Peer-reviewed version available at *Healthcare* **2019**, *7*, 5; doi:10.3390/healthcare7010005

Review

Is Left Ventricular Global Longitudinal Strain by Two-Dimensional Speckle Tracking Echocardiography in Sepsis Cardiomyopathy ready for prime time use in the ICU?

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Abstract: Myocardial deformation imaging (strain imaging) is a technique to directly quantify the extent of myocardial contractility and overcomes several of the limitations of ejection fraction. The application of the most commonly used strain imaging method; speckle-tracking echocardiography to patients with sepsis cardiomyopathy heralds an exciting development to the field. However; the body of evidence and knowledge on the utility, feasibility and prognostic value of left ventricular global longitudinal strain in sepsis cardiomyopathy is still evolving. We conducted a review of literature on utility of left ventricular global longitudinal strain in sepsis cardiomyopathy. We discuss the role of left ventricular global longitudinal strain in mortality prediction, utility and limitations of the technique in the context of sepsis cardiomyopathy.

Keywords: Sepsis Cardiomyopathy 1; Left ventricular function 2; Global longitudinal strain 3

1. Introduction

Left ventricular (LV) function is a powerful predictor of prognosis in a number of conditions and has been shown specifically to be predictive of outcomes in sepsis [1]. Sepsis cardiomyopathy, the reversible myocardial depression that occurs early in severe sepsis and septic shock was first described in 1970s [2]. Utilizing radionuclide angiography, Parker et al[2]. reported that 50% of patients with septic shock had severely reduced baseline LV ejection fraction which was paradoxically lower in survivors. An accepted definition of sepsis cardiomyopathy is based on an LV ejection fraction of less than 45% to 50% in the absence of previously diagnosed cardiac disease that demonstrates reversibility upon remission in patients without prior cardiomyopathy [3]. This definition was evolved prior to the availability of echocardiographic techniques such as speckle tracking echocardiography[4].

The traditional method used to assess LV function (in the ICU) has been determination of LV ejection fraction, usually based on visual analysis of two-dimensional (2D) images or Simpson biplane method [5]. This long relied-upon parameter to describe LV systolic function is relatively easy to acquire and is a concept familiar to most clinicians. However, significant limitations of using LV ejection fraction to characterize systolic function are recognized. The use of 2D echocardiography to describe cardiac function is influenced by geometric assumptions, and technical issues, such as apical foreshortening and difficulties in proper delineation of the endocardial borders, limit its accuracy. As a parameter to assess LV function, ejection fraction is highly dependent on loading conditions and as such does not directly reflect the underlying lying state of LV myocardial

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contractility. In addition, the reproducibility of this method is quite high with significant inter-observer variability reported [6-8].

Given these limitations, a method that more directly assesses intrinsic myocardial contractility would be desired for clinical use. Myocardial deformation imaging (also known as strain imaging) provides a means to directly quantify the extent of myocardial contractility and overcome several of the limitations of using ejection fraction for this purpose. Strain, a unit-less parameter, is defined as the percentage change in the length (deformation) of a myocardial segment over a given period of time compared to the resting state. The most widely used method to perform strain imaging is speckle-tracking echocardiography, a technique which makes use of the presence of unique acoustic markers ("speckles") within the myocardium to track their position throughout the cardiac cycle. This method offers distinct advantages in comparison to earlier (and now rarely-used) Doppler-based techniques [9] and is now available on most current generation echocardiography platforms. Strain can be assessed in 3 principle directions (longitudinal, circumferential, and radial), however longitudinal strain is the most reproducible. Furthermore, as global strain has much better reproducibility than segmental strains, it is currently recommended that global longitudinal strain (GLS) be the parameter used to describe LV systolic function. [5]. In an effort to provide some guidance, the most recent recommendation from the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) states that a peak GLS in the range -20% can be expected in a healthy person.

Strain-imaging by speckle-tracking echocardiography has been shown to have clinical utility in a variety of settings [9] and to offer superior prognostic value to ejection fraction for predicting major adverse cardiac events [10]. Advantages of using GLS to assess LV systolic function compared to ejection fraction include better reproducibility, ability to identify sub-clinical LV dysfunction, non-reliance on geometric assumptions, and lack of influence by tethering effects.

As the utility of GLS measurement by speckle tracing echocardiography has shown accuracy in predicting outcomes in several pathological conditions, it is logical to examine the role of GLS by speckle tracking 2D echocardiography in ICU patients with sepsis and sepsis cardiomyopathy.

2. Materials and Methods

We conducted a review of current literature on the utility and prognostic value of left ventricular global longitudinal strain in patients with sepsis cardiomyopathy.

3. Review

Several recent studies and a review/meta-analysis [11] shed light on the important question; is GLS is a better predictor of mortality in sepsis cardiomyopathy than the traditional parameter; LV ejection fraction. In their meta-analysis [11], the authors pooled available and eligible observational studies that included 794 patients with severe sepsis and/or septic shock. The pooled data, stratified by survivors/non-survivor, showed that GLS measurements were strongly associated with survival (standard mean difference (SMD) −0.26; 95% confidence interval (CI) −0.47, −0.04; p=0.02) while in contrast, LV ejection fraction was found not to be a predictor of mortality.

Before conclusions can be drawn about GLS's utility and prognostic value, caution should be applied in interpreting the results of the meta-analysis[11] in view of the heterogeneity, observational nature of the component studies, especially differences in image acquisition platforms and inter-vendor variability in speckle tracking algorithms.

To further assess the role of GLS in sepsis and sepsis-related cardiomyopathy, we tabulated available relevant GLS studies in sepsis cardiomyopathy by performing a literature search for GLS and/or sepsis and/or cardiomyopathy and highlight the following: (TABLES 1, 2 and 3)

a) We tabulated 8 studies including 846 subjects with severe sepsis and/or septic shock.

b) With exception of 1 study [12] which utilized the Sepsis -3 definition[13] ; all others were based on Sepsis 2 criteria[14].

c) As in the above referenced meta-analysis, significant heterogeneity in subjects exists: 5 studies included septic shock patients, 2 studies [15-16] included patients with both severe sepsis and/or septic shock (Table 1).

Table 1. Description of studies including design, inclusion criteria, subjects and imaging platforms/software.

Primary Outcome	Secondary outcomes	Cut off thresholded GLS (%)	Echo Machine	Software	Timing	Operator	r^2 intra	r^2 inter	Ventilator	Shock
ICU mortality	Hospital mortality	-13	GE Vivid-I or Q	EchoPAC	<24 hrs	2 blinded	0.88	0.94		
ICU mortality	30 day, 90 day mortality	-15	GE Vivid E9	EchoPAC 112	<24 hrs	1	0.92		84%(37)	
hs-cardiac troponin elevation	Hospital mortality		Philips IE33	Philips Qlab 8.1	<24 hrs	2 blinded			100% (106)	
30 day mortality	6 month mortality	-17	GE Vivid 7	Syngo Velocity Vector	<24 hrs	3	0.9 +/- 0.9	0.8 +/- 0.5	65%(39)	
28 day mortality	7 day mortality		Philips IE33	Philips Qlab 8.1	<24 hrs	3 blinded	0.9	0.82	0	39
In-hospital mortality	duration of mechanical ventilation, ICU and hospital length of stay	-15	Philips IE33	Philips Qlab 4.1	<7 days	5	0.83	0.84		
In-hospital mortality, 28 day mortality	organ failure free days out of 14 days	-17	Philips IE33 or CX50	Image Arena	<24 hrs				31%	39%
28 day mortality			GE Vivid-Q	EchoPAC	<24 hrs, day 1,3,7,14	2				100%

d) Of the 846 patients included in these studies, 297 (35.1%) were eliminated from further analysis by various exclusion criteria (Table 2) illustrating the difficulties in quality image acquisition in a timely manner in this set of severely ill patients

e) With a single exception [15], all studies involved only a single center site.

Table 2. Exclusion Criteria.

Study	Exclusion Criteria
Chang et al. 2015	none
De Geer et al. 2015	death<24 hours, treatment limitations, no consent, HF, IHD
Landesberg et al. 2014	Moderate mitral/aortic diesease, poor windows, AF, arrhythmia, RWMA
Orde et al. 2014	pregnancy, congenital HD, poor image quality, prosthetic valves, cardiomyopathy, moderateor severe valve diease
Palmeieri et al. 2015	poor windows, greater than moderate aortic or mitral valve disease
Zaky et al. 2016	<18 yrs, chronic AF, EF<40%, valve disease, valvle replacement, ICDs, poor Echo views

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Lanspa et al. 2017	echo >24 hrs, poor image quality
Yang et al. 2017	MI, congenital, valvular heart disease, hospitalization<24 hrs, malignancy, liver, kideny failure, pericardial effusion, advanced malignancy, poor image quality

d) These published studies utilized different strain analysis software and echo imaging platforms (Table 1):

Philips Qlab 8.1® was utilized in 3 studies (n=352), EchoPACS® in 3 studies(n=213), Image Arena® in 1 study(n=298) and Syngo Velocity Vector® (n=60)

Philips IE 33® was used for Image acquisition in 4 studies (n=573) and GE Vivid® in 4 studies (n=273)

e) The end points reported were heterogeneous and variable. (Table 3)

Table 3. Outcomes.

Study	**ICU Non Survivor GLS**	**ICU survivor GLS**	**Hospital Non Survivor GLS**	**Hospital Survivor GLS**	**28 day Non Survivor GLS**	**28 day Survivor GLS**	**30 day Non Survivor GLS**	**30 day Survivor GLS**	**90 day Non Survivor GLS**	**90 day Survivor GLS**	**6 month Non Survivor GLS**	**6 month Survivor GLS**	**Abnormal GLS hospital mortality Alive n (%)**	**Abnormal GLS hospital mortality dead n (%)**	**Normal GLS hospital mortality dead n (%)**	**Abnormal GLS 28 day mortality dead n (%)**
	Mean +/- SD in %															
Chang et al. 2015	-11.8 +/- 4.5	-15 +/- 3.6	-12.4 +/- 4.9	-14.9 +/- 3.4												
De Geer et al. 2015							-15(-19.7 to -11)	-17.2(-20 to -13)	-14.7(-19 to -10.6)	-17.4(-20.5 to -13.6)						
Landesberg et al. 2014			-12.3 +/- 3.6	-13.7 +/- 2.7												
Orde et al. 2014							-14.6 +/- 4.3	-13.92 +/- 4.2			-14.28 +/- 4.6	-14 +/- 4				
Palmeieri et al. 2015					-9.1 +/- 3.6	-10.8 +/- 3.2										
Zaky et al. 2016													24 (80%)	12 (66.7)		
Lanspa et al. 2017														47(22)	31(17)	54(25)
Yang et al. 2017					-15.98 +/- 1.41	-17.66 +/- 1.22										

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Another recent systematic review[17] which analyzed total of 455 patients[18] did not combine the data by usage of meta-analysis methods citing significant methodological and statistical differences between the studies which concurs with our concerns.

At present no accepted GLS thresholds that define sepsis cardiomyopathy exist. The traditionally used abnormal threshold of -20% to define Left ventricular dysfunction may not apply to the setting of sepsis cardio myopathy in the critically ill population [19] and ASE-chamber quantification guideline[5]. The common observation in current literature in terms of predicting outcome is that the lower (less negative) the value for GLS, the worse the outcome, especially among patients "normal" LV ejection fractions.

Practical difficulties in obtaining reliable and timely bedside measurements of GLS exist.

Issues with standardization[19], Inter-Vendor differences [20-21], incorporation/availability of required software in point of care ultrasound machines, training of bedside ICU providers on measurements of GLS, the limited echo windows which may be available in ICU subjects and time constraints to measure GLS (currently off-line for the most part) in the critically ill subset of patients should be recognized and need to be overcome to make this assessment more robust.

As the literature on this topic continues to evolve and data accumulates on the value of GLS in sepsis and sepsis cardiomyopathy, the time has arrived to conduct prospective, multi-center investigations to define the role of GLS and potential prognostication thresholds in the management of these critically-ill patients. As such studies are designed, investigators need to take into account the limitations of the prior studies as listed above. Until such studies are performed, GLS remains just another tool in our toolbox in the assessment of these complex, critically-ill patients.

In summary, the parameter of GLS heralds an exciting but evolving new era and appears to represent a significant advance in the field of sepsis cardiomyopathy.

Author Contributions: "conceptualization, V.V. and D.T.; methodology, V.V. and D.T; writing—original draft preparation, V.V, R.P and D.T; writing—review and editing, V.V, R.P and D.T .; supervision, D.T

Funding: "This research received no external funding"

Acknowledgments: None

Conflicts of Interest: "The authors declare no conflict of interest."

References

1. Sevilla Berrios, R. A.; O'Horo, J. C.; Velagapudi, V.; Pulido, J. N., Correlation of left ventricular systolic dysfunction determined by low ejection fraction and 30-day mortality in patients with severe sepsis and septic shock: a systematic review and meta-analysis. *J Crit Care* 2014, *29* (4), 495-9.
2. Parker, M. M.; Shelhamer, J. H.; Bacharach, S. L.; Green, M. V.; Natanson, C.; Frederick, T. M.; Damske, B. A.; Parrillo, J. E., Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med* 1984, *100* (4), 483-90.
3. Paulus, W. J.; Tschope, C.; Sanderson, J. E.; Rusconi, C.; Flachskampf, F. A.; Rademakers, F. E.; Marino, P.; Smiseth, O. A.; De Keulenaer, G.; Leite-Moreira, A. F.; Borbely, A.; Edes, I.; Handoko, M. L.; Heymans, S.; Pezzali, N.; Pieske, B.; Dickstein, K.; Fraser, A. G.; Brutsaert, D. L., How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007, *28* (20), 2539-50.
4. Vignon, P.; Huang, S. J., Global longitudinal strain in septic cardiomyopathy: the hidden part of the iceberg? *Intensive Care Med* 2015, *41* (10), 1851-3.
5. Lang, R. M.; Badano, L. P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Flachskampf, F. A.; Foster, E.; Goldstein, S. A.; Kuznetsova, T.; Lancellotti, P.; Muraru, D.; Picard, M. H.; Rietzschel, E. R.; Rudski, L.; Spencer, K. T.; Tsang, W.; Voigt, J. U., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015, *28* (1), 1-39 e14.

Peer-reviewed version available at *Healthcare* **2019**, *7*, 5; doi:10.3390/healthcare7010005

6. McGowan, J. H.; Cleland, J. G., Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J* 2003, *146* (3), 388-97.

7. Thavendiranathan, P.; Grant, A. D.; Negishi, T.; Plana, J. C.; Popovic, Z. B.; Marwick, T. H., Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. *J Am Coll Cardiol* 2013, *61* (1), 77-84.

8. Wood, P. W.; Choy, J. B.; Nanda, N. C.; Becher, H., Left ventricular ejection fraction and volumes: it depends on the imaging method. *Echocardiography* 2014, *31* (1), 87-100.

9. Collier, P.; Phelan, D.; Klein, A., A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. *J Am Coll Cardiol* 2017, *69* (8), 1043-1056.

10. Kalam, K.; Otahal, P.; Marwick, T. H., Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* 2014, *100* (21), 1673-80.

11. Sanfilippo, F.; Corredor, C.; Fletcher, N.; Tritapepe, L.; Lorini, F. L.; Arcadipane, A.; Vieillard-Baron, A.; Cecconi, M., Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: a systematic review and meta-analysis. *Crit Care* 2018, *22* (1), 183.

12. Yang, F.; Chen, Y.; Zheng, R.; Ma, Y.; Yu, H.; Zhang, W.; Zhang, Y., [Two-dimensional speckle tracking imaging in assessing the left ventricular systolic function and its dynamic changes of patients with septic shock]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2017, *29* (8), 721-725.

13. Singer, M.; Deutschman, C. S.; Seymour, C. W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G. R.; Chiche, J. D.; Coopersmith, C. M.; Hotchkiss, R. S.; Levy, M. M.; Marshall, J. C.; Martin, G. S.; Opal, S. M.; Rubenfeld, G. D.; van der Poll, T.; Vincent, J. L.; Angus, D. C., The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016, *315* (8), 801-10.

14. Levy, M. M.; Fink, M. P.; Marshall, J. C.; Abraham, E.; Angus, D.; Cook, D.; Cohen, J.; Opal, S. M.; Vincent, J. L.; Ramsay, G.; Sccm/Esicm/Accp/Ats/Sis, 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003, *31* (4), 1250-6.

15. Lanspa, M. J.; Shahul, S.; Hersh, A.; Wilson, E. L.; Olsen, T. D.; Hirshberg, E. L.; Grissom, C. K.; Brown, S. M., Associations among left ventricular systolic function, tachycardia, and cardiac preload in septic patients. *Ann Intensive Care* 2017, *7* (1), 17.

16. Zaky, A.; Gill, E. A.; Lin, C. P.; Paul, C. P.; Bendjelid, K.; Treggiari, M. M., Characteristics of sepsis-induced cardiac dysfunction using speckle-tracking echocardiography: a feasibility study. *Anaesth Intensive Care* 2016, *44* (1), 65-76.

17. Vallabhajosyula, S.; Jentzer, J. C., Global Longitudinal Strain Using Speckle-Tracking Echocardiography in Sepsis. *J Intensive Care Med* 2018, 885066618799636.

18. Velagapudi, V. M.; Tighe, D., Data Abstraction Error in Systematic Review of Global Longitudinal Strain Using Speckle-Tracking Echocardiography as a Mortality Predictor in Sepsis. *J Intensive Care Med* 2018, 885066618799638.

19. Voigt, J. U.; Pedrizzetti, G.; Lysyansky, P.; Marwick, T. H.; Houle, H.; Baumann, R.; Pedri, S.; Ito, Y.; Abe, Y.; Metz, S.; Song, J. H.; Hamilton, J.; Sengupta, P. P.; Kolias, T. J.; d'Hooge, J.; Aurigemma, G. P.; Thomas, J. D.; Badano, L. P., Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2015, *16* (1), 1-11.

20. Nagata, Y.; Takeuchi, M.; Mizukoshi, K.; Wu, V. C.; Lin, F. C.; Negishi, K.; Nakatani, S.; Otsuji, Y., Intervendor variability of two-dimensional strain using vendor-specific and vendor-independent software. *J Am Soc Echocardiogr* 2015, *28* (6), 630-41.

21. Farsalinos, K. E.; Daraban, A. M.; Unlu, S.; Thomas, J. D.; Badano, L. P.; Voigt, J. U., Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. *J Am Soc Echocardiogr* 2015, *28* (10), 1171-1181, e2.