Biomarkers, 2011; 16(5): 379–392

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.3109/1354750X.2011.574234

informa
healthcare

REVIEW ARTICLE

Risk stratification and short-term prognosis in acute heart failure syndromes: A review of novel biomarkers

Ariadne Avellino, Sean P. Collins, and Gregory J. Fermann

Department of Emergency Medicine, University of Cincinnati, Cincinnati, Ohio, USA

Abstract

Background: Early risk stratification of patients with acute heart failure syndrome (AHFS) can guide the decision to admit the patient to hospital and the choice of therapy.

Methods: Standard review methodology using Medline and Google scholar from the years 2006–present. Papers before 2006 were reviewed when necessary.

Results: Biomarkers used in AHFS are broadly classified based on their mechanism of action: inflammation, renal stress, extracellular matrix remodeling, oxidative stress, cardiac myocyte stress, and neurohormonal regulation.

Conclusion: This paper provides a review for clinicians and medical scientists highlighting the most recent advances in biomarkers with application in AHFS.

Keywords: Heart failure, risk stratification, biomarkers

Introduction

Acute heart failure syndrome (AHFS) is the new onset or worsening of the signs and symptoms attributed to functional or structural impairment of the left ventricle. Ischemic heart disease, hypertension, and valvular disease most commonly contribute to its presence (Blum 2009). AHFS is a significant health-care challenge, posing substantial concern for individuals, health-care systems, and public health (McMurray and Stewart 2002; Bui et al. 2010). The survival rate of heart failure is far less than most forms of cancer; patients who have been hospitalized for the first time with the primary diagnosis of heart failure have a 5-year mortality rate of 75% (McMurray et al. 1998; McMurray and Stewart 2000; McMurray and Stewart 2002; Petrie and McMurray 2001). In 2009 alone, the estimated cost of heart failure care in USA was greater than $37 billion (Lloyd-Jones et al. 2010).

AHFS often presents with nonspecific signs and symptoms (Thomas et al. 2002), in part, because it is a complex disorder involving the interplay of various mechanisms and substances produced by the cardiovascular, the respiratory, the neuroendocrine, and the renal systems. There is no one single diagnostic test for AHFS. Because of the intricacies of this syndrome, biomarkers, particularly when used in combination with physical examination and ancillary diagnostics, have potential for utilization in the diagnosis, management, and risk stratification in AHFS. By definition, biomarkers include enzymes, hormones, and other biologic substances that indicate stress (Braunwald 2008), synthesized either by cause or result at the cellular, single organ, multisystem, and organism levels. According to Morrow and de Lemos (2007), there are three fundamental criteria necessary to evaluate the utility of a biomarker. These criteria include that the biomarker (1) be quantifiable, (2) adds new information not inclusive of other clinical aspects of assessment, and (3) aids in the management of patients with the disease process. Ideally, biomarkers associated with AHFS would specifically include the following optimal characteristics: (1) confirming the presence of heart failure, (2) identifying the underlying disease, (3) characterizing the severity of disease

Address for Correspondence: Dr. Gregory J. Fermann, MD, Associate Professor, Department of Emergency Medicine, University of Cincinnati, 231 Albert Sabin Way ML 0769, Cincinnati, Ohio 45267-0769, USA. Tel.: 1 513 558 8102; Fax: 1 513 558 5791. E-mail: Gregory.fermann@uc.edu

(Received 18 January 2011; revised 18 March 2011; accepted 19 March 2011)

and monitor treatment, and (4) supporting risk assessment of disease progression and prognosis (Tang et al. 2007a).

The remainder of this article will discuss recent advances in the AHFS biomarkers with reference to their mechanism, pathophysiology, and risk stratification potential. Discussion will focus on biomarkers associated with the following processes: inflammation, renal stress, extracellular matrix remodeling, oxidative stress, cardiac myocyte stress, and neurohormonal regulation (Table 1). Although some biomarkers may be associated with more than one process, each biomarker will only be discussed within the context of physiology with which it is most commonly associated. Additionally, Table 1 specifies biomarkers currently in use or those where the authors think they may be of use clinically in the near future. Literature supporting this review was identified using Pubmed and Google Scholar from 2006 to 2010 using English language search terms that included but not limited to: heart failure, biomarkers, inflammation, oxidative stress, renal stress, myocyte stress, extracellular matrix remodeling, neurohormonal regulation, prognosis of heart failure, and risk stratification heart failure. Additional literature was identified by review of bibliographies of articles provided from the above search specifications.

Biomarkers linked with inflammation

Inflammation is one of the core homeostatic phenomena in human disease. In AHFS, immune activation causes an overproduction systemic and cardiac proinflammatory substances (Khaper et al. 2010). Elevated inflammatory cytokine levels have been shown to be detectable earlier than neurohormonal biomarkers, making these inflammatory molecules potentially more sensitive determinants of cardiac function (Wang et al. 2009). Much recent attention has been directed at proinflammatory biomarkers such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), and lipoprotein-associated phospholipase A2 (LP-PLA2) antigen.

TNF-α, IL-6, and CRP

TNF-α exerts its effect on cardiac myocytes by downregulating sarcoplasmic reticulum proteins and thereby inhibiting the contractility of the heart (Blum 2009; Vaz Perez et al. 2010). IL-6 directly affects cell-to-cell communications between cardiac myocytes and fibroblasts. Alterations in IL-6 levels have been shown to cause cardiac dysfunction and alteration of cardiac extracellular matrices (Banerjee et al. 2009). CRP has a long half-life (Yeh and Willerson 2003) and offers protection by binding and clearing apoptotic cells and other oxidative species. Although these protective effects have been suggested, CRP also has potentially deleterious effects as seen in its action in both atherosclerosis and AHFS. Specifically, CRP has been shown to upregulate the production of IL-6 and TNF-α, thereby contributing to the pathogenesis of ongoing myocardial damage (Verma et al. 2004; Nakagomi et al. 2010).

Recent research of these biomarkers with regard to AHFS focuses on monitoring them in combination rather than in isolation. Kalogeropoulos et al. (2010) describe a significant independent association between IL-6 and TNF-α and risk of incident AHFS among older persons (age: 70–79 years) across sex and race. Vredevoe et al. (2004) demonstrate that peripheral blood mononuclear cells (PBMCs) cultured from patients with AHFS produce higher levels of IL-6 than PBMCs from normal controls. In AHFS, elevated IL-6 levels correspond with a decrease in natural killer cell function, illustrating a model of IL-6-induced anergy, a concept common in a variety of oncologic and other disease processes, but one that has only newly been described in AHFS. In chronic heart failure, IL-6 has shown to be a better predictor of heart failure–related deaths and hospitalizations than high-sensitivity CRP (Jug et al. 2009), but a poorer prognostic indicator with regard to mortality or new hospital admissions in AHFS (Ruiz-Ruiz et al. 2007a). Although stable heart failure patients with elevated TNF-α have been shown to have high mortality rates (Amir et al. 2010), TNF-α is not accurate in differentiating AHFS with left ventricular systolic dysfunction (LVSD) versus those with AHFS and preserved left ventricular ejection fraction; Matsumoto et al. (2010) find no difference in TNF-α levels between these two groups. They did, however, note elevations in levels of both IL-6 and high-sensitivity CRP in the group with LVSD.

LP-PLA2

LP-PLA2 has not been as extensively studied in AHFS as TNF-α, IL-6, and CRP, but is a candidate for future research and clinical application. LP-PLA2 circulates with low-density lipoprotein molecules and contributes to the formation of harmful lipid mediators in the vasculature (Zalewski et al. 2005).

Recently, the LP-PLA2 antigen has been associated with a 12-year risk of heart failure in patients without cardiovascular disease or heart failure at baseline. This association is independent of other risk factors for heart failure such as increase in levels of other inflammatory biomarkers and incidence of atherosclerosis. Though the antigen shows this relationship, conversely, LP-PLA2 activity is not associated with risk of incident AHFS, except in patients with baseline cardiovascular disease (Suzuki et al. 2009). Though the research on LP-PLA2 in AHFS is somewhat limited at this point, these data suggest that it is has promise for future consideration in both the basic science and clinical setting.

Biomarkers correlated with renal stress

AHFS is hallmarked by pulmonary congestion and volume overload (Ali et al. 2007). Kidney disease, also marked by derangement in the homeostatic fluid balance, shares similar risk factors and pathophysiologic mechanisms

Table 1. AHFS biomarkers.

Category & biomarker	Physiologic importance	Clinical utility	Biomarker level	References
Inflammation				
Tumor necrosis factor-α (TNF-α)	Myocardial damage	Development of AHFS: -increased risk of if 70–79 years Prognosis -assoc with increased mortality	3.49 pg/mL	(Amir et al. 2010; Kalogeropoulos, et al. 2010)
Interleukin-6 (IL-6)	Myocardial damage	Development of AHFS: -increased risk of AHFS if 70–79 years -likely to have LVSD	2.31 pg/mL	(Kalogeropoulos, et al. 2010; Matsumoto et al. 2010)
C-reactive protein (CRP)	Myocardial damage	Risk stratification -likely to have LVSD	1.94 μg/mL	(Kalogeropoulos et al. 2010; Matsumoto et al. 2010)
Lipoprotein-associated phospholipase A2 antigen (LP-PLA2 antigen)**	Vascular damage	Development of heart failure: -12-year risk in patients without baseline cardiovascular disease/heart failure	113.7 ng/mL	(Suzuki et al. 2009)
Renal stress				
Neutrophil gelatinase–associated lipocalin (NGAL)**	Renal dysfunction & cardiac myocyte injury	Prognosis -worsening severity & prognosis	140 ng/mL	(Poniatowski et al. 2009; Shrestha et al. 2010)
Cystatin C**	Renal dysfunction	Development of AHFS: -independent risk factor if >65 yrs	1.26 mg/L	(Dries et al. 2000; Sarnak et al. 2005; Shlipak et al. 2006)
Extracellular matrix remodeling				
Metalloproteinase-3 (MMP-3) & Metalloproteinase-9 (MMP-9)	Dysfunction of cardiac remodeling	Prognosis -higher all-cause mortality in patients with systolic heart failure -MMP-9: independent predictor of poor prognosis	16.8 ng/mL (MMP-3) 89.0 ng/mL (MMP-9)	(Buralli et al. 2010)
Tissue inhibitor for metalloproteinase-1 (TIMP-1)	Dysfunction of cardiac remodeling	Prognosis -allows MMPs to act without inhibition	1640 ng/mL	(Frantz et al. 2008; Yang et al. 2010)
Propeptide of procollagen type I (PIP)**	Dysfunction of cardiac remodeling	Prognosis -higher levels correlate with higher risk of readmission or death	88.12 ng/mL	(Ruiz-Ruiz et al. 2007; Plaksej et al. 2009)
Procollagen type III amino-terminal propeptide (PIIINP)	Dysfunction of cardiac remodeling	Prognosis -predicts risk of death & hospitalization	5.94 μg/L	(Cicoira et al. 2004)
Galectin-3	Dysfunction of cardiac remodeling	Development of AHFS: -correlates with cardiac disease and increase of other ECM markers Prognosis (long-term)	9.2 ng/mL	(van Kimmenade et al. 2006; de Boer et al. 2009; Carrasco Sanchez 2010)
Oxidative stress				
Myeloperoxidase (MPO)	Myocardial remodeling dysfunction	Development of heart failure: -risk over 7 yrs if elevated Prognosis -1 year all-cause mortality	99 pmol/L	(Tang et al. 2007; La Rocca et al. 2009; Tang et al. 2009; ReichLin et al. 2010)
Cardiac myocyte stress				
B-natriuretic peptide (BNP)**	Myocardial dysfunction	Diagnosis Of AHFS: -if BNP >100 pg/mL dyspnea likely due to AHFS Prognosis -BNP >100 pg/mL predicts poor outcome, hospitalization, other cardiac events, and death	480 pg/mL	(Harrison et al. 2002; Maisel et al. 2003; McCullough et al. 2003; Grewal et al. 2008)
N-terminal pro-b-natriuretic peptide (NT-proBNP)**	Myocardial dysfunction	Diagnosis -if NT-proBNP <300 pg/mL, AHFS likely excluded Prognosis	<50 years: 450 pg/mL 50–75 years: 900 pg/mL >75 years: 1800 pg/mL	(Januzzi et al. 2006; Grewal et al. 2008; Bhardwaj et al. 2010)

Table 1. continued on next page

Table 1. Continued.

Category & biomarker	Physiologic importance	Clinical utility	Biomarker level	References
Arginine vasopressin (AVP)	Hemodynamic dysfunction & myocardial dysfunction	Monitoring of therapy -patients on V_2 antagonists may be monitored for therapeutic efficacy	~10 pg/mL	(Cawley 2007; Goldsmith 2006; Kumar & Mather 2009)
C-terminal provasopressin (Copeptin)**	Hemodynamic dysfunction Myocardial dysfunction	Development of AHFS: -increase risk after MI Prognosis -90-day increased mortality	6.30 pmol/L	(Kelly et al. 2008; Voors et al. 2009; Xue et al. 2010)
Adrenomedullin (ADM)	Hemodynamic dysfunction	Development of AHFS: -disease conversion from AHFS to chronic heart failure	14.6 fmol/mL	(Bisping et al. 2007; Nishida et al. 2008)
Proadrenomedullin molecule (MR-proADM)**	Hemodynamic dysfunction	Prognosis -Emergency Department risk stratification of dyspnea -strong predictor of mortality	1.9 nmol/L	(Potocki et al. 2009; Davenport et al. 2010)
Soluble ST2 receptor**	Myocardial dysfunction	Diagnosis -differentiates dyspnea due to AHFS versus other potential causes Prognosis -strongly predictive of 1-year mortality	0.50 ng/mL (diagnosis) >20 ng/mL (1-year mortality)	(Januzzi et al. 2007; Mueller et al. 2008; Rehman et al. 2008)
Neurohormone regulation				
Norepinephrine (NE)	Adverse effects of nervous system compensation	Prognosis -already established in chronic heart failure; needs more study in acute heart failure, but likely to have prognostic value AHFS	473 pg/mL	(Kaye et al. 1995; Tsutamoto et al. 2008)
Endothelin-1 (ET-1)**	Myocardial dysfunction Vascular dysfunction Conduction system dysfunction	Prognosis -not yet being used clinically in chronic heart failure -studies of chronic heart failure suggest its potential in determining prognosis of disease; likely to have prognostic value also in AHFS	2.29 pM	(Cody et al. 1992; Pacher et al. 1996; Tang et al. 2010)
Urocortin-1 (UCN-1)	Myocardial dysfunction	Prognosis -already established in chronic heart failure; needs more study in acute heart failure, but likely to have prognostic value AHFS	1.7 pmol/L	(Wright et al. 2009; Tang et al. 2010)

**Refers to biomarker likely of benefit to be of clinical use currently or in the near future for AHFS.

with AHFS (Poniatowski et al. 2009). It is common for AHFS patients to have underlying renal dysfunction (Damman et al. 2008), and for patients with a failing renal system to be more susceptible to AHFS (Davenport et al. 2010). Several biomarkers currently under study may have application as indicators of AHFS risk prognosis, including neutrophil gelatinase–associated lipocalin (NGAL), cystatin C kidney injury molecule-1, and podocin (Chaudhary et al. 2010). However, the majority of recent literature of markers of global renal dysfunction and AHFS has focused on NGAL and cystatin C.

NGAL

NGAL is a bacteriostatic protein released not only by the lung, trachea, stomach, and colon, but also by renal tubular cells as a marker of (Schmidt-Ott et al. 2007) acute kidney injury. It has also been suggested as a potential marker of progression in chronic kidney disease (Bolignano et al. 2010). Initially, the presence of NGAL was only considered in AHFS as an indicator of concurrent early renal injury (Damman et al. 2008; Aghel et al. 2010; Bolignano et al. 2010). However, in animal models, Bu et al. (2006) report the release of high levels of NGAL in response to experimental angioplasty of rat aorta independent of renal injury. In humans, the debate continues regarding whether increased NGAL levels are an expression of kidney injury in AHFS or whether cardiac failure alone produces increased systemic levels. It is suspected that NGAL is released not only in response to renal injury, but also as an independent response to cardiac myocyte injury in AHFS (Shrestha et al. 2010).

Recent studies show a positive correlation of increasing levels of NGAL and worsening severity and prognosis of AHFS (Poniatowski et al. 2009; Shrestha et al. 2010). According to Poniatowsky et al. (2010), increased NGAL levels in both urine and serum directly correlate with the severity the of chronic heart failure as characterized by New York Heart Association (NYHA) classification. Additionally, elevated NGAL levels are specifically associated with worsening left ventricular diastolic dysfunction in patients with systolic heart failure and independently predictive of adverse long-term outcomes (Shrestha et al. 2010).

Cystatin C

Cystatin C is a cysteine proteinase inhibitor produced by most human cells and released into the bloodstream. Filtered by the glomerulus and metabolized by the proximal renal tubules (Burkhardt et al. 2002) cystatin C levels increase abnormally in renal dysfunction (Sarnak et al. 2005). Increased cystatin C levels indicate renal dysfunction and are associated with salt retention, ventricular remodeling, and the development of AHFS (Dries et al. 2000; Sarnak et al. 2005).

Sarnak et al. (2005) propose that cystatin C concentrations are an independent risk factor for AHFS in adults older than 65 years. Djousse et al. (2008) suggest that elevated cystatin C could be either an independent risk factor for AHFS or a biomarker for AHFS in those with pre-existing hypertension. However, in a study of over 4400 participants without baseline heart failure, in the 19% who developed cardiac dysfunction over an 8-year follow-up, cystatin C levels were linearly associated with the incidence of systolic heart failure. Cystatin C levels were also associated with the incidence of diastolic heart failure, but not linearly, and only at its highest concentrations (Moran et al. 2008).

Biomarkers accompanying extracellular matrix remodeling

AHFS is characterized by an initial insult to the heart followed by compensatory mechanisms that strive to sustain cardiovascular homeostasis. Transition from compensation to disease progression is marked by change in the size and composition of the cardiac ventricles. Though this transformation becomes evident at the organ level, cardiac modifications begin at myocytes, extracellular matrix, and regulators of cardiac remodeling (Takano et al. 2003; Brower et al. 2006; Mann 2006). Some of the regulators of this process include matrix metalloproteinases (MMPs), galectin-3, plasma procollogen type III, and propeptide procollogen type I (Cicoira et al. 2004; Lin et al. 2010; Lubrano et al. 2010; Yang et al. 2010). Because these substances are important regulators in cardiac renovation, they may also be used as markers of progression of compensation to disease (Chiao et al. 2010).

MMPs and tissue inhibitor for metalloproteinase-1

MMPs are proteolytic enzymes that impact cardiac remodeling by degrading extracellular matrix structures, such as collagen, and regulating signaling pathways involved in the process (Nagase and Woessner 1999; Malemud 2006; Spinale 2007). Although the function of MMPs may at times be considered homeostatic, when their activity is unregulated, they likely play a role in the disease processes. Naturally occurring substances that inhibit MMPs are a group of substances called tissue inhibitor for metalloproteinase-1 (TIMP-1). Several recent studies have suggested that the development of AHFS is associated with the discordance of TIMP-1 and MMPs (Frantz et al. 2008; Yang et al. 2010).

Previous literature in both animal and human models has highlighted the importance of MMPs, specifically MMP-2, MMP-3, and MMP-9, in the development and progression of heart failure (Li et al. 2000; Peterson et al. 2000; Spinale et al. 2000; Sundstrom et al. 2004). Increases in circulating MMP-3 and MMP-9 are associated with higher all-cause mortality in patients with systolic heart failure (Buralli et al. 2010). Interestingly, after adjusting for other confounders, MMP-9 alone proved to be an independent predictor of adverse prognosis in AHFS (Buralli et al. 2010). Future investigations will likely focus on the role of MMP-9 in the study of both AHFS and chronic heart failure.

Propeptide of procollagen type I

Propeptide of procollagen type I (PIP) is a biomarker of extracellular matrix synthesis (Cicoira et al. 2004; Lopez et al. 2010). PIP is a marker only of type I collagen synthesis and is found proportionally to the amount of collagen formed. Ruiz-Ruiz et al. (2007b) suggest that AHFS patients with increased levels of PIP are at a higher risk of death or readmission. Additionally, study suggests that PIP levels predict right ventricular diastolic dysfunction (Plaksej et al. 2009).

Procollagen type III amino-terminal propeptide

Like PIP, procollagen type III amino-terminal propeptide (PIIINP) is not only a marker of type III collagen synthesis but also a marker of its degradation. PIIINP levels are directly proportional to the amount of collagen synthesized or degraded (Jensen & Host 1997; Lopez et al. 2010).

Cicoira et al. (2004) demonstrates that circulating PIIINP levels predict the risk of death and hospitalization for AHFS patients with mild-to-moderate disease independent of the severity of left ventricular dysfunction. Plaksej et al. (2009) postulate that the severity of right and LVSD and left ventricular diastolic dysfunction is directly related to plasma levels of PIIINP.

Galectin-3

Galectin-3 is a carbohydrate binding-lectin, secreted by macrophages that interacts with several extracellular matrix components including laminin, synexin, integrins, and collagen (Ochieng et al. 2004). In non-diseased hearts, galectin-3 levels are low, but increases predictably in cardiac disease (Sharma et al. 2004). Lin et al. (2009) suggest that serum galectin-3 significantly correlates with PIIINP, MMP-2, and TIMP-1 levels. These correlations imply suggest an interplay between inflammation and extracellular matrix remodeling in heart failure.

Some suggest that Galectin-3 has more long-term prognostic value (van Kimmenade et al. 2006; de Boer et al. 2009; Carrasco Sanchez 2010). Recent evidence confirms van Kimmenade, suggesting serum galectin-3 measurements are not only elevated in patients with AHFS, but are also predictive of adverse outcomes in AHFS (Christenson et al. 2010; Vaz Perez et al. 2010).

Biomarkers of oxidative stress

The role of oxidative stress in the pathophysiology of AHFS has been highlighted in literature published before 2008 (Singh et al. 1995; Grieve & Shah 2003). Reactive oxidative species (ROS) damage cellular membranes and proteins causing apoptosis thereby inducing myocardial dysfunction and cardiac hypertrophy, and ROS may moderate the interaction of various substances involved in cellular signaling (Finkel 1999; Spinale 2002; Grieve & Shah 2003). They have also been shown to modulate fibroblast proliferation and collagen synthesis and directly affect MMP activity (Spinale 2002). Recent literature on ROS and AHFS has focused on myeloperoxidase (MPO), biopyrrins (Hokamaki et al. 2004), and oxidized low-density lipoproteins (Tsutsui et al. 2002) as potential biomarkers in AHFS. Though each is a promising biomarker worthy of further evaluation, this discussion will be limited to MPO.

MPO

MPO is an enzyme released by neutrophils, monocytes, and endothelial cells during inflammation. This enzyme catalyzes the formation of reactive oxidants, free radicals, and nitric oxide–derived oxidants, which are active during inflammation and promote tissue injury (Zhang et al. 2002; Nicholls & Hazen 2005; Reichlin et al 2010). In previous research, MPO has been identified as a direct contributor and marker of atherosclerosis and postmyocardial infarction left ventricular remodeling (Podrez et al. 1999; Eiserich et al. 2002; Askari et al. 2003).

Given that this cardiac remodeling also occurs in heart failure, several articles have highlighted it as a potential prognostic biomarker in AHFS (Reichlin et al. 2010; Tang et al. 2007b; Tang et al. 2009; La Rocca et al. 2009). Although previously thought to have low specificity in AHFS, due to its generalized activation in many diseases that increase leukocyte production (Rudolph & Baldus 2010), a recent prospective study of 667 subjects presenting to the emergency department (ED) with dyspnea suggests that it may be useful in risk stratification in patients with AHFS. In AHFS, patients with MPO levels >99 pmol/L are predicted to have a higher rate of an all-cause mortality in 1 year as compared with patients with MPO levels <99 pmol/L (Reichlin et al. 2010). Another study published in 2009 by Tang et al. (2009) proposes that in patients aged 65–75 years, increased systemic MPO at baseline without AHFS is associated with increased risk of developing heart failure over a 7-year period. This risk was determined to be greatest in patients without a history of diabetes mellitus, prior myocardial infarction, or other traditional risk factors of heart failure (Tang et al. 2009).

Biomarkers related to cardiac myocyte stress

In response to cardiac myocyte stress, many biological compounds are released. Some of these compounds, such as the natriuretic peptides, arginine vasopressin (AVP), and C-terminal provasopressin, adrenomedullin, soluble ST2, may be measured for the disease-specific monitoring of AHFS and are thus likely biomarkers of the disease.

B-natriuretic peptide and N-terminal pro-B-natriuretic peptide

The natriuretic peptides, B-natriuretic peptide (BNP) and N-terminal pro-B-natriuretic peptide (NT-proBNP),

are biomarkers of AHFS due to their recognized performance in helping to maintain volume homeostasis (Suttner & Boldt 2004; Dieplinger et al. 2009). BNP and NT-proBNP are cleaved from the same parent molecule, prohormone Pro B-natriuretic peptide (Ruskoaho 2003), which is synthesized in both atrial and ventricular myocytes (Goetze 2004). *In vitro* studies suggest that these compounds exert their regulatory action by affecting natriuresis and diuresis (Beltowski & Wojcicka 2002), causing vasodilation (Suttner & Boldt 2004), and modulating of the sympathetic nervous system (Nishikimi et al. 2006). Natriuretic peptides are secreted from storage granules in response to cardiac wall stretch (Suttner & Boldt 2004) and their release is specifically induced by norepinephrine (NE), epinephrine, acetylcholine, AVP, endothelin-1 (ET-1), angiotensin II, and other inflammatory cytokines (Ruskoaho 2003; Suttner and Boldt 2004). Because heart failure is marked by chronic wall stretch due to an increase in intravascular volume, elevated levels of natriuretic peptides have been purported to reflect the severity (Ruskoaho 2003; Lee & Tkacs 2008; Dieplinger et al. 2009). Though in theory natriuretic peptides seem like ideal biomarkers, their actual value continues to be debated in literature (Hunt et al. 2009) primarily because having high levels may not only be due to AHFS, but also may be due to other diseases that cause inflammation or infection (Jensen et al. 2010). Additionally, some caution must be exercised in using BNP, and to a lesser degree, NT-proBNP levels diagnostically in AHFS as these markers have reduced sensitivity in patients with increased body mass index (Krauser et al. 2005).

Levels of BNP are important in the diagnosis of AHFS (de Sa & Chen 2008). For example, the Breathing Not Properly study established that plasma levels of this biomarker could be used to determine whether patients presenting to the ED with dyspnea was due to AHFS or other pulmonary causes. This study enrolled 1586 patients and suggested that patients with plasma BNP levels of greater than 100 pg/mL (sensitivity 90%, specificity 76%) likely had AHFS as the etiology of their dyspnea (Maisel et al. 2003). Although an important diagnostic indicator, other work suggests that BNP is not as good of a prognostic indicator as one might anticipate. Singer et al. (2009) illustrate that serial BNP measurements do not predict length of stay, mortality, and readmission rate in patients with AHFS. Additionally, BNP levels show a strong inverse association with estimated glomerular filtration rate (eGFR) in patients with AHFS and study suggests that eGFR is a significant confounder of BNP when a patient's renal status is compromised (Wiley et al. 2010). Though despite these results, BNP (greater than 100 pg/mL) levels have been shown to be both strong independent predictors of adverse events such as hospitalization, myocardial infarction, stroke, or mortality (Grewal et al. 2008).

Due to the longer half-life of NT-proBNP in comparison to BNP (Ruskoaho 2003), NT-proBNP levels are subject to less hour-to-hour variation, perhaps making it a more reliable assay in the diagnosis of AHFS (Wiley et al. 2010) (Steinhart, Thorpe, et al 2009). If NT-proBNP level is less than 300 pg/mL then there is 98% negative predictive value to exclude AHFS (Januzzi et al. 2006).

NT-proBNP also has promise as a predictor of poor prognosis in AHFS. Grewal et al. (2008) propose that, in patients with preserved left ventricular ejection fraction, increased plasma NT-proBNP (greater than 600 pg/ml) is a strong independent predictor of adverse events such as hospitalization, cardiac events, and death and is considered to be an overall superior prognostic tool for ADHF than other more traditional methods of evaluation. The International Collaborative of NT-proBNP study proposes age-related cut points of NT-proBNP related to the poor prognosis of AHFS. These cut points are as follows: 450 pg/mL for age <50 years, 900 pg/mL for age 50–75 years, and 1800 pg/mL for age >75 years. Further, in patients with established AHFS, an NT-proBNP concentration of >5180 pg/mL is a strong predictive of death by 76 days (Januzzi et al. 2006). Additionally, in the Pro-B Type Natriuretic Peptide Outpatient Tailored Chronic Heart Failure (PROTECT) study, serial measurements of BNP and NT-proBNP were measured with the goal of clarifying their role in guiding AHFS care. The study concluded that targeting traditional therapy to decrease serial measured NT-proBNP levels to less than 1000 pg/mL improves patient outcomes for a 1-year period of follow-up (Bhardwaj et al. 2010).

AVP and C-terminal provasopressin

Given the role of volume overload and pulmonary congestion in AHFS (Ali et al. 2007), AVP, synthesized by the hypothalamus and secreted by the posterior pituitary, has been implicated as a biomarker of importance. AVP has been shown to contribute to fluid retention, vasoconstriction, platelet aggregation, and hyponatremia (Lee et al. 2003; Cawley 2007). Normally, AVP upregulation in conjunction with the renin–angiotensin–aldosterone system is, at least in part, induced through activation of stretch receptors in the cardiac atria. In AHFS, dysregulation of these systems, which further induces fluid retention and hyponatremia, unfavorably affect systemic hemodynamics and cardiac remodeling (Lee, Watkins et al. 2003). Specifically, AVP has been implicated in the progression of left ventricular dysfunction by increasing wall stress and supporting ventricular hypertrophy (Serradeil-Le Gal, Wagnon et al. 2002). AVP has limited clinical application in the prognosis and risk stratification of AHFS due to assay instability and rapid clearance (Xue, Shah et al. 2010). However, several vasopressin receptor antagonists, conivaptan (Wada et al. 2002; Ali et al. 2007), tolvaptan (Gheorghiade et al. 2006), and lixivaptan (Abraham et al. 2006), have been approved for heart failure therapy, this marker is being explored for its ability to predict response to therapy (Goldsmith 2006; Cawley 2007; Kumar & Mather 2009).

C-terminal provasopressin (copeptin), the C-terminal segment of provasopressin, is a stable, sensitive, and reliable marker of AVP plasma concentrations (Morgenthaler et al. 2007). Given the difficulty measuring AVP in serum, copeptin may be a more useful biomarker in determining risk stratification and prognosis of AHFS as AVP levels are likely associated with poor prognosis (Xue et al. 2010). In the BACH trial of 1600 patients with undifferentiated acute dyspnea, the investigators found an increased 90-day mortality in patients with elevated copeptin (Xue et al. 2010). Previous studies suggest copeptin is associated with left ventricular dysfunction, and cardiac remodeling (Kelly et al. 2008). Newer studies confirm its presence in AHFS and suggests that it, in conjunction with other biomarkers, may be helpful in AHFS prognosis (Stoiser et al. 2006; Katan et al. 2008; Xue et al. 2010) and mortality in patients with symptoms of AHFS after myocardial infarction (Voors et al. 2009).

Adrenomedullin and proadrenomedullin molecule

Adrenomedullin (ADM) is an endogenous vasoactive peptide that causes vasodilation (Ishiyama et al. 1993), stimulates diuresis (Jougasaki et al. 1997) and produces significant hemodynamic effects, which include increased cardiac output and decreased afterload (Lainchbury et al. 2000). Several previous studies confirm that ADM levels are increased in chronic heart failure (Jougasaki et al. 1995; Pousset et al. 2000; Nishikimi et al. 2001; Oie et al. 2010). Nishida et al. (2008) suggest that in high-risk patients, those with known stable coronary artery disease, diabetes mellitus, or hypertension, plasma ADM is a powerful independent predictor of future cardiovascular events such as stroke, transient ischemic attack, and AHFS requiring hospitalization. Elevated plasma ADM levels may also be an independent predictor of prognosis in mild-to-moderate chronic heart failure (Pousset et al. 2000). In the normal human heart, increased ADM causes a positive inotropic effect. Despite significantly elevated circulating ADM levels, AHFS subjects have a decreased atrial and ventricular responsiveness to ADM. (Bisping et al. 2007). Because of this unresponsiveness, it may be possible that ADM as a biomarker could be used as a biomarker not just related to the monitoring of cardiac stress, but also in the conversion from AHFS to chronic heart failure.

Similar to the AVP/copeptin model, the mid-regional fragment of the pro-ADM–molecule (MR-proADM) is far more stable than ADM itself (Potocki et al. 2009). In one prospective study of 287 subjects, Potocki et al. (2009) suggest that MR-proADM provides sufficient evidence to risk stratify patients presenting to the ED with acute dyspnea, related to AHFS or otherwise. Specifically, MR-proADM was a strong predictor of mortality in patients with AHFS (Potocki et al. 2009). Although study of MR-proADM in AHFS has been limited to this point, further study is warranted as this molecule has promise as a potential biomarker of AHFS.

Soluble ST2 receptor

The *ST2* gene, a member of the IL-1 receptor family, is quantifiably measured in the serum as soluble ST2 receptor (ST2) and is detected in the peripheral circulation of patients following cardiac stress such as myocardial infarction and AHFS. Soluble ST2 levels have been shown to be inversely correlated with ejection fraction (Weinberg et al. 2002; Rehman et al. 2008). Rehman et al. (2008) hypothesize that in the normal heart, ST2 signaling works with IL-3 to prevent pressure overload and fibrosis in the myocardium. They infer that in AHFS, overabundance of soluble ST2 levels paradoxically inhibits IL-3 binding to the ST2 ligand (the transmembrane receptor form of ST2) thereby resulting in unwarranted cardiac fibrosis and worse outcomes.

Soluble ST2 has been studied in chronic heart failure. The results of one multicenter 2003 trial shows that in a 2-week period following initial enrollment, an increase in soluble ST2 levels independently predicted the likelihood of mortality or need for transplantation (Weinberg et al. 2003). Newer literature, such as the published Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department (PRIDE) study, suggests that concentrations of soluble ST2 are higher (0.50 ng/mL), on average, in patients with AHFS than those without (0.15 ng/mL). This study also purports that AHFS patients with higher concentrations of ST2 at time of hospitalization had an increased rate of 1-year mortality and specifies that AHFS patients with ST2 concentrations of greater than or equal to 20 ng/mL is strongly predictive of death at 1 year (Januzzi et al. 2007). These results are confirmed by additional studies published in 2008 (Rehman et al. 2008; Mueller et al. 2008).

Biomarkers associated with neurohormone regulation

Neurohormones play an intricate role in AHFS and have substantial implications in the progression of disease pathogenesis (Cohn et al. 1984; Francis et al. 1984; Kaye et al. 1995; Kedzierski & Yanagisawa 2001; Latini et al. 2004; Ng et al. 2004).

NE

In early heart failure, the sympathetic nervous system plays an appropriate compensatory role by increasing heart rate and cardiac contractility, causing vasoconstriction, and increasing salt and water retention with the aims of maintaining left ventricular output, maintaining a stable blood pressure, and enhancing cardiac filling (Floras 1993). As heart failure progresses, however, long-term adverse effects of these compensatory mechanisms prevail. Consideration has been given to not only afferent, but also efferent and central neural pathways affecting sympathetic nervous system modification (Binkley

et al. 1991; Floras 1993) with specific focus on selective increase in plasma NE (Rundqvist et al. 1997).

High plasma NE levels have long been associated as a risk factor in the prognosis of heart failure (Cohn et al. 1984; Francis et al. 1984; Latini et al. 2004; Kaye et al. 1995). More recent studies have looked specifically at transcardiac increase of NE, by measuring its values in the aortic root and coronary sinus, and have confirmed its importance in the prognosis of congestive heart failure (Kaye et al. 1995; Tsutamoto et al. 2008). Ando et al. (2010) suggest the use of metaiodobenzylguanidine to measure NE spillover in blood during exercise to assess the severity of heart failure. Their study showed that increases in metaiodobenzylguanidine were correlated with increases in NYHA classification. Further research has demonstrated that increases in cardiac-specific sympathetic activation are more evident in women than men (Mitoff et al. 2010). Though much of the current literature focuses on NE as a biomarker in chronic heart failure, its further use in monitoring of AHFS is worth further consideration.

ET-1

ET-1 is released by the endothelium (Kedzierski & Yanagisawa 2001) in response to angiotensin II, inflammatory mediators, and vascular shear stress (Gray & Webb 1996). This substance has been shown to upregulate the production of ROS (Kubin et al. 2011), act as a potent vasoconstrictor (Gray & Webb 1996), and cause electrical remodeling in the heart (Mueller et al. 2011), physiologic alterations that may all contribute to the development of AHFS. Other evidence suggests that ET-1 contributes to increases in ventricular remodeling and vascular inflammation and resistance (Pacher et al. 1996).

Several previous studies have correlated circulating ET-1 with the severity of symptoms in chronic heart failure patients with and without pulmonary hypertension (Cody et al. 1992; Pacher et al. 1996). Similar to research with NE, ET-1 has not be significantly studied in AHFS and it is not yet being used clinically. However, Tang et al. (2010) confirm that ET-1 levels have a significant association with severity in chronic systolic dysfunction and predict long-term adverse clinical outcomes in heart failure. Because of the potential highlighted by these studies in chronic heart failure, further study regarding the use of ET-1 in AHFS is warranted in the near future.

Urocortin-1

Urocortin-1 (UCN-1), a vasoactive peptide and member of the corticotrophin-released factor family (Burnett 2005) that binds to corticotrophin-releasing factor receptors concentrated in the left ventricle (Kimura et al. 2002). In animal models, an increase in UCN-1 has been shown to provoke an increase in heart rate, cardiac output, and coronary blood flow in a dose-dependent manner (Parkes et al. 1997). At very high levels, UCN-1 produces a somewhat contradictory overall effect on the cardiovascular system, causing vasodilation and decreases in total peripheral resistence (Rademaker et al. 2005).

Like other biomarkers associated with neurohormone regulation, levels of UCN-1 have been studied as related to the prognosis of chronic heart failure. One study by Tang et al. suggests that UCN-1 levels have a significant association with disease severity in chronic systolic heart failure and further suggests that UCN-1 may independently predict long-term adverse clinical outcomes (Tang et al. 2010). Echoing these results, elevation in UCN-1 was shown to be positively associated with worse left ventricular diastolic activity and worse long-term clinical outcomes in patients with chronic heart failure (Burnett 2005; Wright et al. 2009; Tang et al. 2010). In 2009, Wright et al. proposed that an elevation in UCN-1 levels was positively correlated with severity of cardiac dysfunction independent of age, history, previous myocardial infarction, diabetes, hypertension, and N-terminal proBNP levels (Wright et al. 2009). Given its potential in chronic heart failure, UCN-1 also warrants further investigation with regard to the prognosis of AHFS.

Conclusion

AHFS is complex both in its disease pathogenesis as well as impact on the cardiovascular, renal and neurohormonal systems. Given the increasing prevalence, morbidity, and costs associated with AHFS, continued collaboration between medical scientists and clinicians is needed to identify and investigate biomarkers that aid in the diagnosis, risk stratification, and prognosis of AHFS. Provided the complexity of this syndrome, it is likely that candidate biomarkers will most used in a panel format with selections from several of the pathophysiologic categories. The most mature and promising clinical assays in risk stratification of patients with AHFS include LP-PLA2, NGAL, cystatin C, PIP, BNP, NT-proBNP, MR-proADM, copeptin, soluble ST2 receptor, and ET-1.

Declaration of interest

The authors report no conflict of interest.

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