

Prediction of the short-term and long-term mortality in difficult-to-wean patients by transthoracic echocardiography and diaphragm ultrasound

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High mortality rates of 25% to 50% were reported in patients with extubation failure.^[1] Extubation failure or re-intubation was an independent risk factor for death after extubation, not the precise reason. Common reasons included primary respiratory failure, cardiac dysfunction, ineffective cough, excess secretions, upper airway obstruction, etc. Therefore, death after extubation should be related to these reasons above in theory.

Recently, ultrasound bedside was popularized as a convenient tool to assess cardiac function and diaphragm function accurately. A recent meta-analysis indicated that the ratio (E/Ea) of mitral Doppler inflow velocity (E) to annular tissue Doppler wave velocity (Ea) by transthoracic echocardiography could help identify the cardiac origin of weaning failure.^[2] Another meta-analysis showed that diaphragm thickening fraction or diaphragmatic excursion (DE) could predict extubation failure. Therefore, we hypothesized that E/Ea and DE could predict death after extubation.^[3]

We designed a prospective cohort study to assess the value of DE and E/Ea in predicting death within 30 and 180 days after extubation in difficult-to-wean patients. This study was conducted at four intensive care units (respiratory intensive care unit, surgical intensive care unit, coronary care unit and emergency intensive care unit) in Beijing Chaoyang Hospital between November 2012 and February 2014. This study was approved by the institutional review board of this hospital (No. 2012-ke-88). Informed consent forms were provided from each patient's immediate family members.

The inclusion criteria included difficult-to-wean patients who had been intubated for >48 h and failed the spontaneous breathing trial (SBT) at least once. Moreover, they should succeed on an SBT and be extubated within 24 h. Exclusion criteria included pregnant women, age < 18 years, diaphragm paralysis or cervical spine injury, pneumothorax or pneumomediastinum, severe mitral stenosis or prosthetic mitral valve, poor ultrasonic windows, use of muscle-paralyzing medications within 48 h before enrollment, planned prophylactic noninvasive ventilation after extubation or tracheostomy after SBT, and extubation failure caused by upper airway obstruction. All patients completed the SBT through a T-piece over 30 min in a supine position (30–45°). They were connected to a ventilator set in pressure support ventilation (pressure support 10–12 cmH₂O, positive end expiratory pressure 5 cmH₂O, and proper fraction of inspired oxygen < 40%) before SBT. Both transthoracic echocardiography and diaphragm ultrasound in turn before and after SBT were performed with a 3.0 MHz ultrasonic (US) probe (Vivid i GE Medical Systems Israel Ltd., Tirat Carmel, Israel) by an ultrasound specialist for 15 min. The detailed methods for measuring E/Ea and DE were described in the previously published study.^[4] The attending physicians were blinded to the ultrasonic results.

All patients were followed up with the survival state evaluated by telephone for outpatients or by medical records for inpatients 30 and 180 days after extubation. The causes of death were analyzed by a respiratory specialist according to their medical records or clinical

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manifestations provided by the patient family members. Records were collected including demographic and clinical characteristics, laboratory, and ultrasonic data.

Statistical analysis was performed by using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were described as means (standard deviations) or medians (interquartile ranges). The Student's *t* test or Mann-Whitney *U* tests were used to compare continuous variables. Categorical variables were described as numbers (percentages). Comparisons of proportions were performed with a Chi-square test or Fisher's exact test. Risk factors predicting 30 and 180-day mortality were selected by the backward-Wald method and analyzed with a Cox regression model. Then the area under the curve (AUC) and optimum cutoff value were identified by the receiver operating characteristic curve. The cumulative survival rate was calculated by using the Kaplan-Meier method. The log-rank test was employed to compare the survival rate between subgroups with E/Ea or DE at different levels. The level of significance was fixed at $P < 0.05$.

During the study, 60 patients (aged 18-90 years) were enrolled ultimately, and 15 cases were excluded for relevant reasons [Supplementary Figure 1, <http://links.lww.com/CM9/A865>]. The cumulative deaths after 30 and 180 days were 9 (15%) and 24 (40%), respectively. The major causes of death for these 24 patients were cardiac events (10 cases), refractory pneumonia (9 cases), sepsis (2 cases), gastrointestinal bleeding (1 case), and unknown causes (2 cases).

All patients were divided into death and survival subgroups according to the survival state of 30 and 180 days after extubation. There were significant differences between dead and survival subgroups in age, comorbidities, acute physiology and chronic health evaluation II (APACHE II), Glasgow Coma Scale score, plasma creatinine, potential of hydrogen, N-terminal-pro-B-type natriuretic peptide, and partial ultrasonic data (all $P < 0.05$) [Supplementary Tables 1 and 2, <http://links.lww.com/CM9/A865>]. Cox

regression showed that E/Ea (septal) after SBT (odds ratio [OR]: 1.132, 95% confidence interval [CI]: 1.003–1.278, $P = 0.045$), APACHE II score (OR: 1.269, 95% CI: 1.015–1.588, $P = 0.037$) and age (OR: 1.105, 95% CI: 1.001–1.221, $P = 0.048$) were closely related to the 30-day mortality [Supplementary Table 3, <http://links.lww.com/CM9/A865>]. However, DE (right) after SBT (OR: 0.876, 95% CI: 0.796–0.963, $P = 0.006$), the history of coronary heart disease (OR: 3.520, 95% CI: 1.346–9.204, $P = 0.010$), APACHE II score (OR: 1.131, 95% CI: 1.031–1.240, $P = 0.009$), and age (OR: 1.059, 95% CI: 1.018–1.102, $P = 0.005$) were significantly correlated with the 180-day mortality [Supplementary Table 3, <http://links.lww.com/CM9/A865>]. The AUC of E/Ea (septal) after SBT was 0.782, and a cutoff value > 16.8 showed the highest accuracy in predicting 30-day mortality with a sensitivity and specificity of 88.9% and 66.7%, respectively [Supplementary Figure 2A, <http://links.lww.com/CM9/A865>]. Meanwhile, the AUC of DE (right) after SBT was 0.642, and a cutoff value ≤ 12 mm showed the highest accuracy in predicting 180-day mortality with a sensitivity and specificity of 75.0% and 55.6%, respectively [Supplementary Figure 2B, <http://links.lww.com/CM9/A865>]. The Kaplan-Meier survival curve showed that the 30-day mortality was significantly higher in the subgroup of E/Ea (septal) after SBT > 16.8 , compared with the subgroup of E/Ea (septal) after SBT ≤ 16.8 ($\chi^2 = 9.760$, $P = 0.002$) [Figure 1A]. Meanwhile, the 180-day mortality was significantly higher in the subgroup of DE (right) after SBT ≤ 12 mm than in the subgroup of DE (right) after SBT > 12 mm ($\chi^2 = 4.682$, $P = 0.030$) [Figure 1B].

In this study, 24 patients (40%) died within 180 days after extubation. Frutos-Vivar *et al*^[5] found that the high mortality rate (28%) was closely associated with complications and organ failure in re-intubated patients. Ventilation-associated pneumonia and cardiovascular failure were the main causes, respectively. Similarly, in our study, the two major causes of death were cardiac events (42%) and refractory pneumonia (38%). It implied that the indicators related to cardiac dysfunction and

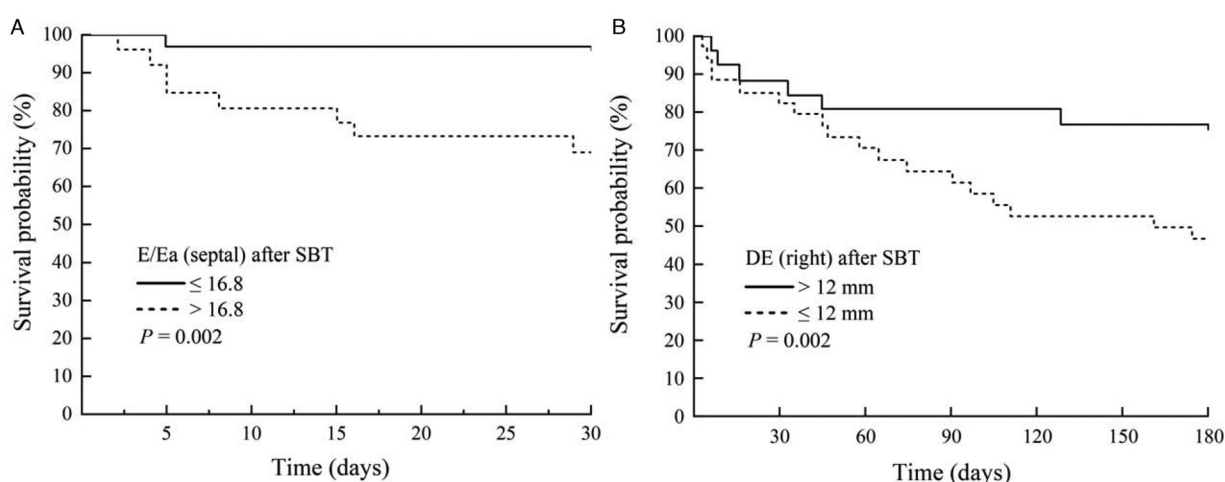


Figure 1: Comparisons of the 30-day survival probability between patients with E/Ea (septal) after SBT at different levels (A) and 180-day survival probability between patients with DE (right) after SBT at different levels (B). DE: Diaphragmatic excursion; E/Ea: Ratio of mitral Doppler inflow velocity (E) to annular tissue Doppler wave velocity (Ea); SBT: Spontaneous breathing trial.

refractory pneumonia might help predict death after extubation.

In this study, E/Ea (septal) after SBT was closely related to the 30-day mortality. It implied that cardiac diastolic dysfunction had an important effect on death after extubation in the early term. During the shift from positive to negative pressure ventilation after extubation, myocardial cells were sensitive to the changes of volume load and pressure load or even intolerable. Unless this issue could be resolved quickly, more deaths would occur rapidly. Actually, in the present study, cardiac event was the first cause of death. It was noteworthy that the cutoff value of E/Ea ratio (septal) in this study was 16.8, higher than the reported cut-off values of E/Ea ratio predicting weaning failure which varied from 7.8 to 14.5.^[2] This suggested the more severe the cardiac diastolic dysfunction, the greater the risk of death after extubation.

Additionally, DE (right) after SBT was remarkably associated with the 180-day mortality. In 2020, a meta-analysis by Medrinal *et al*^[6] found that DE could predict overall death with a sensitivity and specificity of 59% and 62%, respectively. The AUC of DE was 0.640. Our results were very similar with the study mentioned above. The diaphragm was vulnerable to damage from multiple factors such as hypotension, hypoxia, and sepsis. Different from cardiac dysfunction, it was often compensated partially by the accessory inspiratory muscles and expiratory muscles, even by mechanical ventilation. In case the factors which caused diaphragmatic insufficiency could not be corrected, the patient conditions worsened gradually. Then death might happen over a long period. Furthermore, diaphragm dysfunction often appeared as respiratory failure in patients with chronic pulmonary or abdominal diseases. Moreover, as the diaphragm served as the main part in the formation of the cough reflex arc, its dysfunction could markedly limit the ability to cough and discharge sputum. Consequently, refractory pneumonia could often happen. This study confirmed that DE was associated with 180-day mortality after extubation. Actually, refractory pneumonia was the second cause of death in this study.

There was an interesting phenomenon. The previous study showed that E/Ea (average) after SBT could predict respiratory failure within 48 h, and DE (average) after SBT might predict re-intubation within 1 week.^[4] Changes in risk factors for respiratory failure within 48 h and re-intubation within 1 week resembled the changes in risk factors for mortalities between 30 and 180 days. These results implied that clinicians shall closely monitor cardiac diastolic function after extubation and take effective measures to avoid respiratory failure. Meanwhile, they shall persistently focus on diaphragm function to avoid re-intubation. This procedure might be an effective way to improve the survival rate in both the short term and long term.

The death causes in difficult-to-wean patients were often multifactorial. A recent study reported that the combined

indicators including left-atrial pressure, lung ultrasound score, and hemidiaphragm dysfunction could predict extubation failure more accurately than individual indicator.^[7] The initial aim of the present study was to identify whether the combination of E/Ea and DE could improve the predictive accuracy. However, neither DE was related to 30-day mortality nor E/Ea was associated with 180-day mortality. Due to the small sample size in this study, the role of the combined ultrasound in predicting the mortality needed further exploration.

In summary, ultrasound evaluation of severe cardiac and diaphragm dysfunction could help predict death after extubation within 30 and 180 days, respectively. E/Ea (septal) after SBT and DE (right) after SBT were significantly related to 30 and 180-day mortality, respectively.

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Conflicts of interest

None.

References

1. Thille AW, Richard JCM, Brochard L. The decision to extubate in the intensive care unit. *Am J Respir Crit Care Med* 2013;187:1294–1302. doi: 10.1164/rccm.201208-1523CI.
2. Sanfilippo F, Di Falco D, Noto A, Santonocito C, Morelli A, Bignami E, *et al*. Association of weaning failure from mechanical ventilation with transthoracic echocardiography parameters: a systematic review and meta-analysis. *Br J Anaesth* 2021;126:319–330. doi: 10.1016/j.bja.2020.07.059.
3. Le Neindre A, Philippart F, Luperto M, Wormser J, Morel-Sapene J, Aho SL, *et al*. Diagnostic accuracy of diaphragm ultrasound to predict weaning outcome: a systematic review and meta-analysis. *Int J Nurs Stud* 2021;117:103890. doi: 10.1016/j.ijnurstu.2021.103890.
4. Luo L, Li Y, Chen X, Sun B, Li W, Gu W, *et al*. Different effects of cardiac and diaphragm function assessed by ultrasound on extubation outcomes in difficult-to-wean patients: a cohort study. *BMC Pulm Med* 2017;17:161. doi: 10.1186/s12890-017-0501-8.
5. Frutos-Vivar F, Esteban A, Apezteguia C, Gonzalez M, Arabi Y, Restrepo MI, *et al*. Outcome of reintubated patients after scheduled extubation. *J Crit Care* 2011;26:502–509. doi: 10.1016/j.jccr.2010.12.015.
6. Medrinal C, Combret Y, Hilfiker R, Prieur G, Aroichane N, Gravier FE, *et al*. ICU outcomes can be predicted by noninvasive muscle evaluation: a meta-analysis. *Eur Respir J* 2020;56:1902482. doi: 10.1183/13993003.02482-2019.
7. Xu X, Wu R, Zhang YJ, Li HW, He XH, Wang SM. Value of combination of heart, lung, and diaphragm ultrasound in predicting weaning outcome of mechanical ventilation. *Med Sci Monit* 2020;26:e924885. doi: 10.12659/MSM.924885.

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