentraxin 3 [PTX3]) as well as plaque rupture (e.g., myeloperoxidase [MPO], soluble lectin-like oxidized LDL receptor-1 [sLOX-1]) have been studied. Oxidized LDL cholesterol is a general term used to describe the various oxidized lipid and (phospho-)protein epitopes on the apolipoprotein B molecule. Malondialdehyde modification is thought to be one of the major forms of oxidized LDL. Others that have been pursued include oxidized phosphatidylcholine [8] and sLOX-1, the latter being a 50 kDa membrane protein with an extracellular lectin-like structure that is processed to release a soluble peptide. Studies have shown that oxidized LDL markers are generally formidable markers of ACS with marked elevations in this condition.[9,10] A number of oxidized LDL assays are already commercially available.

Inflammatory markers have been equally pursued. CRP, in particular high-sensitivity assays, and its downstream effector protein, IL-6, have been pursued given that vascular inflammation is an important progressive/acceleratory component of vulnerable plaque instability/rupture aside from its formation as reflected by oxidized LDL. CRP and its 'vascular-selective' component, PTX3, belong to the same PTX domain-containing family of proteins. PTX3 is selective to endothelial cells and macrophages among other vascular cells in contrast to CRP, which is produced predominantly in the liver and is an indicator of the systemic inflammatory response. PTX3 has been shown to be selectively elevated in ACS but not in stable angina.[11]

Another protein of interest is MPO. It is released from blood cells, including granulocytes, in response to external stress and insult, which in turn, cause endothelial dysfunction and foam cell accumulation resulting in progression of plaque instability. Granulocyte infiltration is seen in the plaques of ACS patients,[12] and patients deficient in MPO show delayed progression of heart disease. Importantly, studies have shown that dynamics of MPO activity in the circulation seems to be independent of CRP (inflammation) and thus reflects different components of plaque instability

and rupture.[13] As an early marker of the vulnerable plaque, likely elevated even in pre-clinical stages, there are expectations that use of MPO will further assist in risk stratification of ACS patients when used in combination with troponin. As these are biomarkers reflective of pathogenic state, serial measurements to assess evolution of the condition rather than use of certain cut-off levels seem most appropriate. Nonetheless, reflecting use of single measurements on admission, sensitivity, specificity, and positive and negative predictive values for MPO (65.7%, 60.7%, 53.3%, and 72.2%, respectively) in addition to troponin T (58.0%, 100.0%, 100.0%, and 77.7%, respectively), CK-MB (42.4%, 94.7%, 84.6%, and 70.7%, respectively) and CRP (31.7%, 68.9%, 40.6%, and 60.0%, respectively), have been reported as diagnostic performance of cardiac markers in patients with chest pain, whilst acknowledging they may also be elevated in other acute cardiac syndromes, including acute decompensated HF in the absence of chest pain.[13]

In ACS, myocardial injury causes release of microRNAs (miRs) analogous to release of cardiac troponins. miRs are short fragments of non-coding RNA with intricate roles in regulation of gene expression. Alongside their physiological role in individual cell nuclei, they can be isolated from circulating blood or blood components and therein are building momentum as novel biomarkers for a range of clinical scenarios.[14] Several cardiac-specific miRs are released in differing time courses after cell injury, and elegant experiments comparing expression between aortic and coronary sinus venous blood have shown a miR gradient corresponding to release from injured tissue.[15] Amongst others, miR-208, miR-499, miR-1 and miR-133 have been studied as candidates for early diagnosis of ACS, distinguishing patients with myocardial infarction from healthy controls and those with stable coronary artery disease, but existing data fail to provide complete consensus.[16-19] In particular, miR-208 showed promise as an acute diagnostic biomarker with early expression (<3 hours) and greater sensitivity than cardiac troponin at early time points, but in other studies miR-208 was not detected or failed to discriminate.[20,21]. Furthermore, MiR biomarkers might also distinguish ACS from other causes of acute chest pain such as Takotsubo syndrome (TTS). Jaguszewski et al. recently showed a signature of four miRs

that, when assessed together, distinguished STEMI from TTS acutely with good sensitivity and specificity.[22]

Acute ‘non-coronary’ chest pain syndromes

Myocarditis

According to the WHO/ISFC definition, as reported in the recent position statement of the ESC Working Group on Myocardial and Pericardial Diseases, myocarditis is an inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria, and presenting at all ages with a various array of symptoms.[23] The disease is most frequent in young, previously asymptomatic individuals. Clinical presentation and course are diverse and mainly unpredictable, ranging from mild symptoms of chest pain associated with transient ECG changes to life-threatening new-onset HF, cardiogenic shock and ventricular arrhythmia. The ‘ACS-like’ presentation is generally characterized by acute chest pain associated with ST-segment elevation or depression and T-wave changes, with or without common risk factors for coronary artery disease; with or without increased troponin T/I (with a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months); with or without normal global or regional left and/or right ventricular dysfunction on echocardiography or cardiac magnetic resonance (CMR); and in the absence of angiographic evidence of coronary artery disease. These episodes are frequently preceded 1-4 weeks by respiratory or gastrointestinal infection.[23] Recently, new diagnostic biomarkers such as brain natriuretic peptides, circulating cytokines, markers related to extracellular matrix degradation, and new biomarkers such as PTX3, galectin-3, and growth differentiation factor-15 (GDF-15) have been proposed to have a potential diagnostic role, but their sensitivity and specificity need further investigation.[24-27] The diagnosis of myocarditis relies, by definition, on cardiac histology and endomyocardial biopsy as the gold standard.[23] However, according to guidelines, endomyocardial biopsy is recommended only in a precise but limited clinical scenario,[28,29] and non-invasive

imaging techniques such as T2STIR sequences using CMR imaging can be useful in making the diagnosis in ‘focal presentation’ such as ischemic-like or pseudo-infarction.

Acute pericarditis

Acute pericarditis is an inflammation of the pericardium with or without pericardial effusion.[30] It has many causes, including idiopathic pericarditis, infections (most cases are presumed to have a viral etiology), renal failure, myocardial infarction (Dressler’s syndrome), systemic autoimmune disease, post-cardiac injury syndrome (e.g., postcardiotomy, post-myocardial infarction), malignancy, radiation, and trauma.[30] The most common symptoms include prodromic fever and myalgia, pleuritic chest pain that is relieved by sitting forward and radiates to the trapezius ridge, non-productive cough, and shortness of breath. The diagnosis of acute pericarditis remains a clinical one based on history, physical examination, ECG (typical anterior and inferior concave ST-segment elevation) and echocardiography (pericardial effusion confirms diagnosis).[31] Appropriate laboratory tests include a complete blood count with differential count, a high-sensitivity CRP test, measurements of troponin I or T and serum creatinine, and liver function tests. High sensitivity CRP is elevated in only around 75% of cases at clinical presentation, and therefore does not exclude pericarditis, but may show additional benefit when used to monitor therapy. At follow-up, it would be useful to monitor recurrences and to select appropriate therapy duration, preferring non-steroidal anti-inflammatory drug and colchicine.[32] Acute pericarditis may be often accompanied by some degree of myocarditis, which manifests as elevated biomarkers of myocardial injury. In this case, the term “myopericarditis” indicates a primarily pericarditic syndrome with minor myocardial involvement.[30] In this regard, a rise in cardiac troponin T and I is a frequent finding, occurring in one third of patients with idiopathic pericarditis and more commonly in younger age.[33,34] Notwithstanding this, the outcome of myopericardial inflammatory syndromes is usually good and troponin elevation is not a negative prognostic marker.[30,33,34]

Takotsubo syndrome

TTS is an acute cardiac condition characterized by transient and reversible ventricular dysfunction. The clinical picture of TTS mimics ACS despite the evidence of normal coronary arteries.[35]

Although cardiac catheterization is usually required to confirm TTS and to exclude 'culprit' coronary lesions, the profile of cardiac biomarkers can be useful for clinicians in the diagnostic work-up, especially in the early stage.

Compared to acute myocardial infarction where troponin, CK-MB and myoglobin levels are elevated and usually correlated with the extent of myocardial necrosis, TTS is typically associated with mild peak elevations of cardiac enzymes that do not reflect the amount of systolic dysfunction.[35] The striking discrepancy between the degree of myocardial dysfunction on echocardiography or other imaging modalities and the low peak of necrosis enzyme markers is a hallmark of TTS diagnosis.[35-37] The reason for this apparent mismatch likely relies on the pathological mechanism of myocardial stunning hypothesized in TTS, related to catecholamine surge secondary to emotional or physical stress.[38]

The clinical course of TTS patients is characterized not only by reduced left ventricular ejection fraction but also by diastolic dysfunction. B-type natriuretic peptide (BNP) levels appear three- to four-fold higher in patients with TTS than with ST-elevation myocardial infarction (STEMI).[39] The increment of BNP in TTS is probably related to increased myocardial wall stress and distention secondary to volume and pressure overload. Madhavan et al. compared biochemical serum indices in TTS versus STEMI patients. They reported an elevated ratio between high BNP and low troponin levels typically associated with TTS.[39] The ratio of BNP to peak troponin T (cut-off = 502) distinguished TTS from STEMI with a sensitivity of 94% and a specificity of 100%.[39] Similar results were reported by other authors who tested a BNP/CK-MB ratio in a study population including patients with TTS and acute myocardial infarction. In this setting, a cut-off value of ≥38 (obtained from the first simultaneously available serum levels) identified TTS patients with high specificity (99%) but low sensitivity (46%).[40]

Nascimento et al. developed the troponin-ejection fraction product (TEFP) as a new index to differentiate TTS from STEMI.[41] When comparing peak troponin I levels and echocardiographically-derived ejection fraction values in TTS and STEMI patients, they found significantly lower values in the former. Interestingly, TEFP was dramatically lower in TTS (182 ± 380 vs 4088 ± 4244, $p<0.001$). Receiver operating characteristic (ROC) curve analysis showed that TEFP ≥250 had a positive predictive value of 88% for STEMI and TEFP <250 had a negative predictive value of 94%. Therefore, they suggested TEFP as an additional clinical tool to differentiate TTS from STEMI.[41]

The study of biomarker kinetics in TTS aims at increasing the ability to diagnose or suspect TTS without using invasive methods. Besides early diagnostic suspicion, biomarkers in TTS are also useful for prognostic purposes. The N-terminal proBNP (NT-proBNP)/troponin T peak level ratio appeared to predict left ventricular function recovery during hospitalization.[42] Conversely, high levels of BNP as well as a high E/e' ratio, an echocardiographic index of diastolic function, were found to correlate with poor prognosis and in-hospital major adverse cardiac events.[43,44] Very recently, ST2, a receptor of the IL-1 family, has been suggested to improve stratification of in-hospital high-risk patients with TTS.[45] TTS is characterized by a 'unique cardiac biomarker profile' that, when combined with other multimodality imaging parameters, is fundamental for diagnostic orientation and prognostic stratification.

Acute aortic dissection

Acute aortic dissection (AAD) has a high mortality and morbidity due to potentially fatal complications with a mortality rate of approximately 1%/hour within the first 24 hours after symptom onset.[46] Even with modern imaging methods, such as computed tomography (CT) and magnetic resonance, or with echocardiography (primarily transesophageal), which can reliably diagnose this condition, AAD is still often overlooked or misdiagnosed often owing to variability in presentation and lack of suspicion by the attending physician.

Smooth muscle and vascular markers

Smooth muscle markers reflect the release of smooth muscle cell proteins following disruption of aortic media layers during dissection. Smooth muscle myosin heavy chain protein was initially pursued, which showed a wide dynamic range (by as much as 20-fold) allowing for accurate diagnosis but was only elevated in the first 3-6 hours after symptom onset. Serial measurements of smooth muscle myosin heavy chain showed sensitivity of 90%, specificity of 97%, positive likelihood ratio (PLR) of 30 and negative likelihood ratio (NLR) of 0.10 at a cut-off value of 2.5 ng/mL within the first 12 hours.[47-49] A marker with a wider time window was next investigated. The BB-isozyme of C(P)K, which is selective for neurological and smooth muscle tissue, was pursued in analogy to the use of the MB-isozyme in myocardial ischemia/necrosis. Results showed peak concentrations were at 6 hours after AAD onset.[50] Further investigation focused on a troponin-like protein of smooth muscle, calponin, in analogy to cardiac troponins in myocardial ischemia/necrosis. Preliminary experience showed selective elevations in type A AAD patients with a moderate diagnostic performance (sensitivity 50%, specificity 87%, PLR 3.85 and NLR of 0.57 within 6 hours of symptom onset at a cut-off value of 2.8 ng/mL) but with an extended time window of 24 hours.[51] Smooth muscle markers collectively showed promising use in the biochemical diagnosis of AAD and are presently being pursued with hopes of translating to clinical and bedside practice.

Another marker that is elevated in the setting of AAD is elastin, a structural component of the vascular wall.[52] Increasing levels with age and a marginal dynamic range (e.g., 2-fold) with confounding levels have made its clinical use in the present form difficult. However, it is a promising marker that might benefit from improvements. Elastin shows a moderate diagnostic performance with sensitivity of 64.0%, specificity of 94.8%, PLR of 12.3 and NLR of 0.38 at a cut-off point set at the mean +3SD.[52] Matrix metalloproteinase-9, a component of the adventitial remodeling process, has also been shown to be elevated in AAD.[53] Further, CRP as a measure of inflammation was found to be elevated in AAD and to predict outcome.[54-56]

Transforming growth factor beta (TGFβ) is another protein of interest as this factor is the key pathogenic molecule in Marfan syndrome, a genetic disorder affecting fibrillin synthesis in the extracellular matrix of the vascular wall.[57] Studies have identified TGFβ dysregulation and increased circulating markers of this protein in Marfan patients. Recent evidence has also shown that circulating TGFβ levels are increased in adult patients with AAD as well, in particular in patients with type A AAD.[58]

Pro-thrombotic markers

Recent studies have shown that the pro-thrombotic marker D-dimer can be used to both rule in and rule out AAD. The cut-off level generally used to rule out pulmonary embolism (PE) (i.e., 500 ng/mL) can reliably be used to rule out AAD as well.[59] A large study examining D-dimer levels in patients with AAD (IRAD-Bio)[60] showed that a normal D-dimer level can reliably rule out AAD in the first 24 hours after onset with a sensitivity of 96.6% and a NLR of 0.07, but, more importantly, showed that elevated levels (>1600 ng/mL) may also rule in AAD if observed within the first 6 hours of symptom. However, this study only included patients with suspected AAD and did not encompass patients with chest pain in general or those with suspected PE. D-dimer is already widely used in the clinic with available point-of-care (POC) devices, and can be used to rule out both AAD as well as PE.[61]

Heart failure

HF is the primary cardiac-related disease that requires differentiation from pulmonary disease due to the common presenting symptom of breathlessness. BNP and NT-proBNP are natriuretic peptide biomarkers widely used for the diagnosis of HF. Whereas A-type natriuretic peptide, the prototype of the family, is secreted predominantly from the cardiac atria in response to hemodynamic stress, BNP is released predominantly from the ventricles and thus better reflects HF. With a wide dynamic range, BNP levels are correlated with degree of HF, and show a positive correlation with left ventricular end-diastolic pressure as a hemodynamic measure of HF and with functional impairment

as reflected by NYHA class.[62-64] Initial studies using BNP in Japan, where this biomarker was developed, used radioimmunoassay methods, but in the United States and elsewhere BNP assays have been introduced in POC forms and, thus, have been widely used in the critical care setting. The Breathing Not Properly study, which examined patients presenting with shortness of breath, showed that BNP measurements could be used to accurately differentiate/triage and risk stratify patients with suspicion of pulmonary or non-cardiac cause of dyspnea.[65] Diagnostic performance at a cut-off value of 100 pg/mL showed sensitivity of 90%, specificity of 76%, positive predictive value of 79% and negative predictive value of 89%. BNP is a widely accepted biomarker for HF and is recommended for use in diagnosis of acute HF by major cardiology societies (American College of Cardiology/American Heart Association, ESC, etc.).[66,67] Note that the most recent European guidelines recommend use of BNP to mainly rule out HF.[67]

BNP consists of 32 amino acids and is a bioactive hormone that elicits a natriuretic response in addition to vascular relaxation through actions on its receptors and cyclic guanosine monophosphate second messengers. Likely reflective of necessary metabolic processes, BNP is rapidly degraded in the circulation, showing variable levels according to the clinical condition and timing of measurement. NT-proBNP, which is a relatively stable yet biologically inert processed peptide of the precursor protein of BNP, has also been developed as a biomarker much in analogy to CRP and insulin. NT-proBNP generally shows similar diagnostic implications to BNP and has the advantage that it is more stable and therefore can be measured in the community clinics with sample transfer to local hospitals for ‘corelab’ analysis. However, NT-proBNP is affected more by age and renal function/clearance, making careful assessment necessary to avoid misinterpretation in elderly and renal compromised patients as NT-proBNP tends to be higher in these patients.[68] Patients with decompensated right HF associated with PE will generally present with dyspnea and findings of right ventricular load on echocardiography. BNP (or NT-proBNP) levels are useful because they are elevated in both decompensated right- and left-sided HF.

A new marker that shows potential promise is soluble ST2 as it appears superior to natriuretic peptides for defining prognosis in HF patients. ST2 is a component of the IL-33 signaling pathway, which is active in HF. Importantly, ST2 signaling is involved in regulating the fibrotic response and, hence, the cardiac remodeling process, which differs from the natriuretic peptide pathway elicited by cardiomyocytes in response to hemodynamic stress. ST2 used in combination with BNP increases diagnostic accuracy and risk stratification of patients with HF in the context of chronic remodeling and prognosis.[69] The main advantage is regarding prognosis and risk stratification, although no study has prospectively shown that ST2 should guide treatment decisions. ST2 has been approved by the DA for clinical use in 2011 and is commercially available.

Galectin-3, a biomarker of fibrosis, has received research interest for its association with heart failure progression. Studies involving both chronic and acute heart failure patients have been able to report additive prognostic value of galectin-3 after admission to hospital with an acute disorder. One experiment reported that elevated levels of galectin-3 were measured in patients who died within 1- and 4-years, and that galectin-3 was an independent predictor of 4-year mortality,[70] with another showing that combined use of galectin-3 with NT-proBNP was able to significantly increase prognostic information for short term (60 days) mortality and for a composite of mortality and HF recurrence.[71] However, when galectin-3 was assessed for diagnosis of HF, although median levels were higher in those who were later diagnosed with acute HF, the ROC analysis showed that the diagnostic value of NT-proBNP in these patients was far superior (AUC = 0.94) than galectin-3 (AUC = 0.72). These data suggest that the inclusion of galectin-3 as an emergency department diagnostic test is not likely to provide additive value over the use of NT-proBNP, but its measurement may provide informative data for management of HF progression.

A reasonable emphasis has been placed using miR biomarkers to distinguish HF from respiratory causes. MiR-423-5p has received most attention. It is upregulated in failing human myocardium,[72] and transcoronary gradients suggest that it has a cardiac origin.[73] An initial report showed upregulation in dyspneic patients with HF versus those without HF and healthy

controls, with high sensitivity and specificity and miR-423-5p levels correlating with NT-proBNP concentrations.[74] These findings were later supported by a larger study that identified a panel of four miRs (including miR-423-5p) distinguishing HF patients from healthy controls more accurately.[75] However, there were mixed signals about relation to disease severity (significant correlation with BNP levels, but no relation with NYHA class or ejection fraction), and in a further study of ischemic HF patients, miR-423-5p failed to show an association with markers of HF severity, such as BNP or echocardiographic indices of left ventricular function.[76] miRs show promise as biomarkers in acute cardiac conditions, however larger, correctly powered, prospective clinical studies are required in order to reproduce the findings from the small, largely retrospective experiments. Among other issues is the timescale from sample withdrawal to data output. Technology must be streamlined in order to reduce lengthy processes of RNA isolation and quantification by polymerase chain reaction. Without these improvements to coincide with further research, measurement of miRs cannot become commonplace in the clinical laboratory.

BIOMARKERS OF ACUTE PULMONARY DISEASES

Pulmonary embolism

PE along with ACS and AAD represents one of the three major diseases that manifest chest pain as the presenting symptom. As compared to AAD in which patients can pinpoint time of onset by the typical sharp, ripping and moving pain, PE often presents with non-specific symptoms making prompt diagnosis difficult. Plasma D-dimer, a degradation product of cross-linked fibrin, has been extensively studied as a biomarker to rule out this condition and is presently used routinely. A number of D-dimer assays are available. A negative D-dimer result on either quantitative rapid ELISA or second generation latex agglutination tests is diagnostically useful for the exclusion of PE in patients with low to moderate pre-test probability.[77] Plasma D-dimer measurement has limited clinical significance in hospitalized patients or high pre-test probability.[78] The sensitivity, specificity, and NLR of D-dimer testing for deep vein thrombosis in low probability patients have

been shown to be 88%, 72% and 0.18, respectively; in moderate probability patients to be 90%, 58% and 0.19, respectively; and in high probability patients 92%, 45% and 0.16, respectively.[79] For PE, a sensitivity of 95% and a NLR of 0.13 have been reported for D-dimer.[59]

It has become increasingly recognized that D-dimer levels increase with age; as such, the clinical utility of using a universal cut-off (500 μg/L) for all age populations is reduced.[80,81] In a recent meta-analysis, a proposed age-adjusted cut-off value (age x 10 μg/L above age 50 years) improved performance characteristics of D-dimer testing, increasing specificity from 34% to 46% while maintaining a sensitivity >97%.[82,83] The recent AJDUST-PE trial studied the diagnostic strategy of using clinical prediction tools to identify patients with non-high pre-test probability for PE and then applied an age-adjusted D-dimer cut-off level. The 3-month failure rate was 1 of 331 patients (0.3% [0.1%-1.7%]).[84] Among patients >75 years old, using age-adjusted cut-off rather than traditional 500 μg/L increased proportion of patients in whom PE could be excluded on the basis of D-dimer from 6.4% to 29.7%, without any additional false-negative findings.[78,84]

Diagnostic strategies in patients suspected of having PE initially focus on identification of patients in whom PE can be ruled out.[77,85] In these strategies, the first step is to assess clinical probability by using either empirical clinical assessment or standardized clinical decision rules (e.g., 2-level Wells, simple-revised Geneva, Pisa, Charlotte, PE rule-out criteria).[86] Multidetector CT angiography +/- lower limb compression ultrasonography is recommended for imaging.[61] Outpatients with low clinical probability and a normal chest radiograph, lung scintigraphy (V/Q scan) may be an alternative option, especially in child-bearing women, severe renal failure, and severe contrast-allergic history.[59,78,87,88] As predictive indicators for prognosis of PE, BNP, NT-proBNP, and troponin are useful as they reflect right ventricular overload and subsequent minimal myocardial damage, respectively. While a lower BNP cut-off level of <50 pg/mL in patients with PE is associated with a benign clinical course, NT-proBNP concentrations of 600 pg/mL [81] and elevated troponin I or T levels are associated with risk for short-term death.[89,90]

Like acute chest pain, several studies have sought miR biomarkers to identify etiology of dyspnea at presentation to the emergency department. In a small study, miR-134 distinguished patients with acute PE from healthy controls and patients with other causes of dyspnea;[91] other groups assessed circulating miRs in chronic obstructive pulmonary disease (COPD) versus asthma.[92] However, there remains very little data on miRs in respiratory disease.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) and acute lung injury are characterized by high-permeability pulmonary edema causing hypoxic respiratory failure with high morbidity and mortality.[93] The encompassing lung injury can either be direct (pulmonary: pneumonia, aspiration) or indirect (extrapulmonary: non-pulmonary sepsis, pancreatitis).[93] Among the several inflammatory biomarkers that have been validated in the diagnosis of ARDS, plasma surfactant protein D (SP-D) and IL-8 can be used in combination with clinical variables for risk prediction.[94] SP-D is a hydrophilic glycoprotein mainly produced by the secretory pathway in type II pneumocytes and can be a specific marker for lung injury.[95] IL-8 is a pro-inflammatory cytokine and is produced by macrophages.[96] IL-8 promotes chemotaxis of neutrophils, causing them to migrate toward the focus of infection, and also enhances neutrophil phagocytosis.[97,98] More recently, angiopoietin-2, a mediator of endothelial injury, was found to be a robust indicator of indirect ARDS, while SP-D was a consistent marker of direct ARDS.[99]. This suggests that direct lung injury is better characterized by severe epithelial lung injury (SP-D, RAGE), and conversely, indirect ARDS is defined by more vascular endothelial inflammation (angiopoietin-2, IL-6, IL-8).[99] BNP at low levels may also help to exclude cardiogenic pulmonary edema.[100] As we gain better understanding of ARDS pathogenesis, biomarkers may help identify patients at highest risk of developing ARDS, assess response to therapy and predict outcome.

Chronic obstructive pulmonary disease and asthma

Although COPD and asthma are long-term conditions, both report acute exacerbations (AE) that may lead to presentation to the emergency department. Like other acute cardiovascular events, these can show symptoms of dyspnea, chest discomfort and wheeziness.[101,102] AECOPD have been reported to display elevated levels of GDF-15, CRP and fibrinogen when compared to stable COPD patients, with both acute and stable conditions elevated in comparison to healthy controls.[103] Furthermore, elevated D-dimer levels have been shown to offer both short- and long-term prognostic values post-AECOPD, with those who survived the in-hospital stay reporting 6.5-fold shorter mean post-admission survival periods.[104] Interestingly, COPD patients with prior myocardial infarction reported greater elevation of troponin T and CRP than those without following an AECOPD event.[105] In asthma, sufferers of AE showed higher levels of D-dimer and fibrinogen than individuals with either severe or stable asthma.[106] Increased levels of CRP and procalcitonin have also been used to distinguish between acute asthma and pneumonia presentations and thus aid in the more apt use of antibiotics in these patients.[107] The use of biomarkers such as these can clearly show elevation in both cardiac and pulmonary conditions, and therefore the combined use of biomarkers and clinical investigations is paramount.

The diagnostic and prognostic values of key biomarkers among major cardiovascular diseases are summarized in Tables 2 and 3,[5,6,61,67,78,82,89,108-124] taking into account current guideline recommendations, recent meta-analyses and cohort studies.

SYMPTOM-ORIENTED USE OF BIOMARKERS

Chest pain

When examining a patient with chest pain, ACS, AAD and PE are the three potentially life-threatening conditions that should be considered. ACS, including STEMI, can generally be diagnosed by use of troponin measurements, an electrocardiogram and subsequent coronary

angiography. Ideally, an electrocardiogram should be performed and interpreted as soon as possible at the point of first medical contact. AAD and PE can both be generally targeted by D-dimer testing and further by triple-rule-out CT. Based on these features, when examining a patient with chest pain in the critical setting, in addition to initial interrogation and physical examination, blood tests including troponin and D-dimer along with electrocardiogram and rapid imaging tests such as chest radiograph and, if necessary, echocardiography and/or CT may be warranted. If presenting to a community hospital where resources are limited, biomarkers and imaging will assist in making an early decision whether to transfer to a tertiary center and/or pursue further diagnostic testing (e.g., imaging). The critical role of clinical examination and findings in the interpretation of biomarkers should always be remembered to provide a Bayesian context to the test and results, as the pre-test likelihood of various conditions will be dramatically different based upon clinical data (Figure 1). For example, in the case of a high probability of PE or AAD, subsequent biomarker tests should be by-passed in favor of sending the patient directly for imaging. Similarly, it is not possible to definitively define HF when NT-proBNP is high (e.g. high risk of PE) and therefore this emphasizes the importance of the pre-test probabilities derived from clinical investigations, using the Bayesian approach, when considering subsequent diagnostic pathways.

Shortness of breath

Diagnosing whether shortness of breath or dyspnea is of pulmonary or cardiac origin is often difficult because both are frequently present as a complication or sequelae of the other. When examining a patient in the critical setting, in addition to initial interrogation and physical examination, blood tests including BNP along with electrocardiogram and rapid imaging tests such as chest radiograph and, if necessary, echocardiography may be warranted. BNP levels >400 pg/mL are strongly suggestive of acute cardiac decompensation, and echocardiography is recommended in patients with suspected HF, including those individuals with serum BNP levels <100 pg/mL. It

should be noted that pulmonary diseases with hemodynamic stress on the right ventricle can raise BNP >100 pg/mL.

One condition that should especially be kept in mind when examining patients with suspicion of HF is ARDS. Signs and symptoms of this disease are often similar to lung congestion or abnormal blood gas levels, and may thus mimic HF. However, as rapid deterioration of the condition can occur without appropriate treatment, careful suspicion and observation is warranted. SP-D levels can be helpful, but this is not usually measured routinely in critical care patients with shortness of breath/dyspnea owing to lack of availability of POC tests as compared to cardiac troponins, BNP and D-dimer. At present, given the absence of specific methods to triage patients with ARDS, the suspicion of the attending physician to keep this condition in mind when treating patients with acute shortness of breath, in particular those with no history of heart disease, is of utmost importance. For diagnostic algorithm, see Figure 2.

CONCLUSIONS

In the present review, we discussed the use of biomarkers in the diagnosis of critical chest diseases. Characteristics and availability of assays are shown in Table 4.[4,5,8-11,47-56,59,60,62-67,69,87-90,100,125-129] While much progress has been made in this field, especially for cardiac markers, much more research and development are necessary, in particular for pulmonary diseases. More importantly, as cardiac and pulmonary diseases often acutely affect one another, while the main cause of the condition is diagnosed, there will often be a complex pathophysiology in which both the heart and lungs will be affected. Especially in the critical care setting, deciphering between the two may be challenging and the diagnosis will be made in an evolving and collective manner. Nonetheless, biomarkers, such as cardiac troponins, BNP and D-dimer, have become to play an important role in triaging patients with critical chest diseases. In addition, circulating miRs have emerged as promising novel biomarkers in different disease states, including cardiovascular disease. Further investigations of combined roles with rapid imaging tests and other measures along with

their accurate clinical interpretation should prove to be a formidable working diagnostic algorithm as we look to the future.

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130. FIGURE LEGENDS

Figure 1. Diagnostic algorithm for patients presenting to the emergency room with chest pain using high-sensitivity troponin and D-dimer as well as electrocardiogram and rapid imaging.

ACS, acute coronary syndrome; AD, aortic dissection; EMB, endomyocardial biopsy; CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; PE, pulmonary embolism; STEMI, ST-elevation myocardial infarction.

Figure 2. Diagnostic algorithm for patients presenting to the emergency room with shortness of breath using BNP and D-dimer as well as electrocardiogram and rapid imaging.

AD, aortic dissection; ARDS, acute respiratory distress syndrome; BNP, B-type natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; HF, heart failure; NT-proBNP, N-terminal pro-BNP; PE, pulmonary embolism.