

New Biomarkers in Heart Failure: Applications in Diagnosis, Prognosis, and Guidance of Therapy

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Biomarkers are biological variables which provide information about particular disease states. In heart failure (HF), this may include demographic features (age and sex), cardiac imaging (echocardiography, radiography, radionuclide, and magnetic resonance scanning) or even determination of a particular genetic polymorphism. However, the term “biomarker” is now usually employed in reference to circulating analytes beyond the standard biochemistry and haematology included in routine clinical management. An expanding array of circulating biochemicals reflects differing aspects of HF pathophysiology.

The biomarkers of cardinal significance in HF which are now applied in routine clinical practice, are the B-type natriuretic peptides (BNP and NTproBNP). They illustrate what biomarkers have to offer in heart failure and also demonstrate some shortcomings relative to an ideal marker.

Criteria for Clinical Application of Biomarkers

Recent reviews^{1,2} have defined criteria for the clinical utility of biomarkers. First and foremost, measurement should facilitate clinical management and improve outcomes in one or more of the following ways. New markers may improve diagnostic certainty in comparison with existing tests. Levels may be associated with risk of HF onset or deterioration (ideally this would trigger a response with specific therapy). Monitoring through serial marker measurements should

improve end-point outcomes (ie, reductions in acute decompensation, reduced mortality and/or enhanced quality of life).

Secondly, the marker should provide information not otherwise available. There should be a strong relationship between marker levels and diagnosis and/or prognosis. The marker should improve diagnostic certainty and/or clinical risk stratification beyond existing tests.

Finally, practical, technical, and commercial issues will always be pertinent. Assays must be accurate, reproducible and well-supported. The analyte in serum and/or plasma must be sufficiently stable to avoid excessive post-sampling degradation. Assays have to be accessible and affordable.

Among the flood of candidate biomarkers currently under investigation in HF, few will satisfy these criteria. In addition to the requisite test performance, clinical practicality and fiscal limitations will dictate that a limited number of markers will become established in clinical management of HF. This does not negate the pathophysiological insight offered through researching many biomarkers in HF. Biomarkers reflect one or more of the different aspects of the complex HF syndrome. They potentially offer information regarding the aetiology of the condition and, by reflecting disease processes at whole body, organ, cell or sub-cellular level(s), may identify new therapeutic targets.

Classifying Biomarkers in Heart Failure

Biomarkers in HF can be broadly grouped (Table) according to our current understanding of their role in HF pathophysiology. The best known subgroup is the neurohormones, including the cardiac natriuretic peptides (NP), the components of the renin-angiotensin-aldosterone system (RAAS), the catecholamines, arginine vasopressin, and endothelium-derived vasoactive peptides including endothelin, adrenomedullin, and the

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TABLE 1. Biomarkers in Heart Failure

Neurohormonal markers	
Cardiac natriuretic peptides	B-type natriuretic peptides (BNP ₁₋₃₂ , NTproBNP ₁₋₇₆ , pro-BNP) ANP, NTproANP, mid-region pro-ANP C-type natriuretic peptides (CNP, NTproCNP)
Renin-angiotensin-aldosterone system	plasma renin activity (PRA) Angiotensin II Aldosterone
Adrenergic nervous system	Norepinephrine Epinephrine
Arginine vasopressin	AVP Copeptin
Endothelial derived peptides	Endothelin 1, big endothelin Adrenomedullin, mid region pro-adrenomedullin Urocortins I, II, III
Inflammatory markers	C-reactive protein Tumour necrosis factor alpha Fas (APO-1) Interleukins 1,6, and 18
Oxidative stress markers	Oxidised low density lipoproteins Myeloperoxidase Urine biopyrrins Urine and plasma isoprostanes Plasma malondialdehyde Carbonyl proteins
Interstitial matrix remodelling markers	Matrix metalloproteinases (MMPs) Tissue inhibitors of metalloproteinases (TIMPs) Propeptide procollagen I Procollagen III
Myocyte injury markers	Cardiac Troponins I and T Myosin light-chain kinase I Heart fatty acid binding protein Creatine kinase, creatine kinase MB fraction Ischemia modified albumin
Other/new markers	ST2 Growth differentiation factor 15 Osteoprotegerin Adiponectin Galectin 3 Co-enzyme Q ₁₀

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urocortins. These biologically active endocrine and/or paracrine and/or autocrine entities reflect the systemic and/or cardiac response to acute and/or chronic cardiac injury. Some are predominantly compensatory in nature. The NP facilitate renal filtration and sodium excretion whilst suppressing the vasoconstrictor/sodium, retaining RAAS and

exerting a tonic anti-trophic effect that mitigate interstitial fibrosis and cardiac hypertrophy. Genetically modified animals with deletion of ANP, BNP, or their specific receptors are hypertensive with cardiac hypertrophy and fibrosis and increased mortality. The prime secretory stimulus for the NP is cardiomyocyte stretch and the increased

intracardiac pressures which characterise HF trigger secretion of NP. This mechanism underlies the association between plasma concentrations of the B-type natriuretic peptides with diagnosis of decompensated HF, severity of cardiac structural and functional abnormality and prognosis.³ This relationship is modified by age, sex, renal function, body mass, hypoxemia, arrhythmia, adrenal and thyroid status, inflammation, and severe multi-system disease.

Cardiac impairment with associated reductions in regional blood flow, together with increased renal, cardiac and systemic sympathetic drive, stimulate the RAAS, which is a maladaptive response "aimed" at sustaining arterial pressure and critical organ perfusion. This system is counterpoised to the NP and activation induces systemic vasoconstriction and sodium retention, cardiac hypertrophy and interstitial fibrosis. Along with activation of the sympathetic nervous system and high levels of circulating catecholamines, the RAAS appears to be a major culprit promoting adverse ventricular remodelling after cardiac injury and facilitating the vicious cycle of spiralling cardiac dysfunction, decompensation and high mortality observed in chronic heart failure. Plasma levels of catecholamines, plasma renin activity and aldosterone are related to prognosis in HF.⁴

Arginine vasopressin is activated in HF, becoming regulated by hemodynamic cues and angiotensin 2 rather than plasma osmolarity as HF progresses. This can produce inappropriate antidiuresis (with possible hyponatremia) and peripheral vasoconstriction. Endothelin, a potent endothelial vasoconstrictor peptide, is raised and related to poor prognosis in HF. Acute endothelin blockade in HF lowers pulmonary artery and ventricular filling pressures and increases cardiac output.⁵

Conversely, adrenomedullin (ADM), also elevated in HF with levels related to prognosis, is a vasodilator peptide of endothelial origin. In experimental HF infused ADM has a beneficial hemodynamic profile. It activates renin without elevating aldosterone levels and lowers NP concentrations in parallel with reductions in left atrial pressures.⁶

Plasma levels of urocortins (members of the corticotrophin-releasing factor peptide family) are increased in HF. In experimental heart failure urocortins I, II, and III induce major reductions in right heart and left ventricular filling pressures, large increments in cardiac output, and reduction of cardiac work in concert with suppression of the RAAS, endothelin and arginine vasopressin, and marked improvement in renal filtration. Blockade of urocortin exacerbates the hemodynamic, renal and neurohormonal features of experimental HF, indicating endogenous urocortin is a significant

beneficial contributor to the compensatory response to HF.⁷

Markers of inflammation and oxidative stress are a further group of HF biomarkers. C-reactive protein (CRP), tumour necrosis factor (TNF) alpha and other cytokines are increased in HF and high levels portend a worse prognosis.^{1,8,9} Myeloperoxidase activity, urine and plasma isoprostanes and other markers of oxidative damage also rise with increasing severity of HF. CRP disturbances in cardiovascular disease have been long recognized, whereas associations between cytokines and risk of developing HF (and with prognosis in known HF) have been recognised from the 1990s. These immune system responses may exert deleterious effects through stimulating adverse neurohormonal factors such as endothelin 1 in addition to more direct promotion of cardiomyocyte necrosis and apoptosis.

Adverse ventricular remodelling (partly caused by cardiotoxic effects of neurohormonal and cytokine activation) is mirrored in markers of interstitial matrix degradation and formation. These include circulating levels of matrix metalloproteinases, the tissue inhibitors of metalloproteinases, and the procollagens.¹⁰ TNF alpha may drive cardiac dilatation partly through increased expression and activity of metalloproteinases, again illustrating the complex interplay between different elements of the molecular responses to cardiac impairment. Apoptosis and necrosis of cardiomyocytes are reflected in myocyte injury markers including Troponins I and T. Better known for their role in the diagnosis and management of acute coronary syndromes, troponin levels are clearly prognostic in HF and increasingly sensitive assays will facilitate their wider use in HF for risk stratification.¹¹

New markers continue to emerge from diverse aspects of the pathophysiology of heart failure. ST2 is a soluble form of the receptor for interleukin 33 induced through cardiomyocyte stretch. Interleukin 33 mediates an antifibrotic pathway in the heart.¹² Co-enzyme Q10 is reduced in heart failure, possibly reflecting a fundamental impairment of mitochondrial respiration. Other newcomers include growth differentiation factor 15, osteoprotegerin, adiponectin, galectin 3 and urotensin II.¹³⁻¹⁵

Of this broad array, so far only the B-type peptides have become established as recommended aids to the diagnosis of acute HF.^{1,2} Their independent prognostic power across the clinical spectrum from risk factor to end-stage HF is well established. Serial measurements allow improved management of both acute and chronic HF. A threshold B-type peptide level is now a routine inclusion criterion in therapeutic trials.

Mid-region proatrial natriuretic peptide levels have similar diagnostic power for acute heart failure as do the B-type natriuretic peptides. Mid-region pro-adrenomedullin levels and ST2 levels are equal or superior to the B-type peptides as indicators of prognosis in acute HF. Whether or not one or more biomarkers may replace the B-type natriuretic peptides or will be used in combination with BNP, remains to be seen.

The B-type peptides are the only truly established biomarkers in clinical care of HF. The pivotal causative roles of the RAAS and sympathetic nervous systems in progression of HF are clear. There is no benefit in routine measurement of renin, angiotensin II, aldosterone or plasma catecholamines for diagnosis, in triggering introduction of therapy or in monitoring HF.

Biomarkers may assist in case selection for specific therapies.¹ Sub studies undertaken in association with randomized controlled trials of angiotensin converting enzyme inhibitors (ACEI), indicate greatest relative benefit is obtained when baseline RAAS activity is high. In the “RALES” trial of Spironolactone in severe HF, benefit was confined to those with more elevated plasma procollagen 3.^{1,2} Some evidence from randomised controlled trials suggests that greater elevation of B-type natriuretic peptides identifies those gaining benefit from introduction of carvedilol.¹ Currently HF treatment doses are based on a “one size fits all” approach derived from the outcomes of randomized controlled trials. However, future treatments conceivably will be subject to more specific prescribing guided by biomarker profiling.

Identification of Therapeutic Targets by Biomarkers

Understanding of the role of neurohormonal systems in the evolution of HF has underpinned advances in therapy since the mid-1980s. This has depended on investigation of circulating levels of biomarkers.^{1,2} Blockade of the RAAS using ACEI, angiotensin receptor blockers and aldosterone antagonists has been based upon our gathered understanding of the adverse effects of this system in evolving HF. Beta blockade is another successful therapy logically underpinned by understanding the effects of inappropriate adrenergic drive and circulating catecholamines on cardiac energy balance, peripheral vascular resistance, cellular integrity, and renin secretion in heart failure. Human recombinant BNP (nesiritide) has been introduced as treatment in acute decompensated heart failure. Questions remain regarding its effects on renal function and mortality, but it is clear that nesiritide lowers cardiac filling pressures and relieves dyspnea in acute HF.

Rational pursuit of neurohormonal targets has not always been successful. In the last decade experimental treatments based on impeccable logic (often with compelling preclinical evidence) have failed to reduce morbidity and/or mortality in heart failure.^{1,2} Agents reducing central sympathetic traffic outflow, blockade of TNF alpha and endothelin antagonists have not proven to be useful. Antagonists of arginine vasopressin have not reduced mortality. Whether or not manipulation of plasma or tissue levels of urocortin or adrenomedullin, or blockade of specific mediators of inflammation/oxidation and/or interstitial collagen cross-linking will prove useful in HF remains to be tested. Only rigorously designed randomized controlled trials can provide those answers.

Multi-Markers

Combining 2 or more circulating biomarkers reflecting different aspects of HF pathophysiology and independently associated with clinical outcome, can improve prognostic power. In a recent assessment of NTproBNP and ST2 levels in patients with acute heart failure presenting to the emergency department, it was apparent that concurrent elevation of both biomarkers conferred far higher risk of mortality than elevation of one marker alone.¹² Markers predominantly reflecting acute phase responses to cardiac injury may combine well with markers of hemodynamic load (cardiomyocyte stretch), potentially clarifying acuity, severity and prognosis.

Summary

Few candidate biomarkers will satisfy criteria for widespread application in clinical management of HF. These criteria include: *a*) accessible, standardised, affordable assays amenable to high throughput, and rapid turnaround; *b*) consistent association of levels with the diagnosis and prognosis in HF; and *c*) facilitation of improved outcomes in HF.

Combining markers may well provide information compensating for the shortcomings of individual tests. New markers may or may not point to new therapeutic targets. However, each emerging biomarker will offer some additional insight into the pathophysiology of heart failure. As yet the criteria for clinical utility have been met by the B-type natriuretic peptides alone. It is 20 years since BNP was discovered, with the almost immediate recognition of the association between circulating plasma levels of BNP and degree of cardiac dysfunction. Thousands of publications addressing the basic science and clinical aspects of the B-type peptides followed prior to their current acceptance

and clinical application. This hints at the burden of evidence which will be required of future candidate biomarkers. Fortunately, the pathway from discovery to proof of clinical utility is now well established thanks in large part to the global effort in natriuretic peptide research. The accumulated basic and clinical research experience (including the existing banks of samples from well-characterised patient cohorts) should facilitate more efficient assessment of new candidate biomarkers. The continuing exploration of the genome, coupled with the evolving disciplines of proteomics and metabolomics, ensure there will be no shortage of newly discovered candidate biomarker molecules for the foreseeable future.²

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