Inflammation in Cardiovascular Disease

Cart, Horse or Both–Revisited

Russell P. Tracy

“We know that the tail must wag the dog, for the horse is drawn by the cart; but the Devil whoops, as he whooped of old: ‘It’s clever, but is it Art?”’

(Rudyard Kipling, 1865–1936)

In 1998, I wrote an editorial that attempted to make two points. The first point was biological: there existed at that time an active debate over whether inflammation was a cause or a result of cardiovascular disease (CVD), and I suggested that this debate was in fact based on a false distinction, and that both positions where likely to be correct. While atherothrombotic disease is inflammatory, inflammation mediators actually participate in the disease process. The second point was clinical: the routine use of a marker of inflammation in cardiovascular risk prediction was likely in the near future, since this dimension of vascular disease was important and relatively easy to capture with a blood test. C-reactive protein (CRP) seemed to be a good candidate for reasons that were not so much biological as technical and logistic.

Since that time, much of the debate over cause and effect has subsided and, to my reading at least, most articles addressing inflammation and CVD risk these days either directly or tacitly acknowledge both positions. In addition, CRP has become, if not an accepted component of CVD risk assessment, at least a commonly measured CVD risk factor. The major findings were 1) established CVD risk factors assessed by Bermudez et al also has important implications. However, the article by Bermudez et al does establish this clearly in women free of clinical CVD and goes on to present the data in a way that emphasizes the incremental nature: the greater the number of CVD risk factors present, the higher the CRP and IL-6 values. This powerful presentation has two important implications. The first is that IL-6, CRP, or both may be common mediators (or represent common mediating pathways) of damage for a number of the traditional CVD risk factors such as smoking, obesity, hypertension, and diabetes. In support, an important central role for IL-6 has also been suggested by Yudkin. Even if only partly true, this suggests that interruption of this pathway may have profound effects on atherothrombotic progression. Given the overall importance of IL-6 and inflammation in general, however, this interruption would need exquisite targeting and likely not be easy. Recent experience with cyclooxygenase-2 and tumor necrosis factor-α inhibition supports the importance of this complexity in potential interventions.

The second implication is that if the association between the inflammation marker and underlying “traditional” risk factors were to be strong enough, risk prediction might be simplified to the use of a few simple laboratory tests (for example, LDL cholesterol, HDL cholesterol, and CRP or IL-6), compared with the current recommendation of a more complicated approach. This has been proposed by Ridker and colleagues. While the potential benefits of a simplified approach have been discussed by others, this obviously would not eliminate the need to assess all modifiable risk factors such as smoking, hypertension, and diabetes. It might, however, lead to more comprehensive use of a standardized method of risk assessment, certainly a good outcome.

The lack of complete congruence between IL-6 and CRP as assessed by Bermudez et al also has important implications. Because CRP levels are thought to be driven in large part by IL-6, what is the cause of the differences? Since data from a single time point were used in the analysis, analytical error and day-to-day biological variability are likely to contribute. However, the cause of the differences may also reflect
real pathophysiological differences in how these proteins relate to atherothrombosis. For example, IL-6 has major immune system effects, whereas CRP can participate directly in complement activation. These roles may contribute to differences in associations with other CVD risk factors. Interestingly, the large difference in response to hormone therapy (supported by prospective data from a small study by Walsh et al\textsuperscript{20}) cannot be explained this way and likely represents a first-pass liver effect, since transdermal hormone replacement therapy does not appear to have the same effect on CRP as oral hormone replacement therapy.\textsuperscript{21} Whatever the root cause(s) of these differences, their existence suggests that the use of multiple measures of inflammation might better assess an individual patient’s status. For example, the use of both CRP and IL-6 levels in risk assessment might correct for analytical and biological variance in either individual measurement and, at the same time, gather information from different aspects of “inflammation.”

As summarized elegantly by Ross,\textsuperscript{22} atherosclerosis is an inflammatory disorder. Not only does the disease itself cause an inflammatory response, the inflammatory response exacerbates the disease. It appears that we enter a downward spiral as soon as atherosclerosis starts, the slope of which is powerfully modified by genes and environment. IL-6 and CRP are major participants and markers, reflecting the dual cart-horse nature of this process.

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