

# Diastolic dysfunction and mortality in severe sepsis and septic shock

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## Aims

Systolic dysfunction in septic shock is well recognized and, paradoxically, predicts better outcome. In contrast, diastolic dysfunction is often ignored and its role in determining early mortality from sepsis has not been adequately investigated.

## Methods and results

A cohort of 262 intensive care unit patients with severe sepsis or septic shock underwent two echocardiography examinations early in the course of their disease. All clinical, laboratory, and survival data were prospectively collected. Ninety-five (36%) patients died in the hospital. Reduced mitral annular e'-wave was the strongest predictor of mortality, even after adjusting for the APACHE-II score, low urine output, low left ventricular stroke volume index, and lowest oxygen saturation, the other independent predictors of mortality (Cox's proportional hazards: Wald = 21.5, 16.3, 9.91, 7.0 and 6.6,  $P < 0.0001$ ,  $< 0.0001$ , 0.002, 0.008, and 0.010, respectively). Patients with systolic dysfunction only (left ventricular ejection fraction  $\leq 50\%$ ), diastolic dysfunction only (e'-wave  $< 8$  cm/s), or combined systolic and diastolic dysfunction (9.1, 40.4, and 14.1% of the patients, respectively) had higher mortality than those with no diastolic or systolic dysfunction (hazard ratio = 2.9, 6.0, 6.2,  $P = 0.035$ ,  $< 0.0001$ ,  $< 0.0001$ , respectively) and had significantly higher serum levels of high-sensitivity troponin-T and N-terminal pro-B-type natriuretic peptide (NT-proBNP). High-sensitivity troponin-T was only minimally elevated, whereas serum levels of NT-proBNP were markedly elevated [median (inter-quartile range): 0.07 (0.02–0.17) ng/mL and 5762 (1001–15 962) pg/mL, respectively], though both predicted mortality even after adjusting for highest creatinine levels (Wald = 5.8, 21.4 and 2.3,  $P = 0.015$ ,  $< 0.001$  and 0.13).

## Conclusion

Diastolic dysfunction is common and is a major predictor of mortality in severe sepsis and septic shock.

## Keywords

Sepsis • Diastolic dysfunction • Heart failure with normal ejection fraction • Mortality • Echocardiography

## Introduction

Sepsis affects more than 600 000 patients in the USA each year<sup>1</sup> and is associated with high mortality: up to 70% in seriously ill patients.<sup>2</sup> The entire cardiovascular system is involved in the pathophysiology of severe sepsis and septic shock.<sup>3</sup> Venous and arterial dilatation decrease cardiac preload and afterload; microvascular dysfunction leads to capillary leak, tissue oedema and hypoxia; and myocardial dysfunction<sup>4</sup> may further significantly contribute to the haemodynamic derangement. In the 1980's, Parker

*et al.*,<sup>5</sup> using cineangiography and pulmonary artery catheterization, showed that systolic dysfunction and ventricular dilatation occurred in 50% of septic shock patients despite normal or high cardiac outputs.<sup>6</sup> Paradoxically, however, patients with systolic dysfunction had better survival and myocardial dysfunction recovered if patients survived the septic course.<sup>7</sup> Subsequent echocardiography studies confirmed the presence of depressed left ventricular ejection fraction (LVEF) in 20–60% of septic shock patients, although questioned the findings of marked LV dilatation.<sup>8–10</sup> Diastolic dysfunction is currently recognized as a major cause of heart

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failure despite normal EF and as a serious predictor of long-term mortality and morbidity, particularly in elderly patients with cardiovascular disease. Little data exist on diastolic dysfunction during acute non-cardiac illness and only few, small studies (21–54 patients)<sup>11–15</sup> investigated diastolic dysfunction in septic patients. Still, none of these studies had systematically investigated its prognostic role in an adequately sized cohort. Accordingly, we undertook a comprehensive study to fill this important gap in understanding.

## Methods

With the approval of the Institutional Review Board, patients with severe sepsis and septic shock admitted to the General Intensive Care Unit during the years 2007–2009 were studied. Severe sepsis was defined in the presence of all three of the following criteria: (i) evidence of infection or serious clinical suspicion for infection; (ii) at least two signs of the signs of systemic inflammatory response syndrome: (a) temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ ; (b) pulse  $>90$  b.p.m.; (c) respiratory rate  $>20$  breaths/min or mechanical ventilation; (d) white blood cells  $>12\,000$  or  $<4000$  or  $>10\%$  bands; and (iii) at least one organ dysfunction.<sup>16</sup> Septic shock was defined as severe sepsis plus hypotension (systolic BP  $<90$  mmHg) lasting more than 1 h, not responding to fluid therapy (raising central venous pressure to 12 or 15 mmHg in patients with oliguria) and requiring vasopressor therapy.<sup>17</sup> Pulmonary artery catheters were rarely utilized (6%), only in cases of severe renal failure and oliguria. Excluded were patients with greater than mild mitral and/or aortic valve disease, patients with echocardiographic evidence of regional myocardial wall motion abnormality suggesting regional ischaemia or previous infarction and patients with poor quality echocardiographic images and measurements.

## Echocardiography

All patients underwent two, once daily, trans-thoracic echocardiography examinations using a Phillips' Sonos 5500 machine and a S4 2–4 MHz probe. The first examination was as early as possible after the admission with the diagnosis of sepsis in the ICU. The second echocardiogram was performed on the next day, to confirm stability or differences in results. The echocardiography examinations were performed by one experienced sonographer and data were analysed by echocardiography experts who were blinded to the treatment and outcome of the patients. Differences in interpretations were resolved by agreement. In addition to the qualitative examinations of chambers and valvular pathologies, the following measurements were made via the standard parasternal and apical views: LV end-diastolic and end-systolic volumes (EDV and ESV) using biplane modified Simpson's rule, from which stroke volume (SV) and EF were calculated. Peak mitral inflow E and A velocity waves on pulsed-wave Doppler, E/A ratio, E-wave deceleration time, isovolumic relaxation time, and colour M-mode mitral inflow velocity of propagation were measured from the apical four-chamber view. The systolic  $s'$  and diastolic  $e'$  and  $a'$  peak velocities were obtained by tissue-Doppler imaging (TDI) at both the septal and lateral mitral origins on four-chamber apical view, and the  $e'/a'$  ratio and LV filling index  $E/e'$  ratio were calculated in accordance with the guidelines.<sup>18,19</sup> Peak systolic tricuspid insufficiency gradient was measured and RV end-diastolic and end-systolic areas were calculated off-line from the apical four-chamber views. Patients were treated according to the Surviving Sepsis Campaign Guidelines<sup>17</sup> and, although the echocardiography results were not concealed from the treating physicians, patient therapy was not titrated to reach a specific echocardiographic goal.

## Blood samples

Blood samples were obtained on the 2 days of the echocardiography examinations, centrifuged, and serum stored at  $-70^{\circ}\text{C}$  for measurements of high-sensitivity (hs) troponin-T (hs-troponin-T) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). The normal values for the two assays are  $<0.03$  ng/mL and  $<125$  pg/mL, respectively (Roche Diagnostics, Elecsys Assays).

## Clinical data

All demographic, clinical, haemodynamic, respiratory and lab results, vasopressor therapies, and daily fluids administered and balance from the time of diagnosis of severe sepsis or septic shock until, and including the days of echocardiography were prospectively collected, and the mean, maximal, and minimal values were calculated. SOFA and APACHE-II scores were calculated on the day of admission with the diagnosis of sepsis. Mortality data were collected from the hospital's registry updated by our Ministry of Interior for a minimum period of 6 months and up to 2-year follow-up.

## Statistical analysis

Student's  $t$ -test,  $\chi^2$ , or Mann–Whitney  $U$  tests were used to compare the distributions of continuous and dichotomous variables, as appropriate. Normality of distribution of all continuous variables was explored by examining skewness, kurtosis, and Q–Q plots. Variables with not-normal distribution (skewness or kurtosis  $>2$  or  $<-2$ ) were log-transformed before entering further analyses. Repeated echocardiographic measurements were compared by paired  $t$ -test. Echocardiography measurements of volumes, as well as daily fluid balance and urine output, were indexed (divided by the body surface area). Paired  $t$ -tests were used to compare the measurements of the two consecutive echocardiography examinations. The echocardiography variables were divided into quartiles to compare survival among quartiles. Because of the strong co-linearity among all tissue-Doppler imaging variables (septal and lateral  $s'$ ,  $e'$ , and  $a'$  waves), these signals were first subjected separately to the logistic and Cox's multivariate regression analyses with a stepwise selection method to determine the strongest predictor of mortality among them. Univariate and multivariate (backward stepwise selection method with probability for the removal of 0.10) logistic regression analyses were used to determine the association of variables with in-hospital mortality. Kaplan–Meier log-rank and univariate and multivariate (backward stepwise selection method with probability for removal of 0.10) Cox's proportional hazards regression models were used to identify the strongest predictors of overall, time-tagged mortality using time to death as a continuous variable. Only the variables with statistically significant association with mortality on univariate analysis were included in the multivariate models. Linear regression analyses were used to determine associations among continuous variables. Statistical analyses were performed using SPSS 14.0 software (SPSS Inc., Chicago, IL, USA).

## Results

The study included 262 patients after exclusion of 23 patients with technically inadequate echocardiography images, 13 patients with greater than mild mitral and/or aortic stenosis or insufficiency and 6 patients with regional LV wall motion abnormalities suggesting previous myocardial infarction or concurrent regional myocardial ischaemia. The main sources of sepsis were: gastrointestinal, 107 (41%); multi-trauma with wound infections, 39 (15%); respiratory, 32 (12%); vascular surgery/limb ischaemia, 24 (9%); genitourinary, 18 (7%); and orthopaedic/skeletal, 19 (7%). At least one source of

infection was identified by positive cultures in 245 (93%) patients, and 107 (41%) patients had positive blood cultures. Hypotension (systolic blood pressure <90 mmHg) lasting more than 1 h occurred in 237 (90.4%) patients. Mean duration of hypotension was  $6.2 \pm 5.6$  h/24 h/patient (inter-quartile range: 2–9 h). In 163 (62%) patients, septic shock persisted despite fluid resuscitation requiring one or more vasoactive medications: norepinephrine, 162 (62%) patients; epinephrine, 54 (21%) patients; vasopressin, 43 (16%) patients; dopamine/dobutamine, 22 (8%) patients.

All patients were tracheally intubated and mechanically ventilated at the time of echocardiography examination due to significant respiratory dysfunction or failure. The two echocardiograms were performed  $1.6 \pm 0.9$  and  $2.4 \pm 0.7$  days, respectively, after the diagnosis of sepsis and initiation of treatment. There were no statistically significant differences between the two sequential echocardiography studies in any of the parameters measured and, therefore, the results of all echocardiography measurements from both studies were averaged, and only the averaged results were used for further analysis.

## Predictors of in-hospital and overall mortality

Of the 262 patients, 68 (26%) died in the ICU, 95 (36%) died in the hospital (79 within 30 days), and additional 19 (7%) patients died

during  $13.5 \pm 9.2$  month follow-up. Among septic shock patients, 68 (42%) patients died in the hospital. Table 1 summarizes the main clinical variables collected and Table 2 summarizes all echocardiographic data, comparing patients who died in the hospital with those who survived. In a preliminary Cox's multivariate analysis that included all six TDI variables, such as septal and lateral  $s'$ ,  $e'$ ,  $a'$  waves, septal  $e'$ -wave was the only independent predictor of mortality (Wald statistic = 23.7,  $P = <0.0001$ ). Upon exclusion of septal  $e'$ -wave, lateral  $e'$ -wave was the only predictor of mortality (Cox's: Wald = 19.0,  $P < 0.0001$ ). Henceforth, septal  $e'$ -wave was used in all subsequent survival analyses to represent diastolic function. Among all clinical variables predicting mortality on univariate analysis (Table 1, except hs-troponin-T and NT-proBNP), only APACHE-II score, age, low urine output, and lowest oxygen saturation independently predicted mortality on multivariate analysis (Cox: Wald = 15.6, 12.7, 10.6, 4.3,  $P < 0.001$ ,  $<0.001$ , 0.001, 0.032, respectively). Among all echocardiographic variables significantly predicting mortality on univariate analysis (Table 2), only reduced  $e'$ -wave and low LVSVI independently predicted mortality on multivariate analysis (Cox: Wald = 25.1 and 14.1,  $P < 0.0001$  and  $<0.0001$ , respectively). When all independent clinical and echocardiographic variables were included in the Cox's multivariate survival analysis, reduced septal  $e'$ -wave (or increased  $E/e'$  ratio) was the strongest

**Table 1** Clinical and biochemical data of patients who died or survived the hospitalization

	Survived, <i>n</i> = 167 (64%)	Died, <i>n</i> = 95 (36%)	P-value
Age	56 ± 21	70 ± 17	<0.0001
Gender			
Female (%)	63 (38%)	40 (42%)	0.28
Hypertension	51 (30.5%)	47 (49.5%)	0.002
Diabetes mellitus	37 (22.2%)	26 (27.4%)	0.21
Ischaemic heart disease	33 (19.8%)	20 (21.1%)	0.46
Positive blood cultures	59 (35.3%)	48 (50.5%)	0.012
APACHE-II score	18.8 ± 6.5	24.5 ± 7.6	<0.0001
SOFA score	8.7 ± 3.4	10.9 ± 4.3	<0.0001
Heart rate (b.p.m.) mean/max.	92 ± 18/110 ± 18	89 ± 21/109 ± 21	0.21/0.81
Systolic BP (mmHg), mean/min.	120 ± 22/87 ± 14	114 ± 28/84 ± 15	0.040/0.018
Diastolic BP (mmHg), mean/min	61 ± 13/48 ± 7	55 ± 19/46 ± 16	0.014/0.19
CVP (mmHg), mean	12.6 ± 5.2	13.7 ± 4.3	0.15
Lowest Hb (g%)	9.7 ± 1.2	9.7 ± 1.2	0.93
Lowest SaO <sub>2</sub> (%)	94 ± 3	92 ± 6	0.001
Lowest pH	7.31 ± 0.08	7.16 ± 0.61	0.002
Creatinine (mmol/L), max.	168 ± 148	250 ± 161	<0.0001
Urine output (mL/24 h/m <sup>2</sup> )	1161 ± 624	717 ± 538	<0.0001
Fluid balance (mL/24 h/m <sup>2</sup> )	594 ± 800	924 ± 998	0.005
Dialysis	9 (6.1)	12 (14.5)	0.032
Vasoactive medications	95 (56.9)	68 (71.6)	0.012
Cardiac biomarkers			
High-sensitivity troponin-T (ng/mL)	0.04 (0.01–0.11)	0.15 (0.06–0.25)	<0.0001
NT-proBNP (pg/mL)	2275 (567–9426)	13 980 (5877–34 718)	<0.0001

Values are *n* (%), mean ± SD, and median [inter-quartile range].

**Table 2** Echocardiographic data of patients who died or survived the hospitalization

	Survived, n = 167 (64%)	Died, n = 95 (36%)	P-value
LV end-diastolic diameter (cm)	4.6 ± 1.0	4.5 ± 1.1	0.92
LV end-systolic diameter (cm)	2.9 ± 0.8	2.9 ± 0.9	0.20
Isovolumic relaxation time (ms)	49.6 ± 23.4	61.5 ± 54.6	0.017
E wave (cm/s)	95 ± 33	89 ± 22	0.18
A wave (cm/s)	86 ± 52	78 ± 23	0.10
E/A ratio	1.22 ± 0.55	1.22 ± 0.61	0.99
E wave deceleration time (ms)	147 ± 48	144 ± 49	0.67
Velocity of propagation (cm/s)	76.1 ± 42	85 ± 52	0.34
Septal s' (TDI, cm/s)	10.0 ± 2.9	8.7 ± 3.1	0.003
e' (TDI, cm/s)	9.3 ± 3.4	6.8 ± 2.2	<0.0001
a' (TDI, cm/s)	9.9 ± 3.4	8.5 ± 4.0	0.010
Lateral s' (TDI, cm/s)	11.5 ± 3.7	9.7 ± 3.8	0.001
e' (TDI, cm/s)	11.3 ± 4.1	9.0 ± 3.5	<0.0001
a' (TDI, cm/s)	10.1 ± 3.8	8.6 ± 4.4	0.012
LV end-diastolic volume index (cm <sup>3</sup> /m <sup>2</sup> )	58.6 ± 17.3	51.7 ± 18.4	0.005
LV end-systolic volume index (cm <sup>3</sup> /m <sup>2</sup> )	23.5 ± 12.7	22.6 ± 15.7	0.63
SV index (cm <sup>3</sup> /m <sup>2</sup> )	35.1 ± 8.5	29.1 ± 8.7	<0.0001
LVEF (%)	60 ± 10	57 ± 13	0.14
Cardiac index (L/m <sup>2</sup> )	3.3 ± 0.9	2.7 ± 0.9	<0.0001
Tricuspid insufficiency gradient (mmHg)	27.4 ± 14.3	31.1 ± 13.4	0.09
RV end-diastolic area (cm <sup>2</sup> )	21.2 ± 5.3	20.4 ± 6.7	0.30
RV end-systolic area (cm <sup>2</sup> )	13.9 ± 4.4	13.0 ± 4.7	0.13
RV stroke area change (cm <sup>2</sup> )	7.4 ± 3.6	7.6 ± 3.8	0.7

Values are mean ± SD.

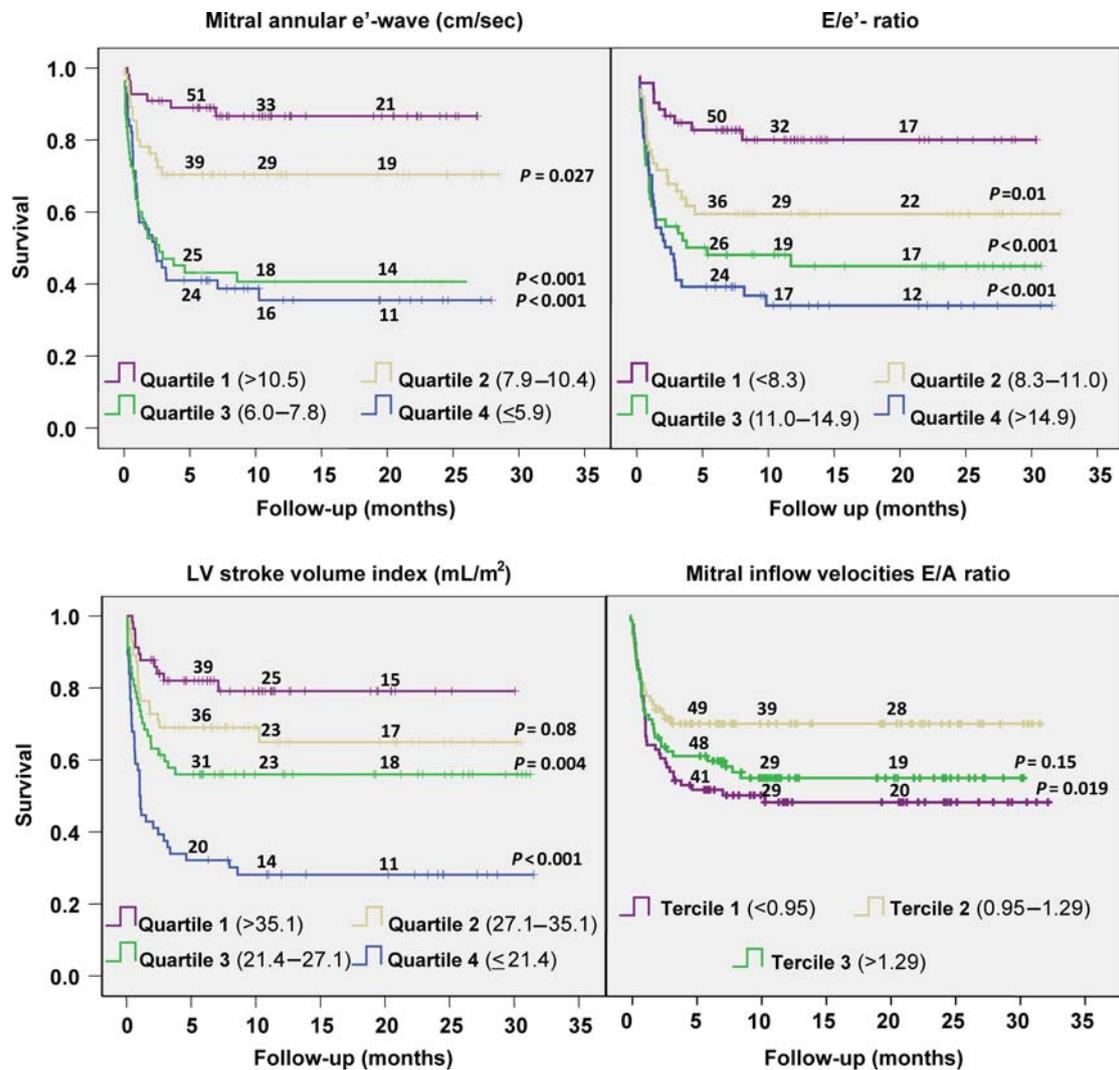
**Table 3** The independent predictors of in-hospital and overall mortality

	In-hospital mortality, multivariate logistic regression			Overall mortality, multivariate Cox's regression		
	Odds ratio [95% CI*]	Wald stat.	P-value	Hazard ratio (95% CI*)	Wald stat.	P-value
e'-wave (TDI)	0.70 (0.59–0.84)	15.1	<0.001	0.76 (0.68–0.99)	21.5	<0.001
E/e' ratio	1.16 (1.07–1.26)*		<0.001	1.08 (1.04–1.13)*		<0.001
APACHE-II score	1.06 (1.01–1.12)	5.7	0.017	1.06 (1.03–1.09)	16.3	<0.001
Urine output (L/24 h/m <sup>2</sup> )	0.54 (0.28–0.99)	9.1	0.003	0.65 (0.42–0.99)	9.91	0.002
LVSVI index	0.95 (0.91–0.98)	3.9	0.040	0.96 (0.93–0.99)	7.0	0.008
Lowest SaO <sub>2</sub> (%)				0.93 (0.87–0.98)	6.6	0.010
Positive blood culture	2.72 (1.28–5.80)	7.1	0.007			

\*CI, confidence interval.

independent predictor followed in a declining order by the APACHE-II score, low urine output, low left ventricular SV index (LVSVI), and lowest arterial oxygen saturation (Cox's: Wald statistic = 21.5, 16.3, 9.91, 7.0, and 6.6,  $P < 0.0001$ ,  $<0.0001$ , 0.002, 0.008, and 0.010, respectively; Table 3). The same variables, except for low oxygen saturation, independently predicted overall mortality when only patients with septic shock were included (Cox's: Wald statistic = 7.5, 10.1, 5.4, and 5.3,  $P = 0.006$ , 0.001,

0.020, and 0.021, respectively). Similarly, the independent predictors of in-hospital mortality as a dichotomous variable were: reduced e'-wave (or increased E/e' ratio), low urine output, the APACHE-II score, positive blood culture, and low SV (logistic regression: Wald = 15.1, 9.1, 7.1, 5.7, and 3.9,  $P < 0.0001$ , 0.003, 0.007, 0.017, and 0.040, respectively). The survival curves of all patients divided into quartile according to their e'-wave, E/e' ratio, and LVSVI are demonstrated in Figure 1A–C. Dividing the



**Figure 1** Kaplan–Meier survival curves of all patients divided into quartiles according to early-diastolic mitral annular peak velocity ( $e'$  wave) (A), the ratio of early diastolic mitral inflow velocity to peak early mitral annular velocity ( $E/e'$  ratio) (B), left-ventricular stroke-volume index (C) or to tertiles according to early-to-late diastolic mitral inflow velocities. The displayed  $P$ -values represent groups with significant difference from the first quartile or tercile by Log-rank test. The numbers on the survival curves represent the number of patients remained after 5, 10, and 20 months of follow-up.

patients into tertiles according to their diastolic mitral inflow velocities  $E/A$  ratio demonstrates that the middle tercile with  $E/A$  at the range of 0.95–1.29 had the best survival (Figure 1D).

### Diastolic and systolic myocardial function

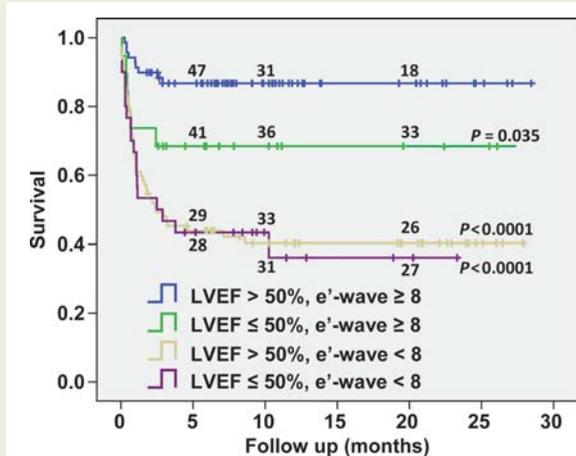
Among all patients, 61 (23.3%) had an LVEF of  $\leq 50\%$  and one half had  $e'$ -wave velocity of  $< 8$  cm/s. Among patients with septic shock, 42 (25.7%) had an LVEF of  $\leq 50\%$  and 58.5% had  $e'$ -wave of  $< 8$  cm/s. Dividing the patients according to these LVEF and  $e'$ -wave cut-off values yielded four subgroups: 95 (36.2%) patients who had an LVEF of  $> 50\%$  and  $e'$ -wave of  $\geq 8$  cm/s (LVEF =  $61 \pm 5\%$ ,  $e'$ -wave =  $11.3 \pm 2.8$  cm/s), 24 (9.1%) patients who had an LVEF of  $\leq 50\%$  only (LVEF =  $46 \pm 5\%$  and  $e'$ -wave =  $10.4 \pm 2.5$  cm/s), 106 (40.4%) patients who had  $e'$ -wave of  $< 8$  cm/s

only (LVEF =  $63 \pm 8\%$ ,  $e'$ -wave =  $6.2 \pm 1.0$  cm/s), and 37 (14.1%) patients who had both LVEF  $\leq 50\%$  and  $e'$ -wave  $< 8$  cm/s (LVEF =  $41 \pm 10\%$  and  $e'$ -wave =  $5.5 \pm 1.3$  cm/s). Patients with LVEF  $\leq 50\%$  only, patients with  $e'$ -wave  $< 8$  cm/s only, and patients with combined LVEF  $\leq 50\%$  and  $e'$ -wave  $< 8$  cm/s had worse survival compared with patients having normal systolic and diastolic function (Cox's regression: hazard ratio = 2.9, 6.0, 6.2,  $P = 0.035$ ,  $< 0.0001$ , and  $< 0.0001$ , respectively, Figure 2).

### Diastolic dysfunction in relation to age and co-morbidities

Reduced  $e'$ -wave velocity correlated strongly with age and less so with hypertension, diabetes mellitus, and history of ischaemic heart disease (IHD) (Pearson's correlation =  $-0.57$ ,  $-0.30$ ,  $-0.22$ , and

–0.33,  $P < 0.0001$ ,  $< 0.0001$ , 0.0008, and  $< 0.0001$ , respectively). Nevertheless, when  $e'$ -wave, age, and the co-morbidities were included in the multivariate survival analyses with backward stepwise selection, only  $e'$ -wave- and age-predicted mortality, and  $e'$ -wave was the strongest predictor (Cox's: Wald statistic = 12.2, and 9.8,  $P = 0.0004$  and 0.002, respectively). The other co-morbidities did not gain statistical significance.



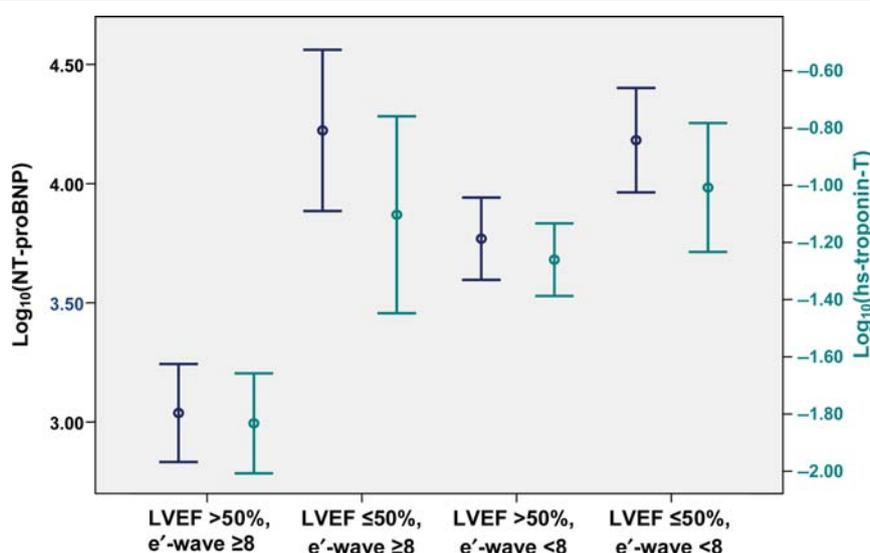
**Figure 2** Kaplan–Meier survival curves of the patients divided into four groups: (A) normal systolic or diastolic function; (B) systolic dysfunction only (LVEF  $< 50\%$ ); (C) diastolic dysfunction only ( $e'$ -wave  $< 8$  cm/s); (D) combined systolic and diastolic dysfunction (LVEF  $< 50\%$  and  $e'$ -wave  $< 8$  cm/s). The numbers on the survival curves represent the number of patients remained after 5, 10, and 20 months of follow-up.

## High-sensitivity Troponin-T and N-terminal pro-B-type natriuretic peptide

Both hs-Troponin-T and NT-proBNP were associated with in-hospital and overall mortality independent of maximal serum creatinine levels when only these three variables were included in the analysis (logistic regression: Wald statistic = 4.9, 7.9 and 1.9,  $P = 0.021$ , 0.004, and 0.16; Cox's regression: Wald statistic = 5.8, 21.4, and 2.3,  $P = 0.015$ ,  $< 0.001$ , and 0.13). However, hs-troponin-T was only mildly elevated (median = 0.07, IQR: 0.02–0.17 ng/mL), whereas NT-proBNP reached very high levels (median = 5762, IQR: 1001–15 962 pg/mL). In addition, patients with isolated low LVEF ( $\leq 50\%$ ), isolated reduced  $e'$ -wave ( $< 8$  cm/s), or both reduced LVEF and  $e'$ -wave had significantly higher serum levels of both hs-troponin-T and NT-proBNP compared with patients having normal systolic or diastolic functions (Figure 3).

## Discussion

The main findings of this study are: (i) patients with severe sepsis and septic shock frequently suffer from diastolic dysfunction and diastolic dysfunction is the strongest independent predictor of early mortality, even after adjusting for the APACHE-II score, low urine output, low left ventricular SV index, and lowest arterial oxygen saturation, the other independent predictors of mortality. (ii) Although diastolic dysfunction is associated with age, hypertension, diabetes mellitus, and IHD, diastolic dysfunction is a stronger independent predictor of mortality than age and the other co-morbidities. (iii) Both hs-troponin-T and NT-proBNP are significantly elevated not only in patients with reduced LVEF but also in patients with isolated diastolic dysfunction, when compared



**Figure 3** Mean  $\pm$  SD of log-transformed NT-proBNP and high-sensitivity troponin-T in each one of the four groups: (A) normal systolic or diastolic dysfunction (LVEF  $\geq 50\%$ ,  $e'$ -wave  $\geq 8$  cm/s); (B) systolic dysfunction only (LVEF  $< 50\%$ ); (C) diastolic dysfunction only ( $e'$ -wave  $< 8$  cm/s); (D) combined systolic and diastolic dysfunction.

with patients having normal systolic and diastolic function. Both hs-troponin-T and NT-proBNP predict mortality, although serum levels of hs-troponin-T are only minimally elevated whereas NT-proBNP is markedly elevated.

### Diastolic vs. systolic dysfunction in sepsis

Since the seminal works of Parker and colleagues<sup>5,7</sup> and Zanotti Cavazzoni,<sup>20</sup> using cineangiography more than 2 decades ago, who demonstrated that systolic dysfunction is common in septic shock and is paradoxically associated with better survival, the mechanisms underlying this paradox have never been elucidated. Later studies using echocardiography also reported a 20–60% incidence of reduced EF in septic shock that was reversible in patients who survive.<sup>8,9,11</sup> In the present study that included patients with severe sepsis and/or septic shock, 9.1% had isolated systolic dysfunction and additional 14.1% had combined systolic and diastolic dysfunction. However, 38% had isolated diastolic dysfunction. Mitral annular peak systolic velocity ( $s'$ -wave), which is another indicator for systolic function, correlated with mortality on univariate analysis. However, the average  $s'$ -wave values in our patients, even in those who died, were greater than those reported previously for young normal adults<sup>21</sup> (Table 2). In addition, studies have showed that minor decreases in  $s'$ -waves (to the range of 8 cm/s) may occur in patients with impaired relaxation (stage I diastolic dysfunction) but normal EF.<sup>22</sup>

Mitral annular early-diastolic peak velocity ( $e'$ -wave) is one of the most load-independent measures of diastolic dysfunction<sup>23,24</sup> and is known to predict long-term mortality in a variety of cardiac diseases.<sup>25–27</sup> The ratio of early mitral inflow velocity to mitral annular motion ( $E/e'$ ) correlates with LV end-diastolic pressure and high  $E/e'$  ratio represents low LV compliance in numerous cardiac conditions,<sup>28</sup> including during sinus tachycardia<sup>29</sup> and septic shock.<sup>30</sup> However, the prognostic importance of diastolic dysfunction during acute non-cardiac illness has not been adequately investigated. Similarly, only few, small studies ( $\leq 54$  patients) investigated diastolic dysfunction in sepsis and septic shock.<sup>11–15</sup> Bouhemad *et al.*<sup>13</sup> found isolated and reversible impairment of LV relaxation, associated with transient increases in troponin-I and inflammatory markers in 20% of 54 septic shock patients studied, yet that study did not provide data on the effect of diastolic dysfunction on mortality. In contrast, Sturgess *et al.*<sup>15</sup> studied 21 septic shock patients and found that diastolic dysfunction was an independent predictor of mortality, better than cardiac biomarkers. None of these studies however had the power and the comprehensive clinical and echocardiographic data analysis to determine the association of various aspects of myocardial function on mortality from severe sepsis and septic shock as in the present study.

### High-sensitivity troponin-T and N-terminal pro-B-type natriuretic peptide

Cardiac troponins and natriuretic peptides elevations are known to predict mortality in septic patients.<sup>31,32</sup> Troponin elevation is particularly common in ICU patients with coronary artery disease.<sup>33</sup> The present study further shows that hs-troponin-T and

NT-proBNP are both significantly elevated in septic patients with isolated diastolic dysfunction, as well as in patients with systolic dysfunction. In addition, an interesting disparity was found between NT-proBNP that reached very high level and hs-troponin-T was only minimally elevated. This disparity suggests that although myocardial wall stress<sup>14,34</sup> can be very high during severe sepsis and septic shock, myocardial necrosis or apoptosis is nevertheless minimal, in accordance with previous studies, showing that coronary perfusion and myocardial blood flow are preserved during sepsis.<sup>35</sup>

### Diastolic dysfunction and cardiovascular dynamics in sepsis

Previous studies as well as the present one have shown that high positive fluid balance is associated with greater mortality in septic patients.<sup>36</sup> Previous studies have also shown in accordance with the present study that low cardiac output and SV are associated with worse survival in septic patients. While fluid loading is one of the mainstays in the haemodynamic management of sepsis to increase cardiac output, it may also be particularly hazardous in septic patients with microvascular dysfunction and increased vascular permeability by causing interstitial oedema with subsequent tissue hypoxia, organ dysfunction, and death.<sup>11,37</sup> Diastolic dysfunction or reduced LV compliance, as observed in the present study, strongly impairs LV dilatation and SV augmentation in response to fluid loading.<sup>38</sup> Excessive fluid loading to the non-compliant LV may aggravates lung congestion and non-cardiogenic pulmonary oedema common in sepsis, leading to pulmonary hypertension, RV dysfunction,<sup>39</sup> and further decrease in LV volumes. It is not surprising therefore that the 'right' amount of fluid resuscitation is frequently debated in septic patients and echocardiography may have an important role in assessing cardiac load and cardiac response to fluids in this setting. Diastolic dysfunction is strongly associated with age, hypertension, diabetes mellitus, and IHD as shown also in the present study. It is conceivable therefore that diastolic dysfunction was a pre-existing condition in the majority of our patients. One cannot rule out, however, that, in addition, diastolic dysfunction was also significantly aggravated by the acute critical and stressful illness in these patients.

### Limitations

This is a single-centre study and therefore it is possible that local management strategies of sepsis may have influenced both myocardial function and outcome. Secondly, although tissue-Doppler velocity parameters are less load-dependent than flow measurements, they are nevertheless not totally load independent. We tried to overcome this limitation by obtaining two echocardiography measurements on two subsequent days. The robust association of diastolic tissue-Doppler variables with mortality in our setting suggests that these were not just instantaneous measurements but represented the cardiac diastolic properties during severe sepsis and septic shock. In addition, we were not able to measure pulmonary venous flows or perform Valsalva manoeuvre in the majority of our patients and were unable therefore to differentiate between

the grades of diastolic dysfunction. Nevertheless, patients with low E/A ratio (impaired relaxation) or high E/A ratio (more restrictive pattern) had higher mortality than patients with E/A ratios around unity (Figure 1D). Another limitation is the inherent difficulty of measuring right ventricular volumes by 2D echocardiography. Although the RV plays an important role in sepsis, our RV area measurements did not differ between survivors and non-survivors. Additionally, since this study did not include follow-up echocardiography examinations, the present data cannot answer whether sepsis was responsible for a transient diastolic dysfunction or whether the observed diastolic dysfunction was a pre-existing condition.

## Summary

Diastolic dysfunction is common and is the strongest independent predictor of early mortality in severe sepsis and septic shock. Although most clinical and investigational efforts in critically ill patients are focused at cardiac systolic function and the majority of cardiovascular monitoring instruments provide data almost exclusively on cardiac output and pressures, the present study shows that diastolic function is at least as important as systolic function and plays a major role in determining outcome, which should not be overlooked. Further studies are required to test whether diastolic dysfunction is merely a pre-existing condition or develops and aggravates as the result of sepsis. Additional studies are also needed to show what therapeutic interventions might improve diastolic function and survival in septic patients.

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