Intensive Care Med (2015) 41:1851–1853
DOI 10.1007/s00134-015-3962-3

EDITORIAL

Philippe Vignon
Stephen J. Huang

Global longitudinal strain in septic cardiomyopathy: the hidden part of the iceberg?

Received: 24 June 2015
Accepted: 30 June 2015
Published online: 17 July 2015

P. Vignon (✉)
Réanimation Polyvalente, CHU Limoges,
2 Avenue Martin Luther King, 87000 Limoges Cedex, France
e-mail: philippe.vignon@unilim.fr

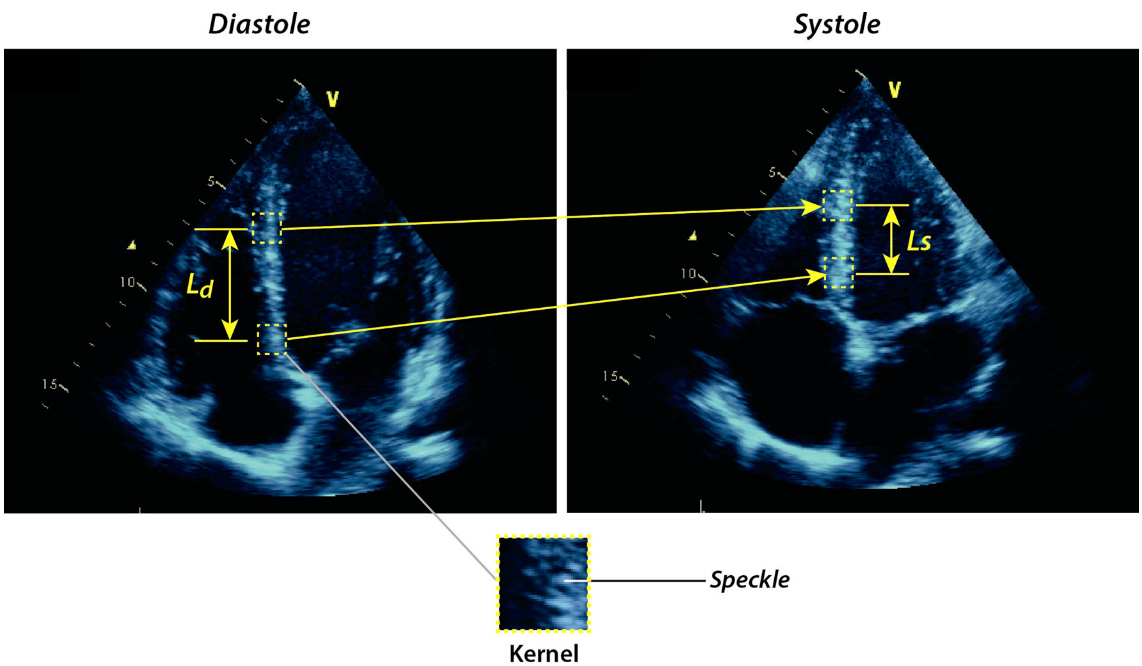
P. Vignon
INSERM, CIC1435, 87000 Limoges, France

P. Vignon
Université Limoges, UMR1092, Limoges, France

S. J. Huang
Department of Intensive Care Medicine, Nepean Hospital,
University of Sydney, Sydney, NSW 2750, Australia

In experimental models, sepsis induces an intrinsic systolic and diastolic myocardial dysfunction whose mechanisms are multiple and complex [1]. Cardiovascular alterations depend on the timing of hemodynamic assessment with respect to the infectious insult and the duration of associated sepsis, and are markedly influenced by initial fluid resuscitation [2]. In healthy humans administered an intravenous injection of endotoxin, hemodynamic alterations developed within 3 h in association with increased cardiac index, low systemic vascular resistance, and early left ventricular (LV) systolic dysfunction unmasked by fluid loading [3]. Echocardiography is a valuable imaging modality for the hemodynamic assessment of septic shock patients. In patients who are admitted to the ICU for septic shock, echocardiography depicts a decreased LV ejection fraction (EF) during the first 48 h in approximately half of the cases [4, 5]. Since both the myocardial contractility and relaxation are impaired during sepsis [1], LVEF is markedly influenced by loading conditions (particularly afterload) in these patients. The prognostic value of LV systolic dysfunction in septic shock remains debated [6]. Initial clinical studies suggested that septic patients with lower LVEF had a better prognosis, presumably owing to relatively preserved arterial tone [7]. More recent studies found similar LVEF values in survivors and in non-survivors [4, 6], and a recent meta-analysis did not suggest that survivors from severe sepsis or septic shock had lower LVEF [8]. In contrast, increased LVEF and high cardiac output secondary to profound vasoplegia were associated with a poor outcome in studies of small sample size [6, 9].

In a recent study published in *Intensive Care Medicine*, Chang et al. [10] investigated whether global longitudinal strain (GLS), a sensitive echocardiographic tool to evaluate LV systolic function, was associated with hospital mortality in septic shock patients. Strain represents the cyclical LV deformation during the cardiac cycle and is measured using echocardiography as a percentage change of the original myocardial length (Fig. 1). Systole (shortening) and diastole (lengthening) result in negative and positive strain values, respectively. GLS measures the entire U-shaped long-axis LV strain and therefore correlates with LVEF. By measuring the peak systolic longitudinal strain of all LV walls in the three standard echocardiographic apical views and subsequently computing GLS as the mean of obtained values in 111 patients with septic shock, Chang et al. [10] showed that GLS (either as a cut-off value >-13 % or as a continuous variable) and APACHE II score constituted independent predictive factors of hospital death, with GLS providing additional prognostic value. In contrast, LVEF was similar between survivors and non-survivors. Interestingly, GLS was also significantly lower in the subset of patients with preserved LVEF (i.e., $\geq$50 %; $n = 100$) who died during their hospitalization when compared to their



$$\text{Systolic strain} = {}^{(L_s - L_d)}/_{L_d} \times 100\%$$

Fig. 1 Left ventricular strain by speckle tracking echocardiography. "Speckles" are an ultrasound interference pattern of minute reflectors within the myocardium and do not represent real physical structures. Modern speckle tracking algorithm tracks the motion of a group of speckles, the kernel, frame by frame (*squares and magnified image*). The relative positions of the speckles within each kernel are fixed (like a fingerprint), rendering the tracking process more accurate. To enhance the speed and accuracy of tracking further, only the nearby areas in the next frame are searched. Strain is measured by comparing the change in distance between two kernels (*double-headed arrows*)

counterparts (OR 1.12; 95 % CI 1.04–1.20; $p = 0.002$). Accordingly, the authors suggested that GLS might be a prognostic factor in septic shock patients providing that echocardiographic image quality is adequately suited [10].

Strain measurement has substantial limitations. Akin to LVEF, GLS also depends on LV loading conditions. For example, increase in LV afterload, as in aortic stenosis or hypertension, reduces (less negative) GLS. Technically, the accuracy and reproducibility of strain measurements are hampered by various factors: frame rate-to-heart rate ratio, random noise, shadowing and clutter artifacts, and translational (motion) artifact (e.g., respiratory motion). Reproducibility and standardization of reference values are not uniform across echocardiography systems because manufacturers use different algorithms [11]. In a critical care setting where patients are predominantly ventilated, mostly lying supine and tachycardiac or arrhythmic, obtaining optimal image quality for strain purposes can be challenging. Consequently, a GLS value which can be obtained regardless of image quality may not accurately reflect actual LV deformation during the cardiac cycle. The acquisition method used by speckle tracking to derive GLS appears more sensitive and more reproducible than LVEF to identify LV systolic dysfunction [12]. GLS analysis is based on a semiautomated, regional, and frame-by-frame basis throughout systole, whereas EF relies on a manual measurement of LV volume at end-diastole and end-systole. In contrast to LVEF, GLS is unaffected by tethering effects (i.e., pulling effect of adjacent myocardium) and does not rely on geometric assumptions [12]. Accordingly, as in the present study [10], low GLS values have been previously reported in adults and children with septic shock and preserved LVEF [13, 14]. Nevertheless, these last two studies failed to identify GLS as an independent prognostic factor [13, 14]. This underlines the difficulty of establishing the prognostic value of septic cardiomyopathy, even when using sensitive echocardiographic tools to identify LV systolic dysfunction. A recent meta-analysis summarized the prognostic values of GLS from 16 studies that recruited patients with mixed cardiac etiologies [15]. GLS, used as a continuous variable, was found to be a predictor for all-cause mortality in these patients (hazard ratio reduction per SD change in GLS = 0.50, 95 % CI 0.36–0.69) with a hazard ratio 1.62 (95 % CI 1.13–2.33; $p = 0.009$) times greater than that of LVEF [15]. Nevertheless, septic cardiomyopathy and other cardiac conditions should be distinguished because they do not share the same pathophysiology. Contrary to congestive heart failure, septic-induced LV dysfunction is typically associated with non-elevated filling pressures and increased LV compliance [7]. Since sepsis alteration of LV mechanics is diffuse and not associated with myocardial ischemia, the greater susceptibility of subendocardial fibers to injury which may be better identified by reduced longitudinal function (i.e., GLS) is presumably not as applicable as in other cardiac conditions [12]. Accordingly, the prognostic value of decreased GLS in septic shock patients remains to be confirmed in larger scale studies over a wide range of LVEF values. To date, GLS has numerous technical limitations including its feasibility in the ICU setting, and the promising results reported by Chang et al. [10] cannot be yet incorporated into clinical practice without further external validation.

References

1. Joulin O, Marechaux S, Hassoun S, Montaigne D, Lancel S, Neviere R (2009) Cardiac force–frequency relationship and frequency-dependent acceleration of relaxation are impaired in LPS-treated rats. Crit Care 13:R14
2. Ricard-Hibon A, Losser MR, Kong R, Beloucif S, Teisseire B, Payen D (1998) Systemic pressure-flow reactivity to norepinephrine in rabbits: impact of endotoxin and fluid loading. Intensive Care Med 24:959–966
3. Suffredini AF, Fromm RE, Parker MM, Brenner M, Kovacs JA, Wesley RA, Parrillo JE (1989) The cardiovascular response of normal humans to the administration of endotoxin. N Engl J Med 321:280–287
4. Etchecopar-Chevreuil C, Francois B, Clavel M, Pichon N, Gastinne H, Vignon P (2008) Cardiac morphological and functional changes during early septic shock: a transesophageal echocardiographic study. Intensive Care Med 34:250–256
5. Vieillard-Baron A, Cecconi M (2014) Understanding cardiac failure in sepsis. Intensive Care Med 40:1560–1563
6. Sanfilippo F, Corredor C, Fletcher N, Landesberg G, Benedetto U, Foex P, Cecconi M (2015) Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis. Intensive Care Med 41:1004–1013. doi:10.1007/s00134-015-3748-7
7. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, Damske BA, Parrillo JE (1984) Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 100:483–490
8. Huang SJ, Nalos M, McLean AS (2013) Is early ventricular dysfunction or dilatation associated with lower mortality rate in adult severe sepsis and septic shock? A meta-analysis. Crit Care 17:R96
9. Vieillard Baron A, Schmitt JM, Beauchet A, Augarde R, Prin S, Page B, Jardin F (2001) Early preload adaptation in septic shock? A transesophageal echocardiographic study. Anesthesiology 94:400–406
10. Chang WT, Lee WH, Lee WT, Chen PS, Su YR, Liu PY et al (2015) Left ventricular global longitudinal strain is independently associated with mortality in septic shock patients. Intensive Care Med. doi:10.1007/s00134-015-3970-3
11. Nelson MR, Hurst RT, Raslan SF, Cha S, Wilansky S, Lester SJ (2012) Echocardiographic measures of myocardial deformation by speckle-tracking technologies: the need for standardization? J Am Soc Echocardiogr 25:1189–1194
12. Nesbitt GC, Mankad S, Oh JK (2009) Strain imaging in echocardiography: methods and clinical applications. Int J Cardiovasc Imaging 25(Suppl 1):9–22
13. Orde SR, Pulido JN, Masaki M, Gillespie S, Spoon JN, Kane GC, Oh JK (2014) Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. Crit Care 18:R149
14. Basu S, Frank LH, Fenton KE, Sable CA, Levy RJ, Berger JT (2012) Two-dimensional speckle tracking imaging detects impaired myocardial performance in children with septic shock, not recognized by conventional echocardiography. Pediatr Crit Care Med 13:259–264
15. Kalam K, Otahal P, Marwick TH (2014) Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 100:1673–1680