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HEART FAILURE:

Pentraxin 3—a diastolic dysfunction and diastolic HF marker?

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Abstract

Inflammation has a pivotal role in cardiac remodeling, and circulating biomarkers of inflammation are independently associated with risk of developing heart failure and with prognosis after onset of the condition. Pentraxin 3 has been suggested as a novel biomarker of left ventricular diastolic dysfunction and heart failure with normal ejection fraction.

Heart failure (HF) is a leading cause of hospital admissions in elderly individuals. Two major forms of HF can be distinguished on the basis of the underlying pathophysiology: HF owing to reduced left ventricular (LV) systolic function (HF with reduced ejection fraction [HFREF]) and HF owing to LV diastolic dysfunction (HF with preserved ejection fraction [HFPEF]). Mild LV diastolic dysfunction without clinical HF is a very common finding (20% prevalence in US general population, 50% in elderly, high-risk patients), and manifest HFPEF accounts approximately for 40–50% of all incident HF in the US and Europe. [1] Both HFPEF and HFREF are characterized by chronic remodeling processes in the myocardium, which often antedate overt HF by many years. Inflammatory pathways are strongly involved in cardiac remodeling, and markers of systemic inflammation, such as C-reactive protein (CRP), interleukin 6 or tumor necrosis factor (TNF) independently predict future HF and prognosis in those with existing HF.[2–4] However, which markers of inflammation, if any, should be used to assess future risk of HF in individuals free of this condition, to facilitate diagnosis in patients with symptoms suggestive of HF, or to estimate prognosis in patients with overt HF is not clear. Also, the pathophysiological role of many biomarkers (including inflammatory markers) in HF is poorly understood, that is, whether a given marker is causally involved in cardiac remodeling, whether it is upregulated in a compensatory manner, or whether it is simply an epiphenomenon of a catabolic state caused by HF is not clear. Furthermore, we do not know whether the increase in circulating levels of many of these biomarkers in the setting of HF reflects increased local cardiac synthesis *per se*, or whether it just reflects a systemic inflammatory state. In this context, Matsubara and colleagues evaluated the relationship between circulating levels of pentraxin 3, a novel marker of inflammation, and the pathophysiology of HF.[5]

Pentraxins are members of a superfamily of multimeric pattern-recognition proteins that have a characteristic molecular ring structure consisting of five monomers and that can be short (such as CRP and serum amyloid associated protein, which are typically produced by the liver) or long (the prototype of this group being pentraxin 3). These proteins are evolutionarily highly conserved and have important roles at the interface of innate immune response, inflammation, and extracellular matrix remodeling.[6] Pentraxin 3 knockout mice

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are highly susceptible to fungal infections,[7] and double pentraxin 3 and apoE knockout mice are also more prone to develop atherosclerosis than single apoE knockout animals.[8] In contrast to CRP, which is mainly produced by the liver in response to stimulation by interleukin 6, pentraxin 3 is produced by a variety of cell types (mainly myeloid dendritic cells, but also mononuclear cells, neutrophils, smooth muscle cells, adipocytes, fibroblasts and others).[9] The expression of pentraxin 3 is stimulated by various inflammatory molecular cascades, in particular toll-like receptor signaling. [9]

In their study, Matsubara and colleagues analyzed circulating levels of pentraxin 3 in a sample of 171 individuals without HF, 82 individuals with HFPEF, and 70 individuals with HFREF.[5] They report that in individuals without HF circulating pentraxin 3—but not circulating CRP, interleukin 6 or TNF—was associated with the E/e' ratio, a quantitative echocardiographic measure of LV diastolic dysfunction. In addition, circulating pentraxin-3 levels were higher in the group with HFPEF than in individuals without HF. Again, the elevation of pentraxin-3 levels in patients with HFPEF was more pronounced than the elevation in blood levels of CRP, interleukin 6 or TNF. However, patients with HFREF had even higher circulating pentraxin-3 levels than those with HFPEF. Lastly, the authors measured higher levels of pentraxin 3 in the coronary sinus than in the aortic root in individuals with diastolic dysfunction but no HF, those with HFPEF and those with HFREF, demonstrating that pentraxin 3 is produced in the coronary circulation in these conditions. The authors conclude that pentraxin 3 is an independent marker of LV diastolic dysfunction and of HFPEF, and that the myocardium is likely to contribute to increase the circulating levels of this protein.

The appraisal of this study involves several aspects. First, the reported relation of pentraxin 3 with LV diastolic dysfunction is a purely statistical association in an observational study. Limited data exist regarding the clinical, biochemical, and echocardiographical correlates of circulating pentraxin 3. Hence, potential confounders of the association between pentraxin 3 and LV diastolic function remain to be identified. Second, the observation that blood pentraxin 3 levels in patients with HFREF were even higher than in those with HFPEF is not easy to interpret. Although LV diastolic dysfunction, which characterizes HFPEF, is also common in patients with HFREF, the concept that pentraxin 3 is primarily a marker of LV diastolic dysfunction is questionable. Indeed, raised pentraxin 3 levels in the setting of HF might simply represent elevated LV filling pressures or increased wall tension. Third, the statistical power of the study was limited to evaluate pentraxin 3 as a screening biomarker of LV diastolic dysfunction or as a discriminatory marker of HFPEF versus HFREF. The HF cases and corresponding controls were not matched with regard to HF risk factors. Whether pentraxin 3 is really a better biomarker of LV diastolic dysfunction than other, previously known biomarkers cannot be reliably answered by this moderate-sized investigation. A major strength of the study is the fact that the authors demonstrated that pentraxin 3 is produced in the coronary circulation, which supports the existence of a myocardial source for this biomarker and strengthens the evidence for the role of this protein in cardiac remodeling.[10] However, since experimental data suggest that pentraxin 3 decreases vascular inflammation and atherosclerosis,[8] this marker is more likely to actually modulate, rather than promote, myocardial remodeling processes.

In conclusion, the clinical application of assessing blood pentraxin 3 remains unclear at present. The data by Matsubara and colleagues[5] indicate that circulating pentraxin 3 is not useful for distinguishing HFPEF from HFREF, but that it correlates with LV diastolic dysfunction (or with elevated LV filling pressures). However, we still do not know whether pentraxin 3 levels can predict the development of HF, help in its clinical diagnosis (when diagnostic uncertainty exists), or carry any prognostic information in the setting of overt HF. How pentraxin 3 would compare with established HF biomarkers, such as the B-type natriuretic peptide, for these different clinical purposes is also not clear. Additional studies are warranted to address these issues.

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