Biochemical Markers in Heart Failure: Are They All the Same?

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In recent years there has been a huge proliferation in the number of studies examining the diagnostic and prognostic value of the numerous and varied biochemical markers of chronic heart failure. These markers are the mediators or expression of the neurohumoral activation associated with this disease—a consequence of left ventricular dysfunction and its hemodynamic and clinical manifestations (reduction in cardiac output and hypotension, an increase in filling pressure, and pulmonary congestion).[1]

Neurohumoral activation in heart failure is maintained over the long term and leads to hemodynamic changes (increased cardiac activity, peripheral vasoconstriction, hydrosaline retention and increased volaemia) mediated by sympathetic hyperactivity, the activation of the renin-angiotensin-aldosterone system, and increased endothelial production of vasopressin and endothelin. This translates into increased plasma concentrations of different markers such as noradrenaline, angiotensin II, aldosterone, vasopressin, and endothelin, among others. In turn, this neurohumoral activation and its effects stimulate other responses with opposing effects (e.g., those involving vasodilators, diuretics, natriuretics and antiproliferative molecules), which results in increased plasma concentrations of the different natriuretic peptides, bradykinins, adrenomedullin and nitrous oxide etc.[1]

The result of all these regulations and contraregulations is that patients with heart failure show a great quantity of circulating neurohormones and other mediators in high concentrations. These substances can nowadays be measured with precision and may perhaps serve as markers of clinical status, disease progress, prognosis and even the response that might be expected to treatment. In fact, the prognostic value of noradrenaline and atrial natriuretic peptide have been known for 20 years (since the classic work of Cohn et al[2] and Keogh[3]). More recently, papers have been published on the prognostic value of angiotensin II,[4] aldosterone,[1] endothelin,[5] and the brain natriuretic peptides BNP and NT-proBNP.[6] These last two are also of great value in the diagnosis of heart failure and ventricular dysfunction,[7] and are very useful for monitoring the efficacy of treatment.[8]

However, a basic question (which might have important practical and economic implications) needs to be answered: are all biochemical neurohumoral markers of heart failure as good as one another, or does each have a different meaning with respect to the stratification of prognosis or the monitoring of treatment etc? In other words, does any particular marker have greater prognostic value than any other? Are some markers more useful for diagnostic screening for heart failure, etc? From a conceptual and pathophysiological standpoint, it is clear that not all markers are equal since they are activated in response to very different stimuli (some common to all of them), since they are an expression of the activity of very different systems (vasoconstrictors or vasodilators, natriuretics or retainers of salt and water, etc), and since they have very varied and complex effects (albeit with important overlaps). In addition, in clinical studies that have tried to correlate the levels of these neurohormones with the prognosis of heart disease, the results have been very variable. In some, for example, noradrenaline was found to be the most powerful prognostic marker, whereas in others, natriuretic peptides, angiotensin II or endothelin were shown to have significant value.[1] Although the different designs of these studies and the different methods used in laboratory determinations could account for some of the variability of these results, it would appear clear that patient characteristics such as

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age, sex, weight, functional class, the duration of disease and its etiology also have an important influence. For example, it is well known that brain natriuretic peptide levels in patients with heart failure but conserved systolic function are lower than in those with systolic dysfunction[9]; it may be that something similar occurs with other markers.[1] Another (possibly more important) influence on the relative value of these markers is the treatment that patients receive. In the early studies in which the prognostic value of noradrenaline was documented,[2] beta-blockers were not in use. By reducing sympathetic activation, these drugs might reduce the levels of this hormone and reduce its prognostic power.[1] The same can be said of inhibitors of angiotensin converting enzyme and the levels of angiotensin 2, or those of aldosterone and anti-aldosterone drugs.[1] When these medications are used, the corresponding marker levels are reduced. Therefore, the current value of noradrenaline, aldosterone or angiotensin 2 might be less than that of brain natriuretic peptide or endothelin since these are still not influenced by inhibitory drugs (these have not been introduced into heart failure treatment regimens since they show no advantages over standard treatment; such is the case of omapatrilate and bosentan). The only role that remains for these particular markers is the detection of subgroups of patients who are not well controlled by standard treatment (aldosterone and angiotensin escape phenomena).[1]

Nevertheless, numerous biochemical, neurohumoral (endothelin, vasopressin, natriuretic peptides, adrenomedullin, etc), and inflammatory (tumor necrosis factor α, interleukins, adhesion molecules) markers[1] remain, whose relative role in the prognosis of heart failure is still to be defined. The work of Rivera et al[10] in this issue of the REVISTA offers data of interest. The authors determine the levels of 3 biochemical markers, proendothelin (or *big* endothelin, a precursor of endothelin-1, which is then turned into endothelin by the action of endothelin converting enzyme), NT-proBNP (the terminal fragment of proBNP, the precursor of BNP), and aldosterone in 103 patients with mild-moderate heart failure (the majority falling into functional class II) and with a moderately depressed ejection fraction (mean, 37±10%). The authors' hypothesis is that increased endothelin-1 concentrations are related to disease severity and prognosis in heart failure (which is true), whereas NT-proBNP levels act as a marker of ventricular remodeling (which is also true, although BNP is also of clinical prognostic value). The results obtained in this work show a strong relationship between plasma levels of both markers and left ventricular systolic (ejection fraction) and diastolic (mitral flow propagation velocity and atrioventricular plane displacement) functional variables. However, they show no significant relationship to exist between proendothelin and aldosterone (the levels of which remained low, probably due to the not-too-severe functional status of the patients involved).

Though the conclusion of the authors that elevated proendothelin levels are associated with greater ventricular dysfunction is valid, the same could be said of the NT-proBNP levels; similar results have been published regarding other markers.

Many aspects of the prognostic value of biochemical markers are still to be clarified. For example, when should biochemical determinations be made? During a period of instability or admission to hospital? After the start of treatment? Randomly when the patient is stable (as in this study)? And in addition, what is the influence of pharmacological treatment or of the several drugs that can influence neurohumoral activity (beta-blockers, inhibitors of angiotensin converting enzyme, anti-aldosterone drugs, etc)? Is the value of a marker the same in patients with systolic or diastolic dysfunction? To cite but one example, a recent study reported that BNP levels were significantly elevated after starting treatment with beta-blockers, although this did not indicate a clinical deterioration or a poor prognosis.[11]

Answers to these and many other questions need to be found, and therefore it would seem unwise to routinely perform an analysis of all possible neurohumoral markers in patients with heart failure: rather than helping, the results would probably introduce confusion. Work like that of Rivera et al,[10] with well defined hypotheses, could eventually provide us with the certainty required in this interesting area of medicine.

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