



# Role of Stress-induced Diastolic Dysfunction in Weaning Failure from Mechanical Ventilation

Mostafa Rafea\*, Karim Mashhour, Mohamed Fawzy, Hanan Zaghla, Sherin El-Genghi

Department of Critical Care Medicine, Faculty of Medicine, Cairo University, Giza, Egypt

## Abstract

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**\*Correspondence:** Mostafa Rafea, Department of Critical Care Medicine, Faculty of Medicine, Cairo University, Giza, Egypt. E-mail: rafefii2010@gmail.com  
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**BACKGROUND:** Critically ill patients may suffer varying degrees of myocardial dysfunction which can cause weaning failure. Stress echocardiography may be helpful in detecting silent diastolic dysfunction (DD) while weaning off mechanical ventilation.

**AIM:** The aim of the study was to assess the existence of temporary DD during respiratory weaning using stress echocardiography.

**METHODS:** Our study was conducted on 60 ventilated patients admitted to the department of critical care, Cairo University. Stress echocardiography was done using dobutamine to assess DD and pulmonary capillary wedge pressure using E/e' ratio.

**RESULTS:** A total of 34 patients (56.66%) were successfully weaned of mechanical ventilation. Twenty-six patients (43.3%) had failed weaning of mechanical ventilation. Patients with successful weaning had no statistically significant difference regarding the E/e' ratio before and after stress testing ( $p < 0.001$ ). While patients with failed, weaning had statistically significant difference regarding the E/e' with a mean E/e' ratio of  $11.11 \pm 4.44$  after stress testing versus  $6.5 \pm 1.39$  before stress testing, ( $p < 0.001$ ).

**CONCLUSION:** Diastolic dysfunction is a predisposing factor for weaning failure. In addition, stress echocardiography can detect silent diastolic dysfunction during respiratory weaning.

## Introduction

Mechanical ventilation is a significant life-saving intervention for respiratory failure. Complications resulting from mechanical ventilation increase with the duration of ventilator support; thus, early weaning is a cornerstone in prevention of these complications [2].

Identifying the ideal time to wean a mechanically ventilated patient is a crucial issue in the critical care practice; as both premature and delayed weaning prolong the duration of mechanical ventilation, length of ICU stay, and increased morbidity and mortality [3], [4]. Consequently, accurate prediction of post-extubation distress and the early diagnosis of the causes responsible for failure of weaning are of a great importance in improving the outcome of ventilated [5], [6], [7].

Weaning failure includes patients failing the initial spontaneous breathing trial (SBT) and those with post-extubation respiratory distress that requires reintubation or rescue non-invasive ventilation after extubation [6].

Many mechanisms are incriminated in weaning failure including, that is, alteration of lung

compliance during weaning, lung derecruitment, neuromuscular disorders, and spontaneous breathing induced cardiac dysfunction; including systolic and diastolic dysfunction, along with weaning induced pulmonary edema [6], [8].

Spontaneous breathing trial (SBT) induces an elevation of the filling pressure the left ventricular (LVFP), which, in turn, may lead to weaning failure. At present, transthoracic echocardiography (TTE) can be used to diagnose the weaning failure of cardiac origin [9].

The application of new technologies such as speckle tracking (especially regarding strain [S] and strain rate [SR]) has proven to be useful in the detection of silent cardiac dysfunction in ambulatory patients. So far, this technology is still seldom used in the intensive care setting [10].

The hypothesis of this study is that critically ill patients with failed weaning from mechanical ventilation experience some measurable degree of myocardial dysfunction. We also believe that dobutamine echocardiography in patients with mechanical ventilation could reveal the existence of myocardial dysfunction that may be masked by mechanical ventilation itself [10].

## Methods

### Study design

This prospective, cohort, and single-center study was conducted on 60 patients admitted to the department of critical care medicine, faculty of medicine, Cairo University, from June 2018 to December 2020. The study was approved by the Ethical Committee of Cairo University number I-211017.

### Inclusion criteria

Invasively, mechanically ventilated patients fulfilling the criteria for a spontaneous breathing trial (SBT) [4], which include:

- Improvement of the underlying cause of acute respiratory failure.
- Adequate cough.
- Absence of excessive trachea-bronchial secretion.
- Hemoglobin level > 7G/dl.
- PaO<sub>2</sub> > 60 mmHg, FIO<sub>2</sub> < 40%, positive end expiratory pressure (PEEP) under or equal to 7 cm H<sub>2</sub>O, respiratory rate <35 breathes/min.
- Stable cardiovascular status (heart rate ≤120/min, systolic blood pressure >90 mm Hg and <160 mm Hg) without the need for vasoactive drugs.
- No sedation with a stable neurological status.
- Rapid shallow breathing index <105.

### Exclusion criteria

The following criteria were excluded from the study:

1. Inappropriate acoustic windows.
2. Known ischemic heart disease.
3. Significant valvular heart disease or valve replacement
4. Presence of arrhythmias.
5. E/e<sub>v</sub>.
6. Patients on vasopressors or inotropic support.
7. Left ventricular systolic dysfunction (LVEF < 50%).
8. Neuromuscular disorders, for example: Guillain barre syndrome and myasthenia gravis.
9. No neuromuscular paralyzing agents for 48 h.
10. Refusal of the patient to participate in the study.

We suspected that the cause of respiratory weaning failure was cardiac in nature by the appearance of both clinical and radiological signs during respiratory weaning such as crackles, fluid overload on chest radiography, and rapidly improving hypoxemia. Clinical and demographic characteristics were collected. Regarding to the echocardiographic parameters,

we used the American Society of Echocardiography guidelines for the study of systolic and diastolic heart function [11], [12].

### Study protocol

A total of 60 patients on whom we performed stress echocardiograms. We used dobutamine to assess the existence of silent diastolic dysfunction. A stress echocardiogram was performed while being on assisted controlled ventilation. The weaning protocol in these patients started from assisted controlled mechanical ventilation. When considered by the medical team to be ready to commence respiratory weaning, these patients were switched to PSV (PS 10 cm H<sub>2</sub>O, PEEP 5 cm H<sub>2</sub>O, FIO<sub>2</sub> 0.5) and subsequently to a T-tube trial for 2 h. If they succeeded in the spontaneous breathing trial, they were extubated. Weaning failure was defined by the inability in switching the ventilation mode from assisted controlled ventilation to PSV due to the occurrence of any of the following: Radiological pulmonary congestion, lung crackles on auscultation, respiratory rate 35/min, arterial oxygen saturation below 92%, respiratory acidosis, diaphoresis, increased work of breathing, or hemodynamic instability.

### Bedside monitoring

All patients were mechanically ventilated under volume-controlled ventilation using a Puritan Bennet 840 ventilator, and they were observed till improvement of their conditions and became eligible to initiate the SBT for weaning. During mechanical ventilation, PSV, and T-tube, the level of pressure support, end expiratory pressure, FIO<sub>2</sub>, and respiratory dynamic compliance were recorded just before initiation of the weaning. The heart rate, respiratory rate, blood pressure, and SatO<sub>2</sub> were monitored throughout the study.

### Image acquisition and processing

Trans-thoracic Doppler echocardiographic examination was done using Siemens machine, with a probe 3.5 MHZ. Echocardiographic examination including M-mode, two-dimensional (2D), color flow mapping, TDI, and dobutamine echocardiography was done and parameters were recorded.

- a. LV Global systolic function was assessed by M-mode in the long axis parasternal view for linear measurement of RV and LV. The M-mode cursor was positioned at the level of the mitral valve leaflets tips to measure:
  - The right ventricular end-diastolic diameter (RVEDD).
  - The left ventricular end-systolic (LVESD) and end diastolic dimensions (LVEDD) (normally up to 5.6 cm).

- Left ventricular ejection fraction (EF) percentage was calculated as:  $[(LVEDd - LVESd)/LVEDd] \times 100$  (normally: 55–75%) [3].
- b. Left ventricular diastolic function: Mitral flow velocities were obtained with the sample volume positioned between the tips of the mitral leaflets, where maximal flow velocity is recorded. For all measurements, five cycles were recorded using a sweep speed of 100 mm/s.

The following parameters were measured:

- Peak early (E) and atrial (A) flow velocity (cm/s).
  - E/A ratio.
- Deceleration time (DT): measured as the interval from peak early velocity to the zero intercept of the extrapolated deceleration slope of E and A [13].
- c. Doppler tissue imaging (DTI): DTI of the mitral annulus was obtained from the apical 4-Chamber view. A 1.5-mm sample volume was placed at the lateral and septal mitral annulus.

Analysis was then performed for:

- Lateral E' mitral: normal value is 12.5 ± 3.7 cm/s [14].
  - Lateral E/E' ratio: With normal value is <8 [14].
- The recommended variables for identifying diastolic dysfunction and their abnormal cutoff values are annular e' velocity: septal e' < 7 cm/sec, lateral e' < 10 cm/s, average E/e' ratio > 14, LA volume index > 34 mL/m<sup>2</sup>, and peak TR velocity > 2.8 m/s [14].
- d. The protocol for dobutamine stress echocardiography was done using a graded dobutamine infusion at a starting dose of 5 µg/kg/min and increased every 3–5 min up to 40 µg/kg/min to achieve a heart rate ≥ 85% of the maximal predicted heart rate for the patient's age. The intervention was discontinued if the patient showed any of the following signs:
- a. Decrease in oxygenation.
  - b. Increase in peak or plateau pressures,
  - c. Dysrhythmias.
  - d. Hemodynamic instability.
- e. We compared both the echocardiographic data before and after stress echocardiography.

### Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum and maximum for quantitative variables, and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test

in normally distributed quantitative variables while non-parametric Mann–Whitney test was used for nonnormally distributed quantitative variables. For comparison of paired measurements (before and after stress) within each patient, the non-parametric Wilcoxon signed rank test was used (Chan, 2003a) [15]. For comparing categorical data, Chi-square ( $\chi^2$ ) test was performed. Exact test was used instead when the expected frequency is <5 (Chan, 2003b) [16].  $p < 0.05$  was considered as statistically significant.

## Results

Our study was conducted prospectively to assess the existence of temporary diastolic dysfunction during respiratory weaning and the relationship between DD and weaning from MV.

The used tools in our study had the advantages of being bedside, minimally invasive, and easy to apply. Nevertheless, the target was selection of only the data with maximum benefit and quickest to obtain with minimal stress on the study patients.

All patients included in the study were invasively ventilated for 48 h or more and were ready to go through a SBT according to the readiness criteria. Routine clinical, laboratory, and imaging assessment was performed to the included patients.

The causes of mechanical ventilation were divided between chest infection, disturbed conscious level, hemodynamic instability, status epilepticus, and non-cardiogenic pulmonary edema (Table 1).

The stress echocardiograms of patients who failed respiratory weaning showed an increase in the E/E' ratio and the ejection fraction. In addition, SO<sub>2</sub> and dynamic lung compliance values decreased during the stress echocardiograms in these patients, supporting the hypothesis of heart failure development as the cause of failure in being weaned from the ventilator (Table 2).

**Table 1: Demographic data**

| Demographic data                 | Weaning failure | Successful weaning | p     |
|----------------------------------|-----------------|--------------------|-------|
| n                                | 26              | 34                 |       |
| Age                              | 56.38 ± 18.07   | 50.74 ± 16.03      | 0.206 |
| Gender                           |                 |                    |       |
| Female                           | 16              | 10                 | 0.013 |
| Male                             | 10              | 24                 |       |
| Diabetes                         | 8               | 10                 | 0.909 |
| HTN                              | 19              | 13                 | 0.651 |
| Smoking                          | 10              | 2                  | 0.037 |
| Renal impairment                 | 12              | 11                 | 0.276 |
| Cerebrovascular stroke           | 7               | 5                  | 0.241 |
| Malignancy                       | 6               | 6                  | 0.602 |
| Causes of MV                     |                 |                    |       |
| Non-cardiogenic pulmonary oedema | 4               | 2                  | 0.484 |
| Status epilepticus               | 4               | 3                  |       |
| Severe hemodynamic instability   | 2               | 4                  |       |
| Postoperative                    | 4               | 1                  |       |
| Disturbed conscious level        | 1               | 1                  |       |
| Chest infection                  | 17              | 17                 |       |

HTN: Hypertension, MV: Mitral valve.

**Table 2: Dobutamine echocardiography in patients with weaning failure during assisted controlled mode: Suspicion of diastolic dysfunction**

| Clinical and echocardiographic parameters             | Basal          | Dobutamine     | p      |
|---|----------------|----------------|--------|
| Heart rate (beat/min)                                 | 89.42 ± 13.88  | 156.15 ± 15.45 | <0.001 |
| Systolic arterial pressure (mmHg)                     | 119.23 ± 11.29 | 138.85 ± 10.71 | <0.001 |
| Diastolic arterial pressure (mmHg)                    | 73.08 ± 9.28   | 89.23 ± 6.88   | <0.001 |
| SpO <sub>2</sub>                                      | 97.42 ± 1.98   | 94.38 ± 2.37   | 0.466  |
| Pulmonary dynamic compliance (mL/cm H <sub>2</sub> O) | 42.37 ± 10.49  | 31.63 ± 9.21   | 0.007  |
| Peak velocity E wave (m/s)                            | 0.84 ± 0.29    | 1.78 ± 0.87    | 0.617  |
| A wave velocity (m/s)                                 | 0.81 ± 0.24    | 0.83 ± 0.24    | 0.939  |
| E' (m/s)  | 0.10 ± 0.04    | 0.10 ± 0.04    | 0.531  |
| E/A   | 1.10 ± 0.41    | 1.19 ± 0.60    | 0.281  |
| E-E' ratio  | 6.50 ± 1.39    | 11.11 ± 4.44   | <0.001 |
| LVEF  | 60.62 ± 11.31  | 68.62 ± 10.40  | 0.366  |
| TAPSE (cm)  | 1.94 ± 0.37    | 1.5 ± 0.43     | 0.045  |

LVEF: Left ventricular ejection fraction, TAPSE: Tricuspid annular plane systolic excursion.

On the other hand, the stress echocardiogram that was performed in the group of patients who had successful respiratory weaning showed an increase of fractions of the left ventricular ejection fraction; however, there was no change in the E/E' ratio (Table 3).

**Table 3: Dobutamine stress echocardiography in successful weaning: The patients were in assisted controlled mode**

| Clinical and echocardiographic parameters             | Basal          | Dobutamine     | p       |
|---|----------------|----------------|---------|
| Heart rate (beat/min)                                 | 89.12 ± 12.40  | 153.68 ± 12.99 | < 0.001 |
| Systolic arterial pressure (mmHg)                     | 120.00 ± 14.14 | 140.29 ± 13.59 | < 0.001 |
| Diastolic arterial pressure (mmHg)                    | 72.65 ± 10.24  | 88.53 ± 8.57   | < 0.001 |
| SpO <sub>2</sub>                                      | 97.42 ± 1.52   | 95.88 ± 1.89   | 0.364   |
| Pulmonary dynamic compliance (mL/cm H <sub>2</sub> O) | 53.91 ± 20.72  | 51.06 ± 21.00  | 0.809   |
| Peak velocity E wave (m/s)                            | 0.80 ± 0.25    | 0.75 ± 0.23    | 0.242   |
| A wave velocity (m/s)                                 | 0.77 ± 0.29    | 0.79 ± 0.22    | 0.732   |
| E' (m/s)  | 0.17 ± 0.16    | 0.14 ± 0.08    | 0.477   |
| E/A   | 1.12 ± 0.48    | 1.00 ± 0.38    | 0.195   |
| E-E' ratio  | 5.55 ± 2.42    | 6.28 ± 2.59    | 0.069   |
| LVEF  | 61.91 ± 8.09   | 68.53 ± 7.19   | 0.198   |
| TAPSE (cm)  | 2.26 ± 0.46    | 2.15 ± 0.40    | 0.182   |

LVEF: Left ventricular ejection fraction, TAPSE: Tricuspid annular plane systolic excursion.

## Discussion

Critically ill patients may suffer varying degrees of temporary myocardial dysfunction during respiratory weaning that could play an important role in weaning failure. Success in respiratory weaning depends on multiple factors, such as respiratory status, comorbidities, neuromuscular status, and nutrition [17]. The process of weaning from mechanical ventilation is a challenging decision in ICU. Hence, the decision of when to wean the patient depends on variable and complicated factors that cannot be assessed by a single mean. The ideal time of weaning is a critical point in patient management in ICU as both early weaning and delayed weaning may have an impact on mortality and morbidity.

PCWP values are dynamic, and an increase in PCWP the E/E' ratio has been observed in patients during respiratory weaning [18], [19]. The previous published articles had shown similar results (increased E/E' ratio) with no altered systolic function during the respiratory weaning phase [19], [20].

We used dobutamine stress echocardiography to assess the existence of silent diastolic dysfunction, and to predict patients who may experience diastolic

dysfunction during respiratory weaning by exposing them to stress using dobutamine stress testing.

In our study, it was found that E/e' can predict weaning failure with a p value of (< 0.001) and (0.069) between patient with weaning failure and those with successful weaning respectively. El-Dehily *et al.* 2017 [21], found that E/e' (2) could predict the failure of weaning during SBT at a cutoff point of 6.28, but with lower specificity and sensitivity (AUC = 0.474). In a similar manner, Moschietto *et al.*; 2012 [22]. proved that E/e' could predict the failed weaning at a cutoff value of E/e' ratio during the SBT of 14.5 with a sensitivity of 75% and a specificity of 95.8%. However, E/e' values measured before SBT were significantly higher in the failed group but results of the ROC curve were non-significant. The major finding of this study shows that serial measurements of E/e' accurately predict weaning failure.

In addition, in the present study, TAPSE was found to be significantly lower in the failed weaning group than the successful weaning group (p = 0.045 vs. 0.182, respectively), we believe that the diastolic dysfunction happened in the group with weaning failure most probably caused the decrease in RV systolic function. In the same context, Roche-Campo *et al.*; 2018 [23]. found that TAPSE was significantly higher in the short weaning group than the prolonged weaning group (P = 0.03). Similar to these findings, Daif *et al.*; 2018 [24]. could find that RVSP was higher in the failed weaning group (P < 0.001) most probably due to RV failure associated with shift of the patient from PPV to negative pressure ventilation leading to increased RV preload against a high RVSP. Same results were found with El-Dehily *et al.*; 2017 [21].

The present study demonstrates that echocardiography is a very reliable diagnostic tool during respiratory weaning, as latent diastolic dysfunction can become evident during stress studies.

Besides, this response to dobutamine could suggest new ischemic complications. We believe that these findings have crucial clinical implications for critically ill patients, in addition to serving as a reminder of the benefits of vasodilators, and other cardioprotective medications and of avoiding such medications as bronchodilators, β-stimulants, steroids, and other cardiotoxic drugs.

### Limitations

- The study is a small sample and single-center study.
- Diastolic dysfunction is a common disorder seen in critically ill patients and our findings may be not related to the failed weaning process only; but may express the severity of the case and association of variable risk factors.

- Exclusion of many patients due to the poor echocardiographic window in some patients under mechanical ventilation.
- The diagnosis of weaning induced cardiac dysfunction and pulmonary edema was made using non-invasive techniques without the use of other invasive methods, that is, PAOP that can confirm the findings.

## Conclusion

Stress echocardiography may be helpful in detecting silent diastolic dysfunction. Echocardiography can be used in the evaluation of weaning induced diastolic dysfunction and its impact on the weaning outcome. Finally, the early assessment of cardiopulmonary changes during PPV can direct the management to fluid restrictive strategy to help in decongestion of the lung and facilitate the success of the SBT.

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