

Biomarkers in heart failure

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1. ABSTRACT

Nowadays, heart failure (HF) has an increasing prevalence, particularly in the elderly, and is becoming a clinical problem of epidemic proportion in terms of morbidity and mortality. Developing biological markers, that can aid in the diagnosis of HF and in the differentiation of congestive heart failure (CHF) from other causes of dyspnoea, will reduce the cost of health care. However, an ideal biomarker has not yet been identified. Potential markers of HF include neuro-hormonal mediators, markers of myocyte injury, and indicators of systemic inflammation. Among these, the BNP and NT-pro-BNP are the most widely studied and appear to be useful in patients with dyspnoea of unknown aetiology, and for risk assessment of patients with established HF. However these markers should be used as an addition tool, and not as a substitute of clinical assessment.

2. INTRODUCTION

Heart failure (HF) is today a clinical problem of epidemic dimension in terms of morbidity and mortality with increasing prevalence especially in the elderly. It has a devastating impact on the public health system balance. Based on this, it is mandatory to develop biological markers that can aid in the precocious diagnosis of HF, providing accurate differentiation of congestive HF (CHF) from other causes of dyspnoea and helping in terms of cost-effectiveness of medical management (1).

To date, the ideal biomarker for CHF has not yet been identified; however the strategy of using a combination of multiple markers with different pathophysiologic backgrounds will be of some help in the clinical practice (2).

Biomarkers in heart failure

Markers of heart failure can be distinguished in neuro-hormonal mediators (catecholamines, renin, angiotensin II and aldosterone, endothelin -1 and natriuretic peptide), markers of myocyte injury (I and T troponin), and indicators of systemic inflammation (CRP, TNF alpha, IL6, GM-CSF, MCSF, etc.) (3).

In this review, we will focus our attention on brain natriuretic peptide (BNP) that is the most widely studied and validated marker; in addition, we will discuss novel inflammatory biomarkers that may give interesting and complementary information but whose role is not completely clear.

3. MARKERS OF HEART FAILURE

3.1. Neurohumoral mediators

It is well known that neuro-hormonal adaptations play an important role in determining signs and symptoms of heart failure. In fact, to overcome the deficit in cardiac output, the body compensates through the activation of both the renin-angiotensin-aldosterone and the sympathetic nervous systems (4,5). These anatomical structures can contribute to the maintenance of perfusion of vital organs by vasoconstriction, resulting in the redistribution of blood flow to vital organs and in the preservation of the systemic pressure; they restore cardiac output by increasing myocardial contractility of the heart rate and by expansion of the extracellular fluid volume (via the Frank-Starling mechanism). However, these compensatory mechanisms may lead to a further deterioration in cardiac performance. In fact, there are a number of negative consequences of neuro-hormonal activation:

- the elevation in diastolic pressure is transmitted to the atria and to the pulmonary and systemic venous circulations; the ensuing elevation in capillary pressure promotes the development of pulmonary congestion and peripheral oedema;

- the increase in left ventricular after load, induced by the rise in peripheral resistance, can both directly depress cardiac function and enhance the rate of deterioration of myocardial function (4);

- catecholamine-stimulated contractility and increased heart rate can worsen coronary ischemia and contribute to the pathogenesis of ventricular arrhythmias.

Angiotensin II, norepinephrine (NE), and endothelin are locally generated by the stimulus of myocyte stretch and can be a marker of the amount of neuro-hormonal activation. These mediators may promote the loss of myocyte by apoptosis; stimulate expression of proteins and myocyte hypertrophy (6,7,21,22).

NE concentrations are increased in HF as a response to sympathetic nervous system activation. NE concentrations correlate with the severity of cardiac dysfunction and inversely with survival. In the Val-Heft study it was found that patients with higher NE concentrations had a higher mortality rate (8,9).

Therapy with ACE-I (ramipril) can reduce the degree of neuro-hormonal activation (10,11). Renin release is activated in HF. In addition to the activation of the systemic renin-angiotensin system in heart failure, there is evidence of local cardiac angiotensin II and angiotensin converting enzyme production is in proportion to the severity of heart failure (12-16). Increases in angiotensin II stimulates collagen synthesis, leading to fibrosis and remodelling of the extracellular matrix (17,18). This phenomenon could explain in part why angiotensin converting enzyme inhibitors are more beneficial in patients with HF than other vasodilators and may prevent remodelling.

Secondary hyperaldosteronism in heart failure has been thought to reflect angiotensin II-mediated stimulation of the adrenal glands. However, aldosterone is also produced locally in the failing heart in proportion to the severity of heart failure (16,19).

Adverse effects of aldosterone-induced stimulation of cardiac mineral corticoid receptors are thought to contribute to the survival benefit associated with the administration of mineral corticoid receptor antagonists in some patients with heart failure (20).

Endothelin is produced by the vascular endothelium and it may contribute to the regulation of myocardial function, vascular tone, and peripheral resistance in HF (21). Plasma endothelin concentrations are increased in patients with HF. Experimental studies suggest that endothelin is released in part from cardiac myocyte and coronary vascular endothelium, and that angiotensin II may contribute to the high circulating levels in HF (22). Over the long-term, high levels of endothelin (as with angiotensin II) may be deleterious to the heart, due for example to pathologic remodelling (21,22). ET1 has been identified as a strong predictor of survival in patients with CHF (23). This has led to the evaluation of endothelin inhibition as a therapy for heart failure (24).

3.1.1. Brain natriuretic peptide

Plasma natriuretic peptides are hormones released by myocyte in response to high ventricular filling pressure (25). The concentrations of these hormones are increased in patients with left ventricular dysfunction. They are secreted to counteract neuro-hormonal activation in HF and so inhibit the renin-angiotensin system, endothelin secretion and systemic and renal sympathetic activity (26). Both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) have diuretic, natriuretic and anti-hypertensive effects.

The circulating concentration of BNP is less than 20 percent of that of ANP in normal subjects, but can equal or exceed that of ANP in patients with HF. Its wider range of concentrations makes BNP a more specific marker for myocardial failure (27,28).

BNP is cleaved from the C-terminal end of its pro-hormone, pro-BNP. The N-terminal fragment, NT-pro-BNP, is also released into the circulation. In normal

subjects, the plasma concentrations of BNP and NT-pro-BNP are similar (approximately 10 pmol/L). However, in patients with LV dysfunction, plasma NT-pro-BNP rises more than BNP, with NT-pro-BNP concentrations approximately four times higher than BNP concentrations (29) and has a longer biological half life. Most of the early studies on BNP have focused on the diagnostic role of plasma BNP and NT-proBNP in patients with signs and symptoms of heart failure. In the Multicenter Breathing Not Properly (BNP) Study plasma BNP concentrations above 100 pg/ml diagnosed HF with a sensitivity and specificity of 90% and 76% and a diagnostic accuracy of 81% in patients admitted to the emergency department for dyspnoea (30). Similar findings were reported by Maisel *et al* who found that BNP measurement together with clinical evaluation versus clinical assessment alone reduced the recovery period and the total cost of treatment. Mueller *et al* reported that BNP evaluation improved the diagnostic accuracy by general practitioners as well (31,32). There is consensus among heart failure specialists about the utility of BNP measurement in patients with suspected diagnosis of HF but with ambiguous symptoms or with contradictory disease states (COPD). However a limit in this setting is that it also increases in patients with primary or secondary pulmonary hypertension (33,34).

Plasma BNP levels have been found to be increased in the setting of acute myocardial infarction without overt symptoms of heart failure inversely correlating with post MI ejection fraction (35). Plasma NT-pro-BNP also has a predictive value after a MI or unstable angina (35-42). The largest study of NT-pro-BNP in this setting is an analysis of data on 6809 patients from the GUSTO IV ACS trial (36). Blood samples obtained within 24 hours of symptoms onset in patients with a non-ST elevation ACS were retrospectively assayed for NT-pro-BNP. Patients in the lowest decile of NT-pro-BNP (98ng/L) had a significantly lower mortality rate at one year than those in the highest decile (higher than 4634 ng/L) (0.4 versus 27.1 percent). NT-pro-BNP had a stronger correlation with mortality than any other marker studied, including cTNT and CRP.

BNP and NT-proBNP may also have a diagnostic use for the screening of asymptomatic left ventricular dysfunction in populations at increased risk for developing it (diabetics, in the elderly) (43-45). However at this time, routine testing remains inappropriate in this category of patients and in the former one (acute myocardial infarction).

Elevations in plasma BNP can establish the presence of HF due to diastolic dysfunction with similar accuracy to systolic dysfunction (46-48). However, the values do not differentiate between systolic and diastolic dysfunction.

Plasma BNP and NT-proBNP can provide useful information in addition to clinical assessment, in the risk stratification and prognostication for patients with chronic heart failure and especially to monitor the clinical status of those with a moderate to severe disease. Measured at initial presentation, they provide prognostic information in

patients with chronic HF, including those receiving therapy with a beta blocker and an ACE inhibitor (49-52). Increased plasma BNP also identifies patients at increased risk for sudden death, and may be a better predictor than other parameters, such as NYHA class (53). The prognostic role of plasma NT-pro-BNP in HF was examined in the Australian New Zealand Heart Failure trial of 297 patients with an ischemic cardiomyopathy (54). A plasma NT-pro-BNP above the median at baseline was independently associated with an increased risk of all cause mortality (risk ratio 4.67 compared to levels below the median), HF mortality (risk ratio 22.1) and hospital admission for HF (risk ratio 4.7). Carvedilol reduced the risk of death in patients with supramedian NT-pro-BNP levels (55). Another potential use of plasma BNP is to identify, in patients supported by a left ventricular assist device (LVAD), those who may require heart transplantation (56).

Measurement of plasma BNP and NT-pro-BNP may also be helpful in titrating therapy in HF patients. At six months, a first cardiovascular event occurred less frequently in those undergoing NT-pro-BNP guided therapy (27 versus 53 percent for clinical assessment). The plasma concentrations of BNP and NT-pro-BNP fall after effective pharmacologic treatment of HF, which suggests that the measurement of plasma BNP may be helpful in titrating therapy (51,57-60). Optimized medical therapy was associated with significant reductions in plasma BNP (917 at baseline to 285 pg/mL) as well as other neuro-humoral factors such as norepinephrine (964 to 431 pg/mL) (57). The Val-HeFT trial suggested a hemodynamic benefit from adding an angiotensin II receptor blocker (valsartan) to optimize therapy, which included an ACE inhibitor (60). At up to a 24 months follow up, plasma BNP, in patients treated with valsartan fell by 21 pg/nL compared with baseline values and was increased by 23pg/mL in the placebo group. In the Australian New Zealand Heart Failure study, carvedilol appeared to reduce mortality only in patients with supramedian baseline values of BNP (55). NT-pro-BNP also seems to predict cardiac involvement and prognosis in patients with AL amyloidosis (61) and may be a useful screen for left ventricular dysfunction due to late cardiotoxicity in children who have received anthracycline chemotherapy (62).

Unfortunately BNP and NT-proBNP are not ideal biomarkers because their concentration is influenced by sex and age (63) in fact plasma BNP and NT-pro-BNP values increase with age and are higher in women than men (63). Thus, somewhat higher cutoff values may be needed in these settings, although the optimal discriminatory values that should be used have not been determined. Moreover its concentrations are modified by obesity (64) renal impairment (65) and sleep apnoea (66).

3.2. Markers of myocardial injury

Cardiac troponin I and T, which are released during myocyte injury, are elevated in some patients with HF, even in the absence of coronary artery disease (67-70). They have been found to correlate with clinical severity of the disease (71). Such markers elevation is associated with a progressive decline in left ventricular function and

more frequent cardiac events, suggesting that they are also prognostic markers (70, 72).

3.3. Cytokines and growth factors

A lot of evidence supports the hypothesis that inflammation plays an important role in the development and progression of heart failure. It has been observed that heart failure is often characterized by an increase in circulating proinflammatory cytokines (TNF alpha, interleukin (IL)-6, IL-1-beta, and IL-2) and their soluble receptor or receptor antagonists that become more pronounced as myocardial function deteriorates (73-78). Increased production of proinflammatory cytokines and other inflammatory markers may identify patients at increased risk of developing HF in the future (79, 80).

Plasma TNF alpha concentrations are often elevated in patients with HF (73-75,81). Plasma TNF alpha increases with disease severity, being directly correlated with NYHA functional class (73,81,82). An increase in TNF alpha correlates with the prognosis in patients with HF and the development of HF in patients without the disease (76-78,83). This issue was best addressed in the VEST study that evaluated 1200 patients with advanced heart failure followed by a mean follow-up of 55 weeks (76). Higher TNF alpha plasma levels at baseline were associated with increased mortality. The relationship was influenced by age, sex, and the cause of heart failure. The plasma concentration of soluble TNF alpha receptors was also an adverse prognostic predictor (76-78). TNF alpha may also predict the development of HF in elderly patients. The role in the elderly was evaluated in a prospective review of 732 elderly subjects from the Framingham Heart Study who had no history of myocardial infarction or HF at baseline (79). At a mean follow-up of 5.2 years, 56 patients (7.7 percent) developed HF. After adjustment for risk factors, there was a 60 percent increase in HF risk for each tertile increment in spontaneous production of TNF alpha by peripheral blood mononuclear cells. When biopsy was performed, TNF alpha was expressed in seven of the eight hearts transplanted in patients who developed right ventricular failure afterwards (84). A normal heart does not express TNF alpha, however significant amounts have been found to be expressed by the failing human heart (85). TNF alpha expression may probably be stimulated by the passive stretch of cardiac myocyte (86), moreover, in humans, pressure and volume overload due to aortic stenosis or mitral regurgitation are associated with increased plasma TNF alpha and other cytokine concentrations (81). Inflammation is also likely to be important since increased TNF alpha production by peripheral blood mononuclear cells is also predictive of risk (79). Increased exposure to endotoxins due to altered gut permeability in patients with oedema may be responsible for this (87). Experimental studies suggest that local production of TNF alpha may have toxic effects on the myocardium, which could explain the association of TNF alpha with an adverse prognosis (67, 88-91). The deleterious actions of TNF alpha may be mediated in part by the generation of reactive oxygen intermediates; an effect that might be inhibited by antioxidants (68). Whether or not TNF alpha overproduction contributes to the progression of HF in

humans must still be determined (69,92). IL-6 production is also increased in patients with HF (73-75) and it may contribute to disease progression (76,93,94) and cardiac function decline (95). The increase in plasma IL-6 is at least in part derived from the peripheral circulation, where the rate of production varies with the severity of the heart failure (93). The prognostic value of IL6 in HF was addressed in the above cited VEST trial (76). Higher plasma levels of IL-6 at baseline were significantly associated with enhanced mortality. In a smaller study by Orus *et al* IL6 was identified as a powerful independent predictor of death, new heart failure episodes and the need for heart transplantation (96). The rate of cytokine activation can be reduced by optimal medical therapy but persistently high IL-6 levels are associated with increased mortality (93). As with TNF alpha, plasma IL-6 may also predict the development of HF. This was illustrated in 732 elderly subjects from the Framingham Heart Study with no history of myocardial infarction or HF at baseline (97). At a mean follow-up of 5.2 years, 56 patients (7.7 percent) developed HF. After adjustment for risk factors, there was a 68 percent increase in HF risk for each tertile increment in plasma IL-6. Plasma IL-6 was related to C-reactive protein levels, which could reflect the central role of IL-6 in the acute phase response (98).

As already stated, HF reflects an inflammatory state as can also be confirmed by an increase of CRP levels. Measurement of CRP may be a complementary tool to echocardiography to identify high risk subgroups of patients with a tendency for poor outcome not discriminated by cardiac function (98). Peak CRP levels could be a predictor of adverse remodelling and poor long term prognosis (99).

Newer studies have investigated the role of growth factors in heart failure. Remodeling is associated with a number of cellular changes including myocyte hypertrophy, loss of myocyte due to apoptosis (77-79) or necrosis (80), and fibroblast proliferation (100) and fibrosis (81,101). Growth factors and cytokines may play a pathogenetic role in left ventricle remodelling promoting apoptosis and fibrosis and inducing tissue regeneration and hypertrophy (102,103).

Granulocyte and macrophage colony stimulating factor (GM-CSF) is a polypeptide stimulating proliferation and differentiation of granulocytes and macrophages. It also activates mature haematopoietic cells leading to an increase of phagocytosis and leucocytes chemotaxis. Macrophage colony stimulating factor (M-CSF) promotes the survival, proliferation and differentiation of mononuclear phagocytes (104). GM-CSF and M-CSF as well as other cytokines, may promote monocytopenia and monocytes and macrophages infiltration into the injured tissue promoting inflammation. Excessive infiltration of inflammatory cells may cause an imbalance between synthesis and degradation of extracellular matrix (ECM) resulting in adverse post-myocardial infarction (MI) remodelling (99). Macrophages may accelerate absorption of necrotic tissue and reduce granulation and scar tissue via the expression of metallo-proteinase (MMP) (105).

Monocytes infiltration may inhibit collagen deposition and prolonged macrophage activation may delay myofibroblast proliferation and migration (99). This process may result in infarct expansion. Maekawa *et al* demonstrated that GM-CSF induction in rats facilitates left ventricle (LV) remodeling infarct in association with monocytes recruitment and inappropriate collagen synthesis. Postiglione *et al* found increased GM-CSF levels in end stage heart failure biopsy compared with normal controls and hypothesized that GM-CSF may play a role in apoptotic phenomena and ECM deposition in the myocardium (106).

Recently, elevated levels of G-CSF have been observed in patients with severe HF correlating with the degree of neuro-hormonal activation (106). Oren *et al* revealed that MCSF, CRP and IL 3, are strong predictors of LV remodelling after acute myocardial infarction (107). Wiecek *et al* suggested that growth factors and particularly GM-CSF may induce the release of stem cells from the bone marrow into the peripheral blood. These can play a role in infarct repair (108,109). However the role of growth factor in LV remodelling is still controversial. A preclinical study hypothesized that MCSF treatment after myocardial infarction may attenuate left ventricle deterioration after myocardial infarction by increasing collagen content in the scar and increasing collagen fiber thickness and accelerating infarct repair (110). Some other studies reported that a combination of G-CSF and MCSF attenuate remodelling in the border zone of infarct hearts (111,112). This action could be mediated by collagen deposition (112). Probably cardiac fibrosis lead to different outcomes determined not only by its extent but also by its location (infarcted vs viable regions) and timing (acute vs chronic phase after infarction). Timely increases in scar collagen deposition can be beneficial for left ventricle function (110).

4. PERSPECTIVES

In recent years there has been an enormous accumulation of data exploring the fascinating world of biomarkers involved in diagnosis, risk stratification and prognostication in heart failure. The ideal biomarker has not yet been identified. The role of some biomarkers is better understood while others are still under investigation and at the moment cannot be routinely recommended for the management of patients with heart failure, although their use seems to be very promising. BNP and NT-proBNP are the most widely studied biomarkers. Their measurement can be encouraged especially for clinical evaluation of dyspnoea of uncertain aetiology, and for risk stratification of patients with established diagnosis of HF. However these markers should be used as an addition to, and not a substitute for clinical assessment.

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Abbreviations: HF: Heart failure; CHF: congestive heart failure; BNP: Brain natriuretic peptide; NT-pro BNP: N-terminal pro Brain natriuretic peptide; CRP: C Reactive Protein; TNF alpha: Tumor necrosis factor-alpha; IL6: Interleukin-6; GM-CSF: granulocyte-macrophage colony-stimulating factor; M-CSF: Macrophage colony stimulating factor; NE: Norepinephrine; ET1: endothelin-1; ECM: extracellular matrix; ANP: Atrial natriuretic peptide; COPD: Chronic Obstructive Pulmonary Disease; GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; cTnT: Cardiac troponin T; NYHA: New York Heart Association; LVAD: left ventricular assist device; VEST Study: vesnarinone Study.

Key Words: neuro-hormonal mediators, Brain-Natriuretic Peptide, Cytokines, Growth Factors, Heart Failure, review

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