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INVITED EDITORIAL

Biomarkers of inflammation in heart failure: from risk prediction to possible treatment targets

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This article refers to 'Inflammation across universal definition of heart failure stages: the CASABLANCA study' by R. Mohebi *et al.*, published in this issue on pages 152–160.

Inflammation is a response to tissue damage. As virtually all compensatory responses, it becomes maladaptive when sustained over time, and may become itself a determinant of disease progression. Accordingly, anti-inflammatory therapies have been regarded with interest as possible strategies for cardiovascular disorders ranging from stable coronary artery disease to myocardial infarction (MI), where the pathogenic role of inflammation is well established.[1] Our knowledge on inflammation in patients at risk for heart failure (HF) (besides the specific setting of MI) or with established HF is more limited, the most established notions being that several comorbidities elicit systemic inflammation, and this may contribute to the development of HF with preserved ejection fraction (HFpEF), although it is not completely known whether inflammation plays a key role in HFpEF or is just a by-product of various comorbidities.[2,3] Further studies expanding the evidence on inflammation in HF are then welcome.

In this issue of the Journal, Mohebi and co-workers investigated the inflammatory activation across the HF stages (A to C/D) through the use of an inflammatory panel and a machine learning approach to assess the degree of inflammatory activation.[4] In a cohort of 1231 patients undergoing diagnostic coronary and/or peripheral angiography, those with stage C/D HF had more inflammatory activation. These was an independent association between moderate and high inflammatory activation and the risk of new-onset HF (in stage A/B) or HF decompensation (in stage C/D). The multivariable model in both cases included N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT), and also soluble suppression of tumorigenesis-2 (sST2) in stage C/D.[4]

The authors should be praised for their original approach, including the assessment of a panel of inflammatory biomarkers, their evaluation through an unsupervised machine learning technique, and the assessment of the degree of inflammatory activation on top of strong predictors of outcome such as NT-proBNP, hs-cTnT and sST2.[5,6] This study provides a convincing demonstration that the degree of activation of the inflammatory response is associated with a higher risk of HF hospitalization across the whole phenotypic spectrum of HF, from individuals at risk for this condition to advanced HF. A study limitation, correctly acknowledged by the authors,[4] is the low number of individuals in stage A and the pooled assessment of patients with stages C and D HF (ranging from mildly symptomatic patients to those poorly responsive to optimal treatment). Furthermore, it would be important to differentiate patients from stage B onwards according to their ejection fraction, as the pathophysiological roles of inflammation may differ. *Figure 1* summarizes the main determinants of inflammation in HF with reduced ejection fraction (HFrEF) or HFpEF. A crucial element is the cause–effect relationship between inflammation and cardiac damage. It is generally acknowledged that such relationship exists, but it is still unclear whether it is sufficiently strong to make inflammation a possible treatment target. In other words, can we expect to obtain a meaningful impact on the natural history of HF by giving anti-inflammatory therapies? To answer this question, we must remember that inflammatory pathways are multiple and partially overlapping, and that inflammatory response may be more or less intense in different conditions (HFrEF vs. HFpEF and in individual patients). Randomized clinical trials using tumour necrosis factor inhibitors, almost two decades ago, were terminated prematurely owing to lack of benefit, which became a handicap for future analyses of anti-inflammatory drugs in HF.[1]

The issues of inflammation as a determinant of disease and possible therapeutic target in HF thus remain open. On the other hand,

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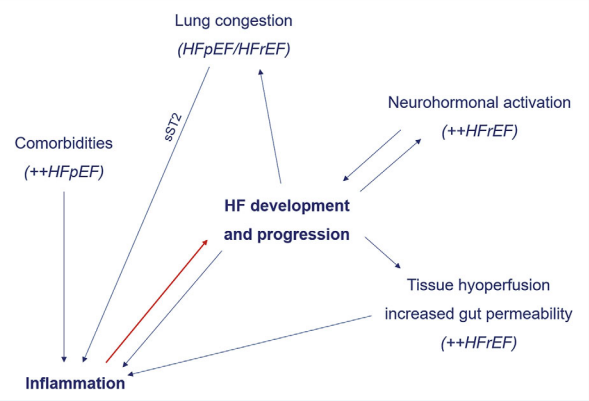

Figure 1 Possible determinants of inflammation and cardiac damage in heart failure (HF). The main possible causes of inflammatory activation and cardiac damage are reported, considering separately HF with reduced or preserved ejection fraction (HFrEF/HFpEF). Both patients with HFrEF or HFpEF may have comorbidities such as chronic obstructive pulmonary disease, obesity or chronic kidney disease, but their pathogenic role is thought to be more relevant in HFpEF. Lung congestion may promote systemic inflammation by the release of soluble suppression of tumorigenesis-2 (sST2). The cause–effect relationship between inflammation and the development or progression of HF (*red arrow*) may require further investigation.

the degree of inflammation is at least an indicator of disease severity, as demonstrated by the relationship between low inflammation levels and earlier HF stages, and the strong, independent association between high inflammation levels and the graded increase in risk of HF hospitalization from low to high inflammation levels. Some elements of novelty in the paper by Mohebi *et al.* are the use of a panel of 24 biomarkers and their pooled assessment through an artificial intelligence (AI) approach.[4] When dissecting the AI-based classification, high-sensitivity C-reactive protein (hs-CRP) emerged as the strongest determinant by far (coefficient > 20), followed by macrophage colony-stimulating factor-1 (M-CSF-1; coefficient lower than 10) and ferritin (coefficient of about 7.5).[4] The prognostic value of hs-CRP is basically in agreement with previous data, reporting for example that hypertensive individuals with higher hs-CRP have an increased risk of developing HF,[7] and that hs-CRP is predictive of outcome in HF regardless of ejection fraction.[8] Less evidence is available on M-CSF, reported to predict outcome in advanced HF,[9] and on ferritin, whose relationship with outcome might be confounded by the development of iron deficiency during HF progression.[10] The outstanding prognostic value of hs-CRP raises the question if we really need a panel of 24 inflammatory biomarkers and the use of an AI approach to stratify inflammatory levels into three categories (low, medium, or high) instead of simply measuring hs-CRP and using continuous hs-CRP levels for outcome prediction. To clarify this point, we may envisage larger biomarker studies, possibly also considering separately patients with acute versus chronic presentations (who were instead pooled together in the present study). Besides confirming that hs-CRP is a strong predictor of outcome, it would be important to check if a cause–effect relationship exists between elevated hs-CRP and HF development or progression. A few Mendelian randomization studies did not find evidence of a relationship between CRP and incident HF,[11,12] and animal studies with direct modulation of this protein (much used to investigate the role of CRP in coronary artery disease)[13] would be important to clarify its causal role in HF. Should this role be confirmed, these findings would provide a strong rationale to target the innate immunity to prevent HF development or progression, particularly in patients with high hs-CRP. A specific inhibitor of CRP (1,6-bis[phosphocholine]-hexane) has been developed and proved effective in preventing HF development following MI in rats,[14] but we are not aware of further studies on this compound as a possible HF therapy. Colchicine is a commonly available drug that can effectively reduce hs-CRP.[1] Colchicine therapy for 6 months did not improve the New York Heart Association class in a small randomized, placebo-controlled trial, where the degree of inflammatory activation at baseline was not evaluated.[15] To our knowledge, there is no further evidence on colchicine for the prevention or treatment of HF, but this drug might warrant consideration for future trials.

Conflict of interest: none declared.

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