

technologies to discover novel prognostic markers and incorporated them in a discrete predictive model. Future innovations will likely push the field to further successes. For example, the incorporation of other factors such as RNA not coding for protein (e.g., noncoding microRNAs) may be important as we take more of a systems biology approach going forward. In systems biology—through a multidimensional view and investigation—the crosstalk of genomic information exchange in the various spaces (e.g., epigenetics, transcriptomics, proteomics, and metabolomics) hold the potential to advance our understanding of sepsis (5). Sepsis remains a growing public health problem, and more studies focusing on the pathophysiology, diagnosis, risk stratification, and treatment are urgently needed.

Omics technologies will be a valuable tool in this search for new diagnostics and therapeutics.

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Cardiac Troponins in Sepsis: An Indication for Echocardiography?*

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Abnormalities of plasma cardiac troponin (cTn) are a common observation in critically ill patients, although the meaning of this finding remains uncertain. Troponin is a protein heterotrimer that regulates muscle contraction, and the specific cTn isoform is a highly specific biomarker for myocardial injury. Raised concentrations of cTn T and I were originally used to diagnose classic myocardial infarction, but the sensitivity of these assays has ultimately led to a completely new definition of this condition (1). We now know that abnormalities of cTns are commonly found in a range of acute illnesses in the absence of myocardial infarction. In most settings, including unselected critically ill patients, these elevations are associated with poor clinical outcomes, even when the abnormality is slight (2).

Sepsis is associated with elevated cTn, with a reported frequency between 43% and 100%, depending on the sensitivity of the assay used (2). The etiology is unclear but initial suspicions of impaired renal clearance have been disproved (3).

*See also p. 790.

Key Words: echocardiography; heart failure; sepsis; troponin

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While cTn rises are more common in septic patients with known coronary artery disease (CAD) (4), elevations can occur in the absence of acute or chronic CAD (5). Proposed mechanisms include ventricular strain, demand ischemia, impaired microvascular flow, and circulating myocytotoxins (6), but the cause is almost certainly multifactorial.

In this issue of *Critical Care Medicine*, Landesberg et al (7) report the findings of an interesting study designed to clarify the etiology of cTn elevations in sepsis by correlating cTn concentrations with echocardiographic findings in patients with severe sepsis or septic shock. They included 106 patients and 225 examinations, encompassing routine as well as more specialized variables describing ventricular size and function. Their findings suggest a relationship between echocardiographic measures of ventricular function and elevated cTn concentrations. Interestingly, they found that left ventricular diastolic rather than systolic dysfunction and right ventricular dilatation were most strongly correlated with plasma cTnT, as measured by mitral E-to-strain-rate e'-wave ratio and right ventricular end-systolic volume index.

The authors note that although both right and left ventricular dysfunction have been associated with cTn abnormalities, their study does not establish a causal relationship between these findings and the release of cTn in sepsis.

These observations certainly progress our understanding of the acute heart failure that occurs in sepsis and will help us to better define the optimal treatments for this life-threatening condition. However, some uncertainty does remain. The correlations between specific variables are not strong, and it is possible that the defined relationship may change in a larger series, affecting our understanding of the mechanics of this cause of heart failure.

It is important to understand whether the observed cTn release specifically relates to sepsis-induced myocardial injury or to additional demands placed on the heart in critical illness. The extent of preexisting cardiac dysfunction may also prove

an important factor. Sepsis is frequently accompanied by systolic and diastolic ventricular dysfunction (8–10). The cause is once again uncertain, but seems likely to be multifactorial (11), and can occur in previously healthy hearts and even in children with septic shock (12). However, since the prevalence of diastolic dysfunction may be as high as 27% in the general population (13), it is possible that preexisting heart failure could be a factor. Similarly, patients with chronic lung disease may have an increased prevalence of right ventricular dysfunction.

A better understanding of the underlying causes of cTn elevation in septic and other critically ill patients is clearly important as we strive to optimize treatment (2). There is some debate whether plasma cTn is an independent prognostic marker in sepsis or simply a surrogate for overall severity of illness (4, 6). cTn abnormalities are also common in the postoperative setting (14), but some clinicians have argued that routine testing may simply increase the risk of harm from inappropriate treatment for myocardial infarction (15). However, the work by Landesberg et al suggests that there may be value in investigating the cause of cTn abnormalities in sepsis using echocardiography to identify and assess potential targets for therapy.

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Early Detection of Deteriorating Patients: Leveraging Clinical Informatics to Improve Outcome*

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*See also p. 801.

Key Words: clinical decision support; critical care informatics; early deterioration; Modified Early Warning System (MEWS); rapid response team
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Over the past 25 years, we have witnessed an abundance of studies demonstrating that significant physiologic deterioration occurs in patients prior to cardiac or respiratory arrest (1). Rapid response systems (RRS) have therefore been introduced to intervene in the care of unexpected deteriorating patients in order to reduce the prevalence of cardiac arrests, unplanned ICU admissions, and deaths (2). The concept of ICU without walls, the core ingredient of the RRS, essentially applies critical care expertise and skills outside the ICU, at the patient's bedside as soon as deterioration is detected. Despite the fact that preventing, recognizing, and treating deteriorating patients early is good common sense, more than a decade after the introduction of such medical emergency teams (3), studies have failed to demonstrate consistent benefit (4).

For an RRS to be effective, it must have a reliable afferent limb whereby early detection and recognition of decompensating

Troponin Elevation in Severe Sepsis and Septic Shock: The Role of Left Ventricular Diastolic Dysfunction and Right Ventricular Dilatation*

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Objective: Serum troponin concentrations predict mortality in almost every clinical setting they have been examined, including sepsis. However, the causes for troponin elevations in sepsis are poorly understood. We hypothesized that detailed investigation of myocardial dysfunction by echocardiography can provide insight into the possible causes of troponin elevation and its association with mortality in sepsis.

Design: Prospective, analytic cohort study.

Setting: Tertiary academic institute.

Patients: A cohort of ICU patients with severe sepsis or septic shock.

Interventions: Advanced echocardiography using global strain, strain-rate imaging and 3D left and right ventricular volume analyses in addition to the standard echocardiography, and con-

comitant high-sensitivity troponin-T measurement in patients with severe sepsis or septic shock.

Measurements and Main Results: Two hundred twenty-five echocardiograms and concomitant high-sensitivity troponin-T measurements were performed in a cohort of 106 patients within the first days of severe sepsis or septic shock (2.1 ± 1.4 measurements/patient). Combining echocardiographic and clinical variables, left ventricular diastolic dysfunction defined as increased mitral E-to-strain-rate e'-wave ratio, right ventricular dilatation (increased right ventricular end-systolic volume index), high Acute Physiology and Chronic Health Evaluation-II score, and low glomerular filtration rate best correlated with elevated log-transformed concomitant high-sensitivity troponin-T concentrations (mixed linear model: $t = 3.8, 3.3, 2.8,$ and -2.1 and $p = 0.001, 0.0002, 0.006,$ and 0.007 , respectively). Left ventricular systolic dysfunction determined by reduced strain-rate s'-wave or low ejection fraction did not significantly correlate with log(concomitant high-sensitivity troponin-T). Forty-one patients (39%) died in-hospital. Right ventricular end-systolic volume index and left ventricular strain-rate e'-wave predicted in-hospital mortality, independent of Acute Physiology and Chronic Health Evaluation-II score (logistic regression: Wald = 8.4, 6.6, and 9.8 and $p = 0.004, 0.010,$ and 0.001 , respectively). Concomitant high-sensitivity troponin-T predicted mortality in univariate analysis (Wald = 8.4; $p = 0.004$), but not when combined with right ventricular end-systolic volume index and strain-rate e'-wave in the multivariate analysis (Wald = 2.3, 4.6, and 6.2 and $p = 0.13, 0.032,$ and 0.012 , respectively).

Conclusions: Left ventricular diastolic dysfunction and right ventricular dilatation are the echocardiographic variables correlating best with concomitant high-sensitivity troponin-T concentrations. Left ventricular diastolic and right ventricular systolic dysfunction seem to explain the association of troponin with mortality in severe sepsis and septic shock. (*Crit Care Med* 2014; 42:790–800)

Key Words: diastolic dysfunction; mortality; myocardial dysfunction; sepsis; troponin

*See also p. 975.

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An abstract of this work was presented in the latest Society of Critical Care Medicine (SCCM) meeting (January 2013) and received the SCCM Annual Scientific Award.

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Cardiac troponins predict mortality in almost every clinical scenario in which they have been investigated. This is true not only for patients with acute coronary syndrome (ACS) but also in non-ACS acute settings such as sepsis (1), pulmonary embolus, stroke, and critical illnesses (2). In ACS, troponin elevations represent myocardial injury or necrosis secondary to coronary artery occlusion, yet the mechanisms leading to troponin elevations and the reasons why troponin is such an important predictor of mortality in non-ACS settings are poorly understood. Hypotheses for troponin elevations in sepsis include inflammation, direct toxicity by drugs or circulating substances, increased myocardial wall stress by pressure or volume overload, and renal dysfunction (3).

We recently showed that in severe sepsis and septic shock, left ventricular (LV) diastolic dysfunction and reduced LV volumes are common and predict mortality better than systolic dysfunction (4). So as to further define what manifestations of myocardial dysfunction correlate with troponin elevation and might explain its association with mortality in sepsis, myocardial function in this new cohort was studied using more comprehensive and advanced echocardiography techniques including 3D LV and right ventricular (RV) volume measurements and strain and strain-rate imaging by speckle tracking.

METHODS

With the approval of the institutional review board, consecutive patients with severe sepsis and septic shock admitted to the general ICU between April 2009 and March 2011 were studied repeatedly. Severe sepsis was defined in the presence of all three criteria: 1) evidence of infection or serious clinical suspicion for infection; 2) at least two signs of systemic inflammatory response syndrome: a) temperature greater than 38°C or less than 36°C; b) pulse greater than 90/min; c) respiratory rate greater than 20/min or the need for mechanical ventilation; and d) WBCs greater than 12,000 or less than 4,000 or greater than 10% bands; and 3) evidence of at least one organ dysfunction (5). Septic shock was defined as severe sepsis plus hypotension (systolic blood pressure < 90 mm Hg) lasting more than 1 hour, not responding to fluid therapy (raising central venous pressure to 12 or 15 mm Hg in patients with oliguria) and requiring vasopressor therapy (6). Excluded were patients with greater than mild mitral and/or aortic valve disease, patients with echocardiographic evidence of regional myocardial wall motion abnormalities suggesting ischemia or previous infarction, patients with poor-quality echocardiographic images and measurements, as well as patients with atrial fibrillation whose uneven cardiac beats interfere with echocardiographic measurements. All echocardiography results were open to the treating physicians but patients were not treated to achieve any specific echocardiographic goal.

Echocardiography

Patients underwent repeated, transthoracic 2D and 3D echocardiography examinations using a Philips' IE33 echocardiograph with the S5-1 sector array and the 3D X3-1 xMatrix array transducers (Philips HealthCare, Eindhoven, The

Netherlands). The first examination was performed on the day of admission or as early as possible after admission to the ICU and diagnosis of severe sepsis. All echocardiography examinations were performed by one experienced sonographer. Data were analyzed by two experienced investigators who were blinded to the treatment of the patients and differences in interpretation and measurements were resolved by agreement. In addition to the qualitative assessments of chambers and valvular pathologies, the following measurements were made: peak mitral inflow E and A velocity waves, E-wave deceleration time, isovolumic relaxation time, color M-mode mitral inflow velocity of propagation, peak systolic tricuspid insufficiency (TI) gradient whenever possible, systolic s' , diastolic e' and a' peak velocities by tissue Doppler imaging (TDI) at both the septal and lateral mitral origins, and LV filling index E/ e' ratio.

Ventricular Volume Acquisition and Measurements

Left ventricular end-diastolic volume, left ventricular end-systolic volume, left ventricular stroke volume, and ejection fraction were calculated using modified biplane Simpson's rule. LV and RV volumes were also acquired from the apical view by the 3D xMatrix transducer (Philips HealthCare), using "full-volume" mode of acquisition during four heart cycles (frame rate, 13–20 Hz). Repeated acquisitions were made for each ventricle so as to obtain the best entire volume of the right and left ventricles separately. LV volumes were calculated off-line using Philips' Qlab 8.1 3DQ-advanced package (Philips HealthCare). RV volumes were measured off-line with TomTec's Image Arena and 4D RV-Function package (TomTec Imaging Systems, Unterschleißheim, Germany). The results of the repeated volume measurements on the same examination were averaged.

Strain and Strain-Rate Imaging

Apical long-axis (four- and two-chamber) and short-axis (midpapillary and basal) clips obtained with a frame rate of greater than or equal to 50 Hz underwent off-line speckle-tracking analyses using the semiautomated Philips' Qlab 8.1 CMQ package (Philips HealthCare). The average of two consecutive heart cycles was used to calculate global longitudinal and global circumferential strains and strain rates. Peak global strain (ϵ_{\max}) and peak systolic, peak early diastolic, and peak late diastolic strain-rate waves (SRs', SRe', and SRa', respectively) were identified and recorded.

Blood Samples

Blood samples were obtained on the days of the echocardiography examinations, centrifuged, and serum stored at -70°C for measurements of concomitant high-sensitivity troponin-T (hs-cTnT) (Roche Diagnostics, Elecsys Assays; Indianapolis, IN). A value of 14 pg/mL, which is the 99th percentile of normal population reported for this assay, was considered as normal (7).

Clinical Data

All demographic, clinical, hemodynamic, respiratory, laboratory results and therapies from the time of diagnosis of severe sepsis or septic shock and on the days of echocardiography

examinations were prospectively collected. Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula (8). Acute Physiology and Chronic Health Evaluation (APACHE)-II scores were calculated on the day of admission and on the days of echocardiography examinations. Mortality data during hospitalization and within 1 year follow-up were collected from the hospital's registry, which is continually updated by the Israeli Ministry of Interior.

Statistical Analyses

Student *t* tests and chi-square tests were used to compare means and distributions of continuous and dichotomous variables, respectively. Values of hs-cTnT with exponential distribution were log-transformed for the purpose of linear analyses. Univariate and multivariate mixed general linear models (GLMs) were used to examine correlations of echocardiographic and clinical variables with $\log_{10}(\text{hs-cTnT})$, due to the ability of mixed GLM to adjust for unbalanced repeated measurements. In the mixed GLM, patient identity was entered as the subject grouping, the dichotomous and continuous variables were entered as factors and covariates, respectively, and their fixed effects were estimated. Multivariate analyses were performed in two stages. First, the variables independently correlating with $\log_{10}(\text{hs-cTnT})$ among clinical and among echocardiography variables were determined separately. Then, the independent clinical and independent echocardiographic variables selected on the first multivariate analyses were subjected together into the multivariate analysis combining both types of variables. Similar steps were employed for multivariate survival analyses. For the purpose of survival analyses only, all clinical and echocardiographic data were averaged per patient across all dates of repeated echocardiography examinations. Univariate and multivariate logistic regression with backward stepwise selection were used to identify predictors of in-hospital mortality. Receiver-operator characteristic (ROC) curve analyses served to assess the main predictors of hs-cTnT elevation, using hs-cTnT as a dichotomous outcome variable at different cutoff levels. Statistical analyses were performed using SPSS 19.0 software (SPSS, Chicago, IL).

RESULTS

The study included 225 echocardiography examinations and concurrent hs-cTnT measurements performed in 106 patients (2.1 ± 1.4 per patient; range, 1–6). Excluded were 14 patients with poor-quality echocardiograms, four with atrial fibrillation, eight with significant regional wall motion abnormalities suggesting old myocardial infarction or ischemia, and six with moderate-severe mitral or aortic valve disease. Off-line 3D LV and RV volumes and longitudinal and circumferential strain-rate imaging were measurable in 216 (96%), 200 (89%), 209 (92%), and 202 (91%), of all 225 examinations, respectively. In 93 patients (88%), hs-cTnT was above 14 pg/mL (the upper limit of normal) and in 77 (73%) hs-cTnT was greater than or equal to 100 pg/mL at least once. Median hs-cTnT was 43

pg/mL (interquartile range [IQR], 22, 101 pg/mL). Forty-one patients (39%) died during hospitalization and 51 (48%) died within 1-year follow-up period. ICU and hospital lengths of stay were 29 ± 45 days (median, 16; IQR, 3, 37) and 47 ± 63 days (median, 30; IQR, 15, 61), respectively.

All patients were tracheally intubated and mechanically ventilated at the time of echocardiography examinations. The main sources of sepsis were gastrointestinal 48 (45%), multitrauma with wound infections 19 (18%), pulmonary 13 (12%), vascular surgery/limb ischemia 10 (9%), genitourinary 8 (8%), orthopedic/skeletal 5 (5%), and burns 3 (3%). Positive cultures were present in 104 patients (98%), 48 (46%) with at least one positive blood culture. Hypotension (systolic blood pressure < 90 mm Hg for > 1 hr) occurred in 93 patients (88%). Mean duration of hypotension was 6.1 ± 3.7 hr/d/patient (IQR, 3.5–8.3 hr). In 67 patients (63%), septic shock persisted despite fluid resuscitation and these patients required one or more vasoactive medications: norepinephrine 66 (62%), epinephrine 27 (25%), vasopressin 20 (19%), and dopamine/dobutamine 6 (6%). **Table 1** compares patients who died or survived the hospitalization.

Correlations With hs-cTnT Concentration

Tables 2 and **3** summarize the clinical and echocardiographic correlations with $\log(\text{hs-cTnT})$. Among clinical variables, only history of ischemic heart disease, eGFR, and APACHE-II score independently correlated with $\log_{10}(\text{hs-cTnT})$ concentrations by multivariate analysis (**Table 2**). Among echocardiographic variables, increased right ventricular end-systolic volume index (RVESVi) and increased E/SRe'-wave ratio independently correlated with $\log_{10}(\text{hs-cTnT})$ (**Table 3** and **Fig. 1**). Among the independent clinical and echocardiographic correlates of $\log_{10}(\text{hs-cTnT})$, RVESVi, E/SRe' ratio, eGFR, and APACHE-II score significantly correlated with $\log_{10}(\text{hs-cTnT})$ (**Table 4**).

ROC curve analyses using hs-cTnT as a dichotomous variable at four different cutoff values—14 pg/mL (99th percentile of normal), 43 pg/mL (median hs-cTnT), 100 and 200 pg/mL—showed that APACHE-II score and eGFR predicted hs-cTnT elevation at all cutoff levels, whereas RVESVi, SRe'-wave, and TDIE'-wave predicted hs-cTnT elevations only at the higher cutoff values (100 and 200 pg/mL), and E/SRe' ratio and E/TDIE' ratio predicted hs-cTnT elevations only at its lower cutoff values (14 and 43 pg/mL) (**Table 5**).

In-Hospital Mortality

Tables 2 and **3** also summarize the clinical and echocardiographic predictors of in-hospital mortality. Among clinical predictors, APACHE-II score and reduced systolic blood pressure predicted in-hospital mortality by multivariate analysis (**Table 3**). Among echocardiographic variables, only RVESVi, longitudinal SRe'-wave, and TI gradient were the independent predictors of in-hospital mortality. TI gradient was measurable in only 79% of the patients, and when TI gradient was excluded from the multivariate analysis, RVESVi was an even stronger predictor of mortality (**Table 3**). Upon submitting the

TABLE 1. Characteristics of Patients Who Died or Survived the Hospitalization

Variables	Survived	Died	p
	n = 65 (mean ± sd)	n = 41 (mean ± sd)	
Age	60.0±20.3	71.3±14.8	0.003
Ischemic heart disease (%)	14 (21)	9 (22)	0.57
Hypertension (%)	17 (26)	12 (29)	0.45
Diabetes mellitus (%)	16 (25)	14 (22)	0.67
Heart rate	105±85	93±15	0.45
Blood pressure—systolic/diastolic	122±22/62±15	112±14/56±10	0.027/0.045
Lowest oxygen saturation	90.9±3.7	87.3±6.6	0.003
Lowest pH	7.33±0.24	7.32±0.11	0.75
Serum creatinine	1.4±1.1	2.4±1.3	<0.0001
Estimated glomerular filtration rate	72±40	36±23	<0.0001
Acute Physiology and Chronic Health Evaluation-II score	17.4±5.4	24.9±6.3	<0.0001
Septic shock and vasopressor therapy	33 (51%)	31 (77%)	0.012
High-sensitivity troponin-T (pg/mL)	59±67	410±81	0.001
Volumes (3D echocardiography—cm ³ /m ²)			
Left ventricular end-diastolic volume index	56.9±13.5	51.1±12.7	0.047
Left ventricular end-systolic volume index	24.5±8.1	22.0±7.7	0.026
Left ventricular stroke volume index/left ventricular ejection fraction	32.4±7.9/56.2±7.8	29.1±8.4/56.9±12.3	0.34/0.98
Right ventricular end-diastolic volume index	55.9±15.2	67.9±22.4	0.005
Right ventricular end-systolic volume index	32.8±10.9	41.0±15.9	0.007
Right ventricular stroke volume index/right ventricular ejection fraction	23.1±7.6/41.5±9.3	26.9±8.5/40.2±7.5	0.041/0.54
Doppler echo cardiography			
E-wave (cm/s)	93±25	80±28	0.022
A-wave (cm/s)	77±30	76±29	0.94
E-wave deceleration time	177±48	176±59	0.86
Velocity of propagation	55±23	46±20	0.069
Isovolumic relaxation time (ms)	60.2±15.6	70.2±18.0	0.006
Tissue Doppler imaging			
Septal s' (cm/s)	10.3±5.0	9.6±2.4	0.49
e' (cm/s)	8.6±2.8	7.5±2.2	0.038
a' (cm/s)	10.5±3.9	10.3±4.7	0.81
E/e' ratio	12.0±4.8	12.2±5.6	0.90
Lateral s' (cm/s)	11.9±3.7	11.2±3.8	0.36
e' (cm/s)	12.5±3.3	10.4±3.2	0.004
a' (cm/s)	11.7±4.7	11.7±4.3	0.95
E/e' ratio	7.9±3.0	9.0±4.6	0.24

(Continued)

TABLE 1. (Continued) Characteristics of Patients Who Died or Survived the Hospitalization

Variables	Survived	Died	p
	n = 65 (mean ± sd)	n = 41 (mean ± sd)	
Speckle tracking			
Strain			
Longitudinal	-13.7 ± 2.7	-12.3 ± 3.6	0.40
Circumferential	-17.3 ± 4.2	-16.4 ± 4.3	0.37
Strain rate			
Longitudinal			
SRs'-wave	-0.84 ± 0.25	-0.79 ± 0.23	0.41
SRe'-wave	0.87 ± 0.28	0.67 ± 0.23	0.001
SRa'-wave	0.62 ± 0.28	0.60 ± 0.28	0.85
E/SRe' ratio	120 ± 45	141 ± 61	0.088
Circumferential			
SRs'-wave	-1.14 ± 0.37	-1.15 ± 0.32	0.96
SRe'-wave	1.10 ± 0.34	0.86 ± 0.31	0.004
SRa'-wave	0.74 ± 0.34	0.67 ± 0.32	0.45
E/SRe' ratio	94 ± 37	137 ± 125	0.038
Tricuspid insufficiency gradient (mm Hg)	21.7 ± 14.3	31.5 ± 14.6	0.003

SR = strain rate.

independent clinical and independent echocardiographic predictors of mortality into the multivariate analysis, APACHE-II score, increased RVESVi, and decreased longitudinal SRe'-wave independently predicted in-hospital mortality (Table 4).

hs-troponin-T and Mortality

hs-cTnT was a univariate predictor of mortality (Table 2 and Fig. 2). However, hs-cTnT lost its prognostic effect when included in the multivariate logistic regression analysis together with RVESVi and longitudinal SRe'-wave (Wald = 2.3, 4.6, and 6.2; odds ratio = 2.6, 1.05, and 0.43; and $p = 0.13$, 0.032, and 0.012, respectively). Additionally, hs-cTnT did not predict mortality independent of APACHE-II score; however, when patients were split according to their mean APACHE-II score to those below or above median APACHE-II score (19.8), hs-cTnT independently predicted mortality in the low APACHE-II group, not in the high APACHE-II group (odds ratio = 16.0 and 1.2 and $p = 0.045$ and 0.88, respectively).

DISCUSSION

The important findings of the present study are as follows: 1) LV diastolic dysfunction and RV dilatation are the echocardiographic features best correlating with concurrent hs-cTnT concentrations in patients with severe sepsis and septic shock, independent of APACHE-II score and independent of eGFR the strongest clinical variables correlating with hs-cTnT. 2) Both LV diastolic dysfunction and RV dilatation predict

in-hospital mortality better than hs-cTnT, suggesting a potential contribution of these cardiac mechanical properties to the hs-cTnT elevations and to its association with mortality in severe sepsis and septic shock.

We have previously shown using less sophisticated echocardiographic techniques that LV diastolic dysfunction and reduced LV volumes predict mortality in septic patients (4). In the present new cohort, we focused on exploring the cardiac abnormalities potentially explaining troponin elevations in sepsis using the advanced and comprehensive echocardiography tools currently available. Systolic and diastolic functions were assessed with global longitudinal and circumferential strain and strain-rate imaging, in addition to the TDI technique used previously. Ventricular volumes were measured by 3D echocardiography rather than the 2D measurements used previously to provide more accurate ventricular volume measurements, particularly of the RV (9).

The sources of troponin elevation in sepsis and septic shock have long been debated. Sepsis and septic shock are associated with marked increase in coronary blood flow with apparent adequate oxygen consumption and delivery (10, 11). Cardiac troponin elevations in sepsis were shown to occur with no evidence of coronary thrombosis (12). Myocardial systolic dysfunction and ventricular dilatation in septic shock were shown to paradoxically predict better survival and complete recovery of systolic dysfunction in surviving patients (13, 14). Serum obtained from patients with septic shock depressed rat cardiomyocytes' contractility in vitro (15, 16),

TABLE 2. Clinical Correlates of \log_{10} (High-Sensitivity Troponin-T) and In-Hospital Mortality

Variables	Correlation With \log_{10} (High-Sensitivity Troponin-T)				Association With In-Hospital Mortality					
	Mixed General Linear Model ($n = 225$)				Logistic Regression Analysis ($n = 106$)					
	Univariate		Multivariate		Univariate			Multivariate		
	<i>t</i>	<i>p</i>	<i>t</i>	<i>p</i>	Wald	OR	<i>p</i>	Wald	OR	<i>p</i>
Age	4.5	< 0.0001			5.9	1.03	0.015			
Ischemic heart disease	4.6	< 0.0001	2.0	0.046	0.4	1.42	0.53			
Hypertension	3.9	0.0001			0.8	0.66	0.37			
Diabetes mellitus	0.8	0.41			0.7	0.68	0.39			
Heart rate	0.3	0.75			0.37	1.00	0.54			
Blood pressure										
Systolic	−1.4	0.17			4.8	0.97	0.028	4.3	0.95	0.037
Diastolic	0.87	0.38			4.4	0.96	0.035			
Lowest O ₂ saturation	−3.1	0.003			6.9	0.85	0.008			
Lowest pH	1.05	0.29			0.1	0.81	0.85			
Lowest hemoglobin	−1.7	0.087			0.7	0.89	0.41			
Creatinine	7.0	< 0.0001			4.3	1.58	0.037			
Estimated glomerular filtration rate	−8.2	< 0.0001	−3.7	< 0.0001	15.1	0.96	< 0.0001			
Septic shock and vasopressor therapy	3.4	0.001			6.4	3.7	0.011			
Acute Physiology and Chronic Health Evaluation-II score	7.8	< 0.0001	4.9	< 0.0001	13.3	1.24	< 0.0001	12.4	1.26	< 0.0001
High-sensitivity troponin-T					8.4	4.8	0.004			

OR = odds ratio.

TABLE 3. Echocardiographic Correlates of \log_{10} (High-Sensitivity Troponin-T) and In-Hospital Mortality

Variables	Correlation With \log_{10} (High-Sensitivity troponin-T)				Association With In-Hospital Mortality					
	Mixed General Linear Model ($n = 225$)				Logistic Regression Analysis ($n = 106$)					
	Univariate		Multivariate		Univariate			Multivariate		
	<i>t</i>	<i>p</i>	<i>t</i>	<i>p</i>	Wald	OR	<i>p</i>	Wald	OR	<i>p</i>
Volumes (3D echocardiography—cm ³ /m ²)										
Left ventricular end-diastolic volume index	−0.3	0.75			1.1	0.98	0.30			
Left ventricular end-systolic volume index	1.5	0.14			0.04	0.99	0.84			
Left ventricular stroke volume index/left ventricular ejection fraction	−0.1/−0.3	0.92/0.76			2.5/0.2	0.95/0.36	0.11/0.69			
Right ventricular end-diastolic volume index	3.5	0.001			6.1	1.04	0.013			

(Continued)

TABLE 3. (Continued). Echocardiographic Correlates of log₁₀(High-Sensitivity Troponin-T) and In-Hospital Mortality

Variables	Correlation With log ₁₀ (High-Sensitivity troponin-T)				Association With In-Hospital Mortality					
	Mixed General Linear Model (n = 225)				Logistic Regression Analysis (n = 106)					
	Univariate		Multivariate		Univariate			Multivariate		
	t	p	t	p	Wald	OR	p	Wald	OR	p
Right ventricular end-systolic volume index	4.5	< 0.0001	4.4	< 0.0001	6.3	1.06	0.012	4.3	1.05	0.038^a
Right ventricular stroke volume index/right ventricular ejection fraction	0.4/-2.4	0.68/0.018			3.3/0.4	1.06/0.18	0.069/0.53			
Doppler echocardiography										
E-wave	0.04	0.95			4.9	0.98	0.027			
A-wave	-0.7	0.47			0.4	1.00	0.49			
E-wave deceleration time	1.5	0.12			0.02	0.99	0.88			
Velocity of propagation	2.7	0.009			2.2	0.98	0.14			
Isovolumic relaxation time	2.4	0.016			5.3	1.03	0.021			
Tissue Doppler										
Septal s' (cm/s)	-2.2	0.028			0.5	0.96	0.47			
e' (cm/s)	-4.1	< 0.0001			2.9	0.85	0.08			
a' (cm/s)	-2.0	0.044			0.2	0.98	0.67			
E/e' ratio	4.0	0.0002			0.01	0.99	0.97			
Lateral s' (cm/s)	-0.24	0.81			0.9	0.94	0.32			
e' (cm/s)	-2.6	0.011			7.3	0.82	0.007			
a' (cm/s)	-0.34	0.74			0.02	0.99	0.89			
E/e' ratio	3.4	0.001			0.95	1.06	0.38			
Speckle tracking										
Strain										
Longitudinal	2.3	0.022			3.7	1.16	0.054			
Circumferential	1.6	0.10			0.52	1.04	0.47			
Strain rate										
Longitudinal										
SRs'	-0.5	0.43			0.6	2.28	0.42			
SRe'	-4.3	-0.0001			7.5	0.06	0.006	8.1	0.02	0.004
SRa'	-1.6	0.10			0.4	0.56	0.54			
E/SRe'	4.8	< 0.0001	4.5	< 0.0001	1.8	1.01	0.17			
Circumferential										
SRs'	-0.7	0.48			0.001	0.99	0.99			
SRe'	-3.6	0.0004			5.6	0.12	0.018			
SRa'	-1.0	0.28			0.9	0.48	0.34			
E/SRe'	4.5	< 0.0001			2.2	1.01	0.14			
Tricuspid insufficiency gradient (mm Hg)	1.2	0.24			9.9	1.06	0.002	7.3	1.07	0.007

OR = odds ratio, SR = strain rate.

^aWhen tricuspid insufficiency gradient is excluded from the multivariate analysis, Wald = 8.2, OR = 1.05, and p = 0.004.

Bold values signify statistical significance.

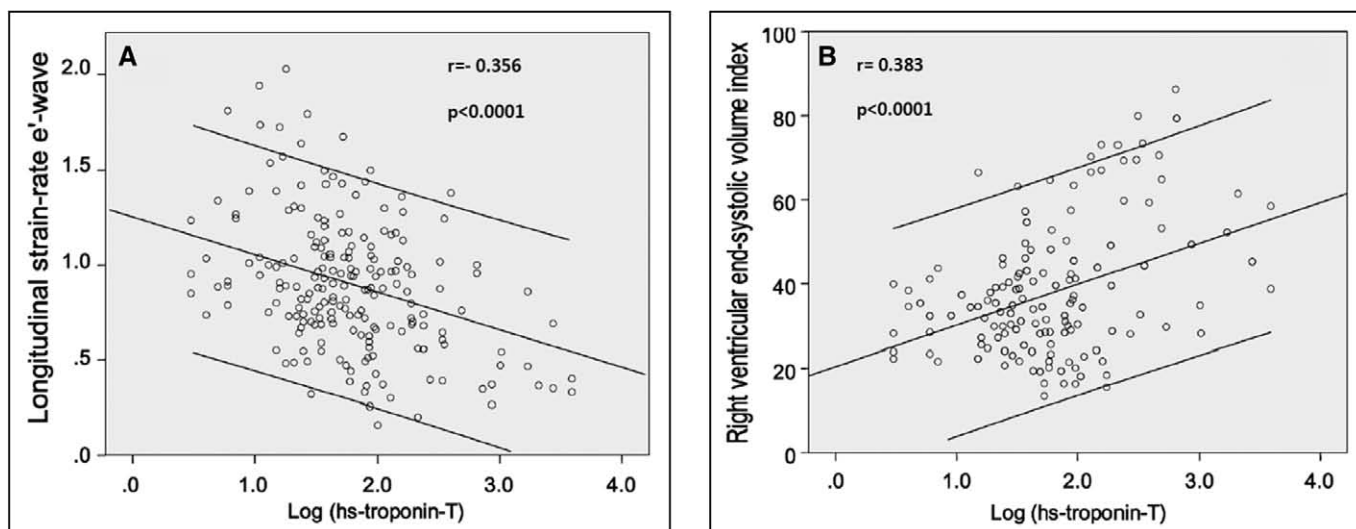


Figure 1. Scatter plots of longitudinal strain-rate e' -wave (s^{-1}) (A) and right ventricular end-systolic volume index (mL/m^2) (B) as functions of log-transformed high-sensitivity troponin-T (hs-troponin-T) (pg/mL).

TABLE 4. Results of Multivariate Analyses When Combining Both Independent Clinical and Independent Echocardiographic Variables

Variables	Correlation With \log_{10} (High-Sensitivity Troponin-T)		Association With In-Hospital Mortality		
	Mixed General Linear Model ($n = 225$)		Logistic Regression Analysis ($n = 106$)		
	<i>t</i>	<i>p</i>	Wald	OR	<i>p</i>
Estimated glomerular filtration rate	-2.1	0.007			
Acute Physiology and Chronic Health Evaluation-II score	2.8	0.006	9.8	1.4	0.001
Right ventricular end-systolic volume index	3.3	0.001	8.4	1.06	0.004
Longitudinal SRe' -wave			6.6	0.02	0.010
Longitudinal E/SRe' -ratio	3.8	0.0002			

OR = odds ratio, SR = strain rate.

Bold values signify statistical significance.

and inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6, cause apoptosis in animal and human cardiac myocytes (17, 18), leading to the notion of circulating depressant substances in septic shock. However, none of these experimental studies showed an association of circulating depressant substances with serum troponin elevation. To the contrary, septic shock simulated in healthy volunteers by IV injection of endotoxin causing high and clinically significant increases in serum TNF- α , IL-6, and IL-8 concentrations failed to cause any increase in serum cardiac troponin (19). Furthermore, circulating depressant substances in these experimental studies were shown to cause systolic, not diastolic dysfunction, while diastolic dysfunction rather than systolic dysfunction correlated with hs-cTnT concentrations in the present study. Renal failure common in severe sepsis and septic shock is frequently blamed for the troponin elevations either due to decreased renal excretion of

troponin or secondary to the presumed cardiotoxic circulating products accumulating in renal failure. Renal dysfunction was associated with hs-cTnT in this study too, but LV diastolic dysfunction and RV dilatation correlated with hs-cTnT concentrations independent of serum creatinine or eGFR. Troponin release from cardiac myocytes is thought to occur as a result of the cardiovascular shock by mechanisms such as myocardial oxygen supply-demand imbalance, apoptosis, and increased cellular permeability, even with no serious coronary artery disease (20). Increases in endogenous or exogenous catecholamines in septic shock were suggested as possible causes of such cardiac toxicity and injury (21). In the present study, all patients with septic shock unresponsive to fluids only received vasopressor therapy, and septic shock (and/or vasopressor therapy) was indeed associated with hs-cTnT concentrations on univariate analysis. However, septic shock (or vasopressor use) failed to independently correlate with

TABLE 5. Predictors of High-Sensitivity Troponin-T Elevation by Receiver-Operator Characteristic Curve Analysis (n = 225)

	hs-Troponin-T ≥ 14 pg/mL (99th Percentile)		hs-Troponin-T ≥ 43 pg/mL (Median Concomitant High-Sensitivity Troponin-T Level)		hs-Troponin-T ≥ 100 pg/mL		hs-Troponin-T ≥ 200 pg/mL	
	c-Index	p	c-Index	p	c-Index	p	c-Index	p
Age	0.61±0.09	0.22	0.51±0.05	0.83	0.56±0.05	0.28	0.59±0.06	0.26
Lowest O ₂ saturation	0.49±0.08	0.87	0.51±0.06	0.79	0.45±0.07	0.48	0.40±0.08	0.24
Estimated glomerular filtration rate	0.21±0.07	0.001	0.31±0.06	0.003	0.23±0.05	< 0.0001	0.19±0.05	< 0.0001
Acute Physiology and Chronic Health Evaluation-II score	0.77±0.07	0.002	0.65±0.04	0.006	0.83±0.04	< 0.0001	0.80±0.06	< 0.0001
Echocardiography								
Right ventricular end- systolic volume index	0.55±0.08	0.62	0.53±0.05	0.58	0.67±0.08	0.019	0.77±0.07	0.0003
SRe-wave (longitudinal)	0.45±0.09	0.60	0.39±0.05	0.027	0.35±0.06	0.012	0.22±0.06	0.0002
E/SRe'-wave	0.68±0.05	0.010	0.66±0.04	0.001	0.57±0.06	0.23	0.61±0.10	0.19
TDIe'-wave (septal)	0.52±0.09	0.82	0.45±0.05	0.36	0.37±0.06	0.041	0.20±0.06	0.0004
E/TDIe'-wave	0.66±0.06	0.025	0.63±0.04	0.003	0.58±0.06	0.14	0.65±0.09	0.083

hs = high sensitivity, SR = strain rate, TDI = tissue Doppler imaging.

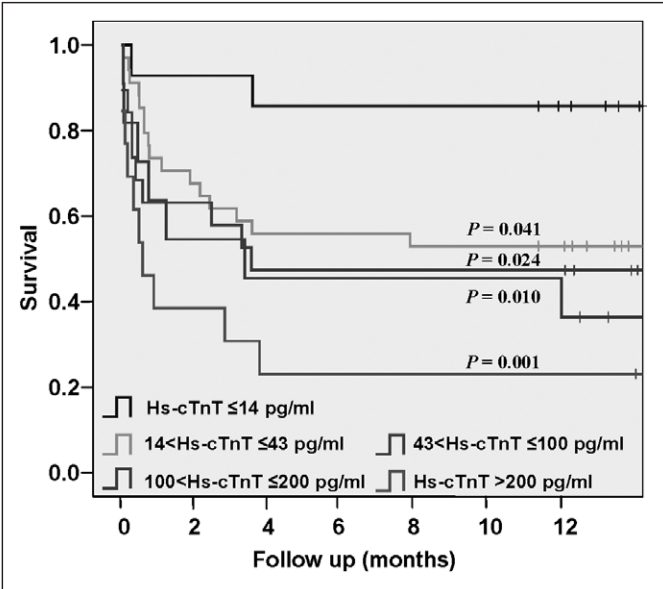


Figure 2. Kaplan-Meier survival curves of all patients divided into five groups according to their highest high-sensitivity troponin-T: < 14 pg/mL, 14–43 pg/mL, 43–100 pg/mL, 100–200 pg/mL, and > 200 pg/mL. Fourteen picograms per milliliter is the 99th percentile of normal distribution with this assay. Forty-three picograms per milliliter was the median concomitant high-sensitivity troponin-T (hs-cTnT) value in the study population. *p* values represent log-rank statistical comparisons with the first group.

hs-cTnT when included with LV diastolic dysfunction and RV dilatation in multivariate analysis. Hence, all the above-mentioned mechanisms likely contribute to serum troponin elevation, yet they do not contradict the probable important

role of LV diastolic RV systolic dysfunction in troponin elevation in septic patients.

Diastolic Dysfunction and Troponin Elevations

TDI-defined diastolic dysfunction in conjunction with elevated hs-cTnT concentrations were reported by a few previous small studies in septic patients (22–25). TDI-defined diastolic dysfunction was also reported in patients with heart failure and normal ejection fraction (26), in chronic kidney disease (27), in subarachnoid hemorrhage (28), and in marathon runners (29). An increase in preload causing troponin degradation was demonstrated in isolated animal hearts in the absence of myocardial ischemia (30). However, none of these studies compared the correlations of all systolic and diastolic echocardiographic features with concurrent hs-cTnT concentrations to show the relative importance of diastolic dysfunction, as in the present study.

Diastolic dysfunction identified by reduced *e'*-waves using both speckle tracking and TDI strongly correlated with hs-cTnT, although in the present study strain-rate *e'*-wave (SRe') on speckle tracking correlated with hs-cTnT concentrations better than TDI (31). The lack of association of systolic strain-rate *s'*-wave (SRs') or LV ejection fraction with hs-cTnT further supports the finding that diastolic, rather than systolic dysfunction, possibly contributes to hs-cTnT elevations in severe sepsis and septic shock (Table 3). Interestingly, ROC analyses showed that both E/TDIe' and E/SRe' ratios correlated better with low-level hs-cTnT elevations, whereas TDIe'-wave and SRe'-wave correlated better with higher levels of hs-cTnT elevations (> 43 pg/mL, Table 5), possibly implying that increased

LV filling pressures are associated more with lower-level troponin elevations while LV relaxation abnormalities are associated with higher hs-cTnT elevations.

RV Dilatation and Troponin Elevation

Cardiac troponin elevations were reported in patients with RV dilatation or dysfunction during acute pulmonary embolism (32) and following strenuous exercise (33). Pulmonary hypertension and RV dilatation occur in severe sepsis and septic shock secondary to the respiratory distress syndrome, hypoxia, hypercarbia, and high-pressure ventilation common in these patients. The 3D echocardiography used in this study demonstrates for the first time the strong and independent correlation of increased RV volumes and reduced RV ejection fraction with hs-cTnT concentrations in sepsis.

Limitations

The observational nature of the study prevents us from conclusively defining causality between the echocardiographic variables and hs-cTnT elevations. All we can conclude is that the independent correlations of LV diastolic and RV systolic dysfunctions with hs-cTnT concentrations as continuous variables strongly suggest that these dysfunctions seem to contribute to the observed hs-cTnT elevations. Patients lacked baseline echocardiography and hs-cTnT examinations prior to the sepsis. Therefore, we cannot ascertain to what extent sepsis was responsible for the observed diastolic dysfunction or whether the dysfunction preexisted and was significantly aggravated as a result of the acute critical illness. It is also notable that although currently available modern echocardiography tools enable transthoracic acquisition and measurements of systolic and diastolic functions in well above 85% of critically ill mechanically ventilated ICU patients (34, 35), the sickest patients who are on high positive end-expiratory pressures are often not amenable to echocardiographic examination.

CONCLUSIONS

The mechanisms causing troponin release from myocardial cells in non-ACS critical illnesses are likely multifactorial. Patients with coronary heart disease are more likely to exhibit troponin elevations during critical illnesses such as sepsis (36). The present study further suggests that myocardial dysfunction contributes to troponin elevations and accounts for troponin's association with mortality. Diastolic dysfunction may also explain the high prevalence of troponin elevations in other serious non-ACS settings such as in high-risk patients undergoing major noncardiac surgery in which even minor troponin elevations are associated with increased 30-day (37) and 5-year mortality (38). Additional studies are required to show whether therapeutic interventions (milrinone? and levosimendan?) aimed at improving diastolic function or RV dilatation can prevent troponin elevation and mortality in severe sepsis and septic shock.

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