Background—In sepsis, whether the assessment of left ventricular global longitudinal systolic strain (GLS) is feasible and prognostically relevant remains controversial.

Methods and Results—Consecutive patients admitted to a high-dependency observational unit with sepsis or septic shock were evaluated. Left ventricular ejection fraction (EF) by planimetry and peak GLS by 2D speckle tracking were available at admission in 115 of 149 (77%) patients. Compared with patients included in the study, those excluded (n=34, 23%) showed higher proportion of chronic obstructive pulmonary disease (P<0.01), but with comparable clinical characteristics and mortality rates. GLS showed lowest variability for low EF and highest for higher EF. By day-28 follow-up, all-cause mortality was 30% (n=34 and n=19 within 7 days from hospitalization). GLS and EF were both more abnormal in deceased than in those alive by day-28 follow-up (both P<0.05, findings consistent using day-7 follow-up data). GLS showed a borderline relationship with mortality by day-28 follow-up (hazard ratio 1.16%/ P=0.05), whereas EF did not (hazard ratio 0.99%/ P=0.63) accounting for age; the lack of association of all-cause mortality with EF was consistent at day-7 follow-up (hazard ratio 0.94%/ P=0.9), whereas more abnormal GLS correlated significantly with higher mortality rate (hazard ratio 1.30%/ P=0.03) independent to age.

Conclusions—In patients with sepsis assisted in a high-dependency observational unit, feasibility of assessments of left ventricular EF and GLS within 24 h from the hospitalization was acceptable and EF showed no prognostic relevance, whereas GLS showed a correlation with mortality rate potentially relevant in shorter more than in longer follow-ups. (Circ Cardiovasc Imaging. 2015;8:e003865. DOI: 10.1161/CIRCIMAGING.115.003865.)

Key Words: echocardiography ■ infection ■ mortality ■ myocardial contractility ■ septic shock
Coronary heart disease was assessed by medical history and charts review and defined based on previous myocardial infarction or myocardial revascularization or presence of significant Q wave (>0.04 s and dipper than 0.1 V) or presence of QS on standard 12-lead ECG (with the exception of aVR and V1 leads) or evidence of regional wall motion abnormalities with previous history of chest pain/myocardial revascularization. Previous history of chronic obstructive pulmonary disease (COPD) was assessed by medical charts review and the use of specific therapy. Previous history of chronic kidney disease was defined by evidence of serum creatinine level above the upper reference limit of the laboratory (in general >1.2 mg/dL or 106.1 μmol/L) on examinations performed in a 12-month time window previous to the hospitalization when the patient could be considered in stable euvelomic conditions; patients on dialysis were excluded apriori from the study. The study protocol was approved by the Toscana–Area vasta–Centro interinstitutional ethic committee (registration number OSS.13.031).

Echocardiography was performed within 24 h from the admission by a standardized protocol following recommendations of the American and European Societies of Echocardiography,26–28 using a single echocardiographic machines (iE33, Philips Medical System, Andover, MA) equipped with an S4 cardiac probe and standardized settings allowing acquisitions of digital loops of at least 2 cardiac cycles with at least 45 frames per second (mean value obtained, 57±5 frames per second). LV EF was assessed by 2-plane method, bedside, as part of the clinical workup at admission, with LV volume reconstruction according to the Simpson’s methodology.29 Speckle-tracking analysis was performed off-line several days or weeks from the admission using a commercially available software (Philips QLAB Advanced Quantification Software version 8.1) by standard methodology previously applied in other studies,19,28,30,31 in random sequence, and by experienced personnel (AA, EG, and VP as final arbiter) blind to clinical data and outcome. Briefly, analysis of LV myocardial deformation was performed from 2-dimensional gray-scale loops by automatic tracking of myocardial speckles after manual selection of landmark points using apical views of the left ventricle. GLS was calculated averaging the negative peak of longitudinal strain from 12 ventricular segments from the apical 4-chamber and 2-chamber views. In-house test–retest reproducibility analyses for assessment of LV EF and GLS were performed as part of the quality control assessment of the data. In a random sample of 22 subjects, EF and GLS were measured twice by a single reader in a random sequence from the same cardiac cycle (R1 and re-R1) and remeasured in a second cardiac cycle stored at the end of the standardized echo-cardiographic protocol (R1 and R2). Intraclass correlation coefficient for R1 and re-R1 (best scenario) was excellent both for EF (0.87, 95% confidence interval 0.52–0.97 for absolute agreement, R1: 72±4% versus re-R1: 73±7%, intraobserver intrastudy coefficient of variability 10%) and for GLS (0.90, 95% confidence interval 0.77–0.99 for absolute agreement, R1: −12±4% versus re-R1: −13±4%, intraobserver intrastudy coefficient of variability 7%). Reproducibility of single-reader measurements repeated on 2 different cardiac cycles acquired at different times within the same echocardiographic examination (worse scenario) were more than good both for EF (0.74, 95% confidence interval 0.27–0.93 for absolute agreement, R1: 72±7% versus re-R1: 70±7%, intraobserver interstudy coefficient of variability 10%) and for GLS (0.63, 95% confidence interval 0.77–0.99 for absolute agreement, R1: −12±4% versus re-R1: −14±4%, interobserver interstudy coefficient of variability 10%).

Outcome was defined as death by any cause recorded by tracing medical records within the hospitalization or by phone calls and chart reviews after hospital discharge, irrespective of rehospitalizations. Mortality rate was evaluated within 28 days from hospitalization and was used as reference for survival analysis; mortality rate by 7 days from hospitalization was also considered as clinically relevant in sepsis. Time to event was computed as the difference between the date of events and the date of hospitalization, whereas for those who survived, the observation time was set at 7 and 28 days. No patient was lost at follow-up.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS software package (version 22). Data in table are mean values±1 standard deviation of the mean or counts and percent. For continuous variables, the null hypothesis was tested using the Student’s t test for independent groups, using log-transformed variables in the case of excessively skewed distribution; Fisher exact test was used to compare counts in cross tables. According to current recommendations,22,23 Cox’s proportional hazard function was used to explore whether GLS or EF predicted time-dependent mortality accounting for age (ie, using only 3 independent variables entered simultaneously). Day-28 follow-up was used as reference. Two-tailed P<0.05 was used to reject null hypotheses.

Results

Demographic and clinical characteristics of the study sample according to day-28 follow-up are summarized in Table. By the clinical setting, the study sample did not include patients on mechanical ventilation. Patients excluded (n=34, 88% as a result of poor image quality) showed clinical and laboratory characteristics comparable to those included in the study, with the exception of a higher prevalence of COPD (31% versus 15%, P<0.05); the SOFA score was also comparable between patients included and those excluded from the study (6.3±3.3 versus 5.9±4.0, respectively, P>0.1); mortality rate (all-cause) was 15% within day-7 follow-up and raised to 24% by day-28 follow-up among the excluded patients (P>0.1 versus mortality rate in the study sample, 17% n=19/115 and 30% n=34/115, respectively).

Patients deceased by day-28 follow-up were older than those who survived (Table). Sex distribution and proportions of those with medical history of diabetes mellitus, coronary heart disease, chronic kidney disease, or COPD were not statistically different between survivors and nonsurvivors. The proportion of those who presented septic shock was comparable between deceased and alive. Heart rate at the time of echocardiogram was higher in deceased compared with survivors, whereas systolic blood pressure tended to be comparable between groups. Troponin I levels were higher

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<th>Table. Clinical Characteristics of the Study Sample, Stratified by Events at Day 28 of Follow-Up</th>
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Nonsurvived were all-cause deaths. CHD indicates coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive disease; EF, ejection fraction; GLS, global longitudinal strain; HR, heart rate; LV, left ventricular; and SBP, systolic blood pressure. Log(10) of Tropinin I was used for statistical analysis.

*P<0.05.
†P<0.01.
in patients who died (median 0.28, interquartile range 63 μg/L) than in those alive (median 0.14, interquartile range 2.8 μg/L) by day-28 follow-up without reaching the statistical significance because of the large variability of the marker of myocardial injury. LV systolic function was more impaired by means of lower EF and less negative GLS (or closer to 0%) in deceased than in patients alive. Analyses comparing clinical characteristics of nonsurvivors (n=19, 17%) versus survivors (n=96) by day-7 follow-up were consistent (data not shown). Coronary heart disease patients showed lower EF (40±18% versus 52±17%) and less negative GLS (−8±3% versus −11±3%, P<0.05) compared with patients without coronary heart disease; no significant differences in EF and GLS were found between patients with or without chronic kidney disease, or with versus without diabetes, or with versus without COPD (data not shown, all P>0.1).

GLS showed a heteroscedastic variability when plotted against EF, with largest variability of GLS for EF>30% and lowest for EF≤20% (Figure 1A and 1B). Moreover, as it may be seen in Figure A, although fatal events by day-28 follow-up were distributed over a wide range of observed EF, almost all the events clustered for GLS >−15%; on the other hand, a large number of patients alive at day-28 follow-up also showed GLS >−15%. Findings looking at events by day-7 follow-up by GLS plotted against EF are reported in Figure B and were substantially consistent.

By day-28 follow-up, mortality rate tended to be higher per unit of GLS closer to 0 (ie, more LV systolic dysfunction, adjusted hazard ratio 1.16%, 95% confidence interval 0.99–1.34, P=0.051), whereas EF was far from being prognostically relevant (adjusted hazard ratio 0.99%/y, 95% confidence interval 0.97–1.02, P=0.6), independent to age (adjusted hazard ratio 1.04/y, 95% confidence interval 1.003–1.07, P=0.03). Survival analysis using day-7 follow-up consistently revealed the lack of significant relationship between EF and the probability of death (hazard ratio 0.94%/y higher EF with a 95% confidence interval of 0.96–1.04, P=0.9), whereas the hazard ratio of all-cause death for GLS was 1.30%/y of GLS closer to 0 with a 95% confidence interval of 1.02 to 1.64 and P value=0.03, accounting for age as potential confounder (adjusted hazard ratio 1.04/y, 95% confidence interval 0.99–1.09, P=0.14).

**Discussion**

In our study in patients with sepsis or septic shock admitted to a subintensive medical care unit and not mechanically ventilated, assessment of GLS and EF was frequently feasible. On average, GLS and EF were significantly more abnormal in those who died versus those who were alive by day-28 follow-ups; data based on day-7 follow-up were consistent. Although GLS showed an age-independent borderline significant relationship with mortality at day-28 follow-up, EF did not predict events. Of note, analyses using mortality rate by day-7 follow-up consistently showed no significant relationship between EF and mortality, whereas more abnormal LV systolic function by means of less negative GLS values, or GLS values closer to 0%, were predictive of increased hazard of fatal events independent to age. LV systolic dysfunction assessment by GLS in sepsis in the short term may be a clinically relevant target for future and larger studies because it might impact decision-making and treatment options during in-hospital management. Our study is underpowered to investigate the prognostic relevance of LV systolic function accounting simultaneously for a larger set of additional potential covariates. However, data in Table clearly showed that deceased and alive patients by day-28 follow-up, as well as by day-7 follow-up, differed essentially by LV systolic function parameters and age.

In a postmortem necropy investigation in sepsis, fatal cardiovascular failure accounted for at least 35% of the events, and myocardial injury was found in 54% of patients. Impaired LV GLS has been reported in acute inflammatory-based injury of the myocardium, which was related to pathophysiological processes, such as myocardial edema, inflammatory cell infiltration, and myocardial damage associated with increased troponin levels and gadolinium-marked regions. Therefore, lower GLS in patients with severe sepsis may not be surprising, may resemble myocardial dysfunction reported in acute myocarditis, and may be mediated by cytokines and microvascular disease, at least in part. Interestingly, in septic shock, vasopressors/inotropes may not protect from fatal events, and actually catecholamine-mediate myocardial injury may be possible in addition to inflammatory-mediated tissue damage. In our study, the GLS showed an heteroscedastic trend when plotted versus EF, with higher variability of GLS for higher EF and lowest for EF<30% (Figure), providing plausibility for investigating GLS as potentially useful tool for risk stratification in sepsis beyond EF and, in particular, in those who may be considered to have substantially preserved LV systolic function. Interestingly, although fatal events were distributed across a wide range of EF, almost all deceased patients showed a baseline GLS >−15% (Figure A and B), an external GLS cut point to identify abnormal GLS. On the other hand, a significant proportion of participants with abnormal LV systolic function according to GLS >−15% were alive at follow-ups; the finding may suggest that GLS, and not EF, may be a useful prognostic indicator in cohort studies, although its contribution to risk stratification in a clinically meaningful window of observation in single subjects needs to be explored further.

A previous report in 60 patients with severe sepsis, GLS was not found to be an independent predictor of all-cause death by day-30 and day-180 follow-up. In our study in 115 patients, the relationship between GLS and time-dependent fatal events by day-28 follow-up was borderline significant with a P value=0.051, accounting for age. Compared with the cohort evaluated by Orde et al, the majority of whom were on mechanical ventilation, our larger study population was on average older by a decade and showed lower SOFA score (mean values 7 versus 11), but more severe LV systolic dysfunction (on average, EF lower by 10 points and GLS less negative by 4 points percent in our cohort). Nevertheless, event rate in the 2 cohorts at 1-month follow-up were almost comparable (30% versus 33%), whereas mortality rate in the shorter follow-up could not be compared because it was not reported by Orde et al.

In our relatively large study cohort of patients with sepsis, not mechanically ventilated and treated in a subintensive medical unit, feasibility of assessment of GLS was acceptable.
compared with the feasibility of the assessment of the more popular EF by planimetry. In another experience in a cohort of septic patients, 65% of whom were on mechanical ventilation, the feasibility was lower than in our experience (55% versus 77%). Novel imaging reconstruction, such as short-lag spatial coherence, has been proved to improve significantly the quality of imaging in volunteers while preserving the possibility of endocardial border recognition and myocardial function quantification by speckle-tracking modality. In our study, for instance, history of COPD was the main factor associated with inability to obtain echocardiographic images suitable for quantitative assessments of both EF and GLS. Moreover, GLS was assessed off-line, so that the information was not immediately available for clinical purpose, whereas EF can be usually estimated bedside in commercially available echocardiographic machines. However, procedures for acquiring cardiac loops to assess GLS are not substantially different from those used for quantitative assessment of EF by

Figure. A, Single cases marked by day-28 follow-up outcome: white circles are patients alive and dark circle deceased. Left ventricular ejection fraction (EF; horizontal axis) was plotted against global longitudinal peak systolic strain (GLS; vertical axis). It can be appreciated that in our study sample, the variability of GLS versus EF was highest for what is generally considered normal or mildly reduced EF, whereas GLS showed the smaller variability for very low EF values. B, Single cases marked by day-7 follow-up outcome: white circles are patients alive and dark circle deceased. Left ventricular EF (horizontal axis) was plotted against GLS (vertical axis) as in Panel A.
planimetry, which provides substrate for systematic attempts of assessments of both measures of LV systolic function in a clinical setting. Currently, off-line GLS analysis by remote workstations and specifically trained medical doctors does not seem to be bedside-ready technique. Nevertheless, after appropriate training, assessment of GLS could be obtained in ≈15 minutes per patient, and new advanced echocardiographic machines may have specific tools for quantitative assessment of LV function onboard, making such an approach bedside-scenario compatible. Actually, tools for GLS assessment may assist the operator for simultaneous and automated estimation of EF, sparing a significant amount of time to be invested in procedures for quantitative estimates of LV systolic function. Relatively high test−retest variability might be another potential issue with GLS. On the other hand, within patients, intrastudy–intraoperator reproducibility of assessment of GLS was comparable to that observed for assessment of EF by the recommended method.27 Of note, EF and GLS were assessed for in-hospital risk stratification in sepsis. but statistically relevant in shorter follow-up. Therefore, more work is needed to investigate whether GLS might be useful for in-hospital risk stratification in sepsis.

Conclusions
Assessments of EF and GLS were frequently feasible in septic patients not mechanically ventilated, assisted in a high-dependency observational unit. Age-adjusted relationship of GLS to mortality was borderline significant by day-28 follow-up, but statistically relevant in shorter follow-up. Therefore, more study is needed to investigate whether GLS might be useful for in-hospital risk stratification in sepsis.

Disclosures
None.

References
In patients admitted to a subintensive medical unit because of sepsis or septic shock, not mechanically ventilated, the assessments of left ventricular ejection fraction and global longitudinal peak systolic strain by 2D speckle tracking were frequently feasible (77% of the 115 cases meeting inclusion criteria) and were both lower in deceased (30%) patients than in patients alive by day-28 follow-up; the finding was consistent using day-7 follow-up mortality data (17%); time-dependent survival analyses suggested that global longitudinal systolic strain was the only measure of left ventricular systolic function with some prognostic relevance accounting for age, potentially more useful for risk assessment in shorter than in longer follow-ups.
Left Ventricular Systolic Longitudinal Function as Predictor of Outcome in Patients With Sepsis
Vittorio Palmieri, Francesca Innocenti, Aurelia Guzzo, Elisa Guerrini, Damiano Vignaroli and Riccardo Pini

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