BIOMARKERS IN HEART FAILURE

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Cardiac biomarkers, including natriuretic peptides and troponins, have become widely used in the treatment of heart failure and acute coronary syndrome. As we learn more about the function of these markers, their use has begun to expand. We can now track and utilise natriuretic peptides throughout hospital admission to monitor progress of heart failure therapy. Troponins and natriuretic peptides can provide useful prognostic data and help stratify more high-risk patients. Novel biomarkers, such as ST2, can also aid in prognostication, and may be beneficial in guiding initiation of therapies that reduce cardiac remodelling, including beta-adrenergic receptor and mineralocorticoid receptor antagonists. Finally, procalcitonin can help distinguish dyspnoea secondary to heart failure from pulmonary infection and can help guide use of antibiotics in patients with heart failure who present with shortness of breath.

Heart failure (HF) is the leading cause of mortality in the United States (Lloyd-Jones et al. 2009). Advances in medical therapies have improved outcomes for patients with heart failure with reduced ejection fraction (HFrEF), but these patients still account for over 1 million hospitalisations annually and generate billions of dollars in healthcare costs (Mozaffarian et al. 2015; Go et al. 2014; Ambrosy et al. 2014). Cardiac biomarkers are noninvasive and inexpensive to measure, and they allow for more accurate and rapid diagnosis of acute heart failure exacerbation in the emergency department (ED), which can reduce rates of hospitalisation and health care costs. Cardiac biomarkers can also improve prognostication and help guide medical therapy for heart failure and this therapeutic guidance may improve patient morbidity and mortality. In this review, we will examine two of the most commonly used cardiac biomarkers in the treatment of heart failure: the natriuretic peptides (NPs) and troponins. We will also discuss two novel cardiac biomarkers: ST2, a marker of cardiac remodelling and fibrosis with prognostic value, and procalcitonin, a marker of inflammation that can help guide treatment of bacterial infections.

Natriuretic Peptides

Brain or B-type natriuretic peptides (BNPs) are proteins synthesised by cardiac ventricular myocytes in response to mechanical stretch (Yasue et al. 1994; Yoshimura et al. 1993). At the cellular level in the setting of volume overload, mechanical stretch on cardiomyocyte membranes activates downstream transcription and translation of a 134 amino acid precursor peptide pre-proBNP (Sudoh et al. 1989). This biologically inactive protein undergoes enzymatic cleavage twice: first producing $proBNP_{1\text{-}108}$, and with a second cleavage producing $BNP_{1\text{-}32}$ (the biologically active carboxy-terminal peptide) and the inactive amino terminal fragment NTproBNP (**Figure 1, Left Panel**). Both peptides are secreted in equimolar amounts into circulation (Daniels and Maisel 2007; Nakagawa et al. 2009; Kojima et al. 1989). Unlike the other natriuretic peptides (Atrial and C-type natriuretic peptides), BNP is minimally stored. It is synthesised and directly secreted in large bursts from the ventricular myocardium (Maisel et al. 2002). NPs act on membrane-bound natriuretic peptide receptors (NPRs) in target tissues to induce vasodilation, diuresis, natriuresis and inhibition of the renin-angiotensin-aldosterone system (RAAS) system. These actions act to reduce cardiac preload and afterload (Daniels and Maisel 2007). BNP is cleared from circulation by binding to NPRs, by degradation by circulating neutral endopeptidases, and to a lesser degree through renal excretion (Daniels and Maisel 2007).

Clinical Use of Natriuretic Peptides

It is now a Class I indication in the American Heart Association / American College of Cardiology (AHA/ACC) guidelines for management of HF that BNP should be measured on hospital admission for all suspected cases of acute HF exacerbation (Yancy et al. 2013). ED providers should utilise BNP levels for risk stratification, with BNP < 400 pg/mL indicating a lower-risk patient that could be safely discharged from the ED with close outpatient follow-up (Maisel et al.

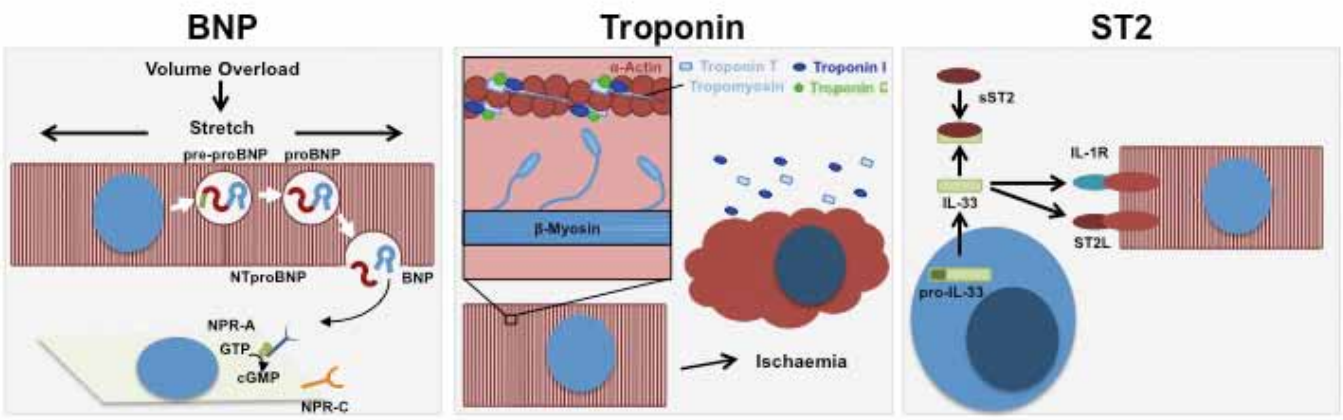

Figure 1. Cardiac Biomarker Production and Signalling

Left Panel: Brain or B-Type natriuretic peptide (BNP) is produced by cardiac myocytes in response to mechanical stretch during volume overload. The peptide is first translated as the precursor peptide pre-proBNP, which is cleaved to proBNP, and a final enzymatic cleavage produces two excreted products: NTproBNP and BNP. **Middle Panel:** Cardiac troponins are calcium-handling proteins associated with the thin filaments (alpha sarcomeric actin) of the myocyte contractile apparatus. During prolonged ischaemia, such as myocardial infarction, myocytes undergo widespread necrosis and release their intracellular proteins (troponin I and T) into circulation. **Right Panel:** ST2 is produced by myocytes and fibroblasts in response to mechanical stress. IL-33 is a cardioprotective cytokine that binds IL-1 receptors on the cardiac myocyte and fibroblasts and has antihypertrophic and antifibrotic affects. Soluble ST2 (sST2), which is overexpressed during heart failure, acts as a decoy receptor for IL-33, blocking its cardioprotective effects.

2015; Maisel et al. 2008). Several clinical trials have demonstrated the utility of BNP measurement in the ED (**Table 1**). In the 2002 Breathing Not Properly multinational study of 1586 patients presenting to the ED with dyspnoea, measurement of serum BNP had higher accuracy in diagnosing heart failure than the ED physicians (Maisel et al. 2002). Using a cutoff of 100 pg/mL, serum BNP was 90% sensitive and 76% specific for heart failure in this trial. The 2005 PRIDE study similarly demonstrated that NT-proBNP was highly sensitive and specific at diagnosing heart failure among 600 ED patients presenting with dyspnoea (Januzzi et al. 2005). This study suggested a cutoff NT-proBNP level of 300 pg/mL to rule out heart failure in these patients. Other studies have demonstrated how measurement of BNP (Mueller et al. 2004) and NT-proBNP (Moe et al. 2007)) in the ED can reduce hospitalisation rates, median length of stay, and thus reduce overall healthcare costs.

BNP has demonstrated prognostic value in both acute (Doust et al. 2005; Maisel et al. 2004) and chronic HF (Berger et al. 2002; Anand et al. 2003), with elevated BNP levels associated with worse outcomes, greater morbidity and higher mortality (**Table 1**). In both the acute and chronic setting, for every 100 pg/mL increase in BNP, there is a 35% increase in risk of death (Doust et al. 2005). Elevated BNP levels in the ED patient should be considered relative to their last baseline outpatient BNP or from prior to discharge from a previous hospitalisation (Maisel et al. 2015). It may not be necessary to trend NPs daily during the hospitalisation, but serial measurements should be considered in patients who are not clinically improving. BNP values should decrease with diuresis, as studies have demonstrated that in acute decompensated heart failure (ADHF), treatment-related decreases in pulmonary capillary wedge pressure (PCWP) are correlated with a drop in NP levels (Kazanegra et al. 2001). Additionally, failure of NP levels to decrease during a hospitalisation is associated with worse prognosis (Bettencourt et al. 2002; Cheng et al. 2016).

In severely volume-overloaded patients, BNP may not immediately decrease, because fluid volume is initially diuresed primarily from interstitial tissues. So in a severely volume overloaded person, they may diurese several litres initially from their lower extremity or pulmonary interstitium without producing any change in intravascular volume or preload (Wettersten and Maisel 2016). As such, their BNP may not begin to decrease until several days into the hospitalisation when diuresis has begun to affect intravascular volume and cardiac preload. Once intravascular volume and preload begin to decrease, ventricular stretch lessens and BNP production by strained cardiac myocytes begins to decline. With continued diuresis, serum BNP levels will decline towards their baseline/outpatient values. BNP levels should be measured in all patients prior to discharge, as elevated serum BNP at discharge is associated with worse outcomes, including increased readmission rates and mortality, regardless of presenting BNP levels (Dokainish et al. 2005; Logeart et al. 2004). This pre-discharge BNP level may also be used to monitor patients at subsequent outpatient follow up visits (Maisel et al. 2015; Wettersten and Maisel 2016; Maisel 2006).

Caveats of BNP Interpretation

Several factors can cause elevated baseline BNP and NT-proBNP levels, including age (Redfield et al. 2002; Wang et al. 2002; Costello-Boerrigter et al. 2006), female gender (Redfield et al. 2002; Wang et al. 2002; Costello-Boerrigter et al. 2006), and renal dysfunction (Tsutamoto et al. 2006). The higher levels of circulating NPs at baseline with advanced age are independent of age-related diastolic dysfunction (Redfield et al. 2002), and may be due to age-related reduction of NPRs, which results in decreased clearance of circulating NPs (Daniels and Maisel 2007). In these studies, age-matched cohorts demonstrated that BNP and NT-proBNP levels are higher in women than men at any age (Redfield et al. 2002; Wang et al. 2002). Several researchers have proposed that oestrogen levels may be involved, as women on hormone replacement therapy (HRT) had higher BNP levels than women not on therapy (Redfield et al. 2002), although oestrogen replacement had only minimal effects on NT-proBNP levels in this same study (Costello-Boerrigter et al. 2006).

Table 1. Clinical Evidence for Use of Biomarkers in Heart Failure

	Trial Name	Methods/Results
BNP	Breathing Not Properly (BNP) (Maisel et al. 2002)	BNP levels improved accuracy in diagnosing HF exacerbation in ED patients presenting with acute shortness of breath (n=1586).
	B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) (Mueller et al. 2004)	Single BNP measurement by ED physicians was associated with 10% decrease in hospital admission and decreased median length of stay.
	Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) (Januzzi et al. 2005)	NT-proBNP levels were sensitive and specific for diagnosing HF exacerbation in 600 ED patients with dyspnoea using a cutoff of 300 pg/mL.
	Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) (Moe et al. 2007)	NT-proBNP had similar improvements in diagnosis and cost savings to BNP.
	Berger et al. (2002)	BNP > 130 pg/mL in patients with chronic HF had higher rates of sudden cardiac death.
	Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) (Maisel et al. 2004)	Elevated BNP level was strong predictor of 90-day outcome (CHF visits, admissions and mortality) in ED patients with dyspnoea.
ST2	Valsartan Heart Failure Trial (Val-HeFT) (Latini et al. 2007)	4053 patients with stable/chronic HF underwent serum analysis for cTnT (10.4% positive) or hsTnT (92.0% positive). Elevated troponins were associated with increased risk of death with both assays, and with hsTnT proving more sensitive and retaining prognostic value.
	Acute Decompensated Heart Failure National Registry (ADHERE) (Peacock et al. 2008)	Troponins were measured in 84,872 patients hospitalised for acute decompensated HF; 4,240 had positive troponins on admission, and this group had lower blood pressure on admission, lower EF and higher in-hospital mortality.
	Xue et al. (2011)	144 patients admitted for acute HF were followed from admission until 90 days post-discharge and had serial troponins and BNPs monitored. Elevated troponin was associated with increased mortality and risk of readmission, even if BNP was low at discharge.
	Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) (Felker et al. 2012)	Troponin I measured in 808 patients hospitalised for ADHF. Elevated troponins were associated with increased length of stay and worsening HF during index hospitalisation, but did not predict worse long-term outcomes (at 30 or 180 days post-discharge).
	Pascual-Figal et al. (2012)	Compared hsTnT to standard cTnT and found similar nearly all patients (98%) had +hsTnT (only 56% had +cTnT), n=202. Elevation of either troponin predicted risk of death.
	Atherosclerosis Risk in Communities (ARIC) (Hoogeveen et al. 2011)	9698 patients age 54-74 in general population who had no known underlying CHD, stroke or HF had hsTnT, BNP and CRP measured. hsTnT was associated with increased risk of CHD, fatal CHD and HF. hsTnT was equally predictive of HF as NT-proBNP.
	Atherosclerosis Risk in Communities (ARIC) (Nambi et al. 2013)	Both hsTnT and NT-proBNP had significant value in predicting HF risk in general population over 10 year follow-up, and combining the two markers had the highest sensitivity at predicting development of HF.
Procalcitonin	Daniels and Bayes-Genisal (2014)	Patients admitted for ADHF with ST>35 ng/mL should receive closer monitoring. ST2 has less variation over time and varies less than BNP relative to age, gender, BMI and renal function.
	Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department (PRIDE) (Januzzi et al. 2007)	ST2 levels were elevated in hospitalised HF patients, and ST2 levels correlate with mortality.
	Gaggin et al. (2013)	Patients with elevated ST2 should have beta blockers maximised to reduce cardiac remodelling.
	Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) (Maisel et al. 2014)	Patients with elevated ST2 should have MRAs maximised to reduce cardiac remodelling.
Troponin	Assicot et al. (1993)	In 79 children (newborn-12 years), elevated PCT was associated with severe bacterial infections, and serum PCT decreased rapidly with antibiotic therapy. PCT was normal or only mildly elevated in patients with viral infections or with peripheral bacterial colonisation.
	Gendrel et al. (1998)	CSF was analysed from 23 children hospitalised for bacterial meningitis and 51 patients hospitalised for viral meningitis, and PCT was elevated in bacterial but not viral infections. PCT dropped to undetectable levels with antibiotic treatment in the bacterial meningitis group.
	Moosig et al. (1998)	Study of 26 patients with granulomatosis with polyangitiis, who had serum taken during active vs inactive disease states. Slight PCT elevations were detected during active disease state. In patients with inactive disease, PCT levels correlated with other inflammatory markers (ESR, CRP, sIL-2, ANCA) suggesting that in inactive disease, PCT correlates with bacterial infections.
	Muller et al. (2000)	Procalcitonin was most reliable marker of infection in 101 ICU patients compared to CRP, IL-6 and lactate. PCT was 89% sensitive and 94% specific for diagnosing sepsis, and PCT elevation was associated with poor prognosis.
	Schwarz et al. (2000)	Procalcitonin was elevated in patients with bacterial meningitis and not in patients with abacterial (viral or aseptic) meningitis. PCT sensitivity of 69% at identifying bacterial meningitis.
	Wang et al. 2014	HF patients have a higher serum PCT than healthy controls. Patients with HF and bacterial infections had the highest serum PCT levels in this study, but the high baseline PCT observed in HF patients complicates the use of PCT as an infectious biomarker in the HF population

ADHF acute decompensated heart failure ANCA antineutrophil cytoplasmic antibodies BNP Brain or B-Type natriuretic peptide CHD coronary heart disease CHF congestive heart failure CRP C-reactive protein cTnT cardiac troponin T ESR erythrocyte sedimentation rate HF heart failure hsTnT high sensitivity troponin T MRA magnetic resonance angiogram PCT Procalcitonin

The relationship of BNP to renal function is more complex and likely multifactorial, as BNP is mostly taken up by NPRs or enzymatically degraded in serum rather than cleared renally (McCullough et al. 2003). Older patients with renal dysfunction may have chronically higher intravascular volume, increased ventricular strain and reduced glomerular filtration, which could all contribute to the elevated BNP levels observed in patients with chronic kidney disease.

Low BNP levels may result in obese patients and during early flash pulmonary oedema. The negative correlation between obesity and baseline serum BNP levels is well documented (Wang et al. 2002; Wang et al. 2004; Mehra e al. 2004; Daniels et al. 2006), but the exact mechanism remains unclear. Some have hypothesised that adipocytes have increased concentration of NPRs, which could increase BNP clearance (Sarzani et al. 1996), but others have demonstrated a positive correlation between BNP levels and lean mass rather than fat mass (Das et al. 2005). There is conflicting evidence as to whether NT-proBNP levels are similarly low in obese patients, which could be explained by the fact that NT-proBNP is not cleared through NPRs. Although BNPs are low in obese patients, they still retain their diagnostic and prognostic values if measured relative to a known baseline (Daniels and Maisel 2004). BNP levels may similarly be low early in flash pulmonary oedema. This is due to the insufficient time for BNP gene expression and translation in the setting of rapid interstitial fluid accumulation (Yoshimura et al. 1993).

Troponins

Troponins are calcium-handling proteins integral to excitation-contraction coupling in the cardiac myocyte (**Figure 1, Middle Panel**) (Sharma et al. 2004; Parmacek and Solaro 2004). Cardiac troponins and other intracellular myocyte proteins are released into circulation after myocardial infarction, in which prolonged ischaemia resulting from coronary artery occlusion causes myocyte necrosis. Detection of cardiac troponins in the blood (Troponin T or I) is useful for diagnosis of acute coronary syndrome (ACS), as troponin I has not been identified in tissues outside the myocardium (Bodor et al. 1995), and troponin T is only minimally expressed in skeletal muscle tissues (Ricchiuti et al. 1998). As these serum markers are specific for myocardial damage (Collinson et al. 2001), they are now considered the gold standard for diagnosis of ACS (Braunwald et al. 2000; Bertrand et al. 2000).

Clinical Scenario

A 79-year-old male with history of heart failure presents to the ED with shortness of breath. The man has known ischaemic cardiomyopathy secondary to coronary artery disease and prior non-ST segment elevation myocardial infarction (NSTEMI), with last known left ventricle ejection fraction (LVEF) of 40% (measured on echocardiography in the last year). His heart failure has been medically managed with a beta-blocker and angiotensin converting enzyme (ACE)-inhibitor for the last 2 years. He says his symptoms began 2 days ago and have become progressively worse. He is unable to lie flat to sleep at night and he is exhausted. He also reports subjective fevers, non-productive cough and swelling around his ankles. He denies chest pain at rest or on exertion. On physical exam, the patient appears uncomfortable, he is tachycardic to the high 90s and afebrile, blood pressures are normotensive and he also appears to have increased work of breathing. His oxygen saturation is 95% on 4L O2 via nasal cannula. He has bibasilar lung crackles, JVP to 10 cm, and 3 mm of lower extremity pitting oedema below the knees bilaterally. Initial CXR shows cephalisation and bibasilar opacifications consistent with pleural effusions, but a consolidative infectious process cannot be ruled out. ECG demonstrates sinus tachycardia with heart rate of 95 bpm, evidence of old inferior wall ischaemia (pathologic Q waves in leads II, III, and aVF that are unchanged from prior ECGs) and no new signs of cardiac ischaemia.

The patient is admitted to the inpatient cardiology service, and initial cardiac biomarker labs are drawn. The patient's BNP is 849 pg/mL in the emergency room, and it was 350 pg/mL at clinic visit 6 months prior. With the elevated BNP and signs of volume overload on exam, diuresis was initiated using intravenous furosemide. Initial hsTnT is also slightly positive at 0.10 mg/dL. Initial ST2 came back at 40 ng/mL. Because initial troponin and ST2 were elevated, the patient is admitted to the Cardiac Critical Care Unit for closer observation, as elevation of BNP, hsTnT and ST2 are associated with worse prognosis. Serum procalcitonin drawn in the ED also came back elevated at 1.8 ug/L, suggesting underlying bacterial infection. Given his clinical history of productive cough, community-acquired pneumonia is strongly suspected even though the patient was initially afebrile and did not have clearly visible consolidations on chest x-ray, and the patient was started on intravenous ceftriaxone.

Serial troponin measurements at 12 and 24 hours after initial presentation are subsequently negative, and it was determined that the patient did not have acute coronary syndrome. As the patient is not at risk of ACS and troponins have normalised, he was downgraded to an intermediate care unit on the cardiology service. After diuresing 2 L of fluid in the first 24 hours, BNP measurement was repeated, and was still elevated at 810 pg/mL. Although the patient had diuresed well, the BNP is likely still elevated because the 2 L lost represents interstitial fluid volume, and the patient is still likely intravascularly volume-overloaded (and thus BNP is still being actively produced in response to ventricular volume overload and myocyte stretch at the cellular level).

Over the next 4 days, the patient diuresed a total of 8.5L in the hospital, he now has only trace pedal oedema, he is breathing comfortably on room air and he is feeling much better. Sputum cultures from admission grew *Strep. pneumoniae*. Cardiac biomarkers are repeated prior to discharge. BNP has dropped to 450 pg/mL, PCT is now undetectable on day 5 of IV ceftriaxone, and ST2 remains elevated at 38 ng/mL. A repeat echocardiogram done during this hospitalisation demonstrated an LVEF of 32% without new regional wall motion abnormalities. The decision was made to discharge the patient with antibiotics, and spironolactone 25 mg daily was added to his current heart failure regimen given his low EF. He was scheduled for follow-up in cardiology clinic in 2 weeks where his primary cardiologist will continue to monitor his BNP and ST2 levels for further optimisation of antihypertrophic medications (beta blockers and MRAs).

Clinical Utility of Troponins in Heart Failure

The AHA/ACC guidelines recommend checking cardiac troponins in patients presenting with acute heart failure, both for ACS rule out and risk stratification (Yancy et al. 2013). In patients presenting with exertional chest pain and dyspnoea, cardiac troponins must be trended over the first 24 hours of hospitalisation to rule out ACS. In patients with acute decompensated HF without ACS (diagnosed by symptoms, ECG changes, and trending cardiac markers), elevated troponins were highly prognostic in several studies (**Table 1**). Patients admitted for ADHF who had troponin elevation on admis-

sion had higher in-hospital mortality in the Acute Decompensated Heart Failure National Registry (ADHERE) trial (Peacock et al. 2008), with increased length of stay and worsening HF during admission in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial (Felker et al. 2012). Both the older cardiac troponin T detection assay (cTnT) and the newer high-sensitivity troponin T assay (hsTnT) have been shown to be useful for prognostication in patients admitted for ADHF. Troponin elevation is detected only in a minority of heart failure patients using the cTnT assay, but hsTnT can detect low concentrations of troponins in the majority of HF patients, and HF patients with elevations of either cTnT or hsTnT demonstrated increased risk of death (Pascual-Figal et al. 2012; Latini et al. 2007). Another study demonstrated that serial troponin measurement, in addition to serial BNP, can add prognostic value. Patients in this study with the highest serum troponins at discharge had increased mortality and higher risk of readmission (Xue et al. 2011). The Atherosclerosis Risk in Communities (ARIC) study evaluated the use of cardiac biomarkers at predicting risk of developing coronary heart disease and heart failure in a pool of 9698 patients without known CHD, stroke or HF. Patients in the general population with elevated hsTnT had significantly increased risk of developing CHD, fatal CHD and HF over 10 year follow-up, and hsTnT had equivalent predictive value as NT-proBNP for detecting development of HF (Saunders et al. 2011). In a follow-up study, the ARIC study authors demonstrated that in this same general population elevation of both hsTnT and NT-proBNP was even more prognostic for prediction of developing HF at 10 year follow-up than either marker individually (Nambi et al. 2013).

ST2

Growth STimulated expressed gene 2 (ST2) is a receptor for interleukin-33 (IL-33) that is expressed by myocytes and fibroblasts in response to mechanical stress. IL-33 is protective against myocardial hypertrophy and fibrosis in animal models of pressure overload (Schmitz et al. 2005; Kuball et al. 2005). ST2, expressed as membrane-bound (ST2L) or soluble (sST2) isoforms through alternative splicing (Kieser et al. 1995; Yanagisawa et al. 1992; Tominaga 1989), is overexpressed in HF, and sST2 acts as a decoy receptor that binds IL-33 and prevents its cardioprotective actions (Sanada et al. 2007; Weir et al. 2010). There are no prospective clinical trials that have examined the utility of ST2 as a clinical biomarker, but many retrospective and observational studies suggest its function as a prognostic indicator and for driving medical therapy.

Clinical Utility of ST2 in Heart Failure

Patients admitted to the hospital with ADHF should have an sST2 level drawn on admission, and patients with serum levels >35 ng/mL should receive closer monitoring, especially if other clinical biomarkers are elevated (i.e. BNP and troponins) (Daniels and Bayes-Genis 2014). In the Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) study, ST2 levels were increased in patients hospitalised for HF, and higher ST2 values were correlated with increased risk of death (Januzzi et al. 2007). Similarly to BNP and troponins, serial ST2 measurements during HF hospitalisation were predictive of mortality (Boisot et al. 2008; Anand and Rector 2014). In several studies (**Table 1**), ST2 has demonstrated some advantages over BNP. There is less variation in sST2 levels relative to age, gender, BMI and renal function, and there is less intra-individual variation in ST2 levels over time (Daniels and Bayes-Genis 2014). Additionally, ST2 is the strongest predictor of mortality both in acute and chronic HF compared to all other biomarkers (Gaggin et al. 2014; Bayes-Genis et al. 2014). Because ST2 is an indicator of cardiac remodelling and fibrosis, antihypertrophic therapies with beta-blockers (Gaggin et al. 2013) and mineralocorticoid receptor antagonists (COACH Trial) (Maisel et al. 2014) should be initiated and maximised in HF patients with elevated ST2 levels.

Procalcitonin

In the critically ill patient, it is often difficult to determine if symptoms of the systemic inflammatory response are due to underlying infection or other aetiologies, and few early markers of infection have proved reliable. Procalcitonin (PCT) may be a useful marker of bacterial infection. Although the exact mechanism of PCT production is unknown, serum levels of the 116 amino acid peptide are increased in the setting of bacterial infection and sepsis (Schwarz et al. 2000; Assicot et al. 1993; Muller et al. 2000). Increased PCT levels can help differentiate between bacterial and viral infections (Gendrel et al. 1998) or between bacterial infection and disease flair of autoimmune disorders (Moosig et al. 1998). Additionally, procalcitonin levels were shown to be normalised in patients with bacterial infection as they were treated with antibiotics (Assicot et al. 1993).

Clinical Use of Procalcitonin in Heart Failure

In patients with a history of CHF presenting with dyspnoea, it is often initially unclear if respiratory symptoms are due to pulmonary oedema or underlying infection. Although many studies suggest PCT can be useful at distinguishing bacterial infection from heart failure exacerbation (**Table 1**), one study, however, did demonstrate that CHF alone could increase PCT levels independently from infection. It was thought to be due to increased endotoxin resorption in the small bowel in volume-overloaded patients, which can cause falsely elevated PCT in the serum, although patients with HF and underlying bacterial infections were found to have the highest PCT levels (Wang et al. 2014). Despite this study's results, there remains compelling evidence that in patients with acute heart failure exacerbation and elevated PCT levels, treatment with antibiotics results in better outcomes. ■

Abbreviations

ACS acute coronary syndrome
ADHF acute decompensated heart failure
BNP Brain or B-Type natriuretic peptide
cTnT cardiac troponin T
ED emergency department
HF heart failure
hsTnT high-sensitivity troponin T
NP natriuretic peptides
NPR natriuretic peptide receptors
NT-proBNP N-terminal pro b-type natriuretic peptide

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