



The prognostic importance of the heart function in sepsis and septic shock: a Dedalus or a window of opportunities?

Vittorio Palmieri¹, Francesca Innocenti², Riccardo Pini²

¹Cardiology Unit, Department of Heart and Vessels, SG Moscati National Hospital, Avellino, Italy; ²High Dependency Observation Unit, Emergency Department-High Dependency Observation Unit, Department of Clinical and Experimental Medicine, Careggi University Hospital, Florence, Italy

Correspondence to: Vittorio Palmieri, MD, PhD. Via Napoli 816, I-81027 San Felice a Cancellò (CE), Italy. Email: vpalmieri68@gmail.com.

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Sepsis is an infection-related clinical condition characterized by severe systemic inflammation, potentially evolving in multi-organ failure through a number of pathophysiological mechanisms. While sepsis is a relatively infrequent disease, it is a world-wide growing and challenging medical issue (1-3), both due to high mortality rate in the short and mid-term follow-ups, and to high costs of medical management (4,5). Hemodynamic instability and sustained hypotension with systemic hypoperfusion not responding to blood volume expansion are the hallmarks of the sepsis-related shock, or septic shock. In sepsis, refractory cardiovascular failure is a frequent cause of fatal events, and myocardial injury can be found in approximately 50% of the patients in necropsy findings (6). Therefore, one cannot infer that sepsis or septic shock is equivalent to myocardial dysfunction.

In 1984, in a group of septic patients, Parker *et al.* (7) reported increased left ventricular (LV) end-diastolic volume and reduced LV ejection fraction (EF) in survivors while the non-survivors showed normal LV volumes and EF, and lower stroke volume, up to fatal events. Increased LV volumes and reduced EF were reversible in survivors to sepsis. A few years later, using radionuclide ventriculography, Parker *et al.* (8) reported that, in patients with sepsis, right ventricular (RV) systolic dysfunction can be as frequent as LV systolic dysfunction. They also found that reversible RV chamber dilatation and systolic dysfunction characterized

survivors rather than non-survivors. Overall, those early investigations on heart systolic function in sepsis and septic shock described the paradox of worse prognosis in those who had early normal systolic chamber function.

Subsequent echocardiographic studies (*Tables 1,2*) on heart structure function failed to confirm relationships of LV and RV dimensions and systolic function with prognosis in sepsis (9). Actually, echocardiographic studies revealed that a significant proportion of non-survivors to sepsis or septic shock actually showed early-depressed LV EF (10,11). With regard to RV function and prognosis in sepsis, echocardiographic studies (12) did not confirm the initial report by Parker *et al.* For instance, Landesberg *et al.* (13) found that RV dilation was independently associated with mortality, altogether with greater Acute Physiology and Chronic Health Evaluation (APACHE) score, impaired renal function and LV diastolic dysfunction. Further studies in sepsis questioned the prevalence and the prognostic significance of impaired RV systolic function as compared to LV systolic dysfunction (14). The lack of consistency in results from different studies (*Tables 1,2*) have raised more skepticism on the real prognostic impact of myocardial function in septic patients. As a consequence, a generalized opinion has been growing that cardiovascular involvement in the septic process may be essentially described by reporting mean arterial pressure and the ongoing treatment with vasoactive medications, to account for cardiovascular

Table 1 Summary of echocardiographic studies which evaluated impact of LV dimensions and function to prognosis

Author, year	Patients (n); mortality rate (%)	Age (years)	Study design; clinical setting	Patients admitted in shock	LV dimension: parameters	LV dimensions: prognostic value	LV function: parameters	LV function: prognostic value	Follow-up
Studies performed by conventional echocardiography									
McLean <i>et al.</i> , 2007	40; NA	63±15	Prospective; ICU	55%	LVDD	Non-significant	LV EF	Non-significant	In-hospital mortality
Etchecopar-Chevreuil <i>et al.</i> , 2008	35; 26	Median 60 years	Prospective, ICU	All	LVDV	Higher in non-survivors	LV EF	Non-significant	In-ICU mortality
Sturgess <i>et al.</i> , 2010	21; 29	65±17	Prospective, ICU	All	LVDV; LVSV	Non-significant	LV EF	Non-significant	In-hospital mortality
Pulido <i>et al.</i> , 2012	106; 38 and 67	65±15	Prospective; ICU	NR	LVDD; LVSD	Non-significant	LV EF	Non-significant	1-month and 1-year mortality
Furian <i>et al.</i> , 2012	45; 33	51±18	Prospective, ICU	72%	LVDD; LVDV	Higher in survivors	LV EF; LV- Sm	Non-significant	In-hospital mortality
Landesberg <i>et al.</i> , 2012	106; 39	NR	Prospective, ICU	63%	LVDV; LVSV	Higher in survivors	LV-EF; LV strain and strain rate	Non-significant	In-hospital mortality
Weng <i>et al.</i> , 2012	61; 33	NR	Prospective, ICU	All	LVDV; LVSV	Non-significant	LV EF; LV Sa	Higher LV Sa in non-survivors	90-day mortality
Studies performed by strain echocardiography									
Orde <i>et al.</i> , 2014	60; 33 and 48	62±15	Prospective; ICU		LVDD; LVSD	Non-significant	LV EF; LV GLS and LV GLS rate	Non-significant	30-day and 6-month mortality
De Geer <i>et al.</i> , 2015	50; 27, 30 and 34	Median 65 years	Prospective; ICU	All	NR		LV EF; LV GLS	Non-significant	In-ICU, 30-day and 90-day mortality
Palmieri <i>et al.</i> , 2015	115; 15 and 24	73±14	Prospective; HDU	39%	NR		LV EF; LV GLS	More compromised GLS in non-survivors	7-day and 28-day mortality
Chang <i>et al.</i> , 2015	111; 32 and 36	NR	Prospective; ICU	All	LVDV	Non-significant	LV EF; LV s; LV GLS	More compromised GLS in non-survivors	ICU- and In-hospital mortality

Sa, peak systolic velocity of the mitral annulus by pulsed tissue Doppler imaging. NR, not reported; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; LV EF, left ventricular ejection fraction; LVDV, left ventricular diastolic volume; LVSV, left ventricular systolic volume; LV-Sm, left ventricular myocardial peak systolic velocity by tissue Doppler imaging; LV GLS, left ventricular global longitudinal peak systolic strain.

Table 2 Summary of the echocardiographic studies evaluating impact of RV dimensions and function to prognosis

Author, year	Patients (n); mortality rate (%)	Age (years)	Study design; clinical setting	Patients admitted in shock	RV dimension: parameters	RV dimensions: prognostic value	RV function: parameters	RV function: prognostic value	Follow-up
Furian <i>et al.</i> , 2011	45; 33	51±18	Prospective; ICU	72%	RV diameter	No prognostic significance	RV-Sm	Significantly lower among non-survivors	In-hospital mortality
Pulido <i>et al.</i> , 2012	106; 36 at 1-month FU; 57 at 1-year FU	65±15	Prospective; ICU	NR	RV to LV size	No prognostic significance	TDI lateral tricuspid annulus peak systolic velocity	Non-significant	1-month and 1-year mortality
Landsberg <i>et al.</i> , 2013	106; 39	NR	Prospective; ICU	63%	RV EDVI; RV ESVI	Significantly higher in non-survivors	RV SVI; RV EF	Significantly lower in non-survivors	In-hospital and 1-year mortality
Harmankaya <i>et al.</i> , 2013	55; 50	67±20	Not specified	Not specified	NR		TD Sm; RV MPI	Both significantly lower among non-survivors	NR
Singh <i>et al.</i> , 2016	88; 59	38±15	Prospective; ICU	All	RV basal diameter; RVOT PLAX proximal diameter and RVOT PSAX distal diameter	No prognostic significance	TAPSE; TD MPI; PD MPI; FAC; PD peak velocity at annulus	Only FAC was significantly lower among non-survivors	28-day mortality
Chang <i>et al.</i> , 2015	111; 32 and 36	NR	Prospective; ICU	All	NR		RV-s'	Non-significant	ICU- and In-hospital mortality
Vallabhajosyula <i>et al.</i> , 2017	388; 30	66	Retrospective; ICU	72%	RV diameter	NR	TAPSE, RV FAC, tricuspid annulus displacement peak systolic velocity	RV dysfunction including RV dilatation, TAPSE <16 mm, tricuspid RV-s' <15 cm/sec, fractional area shortening <35%	1-year mortality
Studies performed by strain echocardiography									
Orde <i>et al.</i> , 2014	60; 33 and 48	62±15	Prospective; ICU		RV diameters	Non-significant	RV FAC; RV free wall strain and strain rate	Non-significant	30-day and 6-month mortality

RV Sm, right ventricular peak systolic velocity; TDI, tissue Doppler imaging; RV EDVI, right ventricular end-diastolic volume index; RV ESVI, right ventricular end-diastolic volume index; RV SVI, right ventricular stroke volume index; RV EF, right ventricular ejection fraction; RV MPI, right ventricular myocardial performance index; RV FAC, right ventricular fractional area change; RV-s', right ventricular peak systolic velocity of the lateral tricuspid annulus by pulsed tissue Doppler imaging.

impairment as one of the potential multi-organ failure in sepsis (Sequential Organ Failure Assessment, SOFA). The recently published Surviving Sepsis Campaign (SSC) considered echocardiography to assess fluid-responsiveness to fluid bolus, recognized the presence of a sepsis-related myocardial dysfunction by means of EF, and stated (cit.) “measurement of cardiac output along with a measure of the adequacy of perfusion is preferable” over echocardiography to identify patients who might benefit from dobutamine administration.

Nonetheless, the issue of a potential link between heart systolic function and prognosis in sepsis or septic shock was raised brought up by a recent retrospective investigation from the Mayo Clinic (15), reporting that RV systolic dysfunction may be common and prognostically relevant in long-term follow-up in septic patients. The study provided interesting data in 388 patients of whom 55% showed RV dysfunction (16) (i.e., tricuspid annulus plane systolic excursion (TAPSE) below 16 mm or its peak velocity below 15 cm/sec or RV fractional area change below 35%). Of the study sample, 26% showed isolated RV dysfunction, i.e. without associated LV dysfunction defined based on LV EF <50% (17). As reported (15), reduced TAPSE (38%) or enlarged RV (31%) were the main contributors to the definition of RV dysfunction, whereas 1 in 5 patients studied showed simultaneously both RV abnormalities. Systemic hemodynamics did not differ significantly among the septic patients stratified based on the absence or the presence of RV systolic dysfunction, independent to the presence or the absence of LV systolic dysfunction. Of note, LV stroke index was on average 40 mL/m² with RV dysfunction, roughly comparable to the mean stroke index measured in septic patients without RV dysfunction. Cardiac index was 3.5 l/min/m² compared to the 3.8 (interquartile range 2.8–4.1) L/min/m² in patients without RV dysfunction, and was lowest in those with LV dysfunction in line with lowest stroke index mean values. LV preload was also comparable among patients stratified according to RV/LV systolic dysfunction, as the peak velocity of the mitral E wave (i.e., the early LV filling wave), and the ratio between the peak velocity of the mitral E wave and the peak velocity of the early diastolic displacement of the mitral annulus (so called $\dot{\epsilon}$), were both comparable among the group of patients independent to ventricular dysfunction. The peak velocity of the mitral E wave represents the instantaneous peak gradient between the left atrium and the LV in proto-diastole, so that, mitral E wave peak velocity can be

assumed as an indirect measure of LV preload, determined by the active LV suction and the passive effect of left atrium blood volume. All groups shared a high percent of patients with shock (80% among those with isolated RV dysfunction, 63% among those without RV dysfunction, 72% among those with both RV and LV dysfunction); SOFA as well as APACHE-III score, blood lactate, mean airway pressure applied, as well as total nor-epinephrine and crystalloid used in 24h, were all comparable among the groups of patients. Therefore, Vallabhajosyula *et al.* (15) described patients differing based on load-dependent indicators of RV and LV systolic chamber function but not in terms of hemodynamics. Ultimately, those data support the hypothesis that subjects with reduced LV or RV systolic function at comparable central hemodynamics may have significant myocardial dysfunction, and worse prognosis at one-year follow-up, independently of APACHE-III score, and with no prognostic contributions from troponins, lactates, LV dysfunction, age, status of shock, and mechanical ventilation. Survival curves did not distinguished patients with versus without RV dysfunction in the first month of observation, whereas curves diverged by the second month of observation, and remained separated up to the 12-month follow-up. The point of long-term survival in sepsis is important. However, for a clinical dynamic condition with a high risk of in-hospital death, such as sepsis and septic shock, short-term predictors of untoward events are potentially more relevant for clinical-decision making than those emerging only in the long-term.

Because investigations on heart chambers structure and function as prognostic indicators in sepsis and septic shock provided inconsistent results, a parallel research focused on laboratory indicators of myocardial injury, myocardial stress and severity of inflammation, such as troponins, natriuretic peptides, and cytokines, for risk stratification, monitoring the process, predicting prognosis. Several experimental studies documented the presence of circulating cytokines, which induce myocardial contractile impairment via mechanisms such as nitric oxide overproduction or calcium ion leakage from the sarcoplasmic reticulum. The issue of circulating myocardial depressant factor(s) emerged (18) as pathophysiological mechanism and target, even though research has been inconclusive (19,20). In fact, a clear correlation between circulating cytokines and LV EF as marker of LV systolic function was substantially inconsistent (21). Furthermore, the time-course of the cardiac-specific troponins has been considered as possible surrogate for the relation between the extent of myocardial damage, risk

stratification and prognosis in sepsis. However, because different processes may end with myocardial damage, it remains to be clarified whether the mechanisms of cytolysis or the cytolysis in itself is relevant in sepsis. Troponin release from cardiac myocytes is supposed to occur by mechanisms such as imbalanced myocardial oxygen supply-demand even in absence of critical coronary stenoses, alteration of oxygen extraction and cellular utilization, inflammation-induced apoptosis, and increased cellular permeability. Additional contribution to myocardial injury in sepsis may be related to increased endogenous or exogenous catecholamines. Myocardial stress with myocardial dysfunction in sepsis may explain in part the increased levels of N-terminal-brain natriuretic peptide (NT-proBNP), whereas a contribution may come from reduced inactivation of NT-proBNP in acute inflammation (13,22-24). Troponins and NT-proBNP both elevated were proven to be associated with worse prognosis and, in a less consistent manner, with the presence of myocardial systolic or diastolic dysfunction in sepsis. However, because cytolyses are invariably elevated in sepsis, and levels of specific markers of inflammation as well as of myocardial necrosis are highly variable intra-patients and between-patients, relationships of plasma levels of those biomarkers with heart function and prognosis in sepsis has not emerged as strong as hypothesized, and the use of those bio-markers have not been turned to be useful in bedside decision-making processes (25-27). Therefore, the attention has remained high on heart structure and function for risk stratification and monitoring disease evolution in sepsis.

As a general concept, EF is the percent of end-diastolic volume ejected in systole, numerically computed as ratio between stroke volume and end-diastolic volume, representing a measure of chamber systolic function. RV fractional area change and TAPSE approximates RV EF, explored today in clinical research by real-time 3D echocardiography (28). Because LV EF, as well as TAPSE or RV area fractional shortening, are sensitive to preload and afterload, they cannot provide reliable information on myocardial systolic performance. For instance, a 50% EF may result from a stroke volume of 120 mL divided by 240 mL of end-diastolic volume, or the result of 60 mL of stroke volume on 120 mL of end-diastolic volume. Moreover, for comparable EF values, as in the latter case, myocardial systolic performance differs according to the *La Place's Law*, because afterload is higher with greater systolic blood pressure and larger end-systolic diameter, but is lower with thicker wall in systole (29-31). Sepsis is a clinical scenario in which loading conditions and myocardial contractility can be largely variable intra-patient

at different times, as well as between-patients. Therefore, a shift in the identification LV function parameters is needed in order to explore whether in sepsis assessment of myocardial performance is useful for triaging patients, following treatments efficacy, and predict prognosis.

Novel technologies in echocardiography have boosted new research in the field of myocardial dysfunction in sepsis and septic shock (*Tables 1,2*) (32-38). Shifting from investigating chamber function to myocardial contractility by minimally operator-dependent techniques, bedside-ready, is the key-element for employing those technologies in patients with sepsis and septic shock. One of the new echocardiographic methods of assessment of ventricular systolic and diastolic function is based on tracking two-dimensional myocardial speckles to describe myocardial deformation through the cardiac cycle (39). The myocardial deformation through the cardiac cycle is defined strain, which can be measured during systole as well as diastole, and can be described as deformation in the dimension of time, therefore called strain-rate. With a sufficient number of speckles traced, semi-automatic procedures allow operators to obtain strain and strain-rate even bed-side. In addition, the contribution of the performance of different myocardial layers to the global function may be explored, granted a sufficient number of speckles are traced in the "space" over time. The global longitudinal peak systolic strain (GLS) is the indicator of systolic myocardial function most commonly used in clinical practice. GLS is significantly less load-independent compared to LV EF or TAPSE (40). Procedures to obtain sections of the heart useful for quantitative analysis (i.e., strain and strain-rate assessments) do not differ substantially from those usually employed in daily practice for heart imaging by ultrasound. As quality of imaging is a key-factor for assessments of EF, TAPSE and heart volumes, a good quality of images of the heart is important for strain and strain *rate* assessments. Such a technology is now available on portable echocardiographic machines, giving the possibility of measuring GLS bedside. GLS should most help in risk stratification of patients beyond load-dependent measure of chamber systolic function, to resolve the initial paradox of worse prognosis in septic patients with preserved LV EF as described by Parker *et al.* (7). There is a possibility that GLS may describe unappreciated myocardial dysfunction in septic patients with normal or nearly normal EF or TAPSE. The relationship between LV GLS and EF was reported to be heteroscedastic toward higher values of both indicators, so that that for EF >30%, information from LV GLS and

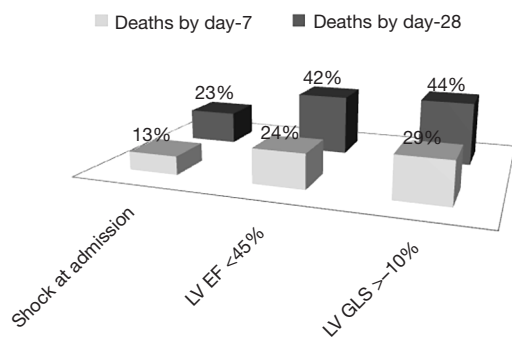


Figure 1 Columns represent prevalence of all-cause deaths at day-7 (light gray columns) and at day-28 (heavy gray columns) among patients grouped by specific characteristics defined at admission to the high-dependency observation unit. Patients were grouped alternatively (horizontal axis) according to shock at admission, or left ventricular (LV) ejection fraction (EF) below 45%, or LV global longitudinal peak systolic strain (GLS) above -10%. GLS closer to 0%, or > -10%, indicates more depressed myocardial contractility compared to those with more negative values of GLS (< -10%). As it can be seen in Figure, the rate of events (numbers in percent on each column) was highest among patients with significantly depressed myocardial systolic function (GLS > -10%) while it was lowest among those who presented with septic shock at admission, both at day-7 as well as at day-28 follow-up.

from LV EF do not overlap, and LV GLS may provide information on short-term prognosis independent and beyond LV EF in septic patients (41). GLS of the RV free wall was also reported to be prognostically relevant in the short term in sepsis and septic shock (42). Actually, in sepsis and septic shock myocardial systolic function predicted prognosis independent to age and sepsis severity based on SOFA, in the very short term (43). Several investigations have demonstrated that GLS was able to identify systolic dysfunction in a significantly higher proportion of septic patients as compared to conventional echocardiography. Nevertheless, the association of impaired LV GLS with adverse prognosis in sepsis may be relatively weak (42,44-46). Investigations on potential contribution of RV GLS to prognosis in sepsis is even more problematic, first of all because RV free wall is thin, and consequently the number of speckles may be relatively low for reliable function quantification.

Notwithstanding, the idea that sepsis could be phenotyped according to GLS is seducing. Fatal events in sepsis in the short term appear to be related to LV systolic function more strongly than the dramatic condition of

shock in itself (Figure 1, data unpublished, abbreviations as in text). Nevertheless, research in the field cannot be considered conclusive, as the use of GLS for clinical decision making in sepsis is far from being established. Correlates and determinants of GLS in sepsis are still under-investigations. Studies using both hemodynamic and heart dysfunction phenotypization in sepsis and septic shock are lacking. To date, risk stratification in sepsis and septic shock remains a challenging task. Such a research field requires a strong joint-invention between cardiology and emergency medicine for the future.

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Footnote

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