C-reactive protein in ischaemic cardiomyopathy: assessing vascular risk in heart failure

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This editorial refers to 'High-sensitivity C-reactive protein: potential adjunct for risk stratification in patients with stable congestive heart failure' by N. Lamblin et al., on page 2245. The paper 'High-sensitivity C-reactive protein: potential adjunct for risk stratification in patients with stable congestive heart failure' by Lamblin et al. clearly demonstrates the prognostic value of this measurement in patients with well-compensated heart failure due to ischaemic cardiomyopathy. Importantly, C-reactive protein did not provide significant prognostic information in the population with dilated cardiomyopathy without evidence of coronary artery disease.

The study included 545 patients referred for evaluation of symptomatic heart failure. During a median follow-up of 972 days, a C-reactive protein >3 mg/L was found to be highly predictive of cardiovascular mortality in patients with ischaemic etiology (113 events, 80% 3-year survival) with a hazard ratio of 2.17 (P < 0.001). In contrast, the hazard ratio of 1.09 was not significant in the rest of the cohort with non-ischaemic etiology. These findings were robust and an elevated C-reactive protein remained a strong, independent predictor in a multivariable model including age, gender, clinical, and echocardiographic variables as well as BNP and peak VO2.

Proper interpretation requires knowledge of the sample recruited and a critical view of the methodology. This was a large cohort of relatively young outpatients (mean age 55) with mild and moderate heart failure (mean ejection fraction 33%). Notably, patients with recent MI or previous revascularization procedures as well as patients with acute infection or inflammatory illness were excluded. All patients underwent coronary angiography. Patients had normal serum sodium, reasonable renal function, and relatively low BNP levels. They were well treated with ACE/A-II inhibition (99%) and beta-blockade (96%). Substantial cytokine activation in such patients is unlikely. Although cardiovascular death is a robust endpoint, the criteria for classifications into sudden cardiac death, vascular death, and fatal pump failure demonstrate overlap and are fraught with controversy. There was no independent Event Committee reviewing all cases.

This publication follows several publications reporting consistent findings evaluating C-reactive protein and vascular risk. Most recently, in a long-term, prospective study in 3971 elderly patients (>65 years), a C-reactive protein level >3 mg/L (26%) at baseline, after adjustment for age, gender, and conventional risk factors, was associated with a hazard ratio of 1.45 for cardiovascular death during 10-year follow-up. The novel finding reported by Lamblin et al. is that cardiovascular death is not predicted by an elevated C-reactive protein in patients with heart failure and normal coronary arteries. The finding that the deleterious impact of elevated C-reactive protein was restricted to patients with ischaemic cardiomyopathy would appear to confirm our mechanistic speculations and represents clinically useful information.

C-reactive protein is an acute phase reactant to inflammation. It is synthesized in the liver and consists of five identical polypeptide chains that form a five-membered ring with a molecular weight of 120 000 Da. Complexed C-reactive protein activates the complement system with a primary function to bind and detoxify endogenous toxic substances produced as a result of tissue damage.

The value of a routinely available, inexpensive biological marker proven to provide strong prognostic information is obviously useful in risk stratification. However, more than satisfying our curiosity about the future, risk stratification permits us to identify and target populations that might benefit from specific pharmacological (including statins) and invasive intervention and treat them accordingly. The two strongest prognostic variables in these patients were C-reactive protein and BNP. This suggests that dual determination of these markers would be rational in that they reflect two different pathological mechanisms (endothelial inflammation and pump dysfunction) both determining prognosis and requiring distinct therapeutic approaches.

Figure 2 in the article demonstrates the potential power of dual determination.

Let us assume that C-reactive protein functions as a surrogate marker for endothelial inflammation and cytokine activation. It would then make biological sense that the success of assaying this marker would differ in assessing prognosis in patients with ischaemic vs. non-ischaemic cardiomyopathy. Interestingly, a very recent publication...
may represent an important step in our understanding of the pathophysiology involved in patients with endothelial inflammation. The demonstration of a group of receptors through which C-reactive protein enters endothelial cells to produce inflammation and atherogenesis is a proof of concept that provides us with a putative mechanism making the results reported by Lamblin et al. biologically plausible and expected.

C-reactive protein is proatherothrombotic through the expression of cell-adhesion molecules, monocyte-chemotactic protein-1, endothelin-1, interleukin-8, and plasminogen activator inhibitor and reduced eNOS expression and prostacyclin release. C-reactive protein levels would therefore function both as a marker and as an effector in patients with heart failure due to coronary artery disease. The prognostic value would therefore be limited to patients with heart failure of ischaemic aetiology. These authors also demonstrated that blocking these receptors (Fc gamma receptors CD32 and CD64) in human aortic endothelial cells with monoclonal antibodies prevents the proinflammatory/prothrombotic effects of C-reactive protein. It becomes intuitively attractive to target these receptors pharmacologically.

Most patients with heart failure in Europe suffer from ischaemic cardiomyopathy. The findings here are consistent with the observation that death in this large population is most often related to the underlying coronary artery disease rather than progressive pump failure. Perhaps, we should consider this group of patients as primarily suffering from ischaemic heart disease with symptoms of heart failure rather than patients with heart failure of ischaemic aetiology. Ischaemia is an active player not another co-morbidity.

Do these findings have any implications for clinical practice today? To a limited degree. High-sensitivity C-reactive protein is already considered part of the routine laboratory evaluation of patients with heart failure. Symptomatic patients frequently have elevated C-reactive protein levels due to associated bacterial infection such as pneumonia. Patients with advanced heart failure may also often have high C-reactive protein levels as far as this measurement serves as a surrogate marker for cytokine activation. However, BNP is more useful in this regard. One could speculate that persistent, low-level C-reactive protein elevation in patients without evidence of infection or inflammation should suggest active coronary disease in patients with heart failure.

Progression in these patients is often stepwise following re-infarction. They are therefore high-risk patients who may need coronary angiography and subsequent revascularization. In symptomatic heart failure patients with multivessel disease, this may mean CABG or alternatively stenting of target, culprit lesions. Clearly, this is a clinical decision based on many considerations. Persistent, modest C-reactive protein elevation in the absence of an obvious cause may indicate substantial vascular risk and strengthen the argument in favour of an invasive procedure.

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References