Cytokine Profile and ST-Elevation Myocardial Infarction

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"Give me fever and I can cure any disease." – Hippocrates

In this issue of Circulation Research, Ammirati et al1 have obtained data from 109 patients with ST-elevation myocardial infarction (STEMI) with the highest interleukin (IL)-6 levels compared with 96 patients with the lowest IL6 levels to identify differences in interacting cytokine levels that might predict clinical outcomes. They identified 2 different modules of patients from their circulating cytokine levels. One module included STEMI patients with increases in IL6(+), IL10(+), greater systolic dysfunction at discharge, and death at 6 months compared with IL6(−) IL10(+ ) STEMI patients. Combining IL10 with IL6 derived from the 2 identified cytokine modules provided a risk index combined-cytokine-index called the “AC-Index” that outperformed any single cytokine in the prediction of systolic dysfunction and death. The authors concluded that simultaneous elevation of IL6 and IL10 levels distinguishes STEMI patients with poorer clinical outcomes from other STEMI patients. They suggest that this information may have potential clinical implications for risk-oriented stratification and for immune-modernating therapies.

IL6 is a cytokine associated with inflammation. Others have reported its value in predicting prognosis in patients during a 3-year follow-up of patients with acute STEMI.2 The IL6 concentrations and 2 promoter polymorphisms of the IL6 gene in STEMI patients treated with thrombolysis3 have also helped to identify higher-risk patients. Lindmark et al4 have shown a relationship between IL6 levels and mortality in patients with unstable coronary artery disease. Biasucci et al5 have shown that IL6 levels are elevated in patients with unstable angina. In the Prospective Epidemiological Study of Myocardial Infarction study, Empana et al6 showed that C-reactive protein, IL6, and fibrinogen levels are related to the risk of sudden death in European middle-aged men. Ridker et al7 have shown that IL6 levels predict the risk of future myocardial infarctions in apparently healthy men. IL6 serum levels are well established as a prognostic marker for patients with acute coronary syndromes. Maseri8 has been an important contributor over many years to this area of work.

We clearly need improved prognostic insights for patients with STEMI after their initial treatment. The new AC-index described by the authors in this article suggests that cytokine profiling may be useful beyond the prognostic insight provided by measurement of IL6 levels.

However, there are some concerns with the AC-index as proposed. First, IL10 suppresses inflammation and cardiac fibrosis.9 Thus, it is a surprise that one would find IL6 and IL10 patients with the highest values as those most at risk for adverse events. It begs the question, “What happens to the IL6(+)IL10(−) patient subset?” One might expect this subset of patients to be those with the most adverse risk biologically. At issue, then, is that statistics appear to collide with anticipated biology. A space-aged evaluation using computational biology is novel and should be applauded. After all, medicine can benefit from the use of artificial intelligence and interpretive computational power. This approach is certainly justified given the complexities of the data interactions at hand, but we must learn to both use such powerful tools and remain solidly focused on observation of palpable clinical benefits.

Second, measurements of left ventricular (LV) function and thrombolysis in myocardial infarction (TIMI) blood flow in this study were not obtained in patients in a rigorous and consistent manner. Only a subset of patients had their LV functional measurements made. Thus, it becomes very difficult to be certain that the degree of LV dysfunction does not play some role in the subsequent cytokine levels. If LV functional measurements were made in a consistent and rigorous manner by 2-dimensional transthoracic echocardiogram or magnetic resonance imaging, would this new cytokine profile index provide information that is additive? In addition, in future studies, comparisons of the AC-index with TIMI and Global Registry for Acute Coronary Events risk scores, with multiclinical variables, and with the Framingham Risk Score will allow one to determine the value of the AC-index in predicting prognosis.

The effort by the authors to develop a cytokine profile index that helps identify patients with significant vascular inflammation and that provides prognostic insight in patients with acute STEMI is an important one. However, additional studies using the cytokine profile index proposed from this study, including rigorous and consistent measurements of LV function and TIMI flow, are needed to allow one to gain confidence in this potential prognostic tool and to determine whether the increased IL6 and IL10 levels are cause or consequence of larger myocardial infarcts, poorer TIMI flow, and, consequently, more LV dysfunction.

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References


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