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Review Article

REVIEW ARTICLE

Association of weaning failure from mechanical ventilation with transthoracic echocardiography parameters: a systematic review and meta-analysis

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Abstract

Background: Weaning from mechanical ventilation is a challenging step during recovery from critical illness. Weaning failure or early reintubation are associated with increased morbidity and mortality, exposing patients to life-threatening complications. Cardiac dysfunction represents the most common cause of weaning failure. We conducted a systematic review and meta-analysis to evaluate the association between transthoracic echocardiographic parameters and weaning failure.

Methods: We performed a systematic search of MEDLINE and EMBASE screening for prospective studies providing echocardiographic data collected just before the beginning of spontaneous breathing trial and outcome of the weaning attempt. We primarily focused on parameters currently recommended for evaluation of left ventricular (LV) systolic or diastolic dysfunction.

Results: We included 11 studies in our primary analysis, which included data on LV ejection fraction (LVEF, n=10 studies) and parameters recommended for the assessment of LV diastolic function (E/e′ ratio n=10; E/A ratio n=9; E wave n=8; and e′ wave n=7). Weaning failure was significantly associated to a higher E/e′ ratio (standardised mean difference [SMD]= 1.70, 95% confidence interval [CI; 0.78–2.62]; P<0.001), lower e′ wave (SMD=−1.22, 95% CI [−2.33 to −0.11]; P=0.03), and higher E wave (SMD=0.97, 95% CI [0.29–1.65]; P=0.005). We found no association between weaning failure and LVEF (SMD=−0.86, 95% CI [−1.92–0.20]; P=0.11) and E/A ratio (SMD=0.00, 95% CI [−0.30–0.31]; P=0.98).

Conclusions: Weaning failure is associated with parameters indicating worse LV diastolic function (E/e′, e′ wave, E wave) and increased LV filling pressure (E/e′ ratio). The association between weaning failure and LV systolic dysfunction as evaluated by LVEF is more unclear. More studies are needed to clarify this aspect and regarding the role of right ventricular function.

Keywords: critical care; echocardiography; extubation; mechanical ventilation; reintubation; spontaneous breathing trial; T-tube; weaning

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Editor's key points

- Failure to wean from ventilation in the ICU is associated with morbidity and mortality. The authors examined evidence on the association between transthoracic echocardiographic parameters and weaning.
- They found a significant association between weaning failure and a higher E/e′ ratio, lower e′ wave, and higher E wave, indicating that left ventricular diastolic dysfunction is associated with weaning failure.
- There was no association between weaning and left ventricular ejection fraction (LVEF), although this result should be considered cautiously as there was a weak (but not statistically significant) association between low LVEF and weaning failure (P=0.11).

Weaning of mechanical ventilation (MV) is a challenging step during the recovery of critically ill patients. Weaning failure and prolonged MV are associated not only with longer ICU length of stay[1,2] and greater healthcare costs,[3,4] but also with increased morbidity and mortality.[3,5] Extubation failure and the need for reintubation exposes patients to life-threatening complications.

The main causes of weaning failure may be grossly divided in respiratory or cardiac origin, although there is increasing evidence on the role of diaphragmatic dysfunction.[6] Cardiac dysfunction seems a key player, possibly representing the majority of the cases of weaning failure; indeed, weaning-induced pulmonary oedema has been reported in the region of 60% of failures by the largest study published so far on this topic.[7] Despite the profound haemodynamic changes induced by the weaning from MV, concomitant myocardial ischemia seems uncommon.[7]

Several algorithms and parameters have been proposed in order to predict successful weaning from MV, and these include patient's clinical characteristics, respiratory functional indices, and laboratory and echocardiographic parameters.[8–13] Echocardiography is increasingly used in the ICU at the bedside[14] and provides real-time measurements immediately integrated by the intensivists into a clinical management plan, with substantial difference from the consultative cardiology echocardiography exam.[15] However, studies investigating the association between findings of transthoracic echocardiography and weaning failure from MV have produced conflicting results. Therefore, we conducted a systematic review and meta-analysis in order to evaluate the association of echocardiographic parameters with weaning failure from MV.

Methods

This systematic review and meta-analysis was performed in accordance with PRISMA guidelines.[16] The review was registered with the international prospective register of systematic reviews (PROSPERO: CRD 42019117832).

Eligibility criteria

We included prospective studies providing echocardiographic data collected just at the beginning of a trial of extubation in our meta-analysis. Data were collected according to the success or failure of the weaning attempt itself. Inclusion criteria were prespecified using the PICOS framework (participants, intervention, comparison, outcomes, study design) (Table 1). Paediatric studies were excluded. Adult case series were included only if they provided acceptable data for at least 10 patients.

In brief, we included studies assessing echocardiographic parameters just before attempting weaning from MV with spontaneous breathing trial (SBT), conducted either as T-tube trial or with low level of pressure support ventilation (PSV). Regarding the latter, we defined low-level PSV a setting where inspiratory support was ≤10 cm H_2O and PEEP was ≤5 cm H_2O. Criteria of weaning failure were failed SBT according to clinical parameters, early reintubation (within 48 h), or both. In the event of studies reporting echocardiographic values only in the overall population, we planned to contact the corresponding author to increase data availability.

Identification of studies

Two systematic independent literature searches of the electronic databases were performed through the *NHS Healthcare Databases Advanced Search*, with a final update on December 4, 2019.

The findings of two search terms groups were combined: the items 'weaning' OR 'spontaneous breathing trial' OR 'mechanical ventilation' were used for the first group, and 'echocardiography' OR 'ejection fraction' OR 'systol*' OR 'diastol*' for the second group. A further independent manual search was performed by four authors (FS, DDF, AN, CS). MEDLINE was the primary database of screening. The search on EMBASE was added to also find conference abstracts not yet published. We applied language restriction to both searches, including only articles in English. We also applied temporal restriction for MEDLINE (2001–19) and EMBASE (2013–19). The latter was applied since it represents an ample timeframe to allow study completion (even of a pilot study) and publication after an adequate peer-review process.

Analysis of outcomes

We primarily focused on parameters used in the definition and grading of left ventricular (LV) systolic dysfunction (LVSD), LV diastolic dysfunction (LVDD), or both, according to their last

Table 1 'PICOS' approach for selecting clinical studies in the systematic search. LV, left ventricle; PSV, pressure support ventilation; RV, right ventricle; SBT, spontaneous breathing trial.

PICOS	
1. Participants	Patients undergoing weaning with SBT (T-tube trial or low level PSV)
2. Intervention	Transthoracic echocardiography performed before the weaning trial is started
3. Comparison	Measurements of echocardiographic parameters of LV and RV function
4. Outcomes	Weaning failure (failed SBT, reintubated, or both within 48 h) *vs* weaning success (studies with longer timeframe for reintubation used for sensitivity analysis)
5. Study design	Prospective clinical studies (retrospective studies only for sensitivity analysis)

Table 2 Summary of characteristics of included studies. The table also summarises two studies included in sensitivity analysis (indicated in *italic font*).

Study (journal and year)	Type of patients/ Total patients (success *vs* fail) SBT method SBT duration	Criteria for SBT failure/ Criteria for reintubation	Echocardiography data reported	Severity scores, overall value (success and failure values)
Caille and colleagues[22] (*Crit Care*, 2010)	Two general ICUs, mixed population Total 117 (94 *vs* 23) T-tube (semi-recumbent, 45°) Last 30 min	• Failed SBT if agitation or depressed mental state, Sp_{O_2}<90%, VF>35 bpm, HR>150 min^{-1} or arrhythmias, SAP>180 mm Hg or <90 mm Hg • Reintubated within 48 h The study included patients at their first SBT	LVEF E/A, DT, E/e′ RV/LV-EDA	SAPS II overall 53, 47–58
TypeZapata and colleagues[30] (*Intensive Care Med*, 2011)	General ICU, mixed population Total 100 (42 *vs* 58) T-tube (semi-recumbent) Last 30 min–2 h	• Failed SBT if VF≥35 bpm with signs of increased work of breathing, Pa_{O_2}≤60 mm Hg with O_2>4 L min^{-1}, arterial pH≤7.30; SAP≥180 mm Hg or <90 mm Hg; HR≥140 min^{-1} or ΔHR≥25%, acute arrhythmia; agitation, anxiety, or diaphoresis • Reintubated within 48 h	LVEF, LV-EDD, LV-ESD E/A, DT	SAPS II (44.2 [13.1] *vs* 45 [15]) APACHE II (18.6 [7.1] *vs* 19.2 [9.3])
Papanikolaou and colleagues[28] (*Intensive Care Med*, 2011)	General ICU, mixed population Total 50 (22 *vs* 28) T-tube Last 30 min	• Failed SBT if VF>35 bpm, Sa_{O_2}<90%, HR>140 min^{-1}, SAP>200 mm Hg or <80 mm Hg, acidosis, arrhythmias, diaphoresis, agitation, depressed mental status, distress • Reintubated within 48 h	LVEF, s′ E, A, E/A, DT, e′, E/e′, Vp, RVFAC, RV/LV-EDA	SOFA overall 5.5 [0.2] APACHE II overall 17.7 [0.5] (16.7 [0.7] *vs* 18.5 [0.7])
Gerbaud and colleagues[23] (*Minerva Anestesiol*, 2010)	Cardiology ICU Total 44 (34 *vs* 10) PS (7 cm H_2O), no PEEP Last 2 h	• Failed SBT if diaphoresis, respiratory distress, discomfort, VF>35 bpm, Sp_{O_2}<90%, HR>140 min^{-1}, SAP>180 mm Hg or <80 mm Hg • Do not report reintubation	LVEF, LV-EDV, LV-ESV E/A, E/e′	SAPS II overall 76 (26)
Moschietto and colleagues[27] (*Crit Care*, 2010)	Medical ICU, mixed population Total 68 (48 *vs* 20) PS (7 cm H_2O), no PEEP Last 1 h	• Failed SBT if VF>35 bpm, Sa_{O_2}<90%, HR>140 min^{-1}, SAP>200 mm Hg or <80 mm Hg, diaphoresis, distress • Reintubated within 48 h	LVEF DT, E/e′, e′	SAPS II (54, 48–72 *vs* 51, 45–55)
Thille and colleagues[29] (*Crit Care Med*, 2015)	General ICU, mixed population Total 225 (194 vs 31) PS 7–10 cm H_2O, no PEEP Last 1 h	• Failed SBT if VF>35 bpm, Sa_{O_2}<90%, HR>130 min^{-1}, SAP>180 or <90 mm Hg, increased accessory muscle activity, major dyspnea, agitation or depressed mental status • Reintubated within 7 days	LVEF	Not reported
Konomi and colleagues[24] (*Anaesth Intensive Care*, 2016)	General ICU, mixed population Total 42 (27 *vs* 15)* T-tube Last 2 h	• Failed SBT if VF>35 bpm, Sa_{O_2}<85–90%, HR>120–140 min^{-1} or ΔHR>20%, SAP>200 mm Hg or <90 mm Hg, arrhythmias, accessory muscles use, diaphoresis, discomfort • Reintubated within 48 h	LVEF E, A, E/A, DT, e′, E/e′	SOFA (8.1 [3.8] *vs* 13 [8.4]) APACHE II (15.6 [6] *vs* 17.7 [6])
Luo and colleagues[26] (*BMC Pulm Med*, 2017)	Four general ICU, mixed population Total 60 (31 *vs* 29) T-tube (supine 30°–45°) Last 30 min	• Failed extubation if onset within 48 h of at least two criteria: acidosis with Pa_{CO_2}>45 mm Hg or ΔPa_{CO_2}>20%; VF>30 bpm or ΔVF≥50%; Pa_{O_2}<60 mm Hg or Sp_{O_2}<90% at Fi_{O_2}≥0.5; decreased consciousness, agitation, or diaphoresis; clinical signs suggestive of respiratory muscle fatigue or increased work of breathing • Reintubated within 48 h (and also within 7 days) The study included only patients passing the SBT and extubated	LVEF E, E/e′	APACHE II (20 [6.4] *vs* 23.9 [4.7])
Haji and colleagues[34] (*Crit Ultrasound J*, 2018)	General ICU, mixed population Total 53 (42 *vs* 11) PS (up to 10 cm H_2O), PEEP (5 cm H_2O) Last 1 h	• Failed SBT if diaphoresis, RASS≥3 or ≤−3, increasing respiratory efforts, Pa_{O_2}<60 mm Hg or Sp_{O_2}<90% with Fi_{O_2}≥0.4, Pa_{CO_2}>50 mm Hg or ΔPa_{CO_2}>8 mm Hg, pH<7.32 or ΔpH≤0.07, Rapid Shallow Breathing Index>105, VF>35 bpm, HR>140 min^{-1} or ΔHR>20%, SAP>180 mm Hg or ΔSAP>20%, SAP<90 mm Hg, arrhythmias • Reintubation, NIV or death within 48 h after extubation	LVEF, E, E/A, DT, E/e′, e′ LA area	SAPS II (46, 36–57 *vs* 42, 33–46) APACHE II (20, 15–23 *vs* 20, 17–23)
Tongyoo and colleagues[35]	General ICU, mixed population		LVEF, LV-EDA E, A, E/A, e′, E/e′	

Continued

Table 2 Continued

Study (journal and year)	Type of patients/ Total patients (success *vs* fail) SBT method SBT duration	Criteria for SBT failure/ Criteria for reintubation	Echocardiography data reported	Severity scores, overall value (success and failure values)
(*Echocardiography*, 2019)	Total 52 (38 *vs* 14) PS 8 cm H_2O, PEEP 5 cm H_2O Last 1–2 h	• Failed SBT if VF>35 bpm, HR>150 min^{-1}, Sa_{O_2}<95%, SAP>180 mm Hg or <90 mm Hg, or deterioration of level of consciousness, or all • Reintubated within 48 h for respiratory distress	RV-EDA, RV/LV-EDA	SOFA overall 4.1 (2.5) (3.9 [2.5] *vs* 4.7 [2.5])
Amarja and colleagues[32] (*Indian J Crit Care Med*, 2019)	General ICU Total 161 (140 *vs* 21) PS with PEEP (support unclear) Duration unclear	• Do not report SBT failure since the study included only patients with successful SBT (clinicians decided to extubate) • Reintubation within 48 h	Eyeball systolic function E, A, E/A, DT, e′, E/e′, a′ TAPSE	APACHE II (18 [6.6] *vs* 20.8 [5.6])
Kaltsi and colleagues[36] (*Crit Care Res Pract*, 2019)	General ICU and CCU, mixed population Total 19 (8 *vs* 11) T-tube Last 2 h	• Failed SBT if VF>35 bpm, Sp_{O_2}≤90%, HR>120 min^{-1} or ΔHR>20%, SAP>180–200 mm Hg or <90 mm Hg, increased accessory muscles use, diaphoresis, discomfort, arrhythmias • Do not report reintubation	LVEF E, A, E/A, e′, E/e′, DT	Not reported
Bedet[33] (Crit Care, 2019)	General ICU, mixed population *Total 208 (76 vs 132)* *T-tube* *Last 2 h*	• Failed SBT if VF≥35 bpm or ΔVF≥50%, HR≥140 min^{-1}, Sp_{O_2}≤90%, SAP>180 or <90 mm Hg, arrhythmia, diaphoresis, respiratory distress, diaphoresis, alteration of consciousness • Reintubation within 7 days or death Included patients failing a first SBT (undergoing a second SBT)	LVEF E, E/A, E/e′	SOFA overall 3, 3–5

Results are indicated as mean (standard deviation) or as median, inter-quartile range.
Δ, (delta) variation from baseline; A, late mitral inflow velocity; APACHE II, Acute Physiology and Chronic Health Disease Classification System II; CCU, coronary care unit; DT, deceleration time; E, early mitral inflow velocity; e′, mitral annular early diastolic velocity; EDV, end-diastolic volume; ESV, end-systolic volume; Fi_{O_2}, fraction of inspired oxygen; LA, left atrial; LV-EDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LV-ESD, left ventricular end-systolic diameter; NIV, noninvasive ventilation; Pa_{CO_2}, arterial blood partial pressure of carbon dioxide; Pa_{O_2}, arterial blood partial pressure of oxygen; PS, pressure support; RASS, Richmond Agitation-Sedation Scale; RVFAC, right ventricular fractional area changes; RV/LV-EDA, right ventricular to the left ventricular end-diastolic areas ratio; SAP, systolic arterial BP; SAPS II, Simplified Acute Physiology Score II; SBT, spontaneous breathing trial; SOFA: Sequential Organ Failure Assessment; Sp_{O_2}, peripheral blood oxygen saturation; s′, mitral annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion; VF, ventilatory frequency; Vp, colour M-mode Doppler velocity of propagation.
* Echocardiographic data available for 12 failures and 22 successes.

guidelines update.[17,18] The LV ejection fraction (LVEF) was considered the primary echocardiographic outcome for the evaluation of LVSD. Since the diagnosis of LVDD relies on the integration of several parameters, we primarily focused on the six parameters currently recommended for diagnosis and grading: left atrial volume, tricuspid regurgitant jet velocity, E wave velocity, E/A ratio, and two tissue Doppler imaging (TDI) variables (e′ and E/e′). Other echocardiographic parameters, including those evaluating the right ventricular (RV) function, were considered as secondary outcomes of our meta-analysis. Analyses were conducted dividing in subgroups according to the type of SBT (T-Tube or PSV). Regarding the TDI variables, further subgroup analyses were conducted dividing studies according to the regional criteria of TDI sampling (average, lateral, or septal).

Four types of sensitivity analyses were preventively planned: the first conducted including studies with criteria for reintubation extended to a longer timeframe (i.e. 1 week); the second including studies with non-prospective design; a third analysis excluding studies with a high risk of bias; a fourth performed with ‘leave-one-out at a time’ approach.

Study selection and data extraction

Three investigators (FS, DDF, CS) independently screened titles and abstracts produced by the automated search and identified potentially relevant articles. Full text articles that were identified as relevant were then assessed against the eligibility criteria. Relevant titles were also identified by hand-searching reviews on the topic and exploring the list of the references of the selected papers. Discrepancies were resolved by consensus, involving other authors (AN, MA), or both. All the authors also conducted an independent search on Medline to check for further evidence. Two reviewers (FS, DDF) independently extracted data from individual studies, contacted corresponding authors, and entered information into a pre-designed data collection form, which was cross-checked by other three authors (AN, CS, AM). As shown in Table 2, data extracted from each study included the setting of critically ill patients included, the number of patients examined, the mode of SBT and the criteria for SBT failure, the echocardiography parameters evaluated, and the severity scores.

Quality assessment

Methodological design quality of the included observational studies was performed by four authors (FS, AN, AM, SS) according the Newcastle-Ottawa scale (NOS).[19] Briefly, the NOS appraises methodological quality in three domains: selection, comparability, and outcome. Studies score points for each subset domains with a maximum of nine points possible for assessing the quality of non-randomized studies in meta-analyses, and in particular they are classified as high-risk (one to three points), intermediate-risk (four to five points), or low-risk of bias (six to nine points).

Statistical analysis

Mean values and standard deviation of the variables of interest were collected for the outcome analysis. If data were reported only as median and inter-quartile range or confidence interval (CI), we followed the Cochrane's recommendation to approximate the values of mean and standard deviation.[20]

Continuous outcome differences were analysed using an inverse variance model with a 95% CI. Values are reported as standard mean difference (SMD), P-values were two-tailed and considered significant if <0.05. The presence of statistical heterogeneity was assessed using the χ^2 (Cochran Q) test. Heterogeneity was likely if Q>degrees of freedom suggested and confirmed if $P \leq 0.10$. Quantification of heterogeneity was performed using the I^2 statistic. Values of 0–24.9%, 25–49.9%, 50–74.9%, and >75% were considered as none, low, moderate, and high heterogeneity respectively.[21] If heterogeneity was quantified as low or above, a more conservative random model was used. Publication bias was investigated inspecting the funnel plot. Meta-analysis was performed using review manager (Revman, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The flow of references was managed with the Endnote X7 citation manager.

Results

The two independent literature searches produced 995 titles on Medline and 1843 on EMBASE. The PRISMA flowchart of the systematic search and qualitative synthesis and the PRISMA checklist are reported as Supplementary material. After screening of titles and abstracts from Medline, 911 articles were excluded because they were not relevant, and a further 74 were subsequently excluded for various reasons (18 paediatric studies, 18 reviews, and 38 case reports/series or letter to editor/editorials), leaving only 10 findings for inclusion,[22–30] but one was excluded because the baseline echocardiography data were collected with very high PSV (15–20 cm H_2O).[31] The search on EMBASE produced a further four studies not identified on MEDLINE.[32–35] Two extra findings were retrieved by the independent manual search.[36,37]

Therefore, we identified 15 studies as potentially eligible in our study, but four were not included in the primary analysis. One study did not explicitly report echocardiographic findings according to weaning failure or success. We contacted the corresponding authors but we were not successful in retrieving data of interest, and therefore the study was fully excluded.[25] Three other studies were included only in sensitivity analysis, the first one because it was published in Chinese language (only abstract available)[37] while the other two since reported reintubation at 1 week (longer timeframe).[29,33] The remaining 11 studies were included for the primary analysis. All the studies included were performed with transthoracic echocardiography and none with transoesophageal echocardiography.

Table 2 shows characteristics of the studies. Among the primary echocardiographic parameters of interest, LVEF and E/e′ ratio were the most commonly reported (n=10 for both), followed by E/A ratio (n=9), E wave (n=8), and TDI e′ wave (n=7). Only one reported measure of left atrial size,[34] while none reported tricuspid regurgitant jet velocity.

The methodological quality of the included studies performed with the NOS showed that four studies had the maximum score (nine points), six scored eight points,[22,23,30,32,35,36] and one scored seven points[34]; thus, all studies were judged at low risk of bias. Also, the two studies using a longer timeframe for reintubation and used for sensitivity analysis had a low risk of bias.[29,33]

Outcome analyses

We found enough data to conduct meaningful analysis for the following echocardiography parameters of primary interest: LVEF, and four parameters used for the diagnosis, grading, or both of LV diastolic function (E/A ratio, E wave, E/e′ ratio, and e′ wave). Secondary analysis was performed on two other parameters (deceleration time—DT, and RV/LV end-diastolic area ratio). We found not enough data on the RV function in the setting of weaning from MV to conduct meaningful analysis.

Parameters describing LV systolic function

Among the included studies, we found LVEF data on 597 patients from 10 studies,[22–24,26–28,30,34–36] with an overall weaning failure of 33.5% (n=200). Weaning failure was not significantly associated with LVEF: SMD −0.86, 95% CI −1.92–0.20; P=0.11 (Fig. 1), with high heterogeneity (I^2=96%, P<0.0001). There were no subgroup differences according to the type of SBT, with no heterogeneity.

Parameters that are surrogates for the evaluation of LV diastolic function

Data on E/e′ ratio were reported from 658 patients included in 10 studies,[22–24,26–28,32,34–36] with an overall weaning failure of 27.2% (n=179). Weaning failure was significantly associated with higher E/e′ ratio: SMD 1.70, 95% CI 0.78–2.62; P=0.0003, Figure 2, with high heterogeneity (I^2=94%, P<0.0001). There were no subgroup differences according to the type of SBT, with no heterogeneity (Fig. 2a). The subgroup analysis performed according to the regional criteria of TDI sampling showed significant differences between subgroups (P=0.04), with moderate heterogeneity (I^2=68.6%). The overall result was driven by studies reporting E/e′ using average TDI values (Fig. 2b).

Data on TDI e′ wave were available from 437 patients included in seven studies,[24,27,28,32,34–36] with an overall weaning failure of 26.8% (n=117). Weaning failure was significantly associated with lower e′ wave values: SMD −1.22, 95% CI −2.33 to −0.11; P=0.03, Figure 3, with high heterogeneity (I^2=94%, P<0.0001). There were no subgroup differences according to the type of SBT, with no heterogeneity (Fig. 3a). The subgroup analysis performed according to the regional criteria of TDI sampling showed significant differences between subgroups (P=0.01), with high heterogeneity (I^2=78.2%). As for the E/e′ ratio, the overall result was driven by studies reporting average e′ wave values (Fig. 3b).

The E wave data on 497 patients from eight studies,[24,26–28,32,34–36] with an overall weaning failure rate of 29.4% (n=146). Weaning failure was significantly associated with higher E wave values: SMD 0.97, 95% CI 0.29–1.65; P=0.005, Figure 4a, with high heterogeneity (I^2=89%, P<0.0001).

Study or subgroup	Weaning failure Mean	SD	Total	Weaning success Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
1.1.1 T-tube trial								
Caille et al, 2010	36	7	23	51	2	94	10.0	−4.20 (−4.91 to −3.48)
Kaltsi et al, 2019	30	4	11	38	10	8	9.6	−1.07 (−2.06 to −0.09)
Konomi et al, 2016	52.6	15.6	12	58	9.7	22	10.0	−0.44 (−1.15 to 0.27)
Luo et al, 2017	57	14	29	64	9	31	10.2	−0.59 (−1.11 to −0.07)
Papanikolaou et al, 2011	60.4	1.2	28	58.8	1.3	22	10.1	1.27 (0.65 to 1.88)
Zapata et al, 2011	56.3	12.1	42	57	9	58	10.3	−0.07 (−0.46 to 0.33)
Subtotal (95% CI)			**145**			**235**	**60.4**	**0.84 (−2.15 to 0.48)**
Heterogeneity: Tau^2=2.58; χ^2=141.06, df=5 (P<0.00001); I^2=96%								
Test for overall effect: Z=1.25 (P=0.21)								
1.1.2 Pressure support trial								
Gerbaud et al, 2012	39	1.375	10	40.5	4	34	10.0	−0.41 (−1.12 to 0.30)
Haji et al, 2018	50	2.5	11	65	3	42	9.2	−5.08 (−6.29 to −3.88)
Moschietto et al, 2012	60	3.75	20	55	2.5	48	10.2	1.70 (1.10 to 2.29)
Tongyoo et al, 2019	56.2	15	14	57.7	14.9	38	10.1	−0.10 (−0.71 to 0.51)
Subtotal (95% CI)			**55**			**162**	**39.6**	**−0.91 (−3.01 to 1.19)**
Heterogeneity: Tau^2=4.42; χ^2=100.51, df=3 (P<0.00001); I^2=97%								
Test for overall effect: Z=0.85 (P=0.39)								
Total (95% CI)			**200**			**397**	**100.0**	**−0.86 (−1.92, 0.20)**
Heterogeneity: Tau^2=2.79; χ^2=248.23, df=9 (P<0.00001); I^2=96%								
Test for overall effect: Z=1.58 (P=0.11)								
Test for subgroup differences: χ^2=0.00, df=1 (P=0.95), I^2=0%								

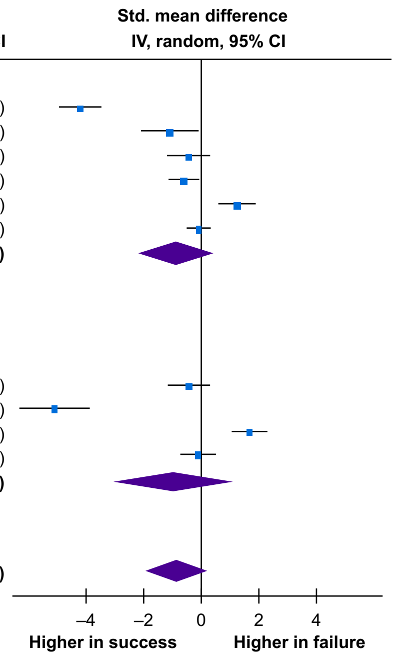


Fig 1. Forest plot comparing values of left ventricular ejection fraction between critically ill patients experiencing weaning failures *vs* success. Studies are analysed in subgroups according to the modality of spontaneous breathing trial. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation, Std., standard.

There were no subgroup differences according to the type of SBT, with no heterogeneity.

Data on E/A ratio were reported by nine studies including 630 patients,[22–24,28,30,32,34–36] with an overall weaning failure of 27.3% (n=172). Weaning failure was not significantly associated with E/A ratio: SMD 0.00, 95% CI −0.30–0.30; P=0.99, with moderate heterogeneity (I^2=59%, P=0.01). There was a trend towards subgroup differences according to the type of SBT (P=0.06), with moderate heterogeneity (I^2=72.5%).

Secondary outcomes

As secondary outcome, we evaluated two other parameters. DT data were available from 602 patients from eight studies,[22,24,27,28,30,32,34,36] with an overall weaning failure of 27.9% (n=168). Weaning failure was significantly associated with lower DT: SMD −0.85, 95% CI −1.60 to −0.10; P=0.03, Figure 4b, with high heterogeneity (I^2=92%, P<0.0001). There were no subgroup differences according to the type of SBT, with no heterogeneity.

The second parameter evaluated as secondary outcome was the RV/LV end-diastolic area ratio. This parameter was reported by three studies with data on 219 patients,[22,28,35] with an overall weaning failure of 29.7% (n=65), and was not significantly different between weaning failure and success (SMD 0.23, 95% CI −0.27–0.74; P=0.37), with moderate heterogeneity (I^2=62%, P<0.007). As there were only three studies, analysis in subgroups was not performed.

The forest plots which are not included as figures in the article and all the funnel plots are available as Supplementary material.

Sensitivity analyses

Two studies used a longer timeframe for reintubation criteria (1 week, rather than 48 h).[29,33] The inclusion of these two studies did not statistically change any result. Also the inclusion of the study by Wang and colleagues[37] (Chinese language, only abstract available in English) did not statistically change any result. All the included studies scored with a low risk of bias according to the NOS (Supplementary material), thus we did not perform sensitivity analyses according to risk of bias.

The majority of the 52 sensitivity analyses conducted with 'leave-one-out at a time' did not change the results. The results of the two ratios (E/e′ and E/A) and of E wave were never affected. The only statistically meaningful changes were:

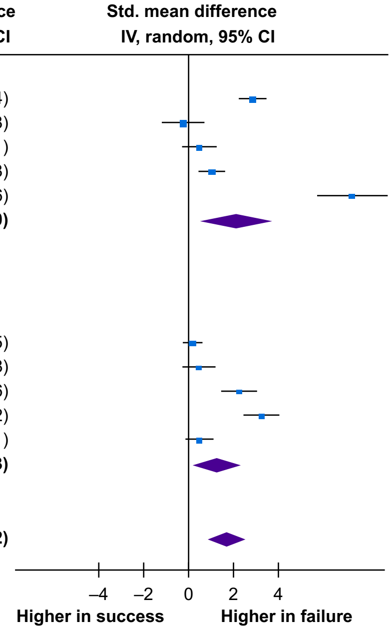
- LVEF, where the exclusion of the study by Moschietto and colleagues[27] changed the result to significant association between lower LVEF and weaning failure (P=0.04)
- TDI e′ wave, where the exclusion of any one of these three studies[27,28,34] changed the result to no significant association between e′ wave values and weaning failure (P values ranging between 0.08 and 0.17)
- DT, where the exclusion of any one of these three studies[22,27,28] changed the result to a P-value ranging between 0.06 and 0.09.

Discussion

The physiological increase in venous return during the shift from positive to negative pressure ventilation determines unfavourable LV loading conditions with possibly higher filling pressures if LV compliance is reduced. Moreover, a steep increase in LV afterload is seen when significant inspiratory

a

Study or subgroup	Weaning failure Mean	SD	Total	Weaning success Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
2.7.1 T-tube trial								
Caille et al, 2010	7	1.05	23	5.6	0.18	94	10.4	2.86 (2.27-3.44)
Kaltsi et al, 2019	10.51	3.18	11	11.2	2.32	8	9.8	−0.23 (−1.15-0.68)
Konomi et al, 2016	11.04	4.71	12	9.29	2.6	22	10.2	0.49 (−0.22-1.21)
Luo et al, 2017	14.7	5.6	29	10.1	2.8	31	10.4	1.04 (0.49-1.58)
Papanikolaou et al, 2011	10.98	0.83	28	6.18	0.28	22	8.2	7.27 (5.69-8.86)
Subtotal (95% CI)			**103**			**177**	**48.9**	**2.16 (0.52-3.80)**
Heterogeneity: Tau^2=3.27; χ^2=95.35, df=4 (P<0.00001); I^2=96%								
Test for overall effect: Z=2.58 (P=0.010)								
2.7.2 Pressure support trial								
Amarja et al, 2019	8.21	2.95	21	7.68	2.79	140	10.5	0.19 (−0.27-0.65)
Gerbaud et al, 2012	10.7	3.45	10	9.5	2.175	34	10.2	0.47 (−0.24-1.18)
Haji et al, 2018	10.9	2.325	11	7.7	1.05	42	10.0	2.26 (1.46-3.06)
Moschietto et al, 2012	13.4	1.975	20	8.9	1.025	48	10.1	3.25 (2.48-4.02)
Tongyoo et al, 2019	19	8.3	14	15.5	6.5	38	10.3	0.49 (−0.13-1.11)
Subtotal (95% CI)			**76**			**302**	**51.1**	**1.31 (0.19-2.43)**
Heterogeneity: Tau^2=1.51; χ^2=59.26, df=4 (P<0.00001); I^2=93%								
Test for overall effect: Z=2.29 (P=0.02)								
Total (95% CI)			**179**			**479**	**100.0**	**1.70 (0.78-2.62)**
Heterogeneity: Tau^2=2.04; χ^2=162.06, df=9 (P<0.00001); I^2=94%								
Test for overall effect: Z=3.62 (P=0.0003)								
Test for subgroup differences: Chi^2=0.70, df=1 (P=0.40), I^2=0%								



b

Study or subgroup	Weaning failure Mean	SD	Total	Weaning success Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
2.1.1 Average								
Gerbaud et al, 2012	10.7	3.45	10	9.5	2.175	34	10.2	0.47 (−0.24-1.18)
Haji et al, 2018	10.9	2.325	11	7.7	1.05	42	10.0	2.26 (1.46-3.06)
Luo et al, 2017	14.7	5.6	29	10.1	2.8	31	10.4	1.04 (0.49-1.58)
Moschietto et al, 2012	13.4	1.975	20	8.9	1.025	48	10.1	3.25 (2.48-4.02)
Papanikolaou et al, 2011	10.98	0.83	28	6.18	0.28	22	8.2	7.27 (5.69-8.86)
Subtotal (95% CI)			**98**			**177**	**48.8**	**2.72 (1.15-4.30)**
Heterogeneity: Tau^2=3.01; χ^2=81.73, df=4 (P<0.00001); I^2=95%								
Test for overall effect: Z=3.38 (P=0.0007)								
2.1.2 Lateral								
Amarja et al, 2019	8.21	2.95	21	7.68	2.79	140	10.5	0.19 (−0.27-0.65)
Caille et al, 2010	7	1.05	23	5.6	0.18	94	10.4	2.86 (2.27-3.44)
Kaltsi et al, 2019	10.51	3.18	11	11.2	2.32	8	9.8	−0.23 (−1.15-0.68)
Tongyoo et al, 2019	19	8.3	14	15.5	6.5	38	10.3	0.49 (−0.13-1.11)
Subtotal (95% CI)			**69**			**280**	**41.0**	**0.84 (−0.53-2.21)**
Heterogeneity: Tau^2=1.83; χ^2=59.21, df=3 (P<0.00001); I^2=95%								
Test for overall effect: Z=1.21 (P=0.23)								
2.1.3 Septal								
Konomi et al, 2016	11.04	4.71	12	9.29	2.6	22	10.2	0.49 (−0.22-1.21)
Subtotal (95% CI)			**12**			**22**	**10.2**	**0.49 (−0.22-1.21)**
Heterogeneity: Not applicable								
Test for overall effect: Z=1.35 (P=0.18)								
Total (95% CI)			**179**			**479**	**100.0**	**1.70 (0.78-2.62)**
Heterogeneity: Tau^2=2.04; χ^2=162.06, df=9 (P<0.00001); I^2=94%								
Test for overall effect: Z=3.62 (P=0.0003)								
Test for subgroup differences: χ^2=6.38, df=2 (P=0.04), I^2=68.6%								

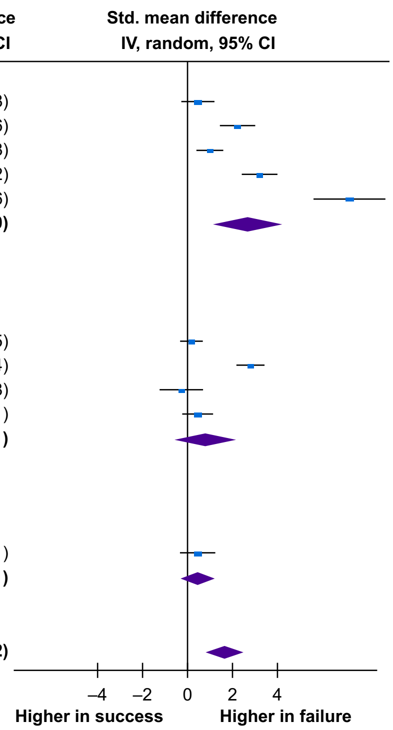


Fig 2. Forest plot comparing values of E/e′ ratio between critically ill patients experiencing weaning failures *vs* success. In the top part of the figure (2a), analysis is performed dividing studies in subgroups according to the modality of spontaneous breathing trial. In the bottom part of the figure (2b), analysis is performed dividing studies in subgroups according to the regional criteria of sampling for the tissue Doppler analysis. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation, Std., standard.

a

Study or subgroup	Weaning failure Mean	SD	Total	Weaning success Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
2.8.1 T-tube trial								
Kaltsi et al, 2019	8	2	11	7	1	8	13.9	0.57 (–0.36 to 1.51)
Konomi et al, 2016	13.8	18.9	12	12.3	15.4	22	14.5	0.09 (–0.62 to 0.79)
Papanikolaou et al, 2011	9.8	0.8	28	14.5	0.9	22	12.9	–5.47 (–6.72 to –4.22)
Subtotal (95% CI)			**51**			**52**	**41.3**	**–1.57 (–4.72 to 1.59)**
Heterogeneity: Tau^2=7.53; χ^2=68.04, df=2 (*P*<0.00001); I^2=97%								
Test for overall effect: Z=0.97 (*P*=0.33)								
2.8.2 Pressure support trial								
Amarja et al, 2019	11.43	3.17	21	11.38	3.24	140	15.0	0.02 (–0.44 to 0.47)
Haji et al, 2018	7	1.5	11	10	1	42	14.1	–2.65 (–3.49 to –1.80)
Moschietto et al, 2012	7	0.5	20	8	0.75	48	14.8	–1.44 (–2.02 to –0.86)
Tongyoo et al, 2019	6.4	3.9	14	6.8	2.8	38	14.7	–0.13 (–0.74 to 0.49)
Subtotal (95% CI)			**66**			**268**	**58.7**	**–1.01 (–2.10 to 0.08)**
Heterogeneity: Tau^2=1.13; χ^2=39.37, df=3 (*P*<0.00001); I^2=92%								
Test for overall effect: Z=1.82 (*P*=0.07)								
Total (95% CI)			**117**			**320**	**100.0**	**–1.22 (–2.33 to –0.11)**
Heterogeneity: Tau^2=2.09; χ^2=107.41, df=6 (*P*<0.00001); I^2=94%								
Test for overall effect: Z=2.15 (*P*=0.03)								
Test for subgroup differences: χ^2=0.11, df=1 (*P*=0.75), I^2=0%								

b

Study or subgroup	Weaning failure Mean	SD	Total	Weaning success Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
2.2.1 Average								
Haji et al, 2018	7	1.5	11	10	1	42	14.1	–2.65 (–3.49 to –1.80)
Moschietto et al, 2012	7	0.5	20	8	0.75	48	14.8	–1.44 (–2.02 to –0.86)
Papanikolaou et al, 2011	9.8	0.8	28	14.5	0.9	22	12.9	–5.47 (–6.72 to –4.22)
Subtotal (95% CI)			**59**			**112**	**41.8**	**–3.12 (–5.15 to –1.09)**
Heterogeneity: Tau^2=2.99; χ^2=33.97, df=2 (*P*<0.00001); I^2=94%								
Test for overall effect: Z=3.01 (*P*=0.003)								
2.2.2 Lateral								
Amarja et al, 2019	11.43	3.17	21	11.38	3.24	140	15.0	0.02 (–0.44 to 0.47)
Kaltsi et al, 2019	8	2	11	7	1	8	13.9	0.57 (–0.36 to 1.51)
Tongyoo et al, 2019	6.4	3.9	14	6.8	2.8	38	14.7	–0.13 (–0.74 to 0.49)
Subtotal (95% CI)			**46**			**186**	**43.6**	**0.05 (–0.30 to 0.39)**
Heterogeneity: Tau^2=0.00; χ^2=1.55, df=2 (*P*=0.46); I^2=0%								
Test for overall effect: Z=0.27 (*P*=0.79)								
2.2.3 Septal								
Konomi et al, 2016	13.8	18.9	12	12.3	15.4	22	14.5	0.09 (–0.62 to 0.79)
Subtotal (95% CI)			**12**			**22**	**14.5**	**0.09 (–0.62 to 0.79)**
Heterogeneity: Not applicable								
Test for overall effect: Z=0.24 (*P*=0.81)								
Total (95% CI)			**117**			**320**	**100.0**	**–1.22 (–2.33 to –0.11)**
Heterogeneity: Tau^2=2.09; χ^2=107.41, df=6 (*P*<0.00001); I^2=94%								
Test for overall effect: Z=2.15 (*P*=0.03)								
Test for subgroup differences: χ^2=9.19, df=2 (*P*=0.01), I^2=78.2%								

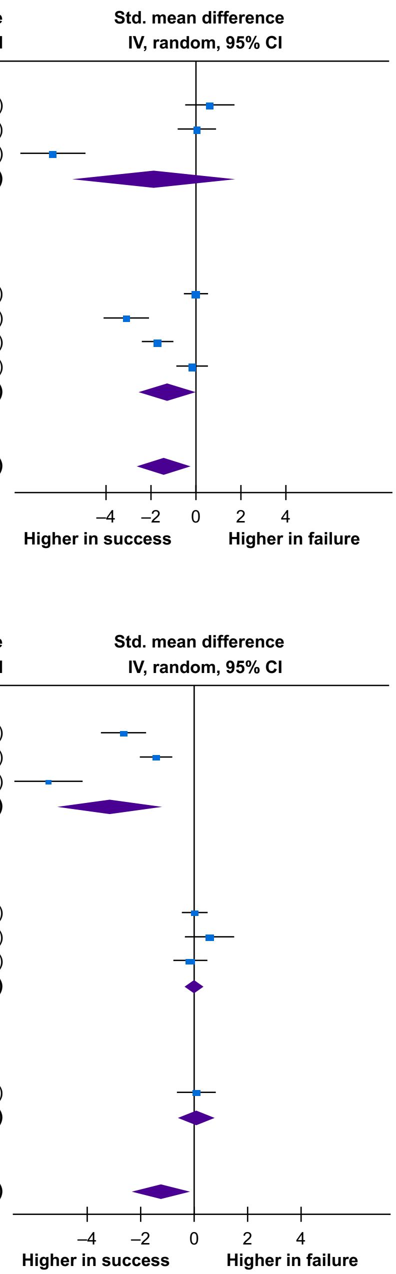


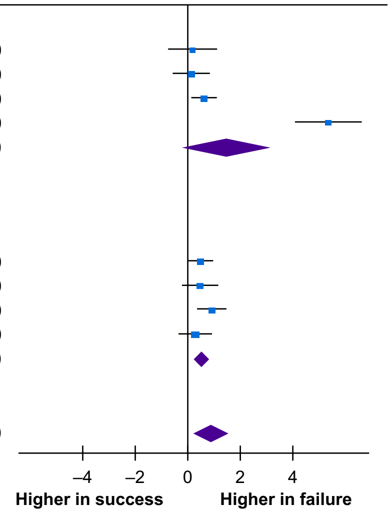
Fig 3. Forest plot comparing values of e′ wave between critically ill patients experiencing weaning failures *vs* success. In the top part of the figure (3a), analysis is performed dividing studies in subgroups according to the modality of spontaneous breathing trial. In the bottom part of the figure (3b), analysis is performed dividing studies in subgroups according to the regional criteria of sampling for the tissue Doppler analysis. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation, Std., standard.

efforts (clinically relevant dyspnoea) generate a large drop in pleural pressure.[38] The increased venous return may result in RV dilatation, particularly when baseline RV function is already impaired. All these haemodynamic changes—together with greater sympathetic stimulation after weaning—increase the overall cardiac workload and could be poorly tolerated.

The main findings of our meta-analysis are that parameters suggesting LV diastolic function and elevated LV filling pressures are associated with higher weaning failure rates, while the role of LV systolic function (as evaluated by LVEF) is less clear. In our study, the strongest association for weaning failure was found for higher values of E/e′ ratio. This is not surprising since E/e′ ratio is not just one of the four parameters indicated by the newest guidelines for the diagnosis of LV diastolic dysfunction,[18] but also a surrogate marker of increased LV end-diastolic pressure (filling pressure). During

a

Study or subgroup	Weaning failure Mean	SD	Total	Weaning success Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
2.3.1 T-tube trial								
Kaltsi et al, 2019	86	34	11	80	15	8	11.5	0.21 (–0.71-1.12)
Konomi et al, 2016	81	26	12	77	22	22	12.6	0.17 (–0.54-0.87)
Luo et al, 2017	92.9	25.6	29	78.2	18.4	31	13.4	0.65 (0.13-1.18)
Papanikolaou et al, 2011	90.6	3.6	28	74	2	22	9.8	5.43 (4.19-6.68)
Subtotal (95% CI)			**80**			**83**	**47.3**	**1.54 (–0.19-3.27)**
Heterogeneity: Tau^2=2.90; χ^2=58.37, df=3 (*P*<0.00001); I^2=95%								
Test for overall effect: Z=1.75 (*P*=0.08)								
2.3.2 Pressure support trial								
Amarja et al, 2019	92.5	24.9	21	81.9	19.3	140	13.6	0.53 (0.06-0.99)
Haji et al, 2018	87	9	11	83	7.75	42	12.7	0.49 (–0.18-1.16)
Moschietto et al, 2012	80	10.25	20	72	7.25	48	13.3	0.96 (0.41-1.51)
Tongyoo et al, 2019	96.5	30.8	14	87.3	27.5	38	13.0	0.32 (–0.30-0.94)
Subtotal (95% CI)			**66**			**268**	**52.7**	**0.59 (0.31-0.87)**
Heterogeneity: Tau^2=0.00; χ^2=2.67, df=3 (*P*=0.45); I^2=0%								
Test for overall effect: Z=4.15 (*P*<0.0001)								
Total (95% CI)			**146**			**351**	**100.0**	**0.97 (0.29-1.65)**
Heterogeneity: Tau^2=0.84; χ^2=62.40, df=7 (*P*<0.00001); I^2=89%								
Test for overall effect: Z=2.78 (*P*=0.005)								
Test for subgroup differences: χ^2=1.13, df=1 (*P*=0.29), I^2=11.8%								



b

Study or subgroup	Weaning failure Mean	SD	Total	Weaning success Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
2.5.1 T-tube trial								
Caille et al, 2010	138	24.2	23	170	6.5	94	12.7	–2.63 (–3.20 to –2.06)
Kaltsi et al, 2019	234	66	11	214	60	8	11.4	0.30 (–0.62 to 1.22)
Konomi et al, 2016	173.8	76.5	12	192.5	63.4	22	12.2	–0.27 (–0.97 to 0.44)
Papanikolaou et al, 2011	194	9	28	205	5	22	12.5	–1.44 (–2.07 to –0.81)
Zapata et al, 2011	193	49	42	202	52	58	13.2	–0.18 (–0.57 to 0.22)
Subtotal (95% CI)			**116**			**204**	**62.1**	**–0.86 (–1.91 to 0.19)**
Heterogeneity: Tau^2=1.33; χ^2=60.41, df=4 (*P*<0.00001); I^2=93%								
Test for overall effect: Z=1.60 (*P*=0.11)								
2.5.2 Pressure support trial								
Amarja et al, 2019	116.5	36	21	119.2	38.2	140	13.1	–0.07 (–0.53 to 0.39)
Haji et al, 2018	175	33.5	11	180	15.5	42	12.4	–0.24 (–0.91 to 0.42)
Moschietto et al, 2012	170	15.7	20	215	21.7	48	12.5	–2.21 (–2.85 to –1.56)
Subtotal (95% CI)			**52**			**230**	**37.9**	**–0.83 (–2.14 to 0.48)**
Heterogeneity: Tau^2=1.24; χ^2=29.84, df=2 (*P*<0.00001); I^2=93%								
Test for overall effect: Z=1.25 (*P*=0.21)								
Total (95% CI)			**168**			**434**	**100.0**	**–0.85 (–1.60 to –0.10)**
Heterogeneity: Tau^2=1.06; χ^2=91.19, df=7 (*P*<0.00001); I^2=92%								
Test for overall effect: Z=2.23 (*P*=0.03)								
Test for subgroup differences: χ^2=0.00, df=1 (*P*=0.97), I^2=0%								

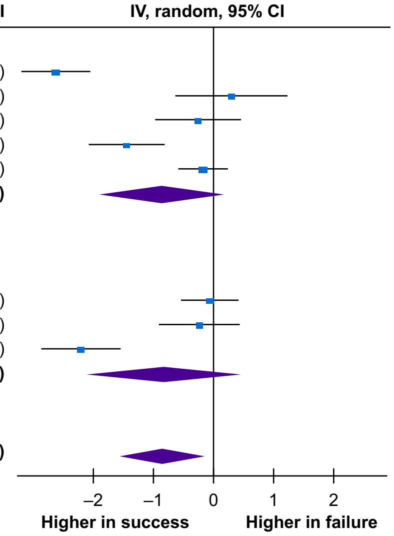


Fig 4. Forest plot comparing values of E wave (4a) and deceleration time (4b) between critically ill patients experiencing weaning failures *vs* success. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation, Std., standard.

the weaning trial, the increased pool of blood returning to the LV may not be accommodated by if the compliance of LV is poor.

The second stronger association with weaning failure was found with lower e′ wave values, another TDI parameter recommended for the diagnosis of LVDD,[18] again suggesting that diastolic function has a pivotal role during weaning from MV. However, some caution is needed as we found a lower number of studies regarding the e′ wave and, more importantly, that three out of the 10 sensitivity analyses conducted on this parameter changed the result to not statistically significant. As subgroup analysis, we noted a stronger association between weaning failure and average values of E/e′ or e′, but this result is difficult to interpret, also because only one study reported septal TDI values. The other two recommended parameters for the echocardiographic diagnosis of LVDD according to the recent guidelines[18] are left atrial size and velocity of the tricuspid regurgitation jet. However, we did not find enough data to analyse these parameters in the context of weaning from MV. This result was somehow expected, as they have been recommended only recently and were not considered by previous guidelines.[39] More importantly, these parameters are difficult to interpret in critically ill patients.[40]

According to these newest guidelines on LVDD,[18] E wave velocity and E/A ratio are useful in the grading of dysfunction, but not for its diagnosis.[18] We found an association between higher E wave values and weaning failure, reinforcing the above-mentioned link. On the contrary, E/A ratio (used widely in the past guidelines[39]) was not associated with weaning failure, but this is easily explained by at least two reasons. First, the E/A ratio should not be interpreted as a continuous variable and its main utility is the pattern recognition with a semi-quantitative approach. However, we had no data to perform the analysis in such a way. Second, this parameter suffers from the 'pseudo-normalisation' issue (increased left atrial pressures in patients with LVDD of second degree produces an E/A ratio with similar values to patients with normal LV diastolic function). Therefore, it is not surprising that E/A ratio was not associated with weaning failure.

We also found a significant association between weaning failure with lower DT values. As for the E/A ratio, this parameter was recommended by past guidelines,[39] and it decreases progressively while LVDD progresses. Therefore, this result further supports the link between LVDD and weaning failure.

From a clinical standpoint, our results suggest paying particular attention to the weaning in patients with LVDD. Importantly, the causative effect of LVDD on weaning failure cannot be fully established by our meta-analysis, as it is possible that such association is the result of a higher incidence of comorbidities (i.e. hypertension) in the group with LVDD. However, it seems reasonable that clinicians remain careful during the process of weaning from MV in critically ill patients with advanced LVDD. The management of these patients is not simple as it relies mainly on reduction of afterload, prevention of arrhythmias and tachycardia, cautious fluid administration, and avoidance of positive fluid balance whenever possible. For instance, pharmacological control of HR may be a reasonable therapeutic option in a selected population of patients, especially those with advanced LVDD as the main cause of weaning failure. Kaltsi and colleagues[36] described infusion of levosimendan in 11 patients with severely decreased LVEF and failing the first SBT; the authors described a success rate of weaning in 82% of patients (n=9) after levosimendan. Interestingly, in this study levosimendan significantly increased LVEF by almost 5%, but also significantly ameliorated the e′ wave (increased by 2 cm s^{-1}) and E/e′ ratio (lowered by almost three points), suggesting good effects on both LVSD and LVDD.

The absence of association between LVEF and weaning failure in our meta-analysis warrants caution in its interpretation, since the P-value showed a trend toward significant association (P=0.11) and one of the sensitivity analyses changed the result to a significant association. It is possible that increased LV afterload after the shift from positive to negative pressure ventilation plays a role in weaning failure, mainly in patients with decreased LVEF. However, all results on LVEF in critically ill patients should be interpreted cautiously since the parameter is highly dependent on loading conditions. Other parameters focusing on LV systolic function such as s′ wave or strain with speckle tracking echocardiography may deserve investigation in the context of weaning from MV.

Gaps of knowledge

Our systematic review also has the value of identifying gaps in knowledge that may boost further research in the field of echocardiography during weaning from MV. Apart from LVEF, no other parameters describing an association between LVSD and weaning from MV were reported clearly enough to produce pooled evidence by our study. In particular the TDI s′ wave was described in one study only,[28] LV end-diastolic volume and end-systolic volume by another study,[23] whereas the use of strain echocardiography is not yet reported. Also, the RV function does not seem to be well explored, since one study only evaluated RV fractional area change,[28] and another evaluated tricuspid annular plane systolic excursion.[32]

Limitations

Our meta-analysis has the main limitation of exploring an association between single echocardiographic variables and weaning failure in critically ill patients. As such, we were not able to adjust for confounders by regression/multivariate analyses since this is unfeasible without accurate access to individual patient data from all studies. This limitation is common to all other meta-analyses conducted in critically care echocardiography,[41–44] also because of the significant heterogeneity in reporting of echocardiography studies.[45]

We included patients performing SBT with either T-tube or PSV. Although some authors suggested that T-tube could be a more stressful test during weaning and a stronger trigger for the cardiorespiratory system as compared with PSV,[46] a recent meta-analysis showed that both approaches have comparable predictive power regarding extubation, rate of reintubation, ICU and hospital length of stay, and ICU and hospital mortality in critically ill patients.[47] In this regard, all our subgroup analyses conducted according to the type of SBT found no differences between T-tube and PSV trial, pointing at their similar impact on cardiac function.

Another consideration is that we included critically ill patients with different pathologies and patients with significant clinical heterogeneity (i.e. may include data on patients with heart failure and those with normal premorbid cardiac function). The clinical heterogeneity is reinforced by the observation of a relatively wide range of some of the echocardiography parameters reported in the included studies. Moreover, from a clinical standpoint, it should be noted that another confounding effect is probably generated by the 'noncardiac' causes of weaning failure (i.e. respiratory, diaphragmatic, or both), even if these are less common than cardiac origin of weaning failure.[7] Finally, we found very high statistical heterogeneity with almost all of our findings, and for a few parameters some of the sensitivity analyses changed the results of the primary analysis.

Conclusions

In conclusion, weaning failure from MV is significantly associated with parameters indicating worse LV diastolic function and increased LV filling pressure. The association with worse LV systolic function, as evaluated by ejection fraction, is more unclear. Our systematic search highlighted significant gaps in the literature regarding the association between weaning failure and other echocardiographic parameters of LV systolic function and of RV function. These gaps could be considered when designing future critical care echocardiography research.

Authors' contribution

Conception and design: FS, AN, EB, SS, AVB, MA
Screening of automated search: FS, DDF, CS
Independent manual search: all authors
Acquisition of data, data cross-check, or both: FS, DDF, AN, CS, AM
Analysis: FS, DDF, AN, EB
Risk of bias assessment: FS, AN, AM, SS
Interpretation of data: FS, AN, CS, AM, EB, SS, AVB, MA
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Critically revising the draft for important intellectual content: AM, EB, SS, AVB, MA
Final approval of the version to be published: all authors.

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.07.059.

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