

# Tissue Doppler assessment of diastolic function and relationship with mortality in critically ill septic patients: a systematic review and meta-analysis

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## Abstract

**Background:** Myocardial dysfunction may contribute to circulatory failure in sepsis. There is growing evidence of an association between left ventricular diastolic dysfunction (LVDD) and mortality in septic patients. Utilizing echocardiography, we know that tissue Doppler imaging (TDI) variables  $e'$  and  $E/e'$  are reliable predictors of LVDD and are useful measurements to estimate left ventricular (LV) filling pressures.

**Methods:** We conducted a systematic review and meta-analysis to investigate the association of  $e'$  and  $E/e'$  with mortality of patients with severe sepsis or septic shock. In the primary analysis, we included studies providing transthoracic TDI data for  $e'$  and  $E/e'$  and their association with mortality. Subgroup analyses were conducted according to myocardial regional focus of TDI assessment (septal, lateral or averaged). Three secondary analyses were performed: one included data from a transoesophageal study, another excluded studies reporting data at a very early (<6 h) or late (>48 h) stage following diagnosis, and the third pooled data only from studies excluding patients with heart valve disease.

**Results:** The primary analysis included 16 studies with 1507 patients with severe sepsis and/or septic shock. A significant association was found between mortality and both lower  $e'$  [standard mean difference (SMD) 0.33; 95% confidence interval (CI): 0.05, 0.62;  $P=0.02$ ] and higher  $E/e'$  (SMD -0.33; 95% CI: -0.57, -0.10;  $P=0.006$ ). In the subgroup analyses, only the lateral TDI values showed significant association with mortality (lower  $e'$  SMD 0.45; 95% CI: 0.11, 0.78;  $P=0.009$ ; higher  $E/e'$  SMD -0.49; 95% CI: -0.76, -0.22;  $P=0.0003$ ). The findings of the primary analysis were confirmed by all secondary analyses.

**Conclusions:** There is a strong association between both lower  $e'$  and higher  $E/e'$  and mortality in septic patients.

**Key words:** diastolic dysfunction; echocardiography; intensive care; septic shock; severe sepsis

### Editor's key points

- Previous data show that left ventricular diastolic dysfunction is common in sepsis and associated with worse outcome.
- New guidelines for determining LVDD by echocardiography include tissue Doppler assessment of the early myocardial diastolic  $e'$  wave and early myocardial relaxation wave ( $E/e'$ ).
- This updated systematic review includes studies reporting to the new echocardiography guidelines.
- The results confirm that LVDD as shown by decreased  $e'$  wave and higher  $E/e'$  ratio is strongly associated with mortality in severe sepsis.
- The significance of LVDD earlier in the evolution of sepsis remains to be established.

Sepsis results from an individual's exaggerated response to an infective process and is associated with profound haemodynamic disturbance, resulting in significant mortality and morbidity when the initial process evolves into circulatory and consequent multi-organ failure. A recent expert consensus has defined septic shock as a subset of septic disease in which the underlying circulatory, cellular and metabolic disturbances are associated with a higher mortality.<sup>1–3</sup> Septic shock is characterized by profound vasoplegia requiring administration of vasoactive agents to maintain organ perfusion.<sup>4</sup> It has become more evident over the past decade that septic patients may exhibit pronounced myocardial dysfunction,<sup>5,6</sup> which could possibly be the result of increased circulating catecholamine and cytokine levels.<sup>7,8</sup> Septic myocardial dysfunction may involve either the left ventricle (LV), the right ventricle (RV) or both. This may manifest as systolic dysfunction,<sup>9</sup> and also as reversible LV diastolic dysfunction (LVDD).<sup>9</sup> A meta-analysis by Huang and colleagues<sup>10</sup> has shown no association between LV or RV systolic dysfunction and mortality in patients with severe sepsis or septic shock, when systolic function is evaluated by ejection fraction. A previous meta-analysis from our group of investigators has demonstrated an association between LVDD and mortality in the same population. We also confirmed the finding of Huang and colleagues<sup>10</sup> showing that there is no association between left ventricular ejection fraction (LVEF) and mortality in septic patients.<sup>11,12</sup> One of the limitations of our previous meta-analysis was the inclusion of only seven studies. Since this publication, a number of further studies in critically ill patients have been published. In addition, our previous work investigated only the effect of abnormal diastolic function, but the recently revised guidelines<sup>13</sup> have significantly changed the methodology for determining LVDD.<sup>14</sup> These recommendations are now based on the assessment of four variables: tricuspid regurgitation jet velocity, left atrial volume,  $e'$  wave, and  $E/e'$  ratio.<sup>13</sup> We feel that it is important to use all the information available from current research to investigate some of the implications of the new guidelines. This provides part of the rationale for this new meta-analysis.

Importantly, the interpretation of echocardiographic measurements in septic patients is challenging because of the variable ventricular loading conditions. Tricuspid regurgitation and left atrial volume may be significantly influenced by mechanical ventilation and loading conditions. As these variables are only

included in these latest guidelines and are rarely reported, we have not included them in this study. We focused on tissue Doppler imaging (TDI) and we feel that the increased reliance on these variables is to be welcomed, because of their relative load independency<sup>15</sup> as compared with blood pool Doppler. The early myocardial diastolic  $e'$  wave provides information on myocardial velocity at the mitral annulus level, and cut-offs of  $<7\text{ cm s}^{-1}$  for septal and  $<10\text{ cm s}^{-1}$  for lateral tissue velocity are considered as abnormal, although using average  $e'$  value should be the preferred approach.<sup>13</sup> The second TDI-derived variable included in the new algorithm for grading LVDD is the ratio of the early transmitral pulse-wave Doppler flow to the early myocardial relaxation wave ( $E/e'$ ). This variable correlates with left atrial pressure (LAP) and pulmonary capillary wedge pressure, and a value below 8 correlates with non-elevated LAP, whereas an averaged ratio above 14 indicates raised left-sided filling pressures.<sup>13</sup>  $E/e'$  ratio has shown good predictive value of LV filling pressures in patients with septic shock,<sup>16</sup> although some controversies remain in patients with heart failure and severe LV systolic dysfunction.<sup>17–19</sup>

Many studies report TDI variables according to survival in septic patients but with conflicting results. We aimed to investigate the predictive value for survival between these two TDI-derived variables in patients with severe sepsis and/or septic shock. The primary hypothesis of our meta-analysis was that lower  $e'$  and higher  $E/e'$  are significantly associated with mortality in this population of patients.

## Methods

We conducted this systematic review and meta-analysis in accordance with the PRISMA guidelines<sup>20</sup> and registered our project with the international prospective register of systematic reviews (PROSPERO – number CRD 42016041712).

### Eligibility criteria and identification of studies

The definition of sepsis and septic shock has changed only recently. We therefore included observational studies providing data on mortality of patients with severe sepsis and/or septic shock as defined by the previous international consensus.<sup>21</sup> Studies were included if they provided one or both TDI variables ( $e'$  and/or  $E/e'$ ), comparing values in survivors and non-survivors. We accepted studies providing values from the septal or lateral annular region as well as averaged TDI values. Inclusion criteria for clinical studies were pre-specified using the PICOS format (Table 1). Exclusion criteria were studies on those under 18 yr and case series reporting data and outcomes from less than 10 patients. By consensus, we only included studies reporting data obtained with transthoracic echocardiography in the primary analysis, but we considered transoesophageal studies in a secondary analysis.

We performed a systematic search of two electronic databases—MEDLINE (PubMed) and EMBASE—using the NHS Healthcare Databases Advanced Search tool. Relevant findings were also recognized by manual searching of reviews on the topic and exploring the list of the references of the included studies. We started our search from inception of MEDLINE (PubMed) database, while findings retrieved from EMBASE as conference abstracts were considered only if published after June 2013 to allow a reasonable time for adequate peer-review process. Only articles published in English, Spanish, French, German or Italian were considered. Duplicates were filtered

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