EDITORIAL

Advanced heart failure: the Gordian knot

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Heart failure (HF) is a multifactorial and complex syndrome with poorly understood pathophysiology, often representing the final stage of different cardiovascular conditions. A number of factors lead to adaptative changes that, over time, become maladaptive and eventually drive pathological remodeling and failure. Among these, chronic inflammation, malnutrition, neurohormonal activation, endothelial cell activation, and venous congestion play a key role in advanced HF development beyond, or in addition to, hemodynamic factors.[1]

In this issue of *Polish Archives of Internal Medicine*, Kurkiewicz et al[2] analyzed the prognostic value of a set of biomarkers of malnutrition and inflammation in a cohort of 200 stable patients with advanced HF awaiting heart transplantation. The patients were predominantly young men with ischemic etiology of HF and mostly with severely reduced (median, 17%) left ventricular ejection fraction (LVEF). The neutrophil percentage-to-albumin ratio (NPAR), advanced lung cancer inflammation index (ALI; based on the body mass index, serum albumin, and neutrophil-to-lymphocyte ratio), serum tenascin-C (TNC), and high-sensitivity C-reactive protein (hsCRP) were assessed. Survival analysis showed that a lower ALI, as well as a higher NPAR and higher serum levels of TNC and hsCRP were associated with poorer prognosis. Besides, blood concentration of N-terminal pro–B-type natriuretic peptide, serum bilirubin, and creatinine also correlated with higher mortality in the multivariable analysis.

Chronic inflammation, malnutrition, and end-stage cardiac remodeling were assessed through a simple set of blood biomarkers. As the 3 arms of a triangle, this set of biomarkers delineated a poor prognosis arena, since they enabled identification of a group of patients with a high mortality rate during the follow-up (30% at 1 year).

Nonetheless, several questions arise with respect to the results of the study. Is it possible to track complex pathophysiologic processes with simple biomarkers? Is there any single common link between inflammation, malnutrition, and remodeling? Furthermore, can the results of the study be extrapolated to other HF populations?

TNC is an extracellular matrix glycoprotein, recently shown to be involved in the pathogenesis of cardiovascular diseases, mostly HF, atherosclerosis, and myocardial infarction (MI), as a marker of inflammation and remodeling. It is expressed when tissue damage occurs. In addition, some inflammatory scores, such as the Glasgow Prognostic Score, based on serum albumin and hsCRP, have been applied to patients with MI, with good results.[3] Thus, inflammation and cardiac remodeling have a bidirectional relationship, leading to myocardial damage and, eventually, HF development and progression. Neutrophils also seem pathogenic in HF as markers of acute inflammation and repairing processes. Indeed, NPAR has been shown to be superior to neutrophils or albumin alone in prognosis prediction in HF.[4] In the setting of an established HF, overweight or obesity confers some protective effect (the so-called obesity paradox), especially in advanced cases, in contrast to underweight patients.[5,6] However, malnutrition and sarcopenia are clearly associated with poor prognosis. Both of them may be caused by gastrointestinal disturbances induced by decreased perfusion, local edema, intestinal congestion, and systemic inflammation.[7] The cascade of proinflammatory cytokines triggered by congestion may contribute to cardiovascular dysfunction; however, therapeutic anti-inflammatory interventions have been shown to be futile.[8]

In the search for common elements of organ dysfunction (mainly cardiac and renal), inflammation, and malnutrition, venous congestion arises as a promising candidate.[9] There is evidence of a direct relationship between congestion and inflammation.[1] Colombo et al[1] developed an experimental model in which mechanical occlusion

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of the veins elicited robust activation of inflammatory genes. As a consequence, it is plausible to think that protracted clinical congestion through inflammatory mechanisms, among others, may be associated with malnutrition,[10] renal dysfunction, poorer functional status, and higher mortality.[11]

In this complex interplay, splanchnic congestion[12] may be the critical factor in promoting a systemic inflammatory status and derangement of the renal function,[13] which, in turn, exacerbate malnutrition through the retention of nitrogenated products, hyporegenerative anemia, and anorexia, closing the circle between HF, systemic congestion, malnutrition, and organ dysfunction.

A striking finding of Kurkiewicz et al[2] was the absence of influence of comorbidities on the outcomes. Comorbidities have been proposed as influential factors in defining the final phenotype of HF, with either reduced or preserved LVEF.[14] Besides, among HF patients, comorbidities tend to cluster together beyond simple chance and impair health outcomes.[15] The simplest explanation for the apparently contradictory results of the study by Kurkiewicz et al[2] are the homogeneous characteristics of their cohort, consisting mostly of young men with severely reduced LVEF and poor functional status that put them all on the waiting list for heart transplantation. Accordingly, these results cannot be extrapolated to the current HF patients with a wide age range, different phenotypes, and several comorbidities.

Given the complexity of the HF syndrome and its poor prognosis, a comprehensive approach, including clinical findings, blood biomarkers, echocardiography, and, sometimes, invasive tests, is still needed to get a reliable perspective of the prognosis and treatment of individual patients.

ARTICLE INFORMATION

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