

# Utility of the E/e' index in ventilated patients and those with sepsis

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## Utility of the E/e' index in ventilated patients and those with sepsis

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We thank Sanfilippo and his colleagues for their interest in our paper, and for the opportunity thus afforded to comment on the E/e' index in critically ill patients and in those who have severe sepsis.

We agree that the E/e' index has some utility in predicting successful weaning from mechanical ventilation, as they have shown in their most recent meta-analysis,<sup>1</sup> but published studies show high heterogeneity, there are often only small initial differences in mean E/e' between patients who will remain off ventilation and those who will not, and average E/e' values in both groups are sometimes within normal or intermediate ranges. Earlier systematic reviews also concluded that a higher E/e' ratio is associated with weaning failure in ventilated patients<sup>2</sup> and that E/e' (as well as other markers of diastolic dysfunction) predicts mortality in critically ill patients.<sup>3</sup> In a large study of 161 patients, however, neither E/e' at the lateral mitral annulus nor any other echocardiographic index predicted success in weaning.<sup>4</sup> The heterogeneity of criteria for diastolic dysfunction in these studies is illustrated by cut-points for abnormal E/e' varying between 8 and 12 at the lateral mitral annulus and 8 and 9.6 at the medial (septal) annulus.<sup>3</sup>

In ventilated as in other patients, both E and e' are preload-dependent.<sup>5</sup> Positive end-expiratory pressure (PEEP) reduces both; for example PEEP of 12 cm H<sub>2</sub>O decreased lateral e' by 19.7% and E by 13.7%, so

E/e' was unchanged.<sup>6</sup> An increase in e' when a patient is taken off a ventilator could indicate a response to changed loading rather than an improvement in intrinsic diastolic function. Before concluding that observed changes in E/e' imply corresponding changes in left ventricular (LV) filling pressures, we should consider if E/e' has been validated by correlation with pulmonary capillary wedge pressure (PCW) measured with Swan Ganz catheters, specifically in ventilated and critically ill patients.

In 39 patients there was no difference in E/e' before a trial of spontaneous breathing, between those subjects in whom it was successful (defined as PCW remaining <18 mmHg after 60 minutes; mean baseline E/e' 8.0) and those in whom it was not (PCW increasing to >18 mmHg; baseline E/e' 7.6).<sup>7</sup> The area under the receiver operating characteristic curve (AUC) for E/e' as a guide to PCW at the end of the trial of spontaneous breathing was 0.8. In an earlier study of patients in intensive care who were also breathing spontaneously, E/e' had a modest correlation with PCW ( $r=0.69$ ); a patient with E/e' of around 10 could have a PCW ranging from <10 to >20 mmHg.<sup>8</sup> In other studies of ventilated patients, the correlation of lateral E/e' with PCW was 0.84<sup>9</sup> and its AUC was 0.91.<sup>10</sup> Recently, Brault et al reported that the 2016 American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines for diastolic dysfunction did not accurately assess PCW in 98 ventilated and critically ill patients, of whom 54% experienced septic shock. The diagnostic score was indeterminate in 49% of patients, sensitivity and specificity were both 74%, and agreement between echocardiography and PCW was moderate (Cohen's Kappa, 0.48). The best echocardiographic predictor of a normal PCW was not the E/e' ratio but a lateral e' >8.<sup>11</sup>

From experimental and clinical observations it is clear that severe sepsis can depress myocardial contractile function, probably through multiple mechanisms.<sup>12</sup> In 40 patients with sepsis, however, there were no significant correlations between serum concentrations of inflammatory cytokines and measurements of e' or calculated E/e'.<sup>13</sup> In another study, mortality was predicted by the APACHE II score and mitral annular systolic excursion (MAPSE) with an AUC of 0.88, while the E/e' index was not selected as a predictor in a logistic regression analysis.<sup>14</sup> Reproducibility of echocardiographic measurements in patients with septic shock is moderate to good<sup>15</sup> but it is difficult to rely on single observations to guide clinical decisions.

In patients with sepsis and severe diastolic dysfunction, failure to respond to volume replacement may be caused by impaired early diastolic relaxation and LV suction, which cannot be detected by the E/e' index. In a randomised trial, an intravenous infusion of esmolol to slow the heart rate prolonged LV filling and increased stroke volume, with a subsequent reduction in mortality.<sup>16</sup> In a prospective observational study, levosimendan increased the probability of successful weaning from ventilation, and averted any increase in E/e';<sup>17</sup> that could also be explained by improved early diastolic relaxation and filling, since levosimendan is positively lusitropic.<sup>18</sup> Detailed echocardiographic assessment of ventilated patients after cardiac surgery showed that levosimendan increased early diastolic strain rate by 30%.<sup>19</sup> Thus changes in E/e' as a marker of mean PCW do not necessarily confirm a causal relationship with any particular aspect of LV diastolic function, while more comprehensive echocardiographic analysis of pathophysiological mechanisms may be more informative.

These thoughts reinforce some of the conclusions that we drew in our review. Many studies are difficult to interpret because the E/e' index is reported without information on changes in its individual components, and because dichotomising patients into normal or diastolic dysfunction (grades) loses information from multiple continuous variables that are inter-related but may change with differing patterns according to particular circumstances. It is unwise to use discrete cut-points especially if they are unadjusted for age and gender, and mistaken to conclude that LV diastolic function has changed when there are significant differences in the E/e' index but its mean values remain within the normal range. The optimal assessment of diastolic dysfunction in septic and ventilated patients requires a multiparametric approach and we caution against over-reliance on E/e'.

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