



Monitoring of biomarkers in heart failure

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KEYWORDS

Heart failure;
Biomarkers;
Monitoring

The role of biomarkers is increasingly recognized in heart failure (HF) management, for diagnosis, prognostication, and screening of high-risk patients. Beyond natriuretic peptides and troponins, the utility of novel, emerging biomarkers is less established. This document reflects the key points of a Heart Failure Association of the European Society of Cardiology (ESC) consensus meeting on biomarker monitoring in HF.

Introduction

The role of biomarkers in heart failure (HF) is increasingly acknowledged. These cardiac markers are used as non-invasive way to assess the status of a patient with HF along with the possibility of monitoring changes induced by patient management.¹ Biomarkers can be used to assess to a variety of pathophysiological processes of relevance to the condition of a HF patient, such as fibrosis, inflammation, myocardial injury, and remodelling.² Specifically, monitoring of biomarkers in HF can be used to make an initial diagnosis, to aid in prognostic stratification, and to identify a patient's response to therapeutic intervention.^{1,3}

A number of HF-related biomarkers have been investigated in the setting of HF (see *Figure 1*). However, the reliability and clinical utility of most and the value of adding biomarker evaluation to routine HF care remains unclear. To review this area a multidisciplinary panel of the Heart Failure Association of the European Society of Cardiology (ESC) met to discuss the issues related to physiological monitoring of biomarkers in HF. The key points of that consensus meeting are described in this document.

Natriuretic peptides

The human natriuretic peptide system is complex. The following have been described: atrial natriuretic peptide

(ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide, and dendroaspis natriuretic peptide. In clinical monitoring most attention has been directed at BNP and N-terminal pro-BNP (NT-proBNP). These biomarkers are peptide hormones synthesized by the heart but also other organs. NP's are the most extensively studied biomarkers that have been used in HF management. As a result of myocardial stretch, the gene coding for BNP is activated and the pro-hormone pro-BNP1-108 is produced. This is cleaved to the biologically active BNP and the biologically inert but stable NT-proBNP1-76.⁴ In addition to inducing natriuresis NP's are vasodilatory via vascular smooth muscle relaxation and they are sympatho-inhibitory. Atrial natriuretic peptide is more rapidly cleared from the circulation and is now much less used in clinical practice. However, the ANP precursor hormone mid-regional pro A-type natriuretic peptide (MR-proANP) is more stable, and may be of more clinical utility as a result.

The latest ESC guidelines⁵ recommended the measurement of NPs to provide assistance in the diagnosis of HF in suspected patients. Levels of NPs should be measured as an initial diagnostic test, especially in the non-acute setting, when echocardiography is not immediately available.⁴ Indeed, increased plasma levels may help identify patients who need further cardiac investigation. Initial NP assessment is recommended in order to rule out HF, and not to ascertain diagnosis. Also, NPs (along with troponins, see below) can be used to identify patients at higher risk of cardiotoxicity and may be helpful in monitoring the use and dosing of cardiotoxic cytotoxics.⁴

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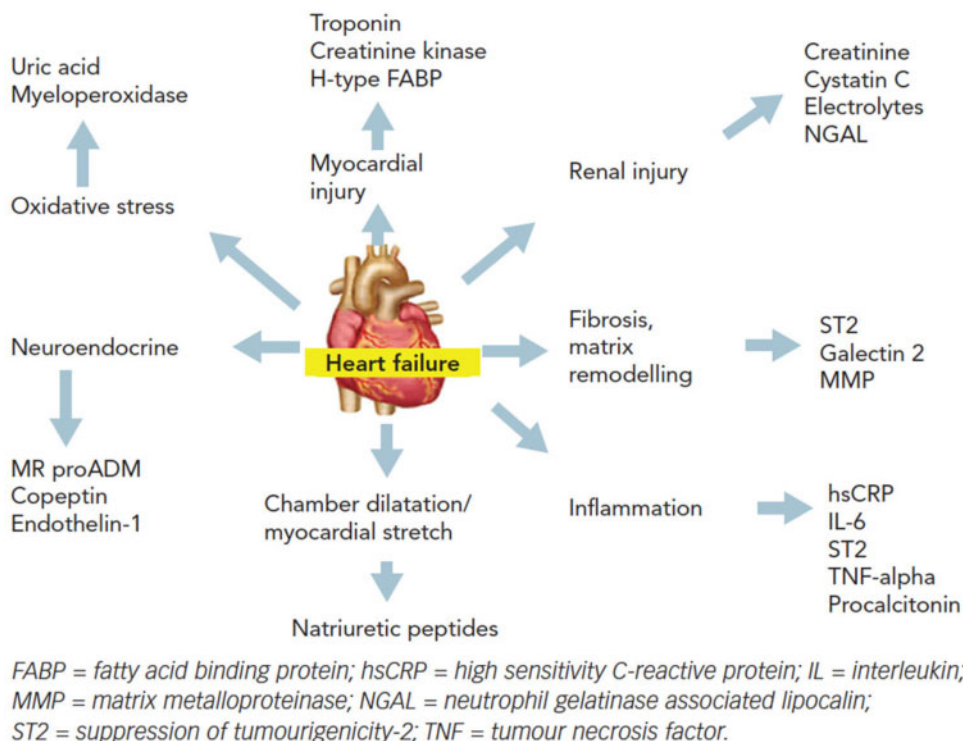


Figure 1 Potential biomarkers in the diagnosis and management of heart failure. Reproduced with permission from Nadar and Shaikh.⁴

Whether NPs are indicated to assist diagnosis and predict severity and prognosis of HF,² their utility in adjusting therapies is less well-established.⁶⁻⁸ Studies on NP-guided treatment in chronic HF have so far yielded promising but inconsistent results.⁹⁻¹¹ An individual patient meta-analysis¹² showed that NP-guided treatment of chronic HF reduced all-cause mortality in patients aged <75 years and overall reduced HF and cardiovascular hospitalization. On the other hand, the randomized GUIDE-IT trial¹³ investigating the effect of NT-proBNP-guided treatment strategy on hospitalization or cardiovascular mortality in high-risk patients with reduced ejection fraction, found that such a strategy was not more effective than standard treatment approach in improving outcomes. The study was therefore discontinued for futility.

Also, NP concentrations may be affected by cardiovascular and non-cardiovascular factors such as patient characteristics, comorbidities, and HF treatments.¹

Despite these limitations, NPs are cost effective, allow repetitive and precise measurements, provide pathophysiological and objective prognostic information, are useful to assist decision-making and enhance clinical care of HF.^{14,15} Integrated with the clinical assessment, serial monitoring of NPs is therefore indicated as part of the routine approach in HF management.

The increasing use of sacubitril/valsartan has meant that NT-proBNP is preferred for BNP levels can be increased after sacubitril/valsartan therapy because the sacubitril component blocks the breakdown of circulating BNP.

The plasma concentrations of NPs have been proven to be useful in the initial evaluation of a patient with possible

or suspected HF. It has a particular role in assessing the acutely dyspnoeic patient as well as the patient with insidious symptoms suggestive of HF in situation where the echocardiography is not immediately available. Elevated NPs can support a working diagnosis of HF, identifying those requiring further cardiac investigation; whereas patients with low values can be reliably considered not to have HF. Various levels have been used. For BNP the upper limit of normal in the non-acute setting is 35 pg/mL and for NT-proBNP it is 125 pg/mL; in the acute setting, however, values are higher and more commonly used are BNP – 100 pg/mL, NT-proBNP – 300 pg/mL, and MR-proANP 120 pmol/L. Below these thresholds ruling-out HF is reasonably reliable and can therefore aid clinical decision-making. In interpreting levels in patients with established HF, such as whether they are deteriorating or whether they are responding beneficially to changes in therapy, the levels of NP's can be useful, but routine measurement for these purposes has not been established as clinically beneficial on major outcomes in large scale RCT's. Other clinical features can affect the interpretation of NP levels such as features that elevate NP levels, such as renal impairment and atrial fibrillation and features that reduce them such as obesity.

Troponin in heart failure

Troponins are proteins involved in the regulation of cardiac muscle contraction.¹⁶

Different isoforms exist within cardiac and skeletal muscle. There is evidence that high-sensitive troponin (hs-troponin) is a marker of myocardial injury or necrosis in HF,

able to identify cardiotoxicity and consequently worse outcomes and prognosis.² In fact, measuring hs-troponin in patients at risk of HF has been found to provide additional predictive value.^{7,17} For these reasons, increased levels of hs-troponin have prognostic value for poor outcomes in both acute and chronic HF with reduced or preserved ejection fraction.^{15,18,19} In acutely decompensated patients, the ADHERE-HF study found increased cardiac troponin to be an independent predictor of in-hospital mortality.²⁰ Subsequent studies have confirmed the presence of high levels of hs-troponin in acute decompensated HF patients to be associated to all-cause mortality.²¹⁻²³ For these reasons, the 2016 ESC guidelines gave a Class Ic recommendation for the use of cardiac troponins in patients with suspected acute HF.⁴

Thus, hs-troponin is a promising biomarker in acute HF, being associated to disease severity, worse clinical outcomes, and increased mortality. Cardiac troponins are also useful for detection of acute coronary syndromes as a precipitant of acute HF. However, elevated concentrations of circulating cardiac troponins do not necessarily prove an ischaemic aetiology for the majority of patients with AHF, even without evident myocardial ischaemia. Troponins can also aid risk stratification in acute pulmonary embolism as a differential diagnosis of acute HF.

Routine monitoring of troponin levels to aid management of chronic HF has not, however, been shown to improve major clinical outcomes.

Soluble suppression of tumorigenesis-2

Suppression of tumorigenesis-2 (ST2) isoforms are markers of left ventricular hypertrophy, fibrosis and ventricular remodelling,²³ all of which are key processes in the pathophysiology of HF.² Soluble ST2 (sST2) is known to be a marker of inflammation and haemodynamic stress as well as cardiomyocyte strain. It is little affected by age, renal function, and body mass.² sST2 is a predictor of adverse clinical outcomes within a HF population.²⁴ Several studies have shown that elevated sST2 levels are associated with an increased risk of developing HF, greater disease severity, and a worse prognosis.²⁵⁻²⁸

For these reasons, sST2 may be potentially used for additive risk stratification beyond the NPs.²⁹ However, caution is needed as this marker is not HF-specific³⁰ as other pathological processes may lead to sST2 rises.²³

Multimarker approach

A multimarker approach incorporates the simultaneous assessment of several biomarkers with the aim of identifying the activity of multiple different pathophysiological pathways and thereby provide integrated information concerning the state of the patient. There is evidence that this combined strategy leads to improved measurement of HF risk compared to traditional risk scores.³¹ The RELAX-AHF trial showed that a multiple score composed of seven different biomarkers provided the more reliable prognostic value compared any single biomarker strategy.³² Thus, combining biomarkers may improve the ability to predict

HF outcomes.^{2,33-35} A multi-biomarker approach based on NT-proBNP, hs-troponin, and ST2 was found to better identify high-risk patients for recurrent hospitalizations than single- or double-biomarkers based scoring systems.³⁶ A multi-biomarker approach is therefore suggested to identify high-risk patients for stratification and prevention.^{37,38}

Conclusions

Many cardiovascular biomarkers have been studied in HF^{39,40} but most do not satisfy the criteria and cannot therefore be recommended.^{2,13} Beyond natriuretic peptides and cardiac troponins, soluble ST2 may be indicated to aid in the diagnosis and risk stratification/prognosis in HF² but additional research is warranted and is in progress. In light of the existing evidence, a multimarker approach is suggested given the complex pathophysiological processes underlying HF.

Conflict of interest: A.J.S.C. declares nothing related to this work. Outside of this work, in the last 3 years, he declares having received honoraria and/or lecture fees from: Astra Zeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Respicardia, Stealth Peptides, V-Wav. The other authors have no declarations to make.

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