Strain Assessment of Myocardial Function: A Better Approach or Just Fun and Games?

Andra E. Duncan, MD, MS

Echocardiographic assessment of myocardial function is frequently used for perioperative management of surgical and critically ill patients. However, the most common echocardiographic measure, left ventricular ejection fraction (LVEF), only assesses volume-based changes during systole and diastole rather than measuring myocardial muscle contraction. LVEF is also limited by its reliance on geometric assumptions that are subject to measurement error. Furthermore, echocardiographic assessment of regional wall motion abnormalities is limited by subjective interpretation.[1] In patients with sepsis, up to two-thirds of whom may experience myocardial impairment,[2,3] early myocardial dysfunction may be masked by sepsis-induced vasodilation and reduced afterload, and thus, LVEF may not fully assess myocardial function.[3,4] A more objective, sensitive, and reproducible measure of myocardial function would be useful.

Myocardial deformation imaging has been used in research for more than a decade, but clinical use of this modality is relatively new for anesthesiologists.[5] This echocardiographic technique assesses the change in ventricular shape (deformation) during myocardial contraction. During systole, the myocardium shortens in the longitudinal and circumferential dimension while thickening radially. Measures of myocardial deformation include strain, defined as the percent change in length of a myocardial segment relative to its resting length, and strain rate, which is the rate of this deformation. Myocardial shortening in the longitudinal and circumferential direction is reported as a negative number, whereas elongation or thickening in the radial direction is positive (Fig. 1). Although normal reference values have not yet been established, longitudinal strain in healthy individuals by transthoracic echocardiography typically is between −18% and −21%,[5–7] whereas strain rate is −1.1 ± 0.2 sec^{-1}.[5,6] Describing a change in myocardial function with negative strain values can cause confusion; thus, the absolute value is considered when determining whether strain increases or decreases[8]; for example, a change from −15% to −12% in longitudinal strain describes a decrease in longitudinal shortening and is referred to as a decrease in strain.

Myocardial deformation imaging initially was based on tissue Doppler echocardiography, but angle dependence and cumbersome analysis techniques impeded its use. Subsequent development of speckle-tracking echocardiography, which assesses changes in the ultrasound backscatter speckle pattern within B-mode echocardiographic images, has overcome these limitations and is more robust than Doppler-based methods.[5,9] Speckle-tracking echocardiography provides semiobjective, quantitative, angle-independent global and regional measurements and allows assessment of 2 orthogonal planes simultaneously. Improved software analysis programs have increased the ease of use and the clinical application of myocardial deformation imaging with speckle-tracking echocardiography.

In this issue of *Anesthesia & Analgesia*, Shahul et al.[10] used myocardial deformation imaging to advance our understanding of sepsis-induced myocardial dysfunction. Myocardial function was assessed in patients with septic shock and those with sepsis alone by the use of longitudinal, circumferential, and radial strain, as well as LVEF on admission and 24 hours later. The authors reported that longitudinal strain decreased in patients with septic shock but not sepsis alone and that LVEF, circumferential, and radial strain were not changed.

Shahul et al.[10] should be commended for using this advanced echocardiographic technique to investigate myocardial impairment in patients with sepsis and septic shock. Several strengths of this investigation include the collection of prospective echocardiographic data and blinding of the echocardiographic analysis to timing (0 vs 24 hours) and diagnosis (sepsis versus septic shock). Because strain is a load-dependent measure, the authors adjusted strain measurements for left ventricular end-diastolic volume and vasopressor use and demonstrated consistent results to further support their conclusions. Unlike longitudinal strain, Shahul et al. [10] found that circumferential and radial strain remained unchanged. However, longitudinal strain has greater reliability and reproducibility than circumferential or radial strain[11] and is a more clinically useful prognostic indicator. As an example, longitudinal strain is a better predictor of mortality than LVEF in patients with valvular heart disease, heart failure, and ischemic cardiomyopathy.[12–14] Although the decrease in longitudinal strain was only seen in patients with septic shock, it is interesting to note that the mean baseline longitudinal

From the Departments of Cardiothoracic Anesthesia and Outcomes Research, Cleveland Clinic, Cleveland, Ohio.

Accepted for publication August 31, 2015.

Funding: Funded by National Institutes of Health HL093065.

The author declares no conflicts of interest.

Reprints will not be available from the author.

Address correspondence to Andra E. Duncan, MD, Departments of Cardiothoracic Anesthesia and Outcomes Research, Cleveland Clinic, 9500 Euclid Ave./J4, Cleveland, OH 44195. Address e-mail to duncana@ccf.org.

DOI: 10.1213/ANE.0000000000001026

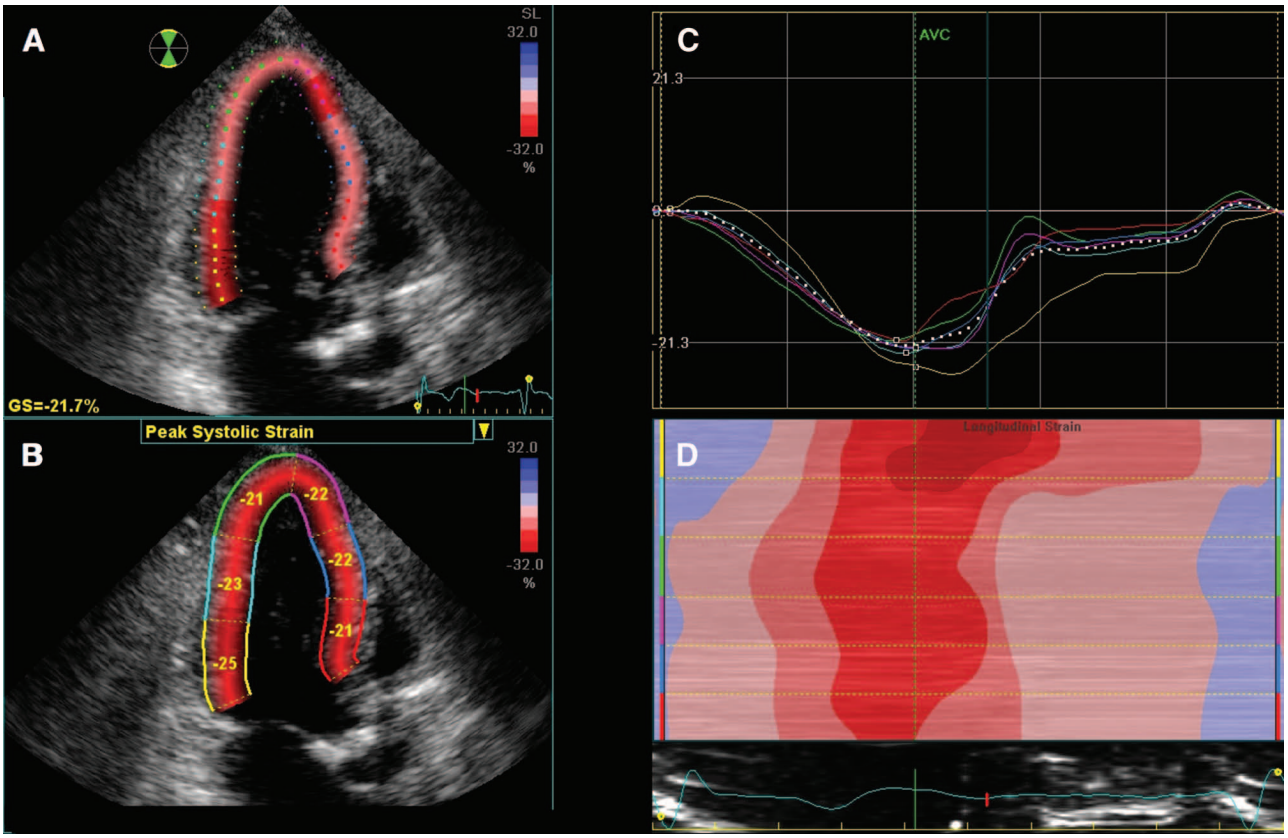

Figure 1. This bright and colorful demonstration of a typical left ventricular (LV) strain analysis from a transthoracic apical long-axis view using speckle-tracking echocardiography looks like fun and games! A, Proper tracking of the LV demonstrating normal global strain (GS) of −21.7%. B, The myocardium is divided into 6 color-coded segments where each segment is labeled with percent segmental strain. C, Strain curves for each myocardial segment (which correspond to color-coded myocardial segments in A and B) demonstrate myocardial shortening (negative curves) during systole peaking at aortic valve closure (AVC). D, Color M-mode display of the LV (segments are color-coded at the left edge to correspond to myocardial segments in A, B, and C), which demonstrates myocardial deformation over time according to the red-to-blue scale in A and B.

strain was abnormal in both groups (approximately −15%) even though LVEF was normal.

An important aspect of this report by Shahul et al.[10] is that patients who had a decrease in longitudinal strain also were more severely ill, as documented by greater Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores, a greater requirement for mechanical ventilation, and higher mortality. In contrast, conventional echocardiography has not identified an association between severity of illness and worsening myocardial function, possibly because LVEF is insensitive to subtle myocardial dysfunction. This investigation also provides evidence that myocardial deformation imaging with speckle-tracking echocardiography offers an early indication of worsening myocardial function before conventional measures of contractility, which may lead to earlier therapeutic intervention. Certainly, myocardial strain imaging detects early signs of myocardial dysfunction in patients with aortic regurgitation[15] and those receiving cancer chemotherapy.[16] Shahul et al.[10] make a case for applying echocardiographic strain measurement more broadly to assess myocardial function during other critical illnesses and the perioperative period.

The authors describe several methodologic limitations to this investigation, such as the potential for confounding by patient comorbidities. Because of the small sample size limited to a single institution, these results may not be widely generalizable and require confirmation in a larger patient population. The analysis did not correct for multiple comparisons, but the actual *P* value for longitudinal strain was highly significant ($P < 0.0001$), reducing the risk of a type I error. This investigation cannot prove that the effects of septic shock on myocardial performance occurred early after the onset of shock because other time periods were not investigated. It is also important to note that a change in myocardial function between hospital admission and 24 hours later reflects not only severity of disease but also response to treatment given during this time period. Evidence supports measurement of global peak systolic strain from a single apical 4-chamber view, although with wide limits of agreement.[17] Thus, analysis of the usual 3 apical views could improve accuracy of the data. Shahul et al.[18] previously reported excellent intra- and interobserver reliability in strain analysis and including a similar result would be useful because this measurement is unfamiliar to many readers.

What's next? This investigation provides a strong rationale for further investigation to examine myocardial function in septic patients. Future studies are needed to elucidate the cause or mechanism of septic shock-associated

myocardial dysfunction and to determine whether this condition is reversible. The clinical impact of sepsis-induced attenuation of longitudinal strain on long-term outcomes, as well as evaluation of potential therapies to improve myocardial function in patients who are critically ill, needs further exploration.

This investigation and others will likely increase the use of strain analysis with speckle-tracking echocardiography in clinical care and research investigations. Significant challenges, however, currently hinder its widespread use. Strain and strain rate are load-dependent measures of myocardial function and thus cannot explicitly state whether contractile function is impaired or whether observed changes in strain are a consequence of altered loading conditions. Speckle-tracking also requires images with excellent endocardial definition, which can be challenging in critically ill or surgical patients. Furthermore, because adequate training and experience are needed, the potential for misinterpretation, especially by a novice user, is high. Although improvements have been made in recent software programs to simplify strain analysis, these techniques are still relatively cumbersome and challenging to perform when caring for a critically ill patient in the intensive care unit or operating room. Moreover, standardization between echocardiographic workstations and software analysis packages is in progress, but more work remains.[8]

Despite the limitations of strain analysis, the ability to measure regional and global myocardial function using a semiobjective, quantitative, and reproducible method provides new opportunities to improve our understanding of myocardial impairment, resulting from sepsis and other critical illnesses. Ultimately, strain analysis with speckle-tracking echocardiography may arise as the superior technique for assessing myocardial function—more than just fun and games.

DISCLOSURES

Name: Andra E. Duncan, MD, MS.
Contribution: This author prepared the manuscript.
Attestation: Andra E. Duncan approved the final manuscript.
This manuscript will be handled by: Avery Tung, MD.

REFERENCES

1. Bergquist BD, Leung JM, Bellows WH. Transesophageal echocardiography in myocardial revascularization: I. Accuracy of intraoperative real-time interpretation. Anesth Analg 1996;82:1132–8
2. Pulido JN, Afessa B, Masaki M, Yuasa T, Gillespie S, Herasevich V, Brown DR, Oh JK. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. Mayo Clin Proc 2012;87:620–8
3. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 2008;36:1701–6
4. Furian T, Aguiar C, Prado K, Ribeiro RV, Becker L, Martinelli N, Clausell N, Rohde LE, Biolo A. Ventricular dysfunction and dilation in severe sepsis and septic shock: relation to endothelial function and mortality. J Crit Care 2012;27:319.e9–15
5. Duncan AE, Alfirevic A, Sessler DI, Popovic ZB, Thomas JD. Perioperative assessment of myocardial deformation. Anesth Analg 2014;118:525–44
6. Marwick TH, Leano RL, Brown J, Sun JP, Hoffmann R, Lysyansky P, Becker M, Thomas JD. Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography: definition of normal range. JACC Cardiovasc Imaging 2009;2:80–4
7. Yingchoncharoen T, Agarwal S, Popović ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr 2013;26:185–91
8. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y, Metz S, Song JH, Hamilton J, Sengupta PP, Kolias TJ, d'Hooge J, Aurigemma GP, Thomas JD, Badano LP. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr 2015;28:183–93
9. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, Støylen A, Ihlen H, Lima JA, Smiseth OA, Slørdahl SA. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789–93
10. Shahul S, Gulati G, Hacker MR, Mahmood F, Canelli R, Nizamuddin J, Mahmood B, Mueller A, Simon BA, Novack V, Talmor D. Detection of myocardial dysfunction in septic shock: a speckle-tracking echocardiography study. Anesth Analg 2015;121:1547–54
11. Risum N, Ali S, Olsen NT, Jons C, Khouri MG, Lauridsen TK, Samad Z, Velazquez EJ, Sogaard P, Kisslo J. Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults. J Am Soc Echocardiogr 2012;25:1195–203
12. Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Møller JE. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. Circ Cardiovasc Imaging 2012;5:613–20
13. Mignot A, Donal E, Zaroui A, Reant P, Salem A, Hamon C, Monzy S, Roudaut R, Habib G, Lafitte S. Global longitudinal strain as a major predictor of cardiac events in patients with depressed left ventricular function: a multicenter study. J Am Soc Echocardiogr 2010;23:1019–24
14. Bertini M, Ng AC, Antoni ML, Nucifora G, Ewe SH, Auger D, Marsan NA, Schalij MJ, Bax JJ, Delgado V. Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy. Circ Cardiovasc Imaging 2012;5:383–91
15. Marciniak A, Sutherland GR, Marciniak M, Claus P, Bijnens B, Jahangiri M. Myocardial deformation abnormalities in patients with aortic regurgitation: a strain rate imaging study. Eur J Echocardiogr 2009;10:112–9
16. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63:2751–68
17. Bagger T, Sloth E, Jakobsen CJ. Left ventricular longitudinal function assessed by speckle tracking ultrasound from a single apical imaging plane. Crit Care Res Pract 2012;2012:361824
18. Shahul S, Rhee J, Hacker MR, Gulati G, Mitchell JD, Hess P, Mahmood F, Arany Z, Rana S, Talmor D. Subclinical left ventricular dysfunction in preeclamptic women with preserved left ventricular ejection fraction: a 2D speckle-tracking imaging study. Circ Cardiovasc Imaging 2012;5:734–9

Detection of Myocardial Dysfunction in Septic Shock: A Speckle-Tracking Echocardiography Study

Sajid Shahul, MD, MPH,* Gaurav Gulati, MD,† Michele R. Hacker, ScD, MSPH,‡ Feroze Mahmood, MD,* Robert Canelli, MD,* Junaid Nizamuddin, MD,* Bilal Mahmood, BA,§ Ariel Mueller, MA,* Brett A. Simon, MD, PhD,* Victor Novack, MD, PhD,‖¶ and Daniel Talmor, MD, MPH*

BACKGROUND: Patients with septic shock are at increased risk of myocardial dysfunction. However, the left ventricular ejection fraction (EF) typically remains preserved in septic shock. Strain measurement using speckle-tracking echocardiography may quantify abnormalities in myocardial function not detected by conventional echocardiography. To investigate whether septic shock results in greater strain changes than sepsis alone, we evaluated strain in patients with sepsis and septic shock.

METHODS: We prospectively identified 35 patients with septic shock and 15 with sepsis. These patients underwent serial transthoracic echocardiograms at enrollment and 24 hours later. Measurements included longitudinal, radial, and circumferential strain in addition to standard echocardiographic assessments of left ventricular function.

RESULTS: Longitudinal strain worsened significantly over 24 hours in patients with septic shock ($P < 0.0001$) but did not change in patients with sepsis alone ($P = 0.43$). No significant changes in radial or circumferential strain or EF were observed in either group over the 24-hour measurement period. In patients with septic shock, the significant worsening in longitudinal strain persisted after adjustment for left ventricular end-diastolic volume and vasopressor use ($P < 0.0001$). In patients with sepsis, adjustment for left ventricular end-diastolic volume and vasopressor use did not alter the finding of no significant differences in longitudinal strain ($P = 0.48$) or EF ($P = 0.96$).

CONCLUSIONS: In patients with septic shock, but not sepsis, myocardial strain imaging using speckle-tracking echocardiography identified myocardial dysfunction in the absence of changes in EF. These data suggest that strain imaging may play a role in cardiovascular assessment during septic shock. (Anesth Analg 2015;121:1547–54)

Key recommendations of the current Surviving Sepsis Campaign guidelines include early recognition and treatment of sepsis-induced myocardial dysfunction.[1] Although the exact mechanism of sepsis-induced myocardial dysfunction is unclear, current evidence suggests that intrinsic cellular depression (e.g., mitochondrial or β-receptor downregulation), circulating tumor necrosis factor-α, interleukin-6β, and volume resuscitation may be involved.[2] Evidence from cardiac magnetic resonance imaging also suggests that this dysfunction may be because of a combination of myocardial inflammation and acidosis.[3] However, despite these processes, the ejection fraction typically remains preserved in septic shock,[4,5] preventing ready diagnosis and treatment. The importance of early recognition is supported by autopsy studies in patients dying from septic shock that demonstrate potentially reversible mitochondrial injury.[6,7] Potential benefits of early recognition may include optimized coronary perfusion, tailored volume resuscitation, appropriately targeted use of inotropes and vasopressors, and possibly, the use of cardioprotective agents such as β-blockers.[8]

Previous investigations have characterized many aspects of myocardial function in sepsis[5,9,10]; however, few data have detailed the evolution of myocardial dysfunction in septic shock and whether these changes depend on initial sepsis severity. Such information may be valuable in sepsis management, because recent studies have shown that ejection fraction at the onset of septic shock does not differ between survivors and nonsurvivors.[4,5] This contrast between ongoing myocardial dysfunction during sepsis and the lack of detectable changes in ejection fraction may potentially be resolved with more sophisticated measures of myocardial dysfunction such as myocardial strain. In other disease states, echocardiographic assessment of myocardial strain can detect changes in myocardial function not measured by conventional echocardiographic indices of systolic function.[11]

Strain measurement using speckle-tracking echocardiography is a recently developed technique based on the generation of ultrasound B-mode echoes called "speckles" that represent discrete myocardial areas and are tracked throughout the cardiac cycle.[12] Changes in the distance between individual speckles can then be used to assess changes in the

From the *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; †University of Pennsylvania, Philadelphia, Pennsylvania; ‡Beth Israel Deaconess Medical Center Harvard Medical School, Boston, Massachusetts; §University of Albany Medical School, Albany, New York; ‖Clinical Research Center, Soroka University Medical Center, Beer-Sheva, Israel; and ¶Faculty of Health Sciences, Ben–Gurion University of Negev, Israel.

Accepted for publication June 15, 2015.

Funding: This work was conducted with support from FAER (Foundation for Anesthesia Research) and Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award 8UL1TR000170-05 and financial contributions from Harvard University and its affiliated academic health care).

The authors declare no conflicts of interests.

Reprints will not be available from the authors.

Address correspondence to Sajid Shahul, MD, MPH, Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215. Address e-mail to sshahul@bidmc.harvard.edu.

DOI: 10.1213/ANE.0000000000000943

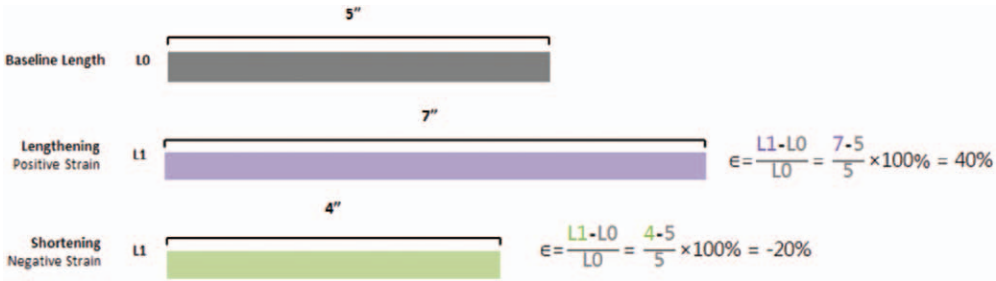

Figure 1. Strain lengthening and shortening. L0 represents the baseline, end-diastolic fiber length. L1 represents the end-systolic fiber length. Positive strain (indicated in purple) occurs when the end-systolic fiber length (L1) is longer than the resting fiber length (L0). On the contrary, negative strain occurs when the end-systolic fiber length (L1) is shorter than the resting fiber length (L0), as demonstrated in green.

length of segments in longitudinal (long axis from base to apex), radial (inward short axis), and circumferential (rotational short axis) planes (Fig. 1).[13] Strain is defined as the difference between the final length of the cardiac segment relative to its resting length. Because the myocardial length shortens in ventricular systole, longitudinal and circumferential strain values are negative with normal heart function, whereas radial strain is positive (Fig. 2).[13] This method is more sensitive than ejection fraction, which is based on fractional change in volume between systole and diastole. Because inward movement in systole tethers diseased and normal segments together, ejection fraction can be relatively insensitive to subtle changes in myocardial function.[14] In contrast to left ventricular ejection fraction, which measures global function, strain with speckle-tracking measures both regional and global functions. Measurement of global longitudinal strain also assesses the function of subendocardial longitudinal fibers that are particularly disposed to ischemia and changes in wall stress.[15] Furthermore, this calculation may detect myocardial dysfunction under conditions of reduced afterload, such as in sepsis.[16] Longitudinal, radial, and circumferential strain measurements are also less prone to measurement error because they avoid the geometric assumptions used in the calculation of left ventricular ejection fraction.[17–19] Speckle tracking has been used to detect subclinical myocardial dysfunction in other disease states[19–21] and can prognosticate mortality and heart failure in patients with preserved ejection fractions.[22,23]

To better describe changes in strain in septic patients, we examined changes in myocardial strain over 24 hours in patients with a diagnosis of sepsis or septic shock. We hypothesized that we would detect changes in left ventricular myocardial strain in patients with septic shock despite normal ejection fractions, whereas patients with sepsis without associated shock would not show such changes.

METHODS

Assembly of the Cohort

The IRB of Beth Israel Deaconess Medical Center in Boston, Massachusetts, approved this prospective study via a verbal consent process. We offered participation to all patients who met eligibility criteria. The study was conducted between March 2010 and July 2014. From March 2010 to April 2012, we enrolled 35 subjects. An interim analysis of the data was performed, and the sample size was recalculated. We then resumed enrollment from July 2013 to 2014 and enrolled an additional 15 subjects.

Patients were eligible if they were at least 18 years of age, not pregnant, without significant valvular stenosis or regurgitation, without ST-segment elevation or arrhythmia, which included bundle branch blocks on the monitor and met the Surviving Sepsis Campaign definition of sepsis or septic shock.[24] Sepsis was defined as probable or documented infection combined with systemic manifestations of infection. Septic shock was defined as sepsis-induced hypotension, despite appropriate fluid management. Participants were recruited consecutively from the intensive care units (ICUs) or emergency department/wards.

Echocardiography

Transthoracic echocardiography was performed in the ICUs and wards on the day of admission with a Philips CX50 machine by 1 of 3 expert sonographers at enrollment (hour 0) and 24 hours later. At the conclusion of the study, strain measurements were read in a blinded manner as related to both timing (0 vs 24 hours) and diagnosis (sepsis versus septic shock). Images were obtained with the patient lying in the supine or left lateral position and reported according to the American Society of Echocardiography guidelines.[25] Images were stored in a cine-loop format of 3 cardiac cycles of uncompressed data with associated electrocardiogram information. A comprehensive examination for each patient was performed, including a complete 2-dimensional (2D) and color flow Doppler valvular assessment.

Ejection fraction was calculated using the Simpson biplane disc method. The tracking quality of all images was assessed before analysis. Strain measurement was performed using a validated, vendor-independent, 2D speckle-tracking echocardiographic tracking software (2D Cardiac Performance Analysis v1.1; TomTec Imaging Systems, Unterschleissheim, Germany).[26] This software can use ultrasound data from any echocardiography machine and produces strain values that are in good agreement with other frequently used software packages.[27] Strain was measured by tracing the endocardial border of the left ventricle at the initial frame with the best endocardial border definition across the maximal number of segments. Longitudinal strain was measured in the apical 4-chamber view; radial and circumferential strain were measured in the parasternal short-axis view. Peak systolic strain (longitudinal, radial, and circumferential) was measured using an average of 3 consecutive cardiac cycles. The average of 6 regional values in the apical 4-chamber and parasternal mid-papillary short-axis views was used to measure longitudinal, radial, and circumferential strain. Images with inadequate endocardial

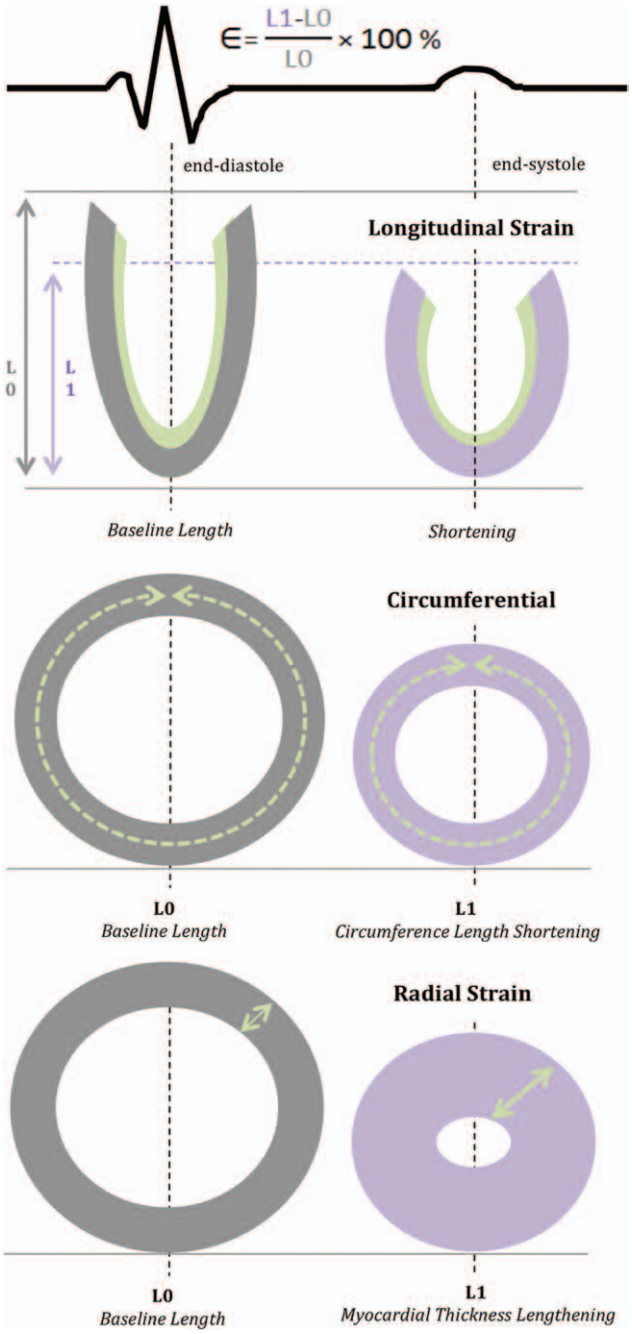

Figure 2. Myocardial strain. L0 represents the baseline, end-diastolic length. Strain is represented by L1 as the end-systolic length. When longitudinal strain occurs, L1 is shorter than L0, causing the difference (L1–L0) to be a negative value. A similar result occurs in circumferential strain, where the circumference decreases in length, causing the difference between L1 and L0 to be negative. In radial strain, the transverse or radial distance thickens, causing the difference between L1 and L0 to be a positive value, unlike longitudinal or circumferential strain.

border tracking (>2 segments) were excluded from strain measurements. The frame rates used for strain acquisition and measurements were between 40 and 70 fps/sec.

Resuscitation Algorithm for Septic Shock and Sepsis

During the first 6 hours, the goals of resuscitation were mean arterial pressure (MAP) ≥65 mm Hg, urine output ≥0.5 mL/kg/h, and superior vena cava oxygen saturation ≥70%. If hypotension persisted despite appropriate fluid resuscitation (30 mL/kg), vasopressors were initiated to target an MAP ≥65 mm Hg. The choice of vasopressors was based on the Surviving Sepsis Campaign guidelines in combination with an interdisciplinary protocol developed at Beth Israel Deaconess Medical Center to manage patients with septic shock. The initial vasopressor in the protocol was norepinephrine, unless contraindicated (e.g., tachyarrhythmia).[28] Subsequent vasopressor choice was determined by patient physiology and Surviving Sepsis Campaign guidelines. During the first 3 hours, the goals of fluid resuscitation were 30 mL/kg in the sepsis group.

Statistical Analysis

Descriptive statistics are presented as mean (±SD), median (interquartile range), or proportion, based on data type and distribution. Normality of continuous variables was assessed with the Shapiro–Wilk test. Comparisons between groups were made using the Student *t*, Wilcoxon rank sum, or χ^2 test, as appropriate. Given the exploratory nature of this study, we did not perform an a priori sample size calculation.

To assess changes in echocardiographic measurements within each group, we created a separate regression model for each of the 3 strain measurements using a repeated measures model with robust standard error estimation and exchangeable correlation structure. For each model, the echocardiographic measurement was the outcome and time (0 or 24 hours) was the explanatory variable. Based on a priori knowledge that prior volume state and vasopressor use (phenylephrine, norepinephrine, and vasopressin) influence strain, the models were adjusted for the dose of each vasopressor and for left ventricular end-diastolic volume. A LOWESS function was used to assess the linearity of the relationship between the continuous predictor and the outcome. The model with the lowest QIC was deemed the best-fitting model. All tests were 2-sided, and *P* values <0.01 were considered statistically significant because of the exploratory nature of this study. Analyses were performed using Stata version 12.1 (Stata Corp., College Station,TX).

RESULTS

All eligible participants whom we approached agreed to participate. We enrolled 59 patients. Six were excluded for inadequate image quality, and 3 were excluded because they died before we obtained echocardiographic measurements (3 patients who died were in the septic shock group; 1 sepsis and 2 septic shock patients were excluded for image quality). Of the included participants, 35 (70.0%) had septic shock and 15 (30.0%) were diagnosed with sepsis. Patients who had ever received vasopressors were included in the septic shock group. One patient who progressed to septic shock after initial enrollment in the sepsis group was analyzed in the septic shock group. The 2 groups were similar with respect to baseline characteristics, including baseline strain and ejection fraction measurements assessed on admission (all $P \geq 0.18$; Table 1). *Acute Physiology and Chronic Health Evaluation* II, troponins, blood pressure, MAP, lactate, and creatinine were measured at the time of enrollment

Table 1. Patient Characteristics by Diagnosis at Admission

	Septic shock (n = 35)	Sepsis (n = 15)	P value
Age	71 (57–81)	74 (43–82)	0.74
Male	18 (51.43)	9 (60.00)	0.58
Body mass index (kg/m^2)	26.1 (25.0–30.7)	23.6 (20.8–29.9)	0.18
Mortality (30 days)	12 (34.29)	2 (13.33)	0.18
APACHE II score	21.73 ± 6.24	17.27 ± 8.45	0.04
SOFA score	6 (2.11–9.00)	0.5 (0–5)	0.0009
Creatinine (mg/dL)	1.40 (0.80–2.60)	0.9 (0.50–1.60)	0.19
Troponin T (ng/mL)	0.01 (0.01–0.08)	0.05 (0.01–0.05)	0.84
Ischemic heart disease	13 (37.14)	4 (26.7)	0.33
Hypertension	25 (71.43)	8 (53.33)	0.22
Diabetes mellitus	8 (22.86)	3 (20.00)	0.82
Longitudinal strain (%)	−15.08 ± 5.74	−15.74 ± 5.72	0.71
Circumferential strain (%)	−22.03 ± 8.48	−21.28 ± 5.58	0.76
Radial strain (%)	29.42± 12.47	28.16±16.66	0.63
Ejection fraction (%)	51.60 ± 18.88	55.47 ± 11.06	0.38
End-diastolic volume (mL)	76.84 ± 31.02	83.53± 46.14	0.56
Infection source			
Not identified	12 (34.29)	6 (40.00)	–
Gram positive	11 (31.43)	5 (33.33)	–
Gram negative	6 (17.14)	3 (20.00)	–
Fungus	6 (17.14)	1 (6.67)	–

Values are presented as median (interquartile range), mean ± SD, or no. (%).
APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment.

and 24 hours later (Table 2). At baseline, the septic shock group had a greater *Acute Physiology and Chronic Health Evaluation* II score (P = 0.04), a greater Sequential Organ Failure Assessment score (P = 0.0009), and lower MAP (P = 0.03). Among patients in the septic shock group, 24 (68.6%) were mechanically ventilated, as were 4 (26.7%) in the sepsis group.

In the crude regression model, longitudinal strain in patients with septic shock significantly worsened over 24 hours (P < 0.0001), whereas in patients with sepsis alone no change in longitudinal strain was observed over 24 hours (P = 0.43). No significant changes during the 24-hour measurement period were observed in either group for radial strain, circumferential strain, or ejection fraction (Table 3).

After multivariate adjustment for vasopressor administration and end-diastolic volume, the change in longitudinal strain observed over 24 hours in patients with septic shock persisted (P < 0.0001). Multivariate adjustment did not alter our findings of no change in radial strain, circumferential strain, or ejection fraction. In the sepsis group, no significant differences in longitudinal strain, radial strain, circumferential strain, or ejection fraction were noted after adjustment for end-diastolic volume.

After we stratified the groups for ischemic heart disease, our findings with respect to longitudinal strain did not change in either group (P = 0.44 for sepsis and 0.10 for septic shock). In addition, no significant differences in troponin between sepsis and septic shock patients were found at enrollment (P = 0.84) or at 24 hours (0.17).

As noted previously, no patients in the sepsis group received vasoconstrictors. Among all septic shock patients, 54.29% received only norepinephrine, 14.29% received only phenylephrine, and no patients received vasopressin only. In our study, 2 patients (5.7%) received both norepinephrine and phenylephrine, whereas 3 patients (8.6%) received both norepinephrine and vasopressin. The proportion of patients receiving norepinephrine, phenylephrine, and vasopressin simultaneously was 11.2%.

DISCUSSION

In this study of critically ill patients, speckle-tracking echocardiography identified worsening myocardial dysfunction over 24 hours in patients with septic shock but not sepsis alone. These changes were not detectable via echocardiographic measurement of ejection fraction but could be identified by assessment of myocardial strain. The time course of our findings also suggests that effects of septic shock on myocardial performance may occur early after the onset of shock. Targeting these patients early for intervention may improve outcomes.

Our study demonstrates the greater sensitivity of longitudinal strain as a measure of cardiac dysfunction in patients with septic shock and sepsis. After adjustment for vasopressor administration and end-diastolic volume, we found significant changes in longitudinal strain but saw no corresponding change in left ventricular ejection fraction over the same time period.

Our results are similar to previous animal and clinical studies in which authors compared strain echocardiography with ejection fraction measurement. Recently, Hestenes et al.[16] demonstrated in a pig model a significant decrease in longitudinal strain without changes in ejection fraction (−17.2 ± 2.8 to −12.3% ± 3.2). Similar results in longitudinal strain were demonstrated by Basu et al.[29] in a retrospective analysis of children admitted with septic shock.

Although left ventricular ejection fraction is used routinely for measuring left ventricular systolic function, newer techniques, such as speckle tracking, are increasingly used to monitor cardiac function in disease states, such as preeclampsia, cardiotoxic chemotherapy and Behcet disease.[20,21,30] Although the mechanisms underlying changes in strain with septic shock are understood incompletely,

Table 2. Values at Enrollment and 24 hours for Patients with Septic Shock and Sepsis

	At enrollment			Hour 24		
	Septic shock (n = 35)	Sepsis (n = 15)	P value	Septic shock (n = 35)	Sepsis (n = 15)	P value
Physiologic						
APACHE II, mean ± SD	21.73 ± 6.24	17.27 ± 8.45	0.04	19.71 ± 7.04	16.67 ± 8.02	0.18
SOFA, median (IQR)	6.0 (2.11–9.00)	0.5 (0–5)	0.0009	—	—	—
MAP, median (IQR)	70.0 (66.0–80.0)	82.3 (70.3–99.7)	0.03	71.7 (65.0–80.7)	79.3 (75.3–93.7)	0.02
Heart rate, mean ± SD	89.66 ± 18.57	89.67 ± 16.37	0.99	89.03 ± 21.86	87.20 ± 22.15	0.79
$Scvo_2$ (%), mean ± SD	75.50 ± 9.89	—	—	77.43 ± 7.28	—	0.86
Lactate (mmol/L), median (IQR)	1.95 (1.30–2.60)	1.50 (1.10–1.90)	0.29	1.90 (1.25–2.55)	1.10 (0.90–1.20)	0.01
Troponin T (ng/mL), median (IQR)	0.01 (0.01–0.08)	0.05 (0.01–0.05)	0.84	0.01 (0.01–0.04)	0.05 (0.04–0.06)	0.17
Pao_2/Fio_2 (mm Hg), mean ± SD	227.79 ± 95.23	287.33 ± 169.36	0.37	222.56 ± 87.01	396.25 ± 129.05	0.02
PEEP, median (IQR)	8 (5–10)	5	0.03	6 (5–10)	5 (5 - 8)	0.48
Creatinine (mg/dL), median (IQR)	1.4 (0.8–2.6)	0.9 (0.5–1.6)	0.19	1.30 (0.90–2.60)	0.9 (0.6–1.9)	0.33
Fluids (mL/kg), mean ± SD	—	—	—	3227.53 ±1893.37	2766.27 ± 1692.24	0.42
Phenylephrine (mcg/kg/min), mean ± SD	0.289 ± 0.787	—	—	0.180 ± 0.459	—	0.49
Norepinephrine (mcg/kg/min), mean ± SD	0.110 ± 0.122	—	—	0.058 ± 0.098	—	0.03
Vasopressin (units/h), mean ± SD	0.274 ± 0.718	—	—	0.206 ± 0.616	—	0.62

For variables not normally distributed, the median (IQR) is presented.

APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; MAP = mean arterial pressure; IQR = interquartile range; $Scvo_2$ = central venous oxygen saturation; Fio_2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure.

one possibility is that microvascular vasoconstriction in the highly vulnerable subendocardial muscle layer might result in ischemic injury.[31] Both coronary vasoconstriction and a decreased response to vasodilators, such as sodium nitroprusside in the coronary circulation, have been observed by Bogle et al.[31] in a rabbit heart model of endotoxemia. This altered coronary microvascular tone may partly explain the changes in strain we observed.[32] That we found changes in strain without corresponding changes in troponin levels suggests that strain identifies focal longitudinal muscle dysfunction rather than myocyte injury. Previous work suggests that the lack of change we observed in radial and circumferential strain represents compensation by the radial and circumferential fibers.[33]

Pulido et al.,[5] Furian et al.,[10] and Landesberg et al.[34] have demonstrated previously the presence of myocardial dysfunction in severe sepsis using conventional echocardiography. The mean ejection fraction and standard deviation in these studies (Pulido et al.,[5] 56.8 ± 16; Furian et al.,[10] 57 ± 13) are in good agreement with our study. Our study further expands their work by demonstrating the presence of ongoing systolic myocardial dysfunction via strain measurement, despite preserved ejection fraction.[5,10]

Although factors affecting myocardial wall stress, such as afterload and volume status, may affect longitudinal or circumferential strain values,[35–37] we observed differences in longitudinal strain even after adjustment for vasopressors. We also note that, despite using different vasopressor resuscitation strategies than Landesberg et al.,[34] we report similar longitudinal strain values at 24 hours (−12.7 ± 5.64 vs −12.3 ± 3.6). Recent data in animals support the utility of strain measurement in the presence of vasopressors. In a rabbit model, Ho et al.[36] found that at comparable blood pressures, strain did not depend on whether norepinephrine or phenylephrine was used or on the dose of vasopressin. In addition, changes in longitudinal strain are not significantly affected by positive end-expiratory pressure titration, which supports the validity of our data.[38,39]

Our study may have clinical implications. Once detected, subclinical myocardial dysfunction may be amenable to cardioprotective strategies, including β-blocker use, even if the ejection fraction remains normal. In one study of patients given cardiotoxic chemotherapy, β-blockers reversed changes in longitudinal strain.[14] Another preliminary study in septic patients receiving norepinephrine found an improved outcome with β-blocker administration.[8]

Myocardial strain measurement may also help with prognosis in septic shock patients. Recently, Orde et al.[40] demonstrated that, despite a normal ejection fraction, severe right ventricular free wall longitudinal strain dysfunction was associated with a high rate of mortality in patients with severe sepsis and septic shock.

Our observational study has limitations. Despite statistically significant differences, our sample size was small, which underscores the need for large-scale prospective studies to replicate our findings. In addition, our initial strain measurement was performed on admission to the ICU, not upon meeting septic shock or sepsis criteria. As a result, we cannot describe changes in longitudinal strain that occurred before or after our 24-hour monitoring period. We also did not measure strain during recovery from septic shock, to determine whether strain values regress to baseline values. Patients in the septic shock group also had a greater proportion of ischemic heart disease, which may have contributed to the changes that we found. Finally, speckle-tracking technology is relatively new, and current implementations require adequate endocardial border definition, which may be challenging because of volume resuscitation, mechanical ventilation, or suboptimal positioning. In addition, no standard values or protocols exist for strain analysis.

In summary, we conclude that early (<24-hour) changes in myocardial function because of septic shock are detectable using echocardiographic speckle-tracking technology. Our data raise the possibility that monitoring strain may better identify patients with myocardial dysfunction because of septic shock than measurement of ejection fraction. Whether early detection of subclinical left ventricular

Table 3. Mean Echocardiography Measurements at Enrollment and 24 hours and Mean Change from 0 to 24 hours

	Hour 0	Hour 24	Crude Change	*P*	Adjusted[a] Change*	*P*
Septic shock (*n* = 35)						
Longitudinal strain (%)	−15.08 (−17.08, −13.07)	−12.67 (−14.63, −10.70)	−2.41 (−3.64, −1.18)	<0.0001	−2.90 (−4.16, −1.65)	<0.0001
Radial strain (%)	29.42 (24.84, 34.00)	27.23 (23.29, 31.16)	2.31 (−1.22, 5.85)	0.20	2.51 (−1.19, 6.21)	0.18
Circumferential strain (%)	−22.03 (−25.14, −18.92)	−21.29 (−24.05, −18.53)	−0.78 (−3.27, 1.71)	0.54	0.01 (−2.81, 2.84)	0.99
Ejection fraction (%)	52.01 (44.92, 59.10)	54.57 (48.90, 60.24)	−2.56 (−8.91, 3.78)	0.43	−3.16 (−10.69, 4.37)	0.41
End-diastolic volume (mL)	76.84 (65.46, 88.22)	84.83 (72.53, 97.13)	−8.64 (−18.28, 0.99)	0.08		
Sepsis (*n* = 15)						
Longitudinal strain (%)	−15.74 (−18.91, −12.57)	−16.66 (−19.04, −14.28)	0.92 (−1.35, 3.20)	0.43	0.85 (−1.50, 3.20)	0.48
Radial strain (%)	28.17 (18.94, 37.40)	35.01 (24.68, 45.33)	−6.84 (−16.85, 3.17)	0.18	−6.69 (−16.94, 3.56)	0.20
Circumferential strain (%)	−21.28 (−24.37, −18.19)	−20.80 (−23.48, −18.13)	−0.48 (−3.56, 2.60)	0.76	−1.03 (−3.92, 1.86)	0.48
Ejection fraction (%)	55.47 (49.34, 61.59)	56.13 (48.56, 63.70)	−0.67 (−6.13, 7.80)	0.17	−0.18 (−7.11, 7.48)	0.96
End-diastolic volume (mL)	83.53 (57.98, 109.09)	85.45 (59.37, 111.53)	−1.57 (−12.00, 8.86)	0.75		

Values are presented as mean (95% confidence interval). The residuals for both the sepsis ($P = 0.13$) and septic shock (0.08) groups were normally distributed when assed using the Shapiro–Wilk test. $P < 0.01$ indicates statistical significance.

[a]Models are adjusted for left ventricular end-diastolic volume (LVEDV) and dose of vasopressors for septic shock and LVEDV for sepsis, which were found to be linear using a LOWESS function. No significant interaction between baseline values of vasopressor dose and left ventricular end-diastolic volume was observed.

dysfunction and subsequent treatment can improve long-term outcome needs to be evaluated in future studies.

DISCLOSURES

Name: Sajid Shahul, MD, MPH.
Contribution: This author helped with conception and design, acquisition of data, analysis and interpretation of data; drafting the article; approving final version of article.
Attestation: Sajid Shahul approved the final manuscript.
Name: Gaurav Gulati, MD.
Contribution: This author helped with the acquisition of data, analysis and interpretation of data; drafting the article.
Attestation: Gaurav Gulati approved the final manuscript.
Name: Michele R. Hacker, ScD, MSPH.
Contribution: This author helped with analysis and interpretation of data and critically revising the article.
Attestation: Michele R. Hacker approved the final manuscript.
Name: Feroze Mahmood, MD.
Contribution: This author helped with the acquisition of data, analysis and interpretation of data, and critically revising the article.
Attestation: Feroze Mahmood approved the final manuscript.
Name: Robert Canelli, MD.
Contribution: This author helped with analysis and interpretation of data and critically revising the article.
Attestation: Robert Canelli approved the final manuscript.
Name: Junaid Nizamuddin, MD.
Contribution: This author helped with analysis and interpretation of data and critically revising the article.
Attestation: Junaid Nizamuddin approved the final manuscript.
Name: Bilal Mahmood, BA.
Contribution: This author helped with analysis and interpretation of data and critically revising the article.
Attestation: Bilal Mahmood approved the final manuscript.
Name: Ariel Mueller, MA.
Contribution: This author helped with analysis and interpretation of data and critically revising the article.
Attestation: Ariel Mueller approved the final manuscript.
Name: Brett A. Simon, MD, PhD.
Contribution: This author helped with the conception and design, analysis and interpretation of data, and critically revising the article.
Attestation: Brett A. Simon approved the final manuscript.
Name: Victor Novack, MD, PhD.
Contribution: This author helped with analysis and interpretation of data and drafting the article.
Attestation: Victor Novack approved the final manuscript.
Name: Daniel Talmor, MD, MPH.
Contribution: This author helped with the conception and design, acquisition of data, analysis, and approving the final version of article.
Attestation: Daniel Talmor approved the final manuscript.
This manuscript was handled by: Avery Tung, MD.

REFERENCES

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580–637

2. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. Crit Care Med 2007;35:1599–608
3. Siddiqui Y, Crouser ED, Raman SV. Nonischemic myocardial changes detected by cardiac magnetic resonance in critical care patients with sepsis. Am J Respir Crit Care Med 2013;188:1037–9
4. Takasu O, Gaut JP, Watanabe E, To K, Fagley RE, Sato B, Jarman S, Efimov IR, Janks DL, Srivastava A, Bhayani SB, Drewry A, Swanson PE, Hotchkiss RS. Mechanisms of cardiac and renal dysfunction in patients dying of sepsis. Am J Respir Crit Care Med 2013;187:509–17
5. Pulido JN, Afessa B, Masaki M, Yuasa T, Gillespie S, Herasevich V, Brown DR, Oh JK. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. Mayo Clin Proc 2012;87:620–8
6. Torgersen C, Moser P, Luckner G, Mayr V, Jochberger S, Hasibeder WR, Dünser MW. Macroscopic postmortem findings in 235 surgical intensive care patients with sepsis. Anesth Analg 2009;108:1841–7
7. Schmittinger CA, Dünser MW, Torgersen C, Luckner G, Lorenz I, Schmid S, Joannidis M, Moser P, Hasibeder WR, Halabi M, Steger CM. Histologic pathologies of the myocardium in septic shock: a prospective observational study. Shock 2013;39:329–35
8. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, Orecchioni A, D'Egidio A, D'Ippoliti F, Raffone C, Venditti M, Guarracino F, Girardis M, Tritapepe L, Pietropaoli P, Mebazaa A, Singer M. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;310:1683–91
9. Brown SM, Pittman JE, Hirshberg EL, Jones JP, Lanspa MJ, Kuttler KG, Litwin SE, Grissom CK. Diastolic dysfunction and mortality in early severe sepsis and septic shock: a prospective, observational echocardiography study. Crit Ultrasound J 2012;4:8
10. Furian T, Aguiar C, Prado K, Ribeiro RV, Becker L, Martinelli N, Clausell N, Rohde LE, Biolo A. Ventricular dysfunction and dilation in severe sepsis and septic shock: relation to endothelial function and mortality. J Crit Care 2012;27:319.e9–15
11. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, McMurray JJ, Solomon SD; PARAMOUNT Investigators. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447–56
12. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, Galderisi M, Marwick T, Nagueh SF, Sengupta PP, Sicari R, Smiseth OA, Smulevitz B, Takeuchi M, Thomas JD, Vannan M, Voigt JU, Zamorano JL. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr 2011;12:167–205
13. Duncan AE, Alfirevic A, Sessler DI, Popovic ZB, Thomas JD. Perioperative assessment of myocardial deformation. Anesth Analg 2014;118:525–44
14. Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. Eur Heart J Cardiovasc Imaging 2014;15:324–31
15. Buckberg G, Hoffman JI, Mahajan A, Saleh S, Coghlan C. Cardiac mechanics revisited: the relationship of cardiac architecture to ventricular function. Circulation 2008;118:2571–87
16. Hestenes SM, Halvorsen PS, Skulstad H, Remme EW, Espinoza A, Hyler S, Bugge JF, Fosse E, Nielsen EW, Edvardsen T. Advantages of strain echocardiography in assessment of myocardial function in severe sepsis: an experimental study. Crit Care Med 2014;42:e432–40
17. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, Nesser HJ, Khandheria B, Narula J, Sengupta PP. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 2010;23:351–69
18. Mondillo S, Galderisi M, Mele D, Cameli M, Lomoriello VS, Zacà V, Ballo P, D'Andrea A, Muraru D, Losi M, Agricola E, D'Errico A, Buralli S, Sciomer S, Nistri S, Badano L; Echocardiography Study Group Of The Italian Society Of Cardiology (Rome, Italy). Speckle-tracking echocardiography: a new technique for assessing myocardial function. J Ultrasound Med 2011;30:71–83
19. Nesbitt GC, Mankad S, Oh JK. Strain imaging in echocardiography: methods and clinical applications. Int J Cardiovasc Imaging 2009;25(suppl 1):9–22
20. Yagmur J, Sener S, Acikgoz N, Cansel M, Ermis N, Karincaoglu Y, Tasolar H, Karakus Y, Pekdemir H, Ozdemir R. Subclinical left ventricular dysfunction in Behcet's disease assessed by two-dimensional speckle tracking echocardiography. Eur J Echocardiogr 2011;12:536–41
21. Shahul S, Rhee J, Hacker MR, Gulati G, Mitchell JD, Hess P, Mahmood F, Arany Z, Rana S, Talmor D. Subclinical left ventricular dysfunction in preeclamptic women with preserved left ventricular ejection fraction: a 2D speckle-tracking imaging study. Circ Cardiovasc Imaging 2012;5:734–9
22. Ersbøll M, Valeur N, Mogensen UM, Andersen MJ, Møller JE, Velazquez EJ, Hassager C, Søgaard P, Køber L. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. J Am Coll Cardiol 2013;61:2365–73
23. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, Gosavi S, Carver JR, Wiegers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol 2011;107:1375–80
24. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296–327
25. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63
26. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, Støylen A, Ihlen H, Lima JA, Smiseth OA, Slørdahl SA. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789–93
27. Risum N, Ali S, Olsen NT, Jons C, Khouri MG, Lauridsen TK, Samad Z, Velazquez EJ, Sogaard P, Kisslo J. Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults. J Am Soc Echocardiogr 2012;25:1195–203
28. Shapiro NI, Howell MD, Talmor D, Lahey D, Ngo L, Buras J, Wolfe RE, Weiss JW, Lisbon A. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. Crit Care Med 2006;34:1025–32
29. Basu S, Frank LH, Fenton KE, Sable CA, Levy RJ, Berger JT. Two-dimensional speckle tracking imaging detects impaired myocardial

performance in children with septic shock, not recognized by conventional echocardiography. Pediatr Crit Care Med 2012;13:259–64
30. Stoodley PW, Richards DA, Hui R, Boyd A, Harnett PR, Meikle SR, Clarke J, Thomas L. Two-dimensional myocardial strain imaging detects changes in left ventricular systolic function immediately after anthracycline chemotherapy. Eur J Echocardiogr 2011;12:945–52
31. Bogle RG, McLean PG, Ahluwalia A, Vallance P. Impaired vascular sensitivity to nitric oxide in the coronary microvasculature after endotoxaemia. Br J Pharmacol 2000;130:118–24
32. Vallet B. Bench-to-bedside review: endothelial cell dysfunction in severe sepsis: a role in organ dysfunction? Crit Care 2003;7:130–8
33. Mizuguchi Y, Oishi Y, Miyoshi H, Iuchi A, Nagase N, Ara N, Oki T. Possible mechanisms of left ventricular torsion evaluated by cardioreparative effects of telmisartan in patients with hypertension. Eur J Echocardiogr 2010;11:690–7
34. Landesberg G, Jaffe AS, Gilon D, Levin PD, Goodman S, Abu-Baih A, Beeri R, Weissman C, Sprung CL, Landesberg A. Troponin elevation in severe sepsis and septic shock: the role of left ventricular diastolic dysfunction and right ventricular dilatation*. Crit Care Med 2014;42:790–800
35. Burns AT, La Gerche A, D'hooge J, MacIsaac AI, Prior DL. Left ventricular strain and strain rate: characterization of the effect of load in human subjects. Eur J Echocardiogr 2010;11:283–9
36. Ho JK, Zhou W, Ashraf M, Swaminathan M, Sahn D, Mahajan A. Effect of pharmacologic increases in afterload on left ventricular rotation and strain in a rabbit model. J Am Soc Echocardiogr 2013;26:674–82
37. Weidemann F, Jamal F, Sutherland GR, Claus P, Kowalski M, Hatle L, De Scheerder I, Bijnens B, Rademakers FE. Myocardial function defined by strain rate and strain during alterations in inotropic states and heart rate. Am J Physiol Heart Circ Physiol 2002;283:H792–9
38. Franchi F, Faltoni A, Cameli M, Muzzi L, Lisi M, Cubattoli L, Cecchini S, Mondillo S, Biagioli B, Taccone FS, Scolletta S. Influence of positive end-expiratory pressure on myocardial strain assessed by speckle tracking echocardiography in mechanically ventilated patients. Biomed Res Int 2013;2013:918548
39. Kiani A, Shabanian R, Seifirad S, Heidari-Bateni G, Rekabi M, Shahbaznejad L, Dastmalchi R, Kocharian A. The impact of preload alteration on the myocardial performance index through implementing positive end expiratory pressure. Echocardiography 2012;29:900–5
40. Orde SR, Pulido JN, Masaki M, Gillespie S, Spoon JN, Kane GC, Oh JK. Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. Crit Care 2014;18:R149