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Diastolic dysfunction as a predictor of weaning failure: A systematic review and meta-analysis

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ABSTRACT

Purpose: Weaning failure and prolonged mechanical ventilation are associated with increased morbidity, cost of care, and high mortality rates. In the last few years, cardiac performance has been recognized as a common etiology of weaning failure, and growing evidence suggests that left ventricular diastolic dysfunction is a key factor that determines weaning outcomes. Therefore, we performed a systematic review and a meta-analysis to evaluate whether diastolic dysfunction in the critically ill patient subjected to mechanical ventilation is an independent predictor of weaning failure.
Materials and methods: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, LILACS, Google Scholar, and ClinicalTrials.gov from inception to September 2014, along with conferences proceeding from January 2005 through September 2014, and included Observational Studies and Randomized Clinical Trials evaluating predictors of weaning failure.
Results: Ten studies were included in the systematic review; and 7, in the meta-analysis (6 observational studies and 1 randomized controlled trial). Patients who developed weaning failure had a higher E/e′ ratio when compared with those who did not (mean difference, 2.65; 95% confidence interval, 0.52-4.79; P= .01); however, there was no difference in the E/A ratio (mean difference, 0.07; 95% confidence interval, −0.04 to 0.18; P= .22). Both the E/e′ and E/A ratios were associated with weaning-induced pulmonary edema at the end of a spontaneous breathing trial.
Conclusion: **A** higher E/e′ ratio is significantly associated with weaning failure, although a high heterogeneity of diastolic dysfunction criteria and different clinical scenarios limit additional conclusions linking diastolic dysfunction with weaning failure.

1. Introduction

Weaning from mechanical ventilation is the process of gradual ventilatory support reduction to the patient subjected to mechanical ventilation for more than 24 hours [1]. It is a crucial moment because prolonged mechanical ventilation and weaning failure are associated with increased morbidity, cost of care, and high mortality rates [2–4]. However, it remains a challenge to identify both the appropriate time for beginning the weaning process and reliable predictors of weaning outcome.

Weaning failure may be caused by several factors and is often multifactorial [5]. In the last few years, disturbances in cardiac performance have been recognized as a common etiology of weaning failure [6–15] and are even considered by some to be the leading cause [16]. The transition from positive to negative thoracic pressure increases venous return and left ventricular (LV) afterload, decreases LV compliance, and may induce cardiac ischemia [1]. All of these factors tend to increase ventricular filling pressures and may consequently lead to weaning-induced pulmonary edema [6,17].

More recently, some authors have suggested that LV diastolic dysfunction is associated with weaning outcomes, and several studies evaluating this hypothesis have been published [9,13,14].

Because diastolic dysfunction is commonly seen in the intensive care unit (ICU) [18] and there is growing evidence that it plays an important role in the weaning process, we decided to systematically review the literature to address whether the presence of diastolic dysfunction in the critically ill patient subjected to mechanical ventilation is an independent predictor of weaning failure.

2. Methods

The protocol for this review can be found at PROSPERO database (registration no. CRD42014014353). We included studies

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(observational and randomized clinical trials) that evaluated patients older than 18 years who (1) were on mechanical ventilation for at least 24 hours, (2) were considered ready to wean, (3) had an echocardiographic evaluation immediately before undergoing a spontaneous breathing trial (SBT) or right after the onset of the test, and (4) were followed up for at least 48 hours after extubation. The main outcome was weaning failure, defined as the failure to pass an SBT or the need for reintubation within 48 hours after extubation. Secondary outcomes included the duration of mechanical ventilation, ICU length of stay, incidence of tracheostomy, and mortality. We excluded studies that included patients with prolonged mechanical ventilation (>21 days).

The systematic review and the eligibility assessment were independently conducted by 2 reviewers (CAM and WLN). Disagreements were resolved by a third reviewer (VDM). Articles were searched from inception to September 2014, with no language restriction, in the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, LILACS, and Google Scholar. Additional studies were searched at conferences from the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the American College of Chest Physicians, and the International Symposium on Intensive Care and Emergency Medicine from the past 10 years (2005-2014). We also checked the reference list of the included articles and contacted experts in the field for information regarding additional trials. Finally, we identified unpublished and ongoing trials by searching clinical trial registries (ClinicalTrials.gov). The strategies used to search the databases are available in the published protocol.

Data from the articles were extracted using a modified data extraction sheet, also found in the study protocol. The entire process was conducted independently by the same 2 reviewers who carried out the eligibility assessment. After the data extraction, the reviewers checked individual data, and any disagreements were resolved in a subsequent meeting. The following data were extracted: study location, enrollment period, sample size, inclusion and exclusion criteria, number of excluded patients, baseline characteristics, duration of mechanical ventilation (before and after the SBT), details of the echocardiographic examination, details of control intervention, length of follow-up, and clinical outcomes. We contacted 6 authors for further information, 5 responded to our questions, and 1 did not.

To ascertain the validity and the risk of bias of the included eligible randomized studies, 2 reviewers working independently used The Cochrane Collaboration's tool for assessing risk of bias (version 5.1.0.). Observational studies were evaluated using the Newcastle-Ottawa quality assessment scale.

The statistical analysis was performed using the MetaView statistical program within the Review Manager software (RevMan 5.3.4) using the Mantel-Haenszel random- and fixed-effects model. Statistical heterogeneity across trials was assessed using the Cochrane's χ^2 test and the inconsistency test proposed by Higgins and Thompson [33].

We analyzed the probability of publication bias using a funnel plot and considered plot asymmetry to be suggestive of reporting bias.

3. Results

We identified 10 934 citations from the databases and 8 citations from the conferences. After adjusting for duplicates, 10 892 studies remained. Of these, 10 866 articles were discarded after reviewing the abstracts. One additional study was excluded because the full text was not available, and the author did not have the complete data to send. The full text of the remaining 25 articles was examined in detail. Fifteen did not meet the inclusion criteria or were duplicates and were excluded. Ten studies met the inclusion criteria and were included in the systematic review, with a total of 731 patients. Seven studies were included in 1 meta-analysis and 6 in other. Three studies were not included in any meta-analysis because of (1) the particular mode of measuring diastolic function [4,14], (2) the authors studied only pulmonary capillary pressure weaning-induced changes, and (3) the authors did not report weaning success within the time frame proposed in our study [6], as shown in Fig. 1.

3.1. Characteristics of the studies

Of the 10 studies, 1 was a randomized controlled clinical trial, and 9 were prospective cohort studies. They were all published between 2009 and 2014, with between 24 and 225 subjects included in each article. The main characteristics of the individual studies are summarized in Table 1. The assessment of risk of bias of the studies included in the meta-analysis is available in Table 2. Most of the observational studies had in general a good methodological quality, as assessed by the Newcastle-Ottawa scale.

The 2 main enrollment criteria in the studies were mechanical ventilation for more than 24 hours and a patient ready to wean. Spontaneous breathing trials were conducted using different methods and varying durations (T-piece, low-level pressure supportive ventilation [PSV] with or without positive end-expiratory pressure with periods ranging from 30 to 120 minutes). The main exclusion criteria included the presence of atrial fibrillation or other arrhythmias, a poor transthoracic echocardiographic window, and the presence of moderate to severe valvulopathies, especially involving the mitral valve. Only 1 study included patients with atrial fibrillation [13].

Most of the studies were carried out in the general ICU of university hospitals, and all but 1 were unicentric. Transthoracic echocardiography was performed by experienced operators. Interobserver reproducibility was satisfactory. The patient's medical assistant was usually blinded to the echocardiography and the pulmonary artery catheter results. The criteria used to begin and interrupt the weaning trial were well specified as well as the criteria to reintubate a patient after extubation.

Caille et al [7] studied 117 patients ready to wean. Fifty percent had LV ejection fraction (LVEF) less than 50%. Twenty-three patients (20%) failed the weaning process. The ratio between baseline maximal flow velocity during early diastole (E wave) and during atrial systole (A wave) (E/A ratio) ($P = .7$) and the e wave deceleration time (DTE) ($P = .07$) were not correlated with weaning failure. However, the ratio between the E wave and the maximal velocity of the mitral annulus displacement during early diastole by pulse wave tissue Doppler (e′ wave) and LVEF was correlated with weaning failure (E/e′ ratio: $P = .038$ and LVEF: $P = .04$). In patients who failed to be weaned from the ventilator due to cardiogenic pulmonary edema (n = 20), both the median E/A and E/e′ ratios increased significantly from baseline to SBT ($P < .01$ and $P < .05$, respectively).

In 3 studies, the assessment of diastolic dysfunction was performed concomitantly with an evaluation of brain natriuretic peptide (BNP), N-terminal pro-BNP, or troponin levels [8,12,14]. In 1 study, the authors reported an association between baseline diastolic dysfunction and blood BNP values and weaning failure ($P < .001$ and $P = .008$, respectively) [14]. In the second study, Gerbaud et al [12] found an association between the elevation from baseline of N-terminal pro-BNP values after an SBT and E/é ratio and weaning failure ($P < .05$ for both). Baseline measures were not significantly correlated with the outcome. The third study was conducted by Zapata et al [8] and reported that baseline echocardiographic findings did not predict SBT failure. However, both baseline BNP and its elevation after SBT predicted weaning failure from a cardiac origin ($P < .05$).

Two studies correlated diastolic filling Doppler-derived variables (E/A and E/e′ ratio) with an elevation in weaning-induced pulmonary artery occlusion pressure (PAOP) (assessed by pulmonary artery catheterization and defined as a PAOP >18 mm Hg after SBT). Both studies reported an association between echocardiographic changes and PAOP elevation [6,11], with values quite different than those proposed in literature (E/A ratio ≥1 and E/e′ ratio > 15).

Moschietto et al [13] defined relaxation impairment as a lateral e′ wave velocity less than or equal to 8 cm/s. Eighty percent of the weaning failure group in his study had this finding, whereas only 35% of patients