CHEST™

Myocardial Dysfunction in Severe Sepsis and Septic Shock

No Correlation With Inflammatory Cytokines in Real-life Clinical Setting

Giora Landesberg, MD, DSc; Phillip D. Levin, MA, BChir; Dan Gilon, MD; Sergey Goodman, MD; Milena Georgieva, MD; Charles Weissman, MD; Allan S. Jaffe, MD; Charles L. Sprung, MD, FCCP; and Vivian Barak, PhD

BACKGROUND: In vitro studies suggested that circulating inflammatory cytokines cause septic myocardial dysfunction. However, no in vivo clinical study has investigated whether serum inflammatory cytokine concentrations correlate with septic myocardial dysfunction.

METHODS: Repeated echocardiograms and concurrent serum inflammatory cytokines (IL-1β, IL-6, IL-8, IL-10, IL-18, tumor necrosis factor-α, and monocyte chemoattractant protein-1) and cardiac biomarkers (high-sensitivity [hs] troponin-T and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) were examined in 105 patients with severe sepsis and septic shock. Cytokines and biomarkers were tested for correlations with systolic and diastolic dysfunction, sepsis severity, and mortality.

RESULTS: Systolic dysfunction defined as reduced left ventricular ejection fraction (LVEF) < 50% or < 55% and diastolic dysfunction defined as e′-wave < 8 cm/s on tissue-Doppler imaging (TDI) or E/e′-ratio were found in 13 (12%), 24 (23%), 53 (50%), and 26 (25%) patients, respectively. Forty-four patients (42%) died in-hospital. All cytokines, except IL-1, correlated with Sequential Organ Failure Assessment and APACHE (Acute Physiology and Chronic Health Evaluation) II scores, and all cytokines predicted mortality. IL-10 and IL-18 independently predicted mortality among cytokines (OR = 3.1 and 28.3, $P = .006$ and < 0.0001). However, none of the cytokines correlated with LVEF, end-diastolic volume index (EDVI), stroke-volume index (SVI), or s′-wave and e′-wave velocities on TDI (Pearson linear and Spearman rank [ρ] nonlinear correlations). Similarly, no differences were found in cytokine concentrations between patients dichotomized to high vs low LVEF, EDVI, SVI, s′-wave, or e′-wave (Mann-Whitney *U* tests). In contrast, NT-proBNP strongly correlated with both reduced LVEF and reduced e′-wave velocity, and hs-troponin-T correlated mainly with reduced e′-wave.

CONCLUSIONS: Unlike cardiac biomarkers, none of the measured inflammatory cytokines correlates with systolic or diastolic myocardial dysfunction in severe sepsis or septic shock.

CHEST 2015; 148(1):93-102

Manuscript received September 12, 2014; revision accepted December 3, 2014; originally published Online First January 15, 2015.

ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; hs = high sensitivity; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SOFA = Sequential Organ Failure Assessment; SVI = stroke volume index; TDI = tissue Doppler imaging; TNF = tumor necrosis factor

AFFILIATIONS: From the Departments of Anesthesiology and Critical Care Medicine (Drs Landesberg, Levin, Goodman, Georgieva, Weissman, and Sprung), the Department of Cardiology (Dr Gilon), and the Immunology Laboratory (Dr Barak), Hadassah – Hebrew University Medical Center, Jerusalem, Israel; and the Cardiovascular Department of Laboratory Medicine and Pathology (Dr Jaffe), Mayo Clinic, Rochester, MN.

FUNDING/SUPPORT: This study was funded in major part by the International Anesthesia Research Association (IARS) 2006 Clinical Scholar Research Award (CSRA) and in part by a grant from Hadassah Hospital.

CORRESPONDENCE TO: Giora Landesberg, MD, DSc, Department of Anesthesiology and Critical Care Medicine, Hadassah – Hebrew

Sepsis is a dysregulated inflammatory overresponse of the immune system to the invasion of pathogenic organisms.[1] Mortality from severe sepsis and septic shock is high (30%-40%) despite the best available treatments and is mostly the result of septic shock and multiorgan failure. The cardiovascular system plays a key role in the pathophysiology of septic shock, organ failure, and death. Since the first clinical demonstrations of septic myocardial depression in the 1980s and the observation that serum obtained from patients with septic shock depresses the contractility of isolated rat myocardial cells,[2,3] numerous experimental in vitro studies attempted to explore the complex molecular-cellular inflammatory pathways potentially leading to septic myocardial dysfunction.[4,5] In vitro studies showed that circulating inflammatory substances, specifically cytokines, possess cardiodepressant effects.[6] Proinflammatory cytokines most intensively studied were tumor necrosis factor (TNF)-α, IL-1β, and IL-6.[7-13] However, despite intensive laboratory efforts, the mechanisms responsible for septic myocardial dysfunction remain elusive, and the paucity of clinical evidence for an association of circulating cytokines with septic myocardial dysfunction is notable.

We have demonstrated that diastolic dysfunction is more common than systolic dysfunction and strongly predicts mortality in patients with severe sepsis and septic shock.[14,15] In this study we aimed to investigate whether diastolic or systolic dysfunction on echocardiography in severe sepsis and septic shock can be explained by increased circulating inflammatory cytokine concentrations.

Materials and Methods

The final 105 patients included in our previously published echocardiography study[14] composed the patient group for this study. As previously reported,[14] after approval by the Institutional Review Board (Hadassah Medical Organization 0034-11-HMO), patients with severe sepsis and septic shock admitted to the general intensive care unit were enrolled. Severe sepsis was defined as the presence of (1) infection or serious clinical suspicion for infection, (2) at least two signs of systemic inflammatory response syndrome, and (3) at least one organ dysfunction.[16] Septic shock was defined as severe sepsis and hypotension (systolic BP $<$ 90 mm Hg) lasting $>$ 1 h, not responding to fluids, and requiring vasopressor therapy.[17] Excluded were patients with more than mild mitral and/or aortic valve disease (insufficiency or stenosis), patients with regional myocardial wall motion abnormality on echocardiography suggesting myocardial ischemia or infarction, and patients with poor quality echocardiographic images.

Echocardiography

As previously reported,[14] all patients underwent two transthoracic echocardiography examinations using a Phillips Sonos 5500 machine and a S4 2-4 MHz probe. The first examination was as early as possible after admission to the ICU with the diagnosis of sepsis and the second was performed on the following day. All echocardiograms were performed by one experienced sonographer, and data were analyzed by two experts who were blinded to the treatment and outcome of the patients. Differences in interpretations were resolved by agreement. Measurements included left ventricular end-diastolic volume, left ventricular end-systolic volume, stroke volume, left ventricular ejection fraction (LVEF), peak mitral inflow E- and A-wave velocities, E-wave deceleration time, isovolumic relaxation time, and mitral inflow velocity of propagation. The systolic s′ and diastolic e′ and a′ peak velocities were obtained by tissue Doppler imaging (TDI) at both the septal and lateral mitral origins on four-chamber apical view, and the left ventricular (LV) filling index E/e′ ratio was calculated.[18,19] Peak systolic tricuspid insufficiency gradient was measured. Echocardiography results were available for the treating physicians, but patients were not treated to reach any specific echocardiographic goal.

Blood samples were obtained in two different aliquots at the time of echocardiography. Samples were immediately centrifuged and serum stored at −70°C. One aliquot was used for measurements of the cardiac biomarkers: high-sensitivity (hs) troponin-T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Elecsys Assays; Roche Diagnostics) and the other for measurements of cytokines: TNF-α, IL-1β, -6, -8, -10, and -18, and monocyte chemoattractant protein-1 (normal values: $\leq$20, $\leq$5, $\leq$6, $\leq$70, $\leq$10, 250, and 722 pg/mL, respectively). Cytokines were measured by solid phase enzyme-linked immunosorbent assay kits (R&D Systems, Inc). These particular cytokines were chosen because they were most frequently cited in the literature in relation to sepsis and to myocardial dysfunction.

Clinical Data

All demographic, clinical, hemodynamic, respiratory and laboratory results, and therapies were prospectively collected. Admission APACHE (Acute Physiology and Chronic Health Evaluation) II score and daily Sequential Organ Failure Assessment (SOFA) were calculated on the days of echocardiography. In-hospital and up to 2 years mortality data were collected from the hospital's registry continually updated by the Ministry of the Interior. LV systolic dysfunction was defined using two cutoffs levels: LVEF $<$ 50% or LVEF $<$ 55%. LV diastolic dysfunction was defined as peak septal e′-wave $<$ 8 cm/s based on previous observation that these patients have significantly worse survival.[14]

Statistics

Student *t*-test, χ^2, or Mann-Whitney *U* tests were used to compare the distributions of continuous and dichotomous variables. Normality of distribution of all continuous variables was explored by examining skewness, kurtosis, and Q-Q plots. Variables with skewed distributions (skewness or kurtosis $>$ 2 or $<$ −2) were log-transformed before further analysis. After $\log_{10}$ transformation, all biomarkers (cardiac and cytokines) had close to normal distribution with skewness or kurtosis $>$ 2 or $<$ −2. Pearson linear correlation and Spearman rank nonparametric correlation were used to assess correlations among all continuous variables. The main echocardiography parameters of systolic and diastolic dysfunction were also dichotomized, and the log-transformed cytokine and biomarker concentrations were compared for the dichotomized variables. Benjamini-Hochberg step-up false-discovery-rate method was used to adjust *P* values for multiple comparisons, and both adjusted and unadjusted *P* values were reported.

University Medical Center, Jerusalem 91120, Israel; e-mail: giora.lan@mail.huji.ac.il

DOI: 10.1378/chest.14-2259