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# Early diastolic dysfunction is associated with intensive care unit mortality in cancer patients presenting with septic shock

M. Mourad[1], L. Chow-Chine[1], M. Faucher[1], A. Sannini[1], J. P. Brun[1], J. M. de Guibert[1], L. Fouche[1], J. Lambert[2], J. L. Blache[1] and D. Mokart[1,3]*

[1] Department of Anaesthesia and Intensive Care Unit, Paoli-Calmettes Institute, 232 bd Sainte Marguerite, 13273 Marseille Cedex 9, France
[2] Department of Biostatistics, Saint Louis Hospital, Paris, France
[3] Groupe de Recherche en Réanimation Respiratoire Onco-Hématologique (Grrr-OH), France (www.grrroh.com)

* Corresponding author. E-mail: mokartd@ipc.unicancer.fr

## Editor's key points

- The body's response to inflammation and sepsis is at least in part dependent on adequate myocardial function.
- Diastolic dysfunction can be detected and quantified by echocardiographic indices such as pulse wave and tissue Doppler.
- The presence or extent of diastolic dysfunction may be an additional factor used to stratify the need for high-level care and response to treatment.
- This study's findings of a strong association between diastolic dysfunction and intensive care unit mortality in patients with sepsis offer inroads into improved treatment options.

**Background.** Cancer patients present a high risk of sepsis and are exposed to cardiotoxic drugs during chemotherapy. Myocardial dysfunction is common during septic shock and can be evaluated at bedside using echocardiography. The aim of this study was to identify early cardiac dysfunctions associated with intensive care unit (ICU) mortality in cancer patients presenting with septic shock.

**Methods.** Seventy-two cancer patients admitted to the ICU underwent echocardiography within 48 h of developing septic shock. History of malignancies, anticancer treatments, and clinical characteristics were prospectively collected.

**Results.** ICU mortality was 48%. Diastolic dysfunction ($e' \leq 8$ cm $s^{-1}$) was an independent echocardiographic parameter associated with ICU mortality {odds ratio (OR) 7.7 [95% confidence interval (CI), 2.58–23.38]; $P<0.001$}. Overall, three factors were independently associated with ICU mortality: sepsis-related organ failure assessment score at admission [OR 1.35 ( 95% CI, 1.05–1.74); $P=0.017$], occurrence of diastolic dysfunction [OR 16.6 (95% CI, 3.28–84.6); $P=0.001$], and need for conventional mechanical ventilation [OR 16.6 (95% CI, 3.6–77.15); $P<0.001$]. Diastolic dysfunction was not associated with exposure to cardiotoxic drugs.

**Conclusions.** Early diastolic dysfunction is a strong and independent predictor of mortality in cancer patients presenting with septic shock. It is not associated with exposure to cardiotoxic drugs. Further studies incorporating monitoring of diastolic function and therapeutic interventions improving cardiac relaxation need to be evaluated in cancer patients presenting with septic shock.

**Keywords:** cancer; diastolic dysfunction; echocardiography; sepsis; septic shock; prognosis

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Cancer is associated with a considerably increased risk of sepsis, especially in patients with haematological malignancies[1] because of immune suppression related to the disease itself or imposed by anticancer treatments. As a result, cancer patients now represent a significant proportion of admissions to the intensive care unit (ICU) for severe infections: 17% of medical admissions associated with severe sepsis in the USA[2] and 15.4% of septic shock patients in a French ICU cohort.[3] Whereas recent advances in the management of severe sepsis and septic shock only have led to a moderate decrease in mortality in general populations, the prognosis of cancer patients in septic shock has markedly improved over recent years. Thus, survival is now similar to the general population in experienced centres and approaches 50%.[4]

Whatever the population studied, the number and the extent of organ failures are the main prognostic factors in ICU cancer patients,[5] and particularly in those presenting with septic shock.[6] Myocardial dysfunction in sepsis is now well described: impairment of systolic, diastolic, and right ventricle (RV) function are described.[7–9] However, little data exist regarding the prognostic value of cardiac dysfunctions in septic shock cancer patients. The aim of this study was to assess the association between echocardiographic measures of cardiac function in cancer patients presenting with septic shock, and ICU mortality.

## Methods

Seventy-six cancer patients with septic shock admitted to the ICU during a 30 month period (January 2009–August 2011) were prospectively included. Septic shock was defined as severe sepsis with persistent hypotension (mean arterial

pressure <60 mm Hg despite adequate volume resuscitation) requiring vasopressor therapy.[10] Exclusion criteria were: age younger than 18 yr; presence of moderate-to-severe valvular heart disease; echocardiographic evidence of regional ischaemia or previous infarction; or decision of therapeutic limitation taken before onset of septic shock. Patients with septic shock were systematically admitted to the ICU, once the diagnosis was made. They came from the haematology or oncology units. All patients received broad-spectrum antibiotic treatment (β-lactam plus an amino glycoside or a quinolone plus a glycopeptide) immediately after initial clinical evaluation. Besides antibiotics, all patients received standard supportive care for the shock according to standard recommendations.[10] Fluid expansion (using crystalloids or colloids) and the use of epinephrine, norepinephrine, and/or dobutamine were decided by the physician in charge of the patient. Haemodynamic evaluation, using echocardiography, was routinely performed in all patients. Both clinical (heart rate, arterial pressure, peripheral perfusion, urine output, central venous pressure, and saturation) and echocardiographic variables were considered in determining the requirement and response to fluid management. In particular, fluid administration was reduced if cardiac filling pressures increase (right ventricular dilatation, $E/e'$ ratio >10, or both) without concurrent haemodynamic improvement. Stress-dose steroids were routinely administered in our patients presenting with septic shock. The study was approved by the Paoli-Calmettes Institute institutional review board which waived the need for informed consent.

## Echocardiography

Transthoracic echocardiography and Doppler examination were performed by experienced physicians using a *General electric Vivid-I* machine as soon as possible within the first 48 h of septic shock diagnosis. All measurements were recorded over four consecutive cardiac cycles and at end-expiration for ventilated patients. Data from the first examination were collected and analysed by two echocardiography experts who were blinded to the treatment and outcome of patients; we averaged the values of both observers. Differences in interpretations were resolved by agreement. The following measurements were made using the standard parasternal and apical views: left ventricle (LV) end-diastolic volume and LV end-systolic volume using the biplane modified Simpson's rule from which LV ejection fraction (LVEF) was calculated; LV and RV end-diastolic areas from which the RV/LV ratio was calculated and LV outflow tract diameter. The peak mitral inflow $E$ and $A$ velocity waves on pulsed-Doppler, $E/A$ ratio, and $E$-wave deceleration time were measured from the apical four-chamber view. Cardiac output and LV outflow tract velocity–time integral were measured from the apical five-chamber view. Using tissue-Doppler imaging at the lateral mitral annulus on the four-chamber view, the systolic $s'$, the diastolic $e'$, and $a'$ peak velocity were measured and the LV filling index $E/e'$ ratio and the Tei tissular index were calculated in accordance with the guidelines.[11–14] Delta $e'$ (theoretical $e'$ − measured $e'$) was calculated using normative reference value for tissue Doppler imaging.[15] This parameter takes into account diastolic dysfunction related to age, and thus reflects non-physiological diastolic dysfunction. The peak systolic tricuspid insufficiency gradient and tricuspid annular plane systolic excursion were measured from the apical chamber view. As previously described,[16] systolic dysfunction was defined by LVEF ≤50%, $s'$ ≤10 cm $s^{-1}$, or both, diastolic dysfunction by $e'$ ≤8 cm $s^{-1}$, and RV dilatation by RV/LV ratio >0.6.

Patient characteristic, clinical, haemodynamic, and outcome data were collected with focus on the clinical context during echocardiographic evaluation: ventilation mode, vasopressor therapy, cumulative, and previous 24 h fluid balance.

## Clinical data and laboratory results

The following clinical data were collected during the ICU stay (Table 1): age and gender; characteristics of the malignancy, the presence of metastatic disease; neutropenia (absolute neutrophil count of $<0.5\times10^9$ litre$^{-1}$); characteristics of sepsis; chronic health status as evaluated using the Knaus scale;[17] severity-of-illness scores using Simplified Acute Physiology Score II (SAPS II)[18] at admission, organ dysfunctions using sepsis-related organ failure assessment (SOFA) score[19] on day 1 (day of ICU admission), cause of ICU admission; therapeutic interventions in ICU, including vasopressor use, need and duration of respiratory support [invasive mechanical ventilation (MV)], and renal replacement therapy (RRT); length of ICU stay; and ICU mortality. Organ failure was defined as a SOFA score of ≥3 for any system. In addition, 24 h fluid balance and cumulative fluid balance and from ICU admission to the time of echocardiographic assessment were also collected. History of anticancer drugs, thoracic radiotherapy, and exposure to cardiotoxic drugs were collected for each patient in accordance with recent data proposed in 2010 by Raschi and colleagues.[20]

## Statistical analysis

All data are presented as frequencies (%) for categorical variables and medians (25th–75th percentiles) for continuous variables. Echocardiographic parameters and characteristics of patients during ICU hospitalization were compared across the groups of ICU survivors and decedents by using Fisher's exact test and the Wilcoxon rank-sum test. We performed logistic regression analyses to identify variables that significantly influenced ICU mortality, as measured by the estimated odds ratio (OR) with the 95% confidence interval (CI). Variables yielding $P$-values of <0.10 in the bivariate analyses were entered into a backward stepwise logistic regression model where ICU mortality was the outcome variable of interest. Lastly, we forced variables of clinical interest that may be suspected to be associated with outcome into the final model. Two models were thus constructed. In the first model ('echocardiographic model'), significant echocardiographic parameters were tested for the variable of interest. In the second model ('classical model'), usual clinical parameters, including those selected by the 'echocardiographic model', were also tested