Cytokine Serum Levels and Septic Myocardial Dysfunction

Is This the Key?

To the Editor:

We read with interest the study by Landesberg et al\(^1\) in a recent issue of CHEST (July 2015) and dealing with the correlation between inflammatory cytokines and myocardial dysfunction in patients with septic shock. In this retrospective analysis, the authors found that biomarkers of cardiac injury, such as high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide, but not plasma concentrations of cytokines were correlated with echocardiographic evidence of systolic myocardial dysfunction, diastolic myocardial dysfunction, or both or with left ventricular dilation, as suggested by increased end-diastolic left ventricular volume. The study offers new perspectives to clarify the complex pathophysiology of septic myocardial dysfunction, and the authors should be commended for their work.

However, some issues need further discussion to better understand whether these findings may be generalizable to all patients with sepsis. These data come from a single-center cohort (N\(=\)262) that had been previously evaluated for the occurrence of diastolic dysfunction.\(^2\) Blood samples obtained at the time of echocardiography examination in 105 patients were used to assess serum concentration of various inflammatory cytokines, including IL-1\(\beta\), IL-6, and tumor necrosis factor (TNF)-\(\alpha\), which have been extensively evaluated in the pathogenesis of septic myocardial dysfunction.\(^3\) The first measurement of plasma cytokines was within 2 days after diagnosis of sepsis, and the second one was on the next working day. Serum concentrations of IL-1\(\beta\) and TNF-\(\alpha\) were surprisingly low; median IL-1\(\beta\) levels were 3.3 (interquartile range [IQR], 1.2-4.1) pg/mL in survivors and 3.3 (IQR, 1.3-5.0) pg/mL in nonsurvivors (normal values \(\leq\) 5 pg/mL), whereas median TNF-\(\alpha\) concentrations were 23.5 (IQR, 15.8-47.8) pg/mL in survivors and 34.0 (IQR, 24.0-60.7) pg/mL in nonsurvivors (normal values \(\leq\) 20 pg/mL).

One may argue that these results might have been influenced by the late timing of blood sampling after the diagnosis of sepsis. Indeed, Michie et al\(^4\) measured circulating TNF-\(\alpha\) 2 h after IV administration of endotoxin in 13 healthy volunteers. Peak TNF-\(\alpha\) concentrations (240 ± 70 pg/mL) were obtained within 180 min since endotoxin administration and decreased to within normal values only 4 h later. Similarly, Cain et al\(^5\) showed that both TNF-\(\alpha\) and IL-1\(\beta\) induced alterations in human myocardial function in a concentration-dependent fashion, and the maximal myocardial alterations were observed 120 min after the highest levels of TNF-\(\alpha\) (250 pg/mL) and IL-1\(\beta\) (200 pg/mL) were achieved. Moreover, the combination of both cytokines could induce the same myocardial dysfunction at lower concentrations than those observed with high TNF-\(\alpha\) and IL-1\(\beta\) levels alone, suggesting a synergistic effect of such mediators on myocardial contractility. Thus, the results of Landesberg et al\(^1\) should be reconsidered with the limitation of delayed cytokine assessment, which may have underestimated the initial peak concentrations. Additionally, the lack of a combined cytokine evaluation, as a synergistic phenomenon that may still contribute to myocardial dysfunction even at low cytokine levels, is another important confounder. Further prospective studies are warranted to investigate the early relationship between cytokine levels and septic myocardial dysfunction in a real-life clinical setting.

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1. Landesberg G, Levin PD, Gilon D, et al. Myocardial dysfunction in severe sepsis and septic shock: no correlation with inflammatory...


