CHEST

Pressure-Controlled vs Volume-Controlled Ventilation in Acute Respiratory Failure

A Physiology-Based Narrative and Systematic Review

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BACKGROUND: Mechanical ventilation is a cornerstone in the management of acute respiratory failure. Both volume-targeted and pressure-targeted ventilations are used, the latter modes being increasingly used. We provide a narrative review of the physiologic principles of these two types of breath delivery, performed a literature search, and analyzed published comparisons between modes.

METHODS: We performed a systematic review and meta-analysis to determine whether pressure control-continuous mandatory ventilation (PC-CMV) or pressure control-inverse ratio ventilation (PC-IRV) has demonstrated advantages over volume control-continuous mandatory ventilation (VC-CMV). The Cochrane tool for risk of bias was used for methodologic quality. We also introduced physiologic criteria as quality indicators for selecting the studies. Outcomes included compliance, gas exchange, hemodynamics, work of breathing, and clinical outcomes. Analyses were completed with RevMan5 using random effects models.

RESULTS: Thirty-four studies met inclusion criteria, many being at high risk of bias. Comparisons of PC-CMV/PC-IRV and VC-CMV did not show any difference for compliance or gas exchange, even when looking at PC-IRV. Calculating the oxygenation index suggested a poorer effect for PC-IRV. There was no difference between modes in terms of hemodynamics, work of breathing, or clinical outcomes.

CONCLUSIONS: The two modes have different working principles but clinical available data do not suggest any difference in the outcomes. We included all identified trials, enhancing generalizability, and attempted to include only sufficient quality physiologic studies. However, included trials were small and varied considerably in quality. These data should help to open the choice of ventilation of patients with acute respiratory failure. CHEST 2015; 148(2):340-355

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ABBREVIATIONS: APRV = airway pressure release ventilation; ARF = acute respiratory failure; CMV = continuous mandatory ventilation; Crs = respiratory system compliance; IMV = intermittent mandatory ventilation; I:E = inspiratory to expiratory; PC = pressure control; PEEP = positive end-expiratory pressure; PEEPi = intrinsic positive end-expiratory pressure; P:F = Pao_2 to FIO_2; PIP = peak inspiratory pressure; PL = transpulmonary pressure; Pplat = plateau pressure; PSV = pressure support ventilation; T_E = expiratory time; T_I = inspiratory time; VC = volume control; V_T = tidal volume

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Acute respiratory failure (ARF) is common in critically ill patients admitted to ICUs and often culminates in mechanical ventilation as respiratory support. Mechanical ventilation is the cornerstone of management, with invasive positive pressure ventilation remaining the most common method of gas delivery. A ventilator breath can be achieved in two ways: flow/volume targeting (volume control [VC]) or pressure targeting (or pressure control [PC]) with either time or flow cycling.[1] Then the ventilator delivers three basic breath sequences including continuous mandatory ventilation (CMV), intermittent mandatory ventilation (IMV), and continuous spontaneous ventilation.[2] In the past decade, VC-CMV remained the most common mode of ventilation during the first few days of mechanical ventilation. Large international observational studies demonstrated that VC-CMV was used in approximately 60% of critically ill patients,[3] but that its use has decreased over time to 40%.[4,5] Data from the most recent international prospective cohort study demonstrated that PC breath (using different modes) use has increased from 7% to 20% in 2010 as the initial mode (PC-CMV), and that after 48 h of mechanical ventilation, pressure-targeted modes (PC-CMV, PC-IMV, and pressure support ventilation [PSV]) are now preferentially used.[5]

PC-CMV is one of several types of pressure-targeted modes of ventilation, which include PC-IMV, airway pressure release ventilation (APRV), biphasic positive airway pressure, PSV, and pressure-regulated VC ventilation.[2] Unfortunately, the nomenclature of pressure-targeted modes is often specific to each ventilator brand (e-Table 1). In addition, the basic principles regarding the breath types and modes are not always well understood and erroneous claims about potential advantages for each mode are still frequently made, such as emphasizing the differences in peak airway pressure.

Our study reviews the physiologic principles surrounding PC and VC breaths. Subsequently, we present a literature search in the form of a systematic review and meta-analysis comparing the physiologic effects and the clinical outcomes of PC-CMV, PC-inverse ratio ventilation (IRV), and VC-CMV in patients with ARF.

Working Principles and Physiology of PC and VC Breaths

Working Principles

A PC breath is patient-triggered or time-triggered, pressure-limited and usually time-cycled or flow-cycled. In PC-CMV, set ventilatory variables include inspiratory pressure, inspiratory time (T_I) or fraction (inspiratory to expiratory [I:E] ratio), pressure rise time, and respiratory rate; set variables that affect mainly oxygenation include positive end-expiratory pressure (PEEP) and F_{IO_2}.[6] The volume and flow in PC-CMV are dependent variables[7] and vary with both respiratory mechanics and patient effort. During the inspiratory phase, flow is rapidly provided by the ventilator until reaching a value close to the preset pressure, at which point the ventilator tries to maintain this pressure constant and flow gradually decreases according to the preset pressure level and the mechanical properties of the respiratory system until the end of inspiration.[8] The pressure waveform during inspiration is virtually constant (square) and the flow waveform is one of decelerating flow.[9] When and only when T_I is long enough for flow to reach zero, the preset pressure is in equilibrium with the peak alveolar pressure at the end of the breath and equals the so-called plateau pressure (Pplat). With PC-CMV, the peak inspiratory pressure (PIP) is guaranteed by the ventilator and will not exceed the preset pressure limit. If the inspiratory flow does not reach zero, the preset pressure is not equal to Pplat and this also affects delivered tidal volume (V_T) (Fig 1). This has been claimed as a possible mechanism for minimizing the risk of alveolar overdistention and barotrauma.[10,11] This, however, does not hold true as soon as the patient exerts some spontaneous activity (vide infra). The cycling from inspiration to expiration is determined by time. During expiration, the pressure is abruptly released and the lung is emptied by the passive recoil forces until the airway pressure is equal to the preset PEEP. If the expiratory time (T_E) is long enough to reach a zero flow, the alveolar pressure will have the same PEEP value.

In VC-CMV, the breath can be patient-triggered or time-triggered by the ventilator. The ventilator then delivers the preset V_T by using the same flow-time waveform in every breath.[12] The airway pressure is a dependent variable and is influenced by respiratory mechanics and patient's effort.[13] Inspiratory flow pattern in VC-CMV is most frequently a square flow; other flow patterns can be used, including ramp (accelerating or decelerating) or sinusoidal in some ventilators.[14] Other set variables include respiratory rate, and either T_I or I:E ratio or the peak flow rate (volume and flow gives insufflation time), PEEP, and F_{IO_2}. VC-CMV is cycled by time or volume. PIP in VC-CMV is the sum of the elastic and resistive pressures plus the initial pressure in the system during flow delivery. When the airway is

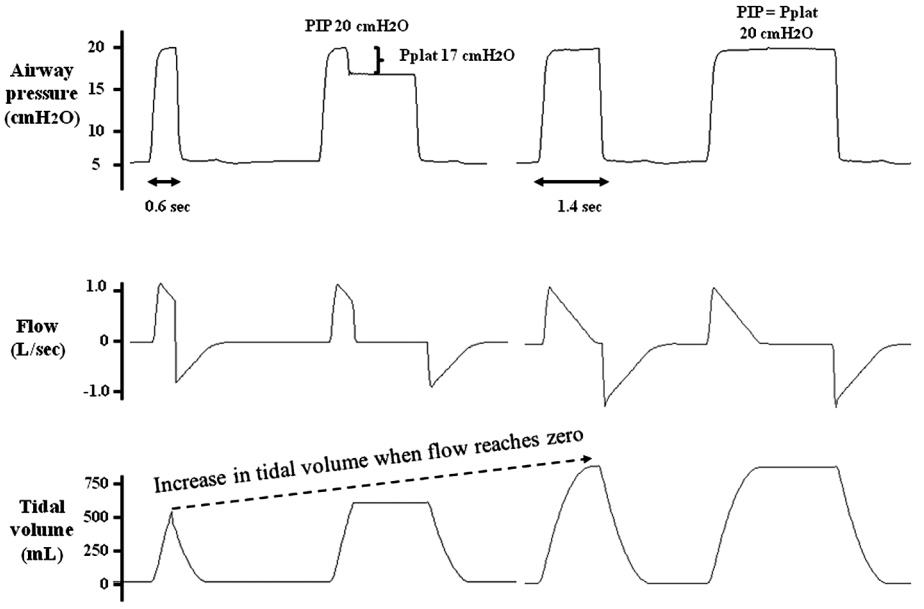

Figure 1 – *The impact of inspiratory time on Pplat during pressure-controlled breath. PIP is only equal to Pplat when inspiratory flow reaches zero because of the equilibrium with alveolar pressure. In addition, tidal volume increases in this condition. PIP = peak inspiratory pressure; Pplat = plateau pressure.*

occluded at the end of inspiration and flow ceases, the airway pressure falls until it reaches Pplat, which reflect the elastic recoil pressure of the respiratory system.[15]

Passive Condition

Under passive conditions, the ventilator entirely substitutes the respiratory muscles for gas delivery. V_T delivered under passive condition in VC-CMV is preset and theoretically constant,[16] whereas V_T in PC-CMV depends on three main factors: the driving pressure, the time constant of the respiratory system (ie, the product of compliance and resistance of the respiratory system), and T_I.

The driving pressure in PC breaths is the pressure difference between the PIP and total PEEP, which is the pressure in the alveoli at the very end of expiration, immediately before the insufflation starts.[17] In PC-CMV, the delivered V_T is proportional to the driving pressure.

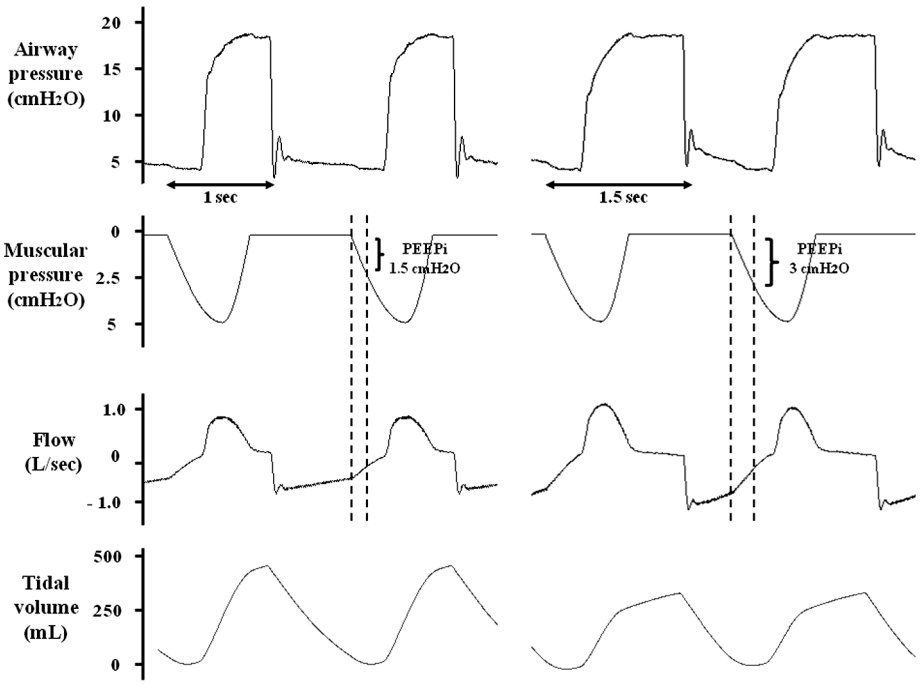

Figure 2 – *Pressure control-continuous mandatory ventilation mode with different inspiratory time (T_I) and expiratory time (T_E). PEEPi increases when T_I increases with inadequate T_E. This phenomenon leads to decreases in driving pressure and delivered tidal volume. PEEPi is measured by the pressure difference between the beginning of muscular pressure and the onset of inspiratory flow (pressure difference between two dotted lines). PEEPi = intrinsic positive end-expiratory pressure.*

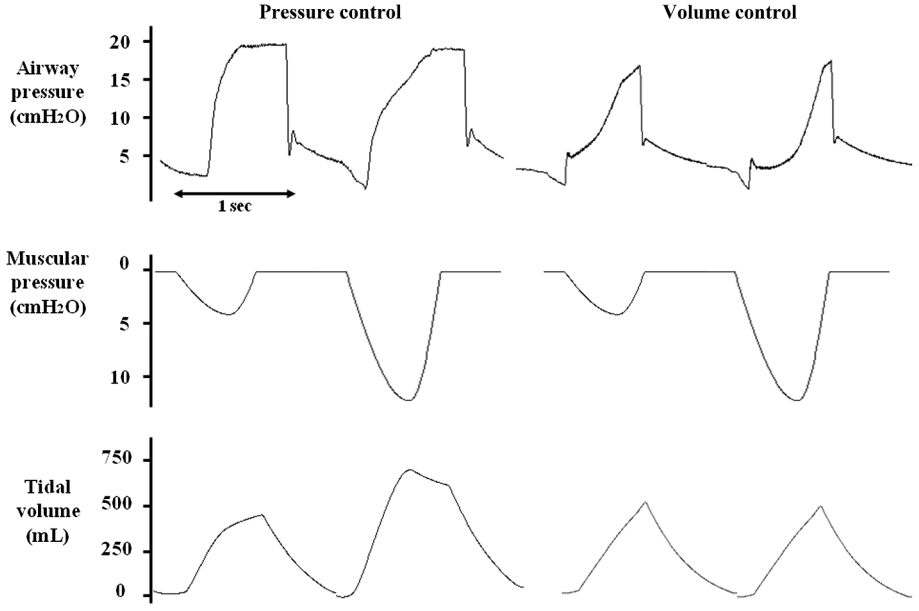

Figure 3 – *Comparison between two levels of muscular pressure in pressure control (PC) breath with the same airway pressure and volume control (VC) breath. Increasing muscular pressure leads to increase delivered tidal volume in PC breath whereas the tidal volume is constant in VC breath.*

Intrinsic PEEP (PEEPi) is a condition during which end-expiratory lung volume remains above functional residual capacity as a result of dynamic hyperinflation.[18] The usual mechanisms for developing PEEPi are increased expiratory resistance causing expiratory flow limitation, and high respiratory rate with inadequate T_E.[19] In PC-CMV, inadequate T_E results in incomplete lung emptying and concomitant PEEPi (Fig 2). To prevent incomplete lung emptying, and in the absence of flow limitation, T_E should theoretically be longer than three time constants.[20-22] PEEPi decreases the driving pressure and, thus, affects the delivered V_T. When PEEPi increases, both the true driving pressure and the delivered V_T decrease. This, for instance, can occur with increasing respiratory rate at constant T_I, or with increasing expiratory resistance or compliance of the respiratory system at constant T_E.[23,24] This can explain the paradoxical effect of increasing the respiratory rate resulting in reduced delivered ventilation. The same physiologic abnormality (PEEPi) will generate a progressive increase in Pplat during VC-CMV without affecting V_T.

Furthermore, changes in compliance and resistance will affect the delivered V_T in PC-CMV in most situations. The equation of motion of the respiratory system dictates that the driving pressure applied to the respiratory system consists of the pressure needed to overcome the elastance and the pressure dissipated against the resistance.[25] The elastance of the respiratory system (inverse of compliance) reflects the "stiffness" of the respiratory system and is influenced by the amount of aerated lung volume. For an identical V_T, the lower the lung volume, the higher the elastance of the respiratory system. The clinician must be aware of this influence and monitor V_T on the ventilator when using PC-CMV, especially in patients with restrictive diseases (eg, ARDS, chest wall stiffness, increased intraabdominal pressure) because V_T may decrease as their disease worsens.[23,26] The effect

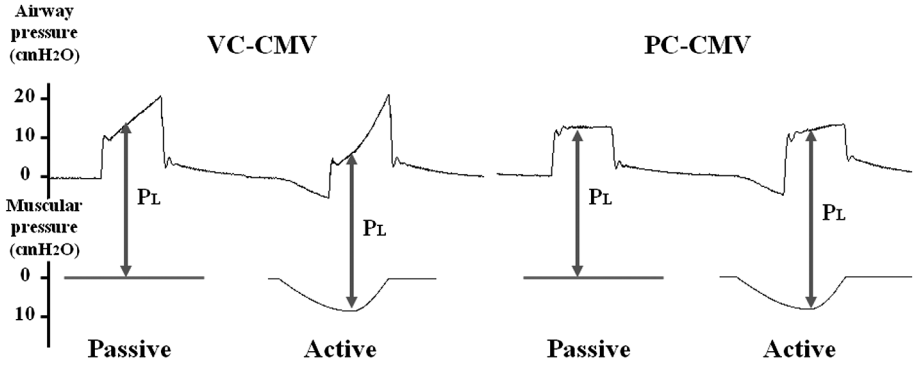

Figure 4 – *Responses to change from passive to active breathing. In VC-CMV, airway pressure drops when muscular pressure increases and P_L is maintained. With PC-CMV, changing from passive to active breathing leads to increase in P_L when airway pressure is constant. PC-CMV = pressure control-continuous mandatory ventilation; P_L = transpulmonary pressure; VC-CMV = volume control-continuous mandatory ventilation.*

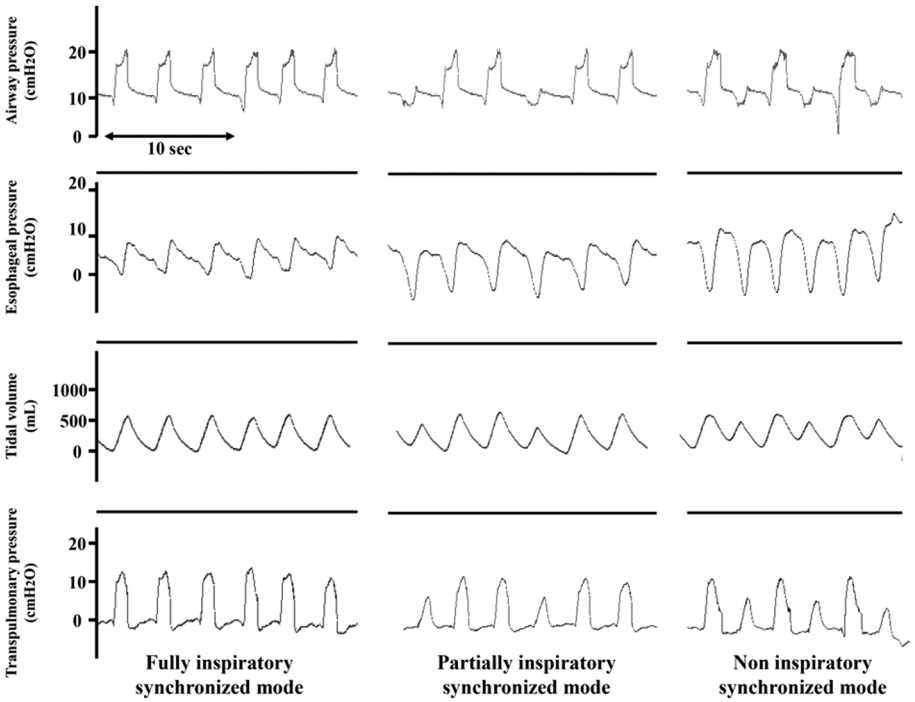

Figure 5 – *Comparison of three different pressure-targeted modes according to inspiratory synchronization (i-sync). Tracings of airway pressure, esophageal pressure, tidal volume, and transpulmonary pressure demonstrated that during fully i-sync mode (PC-CMV), all patient efforts triggered the ventilator. In partially i-sync mode (pressure control-intermittent mandatory ventilation [PC-IMV]) and non i-sync mode (airway pressure release ventilation [APRV]), two types of breaths (synchronized spontaneous and mandatory breath and spontaneous breath at positive end-expiratory pressure [PEEP] or low pressure) are observed. PC-CMV has more constant tidal volume and higher transpulmonary pressure than PC-IMV and APRV despite identical ventilator settings (inspiratory pressure = 20 cm H_2O and PEEP = 10 cm H_2O). See Figure 4 legend for expansion of other abbreviations.*

of the resistance of the respiratory system to delivered VT is dependent on the flow rate and the diameter of endotracheal tube and airways, explaining that most of the resistive pressure is dissipated in the first part of the insufflation. This is why, in contrast with elastance, the effect of resistance on VT will vary depending on TI.[23] If flow is terminated early before the end of insufflation, increasing resistance will initially have no effect on VT; in other cases, it will decrease VT. An increased resistance may also act via its consequence on PEEPi as described previously, especially in the conditions of high respiratory rate and inadequate TE.[8,19]

Finally, a relevant factor for VT delivery with a PC breath is the duration of inspiration. The maximum VT will occur when the lung is at complete inflation, meaning that the airway pressure equilibrates with alveolar pressure at zero flow. Complete inflation requires a TI longer than three time constants.[8,20] This is why, frequently, the flow is still positive at the end of a usual inspiration (often lasting < 1 s). If inspiratory resistance increases, a longer TI is needed to complete inflation and keep the same VT.

Spontaneous Breathing or Partial Ventilatory Support

When the patient develops spontaneous breathing efforts and triggers the ventilator, the real driving pressure becomes the sum of the pressure generated by the ventilator and by the patient's inspiratory muscles.[8] In this scenario, the muscular pressure (which remains hidden to the clinician) becomes an important part of the equation of motion. The physiology of PC-CMV markedly differs from the passive condition when spontaneous breathing activity is present.

In PC-CMV, the patient usually triggers the ventilator at each breath. There are two types of forces inflating the lung: the positive pressure delivered by the ventilator

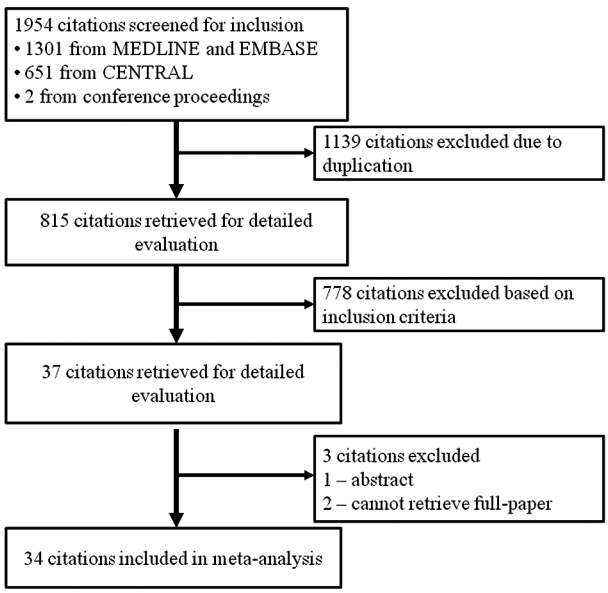

Figure 6 – *Search strategy. CENTRAL = Cochrane Central Register of Controlled Trials; EMBASE = Excerpta Medica dataBASE; MEDLINE = Medical Literature Analysis and Retrieval System Online.*

TABLE 1] Patient Characteristics in the Included Studies

Study/Year	No. of Patients	Population	Study Intervention	Duration of Ventilation in Each Mode	Reported Outcomes
Randomized controlled study					
Rappaport et al[41]/1994	27	Acute hypoxic respiratory failure	VC-CMV and PC-CMV	At least 72 h	Crs, gas exchange, clinical outcomes
Esteban et al[10]/2000	79	ARDS (AECC criteria)	VC-CMV and PC-CMV	Until successful extubation	Crs, clinical outcomes
Castellana et al[50]/2003	61	Post coronary bypass graft surgery with acute hypoxemia	VC-CMV and PC-CMV	2 h	Gas exchange
Ge et al[51]/2004	50	ARDS	VC-CMV and PC-CMV	24 h	Crs, gas exchange, hemodynamics
Gritsan et al[52]/2012	75	Hemorrhagic stroke	VC-CMV and PC-CMV	7 d	Crs, gas exchange, hemodynamics, clinical outcomes
Randomized crossover study					
Mercat et al[53]/1993	10	ARDS with LIS > 2.5	VC-CMV, PC-CMV, and PC-IRV	1 h	Hemodynamics
Lessard et al[54]/1994	9	ARDS with LIS > 2.5	VC-CMV, PC-CMV, and PC-IRV	30 min	Crs, hemodynamics
Vallverdu et al[55]/1994	8	ARDS with LIS > 2.5	VC-CMV and PC-IRV	30-45 min	Crs, gas exchange, hemodynamics
Mancebo et al[56]/1994	8	ARDS with LIS > 2.5	VC-CMV and PC-IRV	At least 45 min	Crs, gas exchange, hemodynamics
Auler Júnior et al[57]/1995	20	Elective postcardiac surgery	VC-CMV and PC-CMV	15 min	Hemodynamics
			Group 1: cardiac index > 2.5 L/min/m^2 (10 patients)		
			Group 2: cardiac index < 2.5 L/min/m^2 (10 patients)		
Cinnella et al[32]/1996	13	Acute respiratory failure of different etiologies	Part 1 (7 patients): VC-CMV and PC-CMV (high and moderate V_T with low inspiratory flow)	20 min	Gas exchange, hemodynamics, work of breathing
			Part 2 (6 patients): VC-CMV and PC-CMV (moderate V_T with low and high inspiratory flow)		

(Continued)

TABLE 1] *(continued)*

Study/Year	No. of Patients	Population	Study Intervention	Duration of Ventilation in Each Mode	Reported Outcomes
Davis et al[39]/1996	25	ARDS	VC-CMV (square and decelerating waveform) and PC-CMV	2 h	Gas exchange, hemodynamics
Kallet et al[45]/2000	18	ARDS (AECC criteria)	VC-CMV and PC-CMV	30 min	Work of breathing
Castañón-González et al[58]/2003	114	Patients mechanically ventilated in the ICU	VC-CMV and PC-CMV	15 min	Crs, gas exchange
Chiumello et al[46]/2002	7	Patients mechanically ventilated in the ICU	VC-CMV, PC-CMV, and PSV	N/A	Gas exchange, work of breathing
Kallet et al[47]/2005	14	ARDS (AECC criteria)	VC-CMV, PC-CMV, and PRVC	20 min	Work of breathing
Nonrandomized parallel study					
Kiehl et al[59]/1996	20	Leukopenic, ARDS with LIS > 2.5	VC-CMV and biphasic positive pressure ventilation	48 h	Gas exchange
Yang et al[60]/2005	40	Traumatic ARDS	VC-CMV and PC-CMV	24 h	Gas exchange, hemodynamics
Armstrong and MacIntyre[61]/1995	14	ARDS (AECC criteria)	VC-CMV and PC-IRV	12 h	Crs, gas exchange, hemodynamics
Sharma et al[62]/1996	21	Pulmonary contusion from blunt trauma	VC-CMV and PC-CMV	N/A	Gas exchange
Karakurt et al[63]/2009	40	COPD with acute respiratory failure	VC-CMV and PC-CMV	Until extubation	Clinical outcomes
Nonrandomized crossover study					
Tharratt et al[64]/1988	31	Severe ARDS	VC-CMV and PC-IRV	N/A	Gas exchange, hemodynamics
Abraham and Yoshihara[65]/1990	10	Severe ARDS	VC-CMV and PC-CMV	60 min	Crs, gas exchange, hemodynamics
Muñoz et al[66]/1993	11	Acute respiratory failure of different etiologies	VC-CMV and PC-CMV	30 min	Crs, gas exchange
Poelaert et al[67]/1993	12	ARDS with LIS > 2.5	VC-CMV and PC-IRV	30 min	Hemodynamics
Clarke[68]/1997	9	Severe head injury (Glasgow Coma Scale < 8)	VC-CMV and PC-IRV	1 h	Gas exchange, hemodynamics
Zavala et al[69]/1998	8	ARDS (AECC criteria)	VC-CMV with and without PEEP and PC-IRV	30 min	Crs, gas exchange, hemodynamics
Jung et al[70]/1999	9	Acute respiratory failure	VC-CMV, PC-CMV, and PC-IRV	20 min	Gas exchange, hemodynamics

(Continued)

TABLE 1 *(continued)*

Study/Year	No. of Patients	Population	Study Intervention	Duration of Ventilation in Each Mode	Reported Outcomes
Kim et al[71]/1999	10	Acute respiratory failure	VC-CMV and PC-CMV with low V_T (6-8 mL/kg) and high V_T (10-12 mL/kg)	N/A	Work of breathing
Prella et al[40]/2002	10	ARDS (AECC criteria)	VC-CMV and PC-CMV	30 min	Crs, gas exchange
Wang and Wei[72]/2002	20	ARDS with LIS > 2.5	VC-CMV and PC-IRV	N/A	Gas exchange
Yang et al[44]/2007	12	Acute respiratory failure	VC-CMV and PC-CMV	1 h	Crs, hemodynamics
Razek et al[73]/2008	50	Orthotropic liver transplantation patients	VC-CMV and PC-CMV at PEEP 5 and 10 cm H_2O	30 min	Crs, gas exchange, hemodynamics
Othman et al[74]/2013	15	Severe head trauma patients	VC-CMV and PC-CMV	12 h	Gas exchange, hemodynamics

AECC = American European Consensus Conference; Crs = respiratory system compliance; LIS = lung injury score; N/A = not applicable; PC-CMV = pressure control-continuous mandatory ventilation; PC-IRV = pressure control-inverse ratio ventilation; PEEP = positive end-expiratory pressure; PRVC = pressure regulated volume control ventilation; PSV = pressure support ventilation; VC-CMV = volume control-continuous mandatory ventilation; V_T = tidal volume.

and the negative intrapleural pressure generated by the respiratory muscles.[27] Because of this, the airway pressure displayed by the ventilator is not anymore a clinically valid surrogate of transpulmonary pressure (PL). If the patient is exerting strong respiratory efforts, the inspiratory PL increases without any change in airway pressure. With increased patient's efforts, V_T will increase dramatically (Fig 3), and can become injurious to the lung if the patient's respiratory drive and muscle output are high. Risk of overdistension or large stretch injury could be particularly important in patients with ARDS or in those at risk for developing ARDS.[28-30] This is different in VC-CMV because, in theory, V_T remains constant despite increasing effort of the patient. In VC-CMV, the airway pressure drops from its passive trajectory as soon as intrathoracic pressure becomes negative, but PL is kept constant in this scenario (Fig 4). The drawback of this response in VC-CMV may be discomfort for the patient, also referred to air hunger due to inadequate flow and the patient's desire for higher flow early during the breath. It is highly dependent on the peak flow rate.[31,32] This is also why an adequate peak-flow setting is so important for patient's comfort in VC-CMV when the patient triggers the ventilator.[32] Setting the flow rate at 1 L/s is usually adequate for most of the patients.

Yoshida et al[33,34] demonstrated in experimental models that strong spontaneous efforts can worsen lung injury by increasing PL and delivered regional V_T. This injury can occur even when Pplat are limited below 30 cm H_2O because of regional PL increase causing pendelluft. The clinician should be cautious of using PC-CMV during lung protective ventilation in patients who are making substantial respiratory efforts. The use of PC-CMV in these patients may worsen the severity of lung injury. Richard et al[35] compared the different types of pressure-targeted modes (PC-CMV, PC-IMV, and APRV) in both bench and clinical studies. They used the same ventilator settings in all three modes and looked at the effects of the interaction with patient's simulated inspiratory activity. These modes have different working principles with respect to inspiratory synchronization between the patient and the ventilator. The fully synchronized mode (PC-CMV) had much higher V_T and PL than partially synchronized (PC-IMV) and nonsynchronized (APRV) modes despite identical ventilator settings and levels of patient effort (Fig 5).

During PC-CMV, with some degree of spontaneous effort, the PIP can become lower than the alveolar pressure or the static recoil pressure at the end of inspiration

(Pplat). In this situation, the PIP does not confer anymore protection against lung distention since the total distending pressure may become much higher.[36]

Gas Exchange

From a physiologic standpoint, a decelerating flow pattern in PC-CMV could allow a different gas distribution than a square flow and initial studies had suggested a possible advantage in terms of gas exchange.[10,37] Al-Saady and Bennett[38] suggested that a decelerating flow resulted in a lower airway resistance, higher compliance, and improvement of oxygenation when compared with a constant flow waveform. Davis et al[39] demonstrated that PC-CMV provided better oxygenation in 25 patients with ARDS when compared with VC-CMV with a square flow but at the expense of higher mean airway pressure. However, several other studies, with a better control of total PEEP and Pplat comparing PC-CMV (with normal I:E ratio) and VC-CMV with a square flow have not observed the purported benefits of PC-CMV in terms of gas exchange.[32,40,41] Thus, the beneficial effect on gas exchange of PC-CMV compared with VC-CMV remains at best inconclusive.

Patient-Ventilator Interaction and Patient's Effort

In PC-CMV, the initial (peak) inspiratory flow rate is usually high at the beginning of inspiration and may more often and more easily overcome patient's demand than VC-CMV using a fixed flow pattern.[29] This is especially relevant in patients with high respiratory drive. A common problem of VC-CMV with a fixed flow pattern is the occurrence of insufficient flow delivery when the set inspiratory flow rate is lower than the peak patient's demand for flow.[13,42] In particular, when using a low tidal volume strategy, PC-CMV may improve patient-ventilator synchrony.[43] Yang et al[44] demonstrated that PC-CMV improved the patient's trigger effort when compared with VC-CMV at the same VT (6-8 mL/kg ideal body weight) in patients with ARDS. The price to pay, however, is the loss of control of VT.

Cinnella et al[32] compared PC-CMV with VC-CMV at both high and moderate VT. They found that PC-CMV reduced the work of breathing, transdiaphragmatic pressure swing, and pressure-time product at moderate VT (8 mL/kg) but only when the set peak flow during VC-CMV was insufficient. Indeed, they found that the same work of breathing could be achieved with one mode or another with properly adjusted settings (ie, similar flow rates in PC-CMV and VC-CMV). Kallet et al[45] also found that PC-CMV significantly reduced patient work of breathing relative to VC-CMV. The advantage of PC-CMV in terms of reducing patient work of breathing in both studies may be explained by the higher initial peak flow rate. However, when flow rates are similar between PC-CMV and VC-CMV, the work of breathing does not differ.[46,47]

Adjustment of the pressure rise time (ie, the rate of inspiratory valve opening) to match the patient's inspiratory flow demand could further improve patient effort. Pressure rise time is defined as how rapidly the inspiratory valve opens and hence how rapidly the pressure changes from its end-expiratory value to the preset

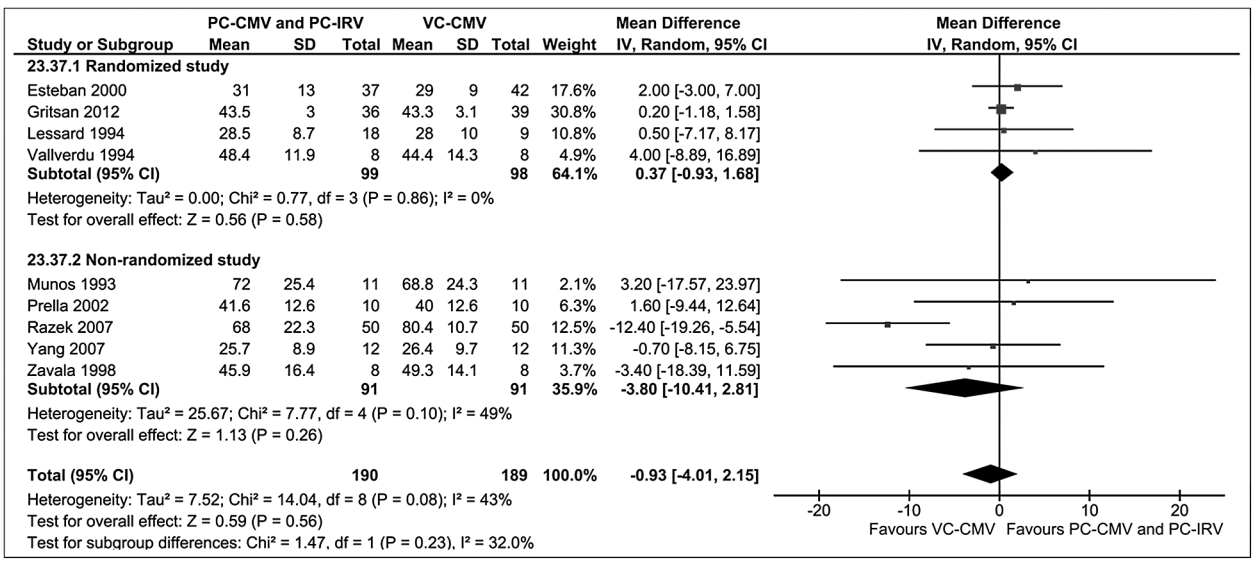

Figure 7 – *Respiratory system compliance. df = degree of freedom; IV = inverse variation; PC-IRV = pressure control-inverse ratio ventilation. See Figure 4 legend for expansion of other abbreviations.*

pressure.[42] A study from Chatmongkolchart et al[48] demonstrated that a slow rise time delayed pressure delivery and increased trigger pressure-time product. Thus, the pressure rise time in PC-CMV can sometimes be used as a method to enhance patient-ventilator synchronization.

Materials and Methods

Methodology of the Literature Search

We present a systematic review and meta-analysis comparing the physiologic effects as well as the clinical outcomes between pressure-targeted modes limiting to PC-CMV and PC-IRV and VC-CMV.

Literature Search Strategy and Trial Identification

We conducted a search of Medical Literature Analysis and Retrieval System Online (MEDLINE; 1948 to January 2014), Excerpta Medica dataBASE (EMBASE; 1980 to January 2014), and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. Details of our search strategy are given in e-Appendix 1.

Eligibility Criteria

All study designs reporting the effect of PC-CMV or PC-IRV to VC-CMV during ARF were considered. Studies were considered suitable if they met the following criteria: (1) patients were >18 years of age, admitted to an ICU or critical care setting, (2) patients were receiving invasive mechanical ventilation for ARF, and (3) the study reported on respiratory system compliance (Crs), gas exchange, hemodynamics, work of breathing, or clinical outcomes. We excluded studies concerning intraoperative ventilation, as we considered this a different population, as well as studies using APRV, which has different working principles.

Data Extraction and Study Quality Assessment

Two independent reviewers (N. R., C. M. K.) abstracted data and assessed study quality using the full text publications of studies. Disagreements on data abstraction were resolved by consensus and authors were contacted for additional information as needed.

To assess risk of bias for all studies, we used the Cochrane tool for risk of bias.[49] For each included trial, we categorized it as "low," "high," or

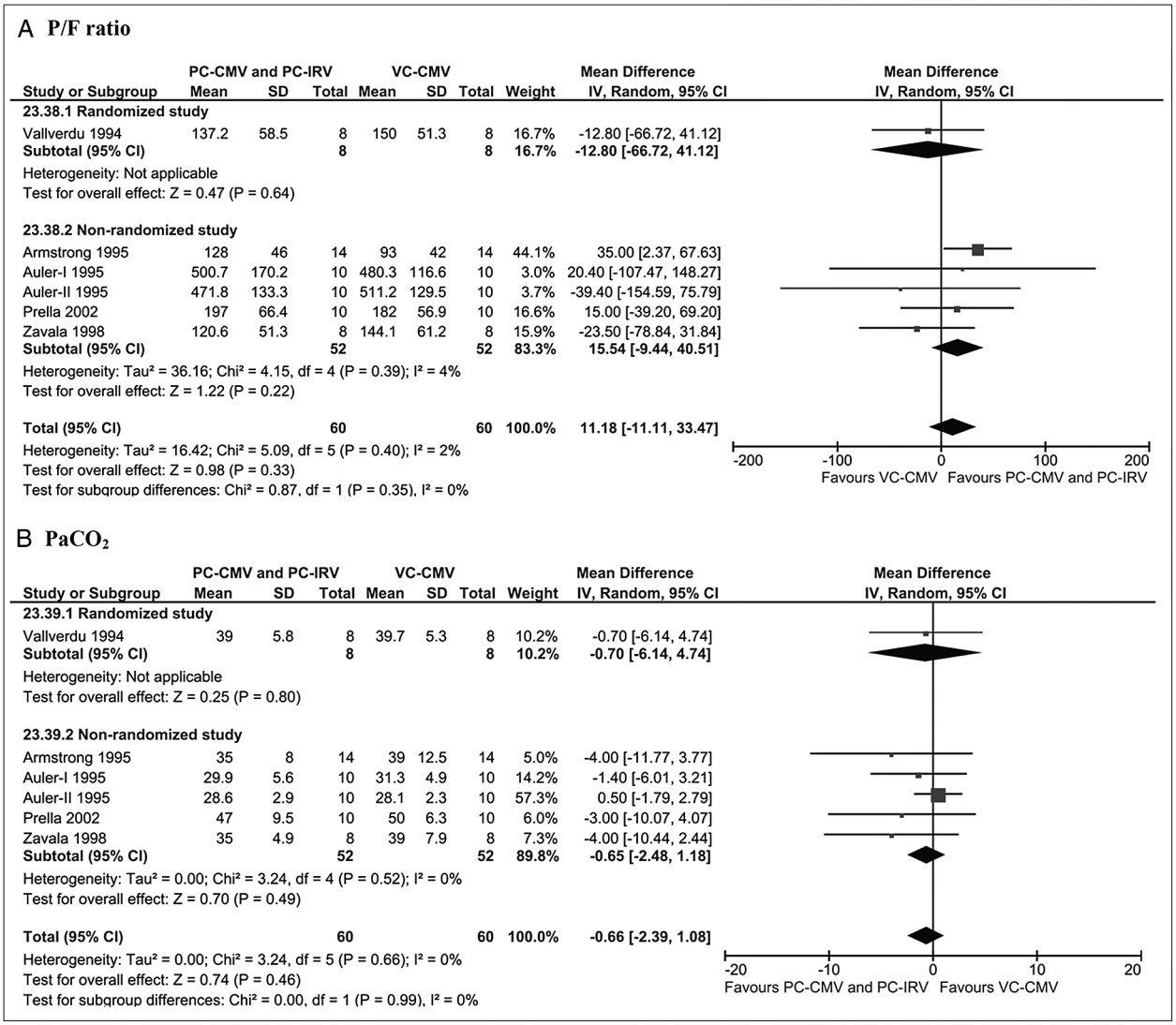

Figure 8 – *A, B, Gas exchange: P/F (A) and $PaCO_2$ (B). P/F = PaO_2 to FIO_2 ratio. See Figure 4 and 7 legends for expansion of other abbreviations.*

"unclear" risk of bias for the following items: sequence generation, allocation concealment, adequate blinding procedures, incomplete outcome data, and selective outcome criteria for parallel-group randomized controlled trials. We report the results by type of studies.

As an additional measure of quality, we established rules for physiologic quality assessment (e-Appendix 1) to make comparisons between modes reliable and interpretable. Studies not meeting these criteria were not retained in the analysis.

Study Outcome

We compared several physiologic outcomes including Crs, gas exchange (Pao_2 to FIo_2 [P:F] ratio, $Paco_2$, and oxygenation index), hemodynamic parameters (mean arterial pressure and cardiac index), and patient work of breathing. Clinical outcomes (ICU mortality and ICU length of stay) were also analyzed.

Statistical Analysis

Data analyses were completed with RevMan5 using random effects models. The I^2 statistic documents statistical heterogeneity of effect sizes in the overall aggregations. An I^2 of $<25\%$ indicates low heterogeneity, and I^2 exceeding 75% indicates high heterogeneity. We prespecified an I^2 statistic of $>50\%$ and $P<.05$ as considerable heterogeneity between included studies. Pooled analyses included trial using PC-CMV, PC-IRV, or both in comparison with VC-CMV. Subgroup analyses are described in e-Appendix 1.

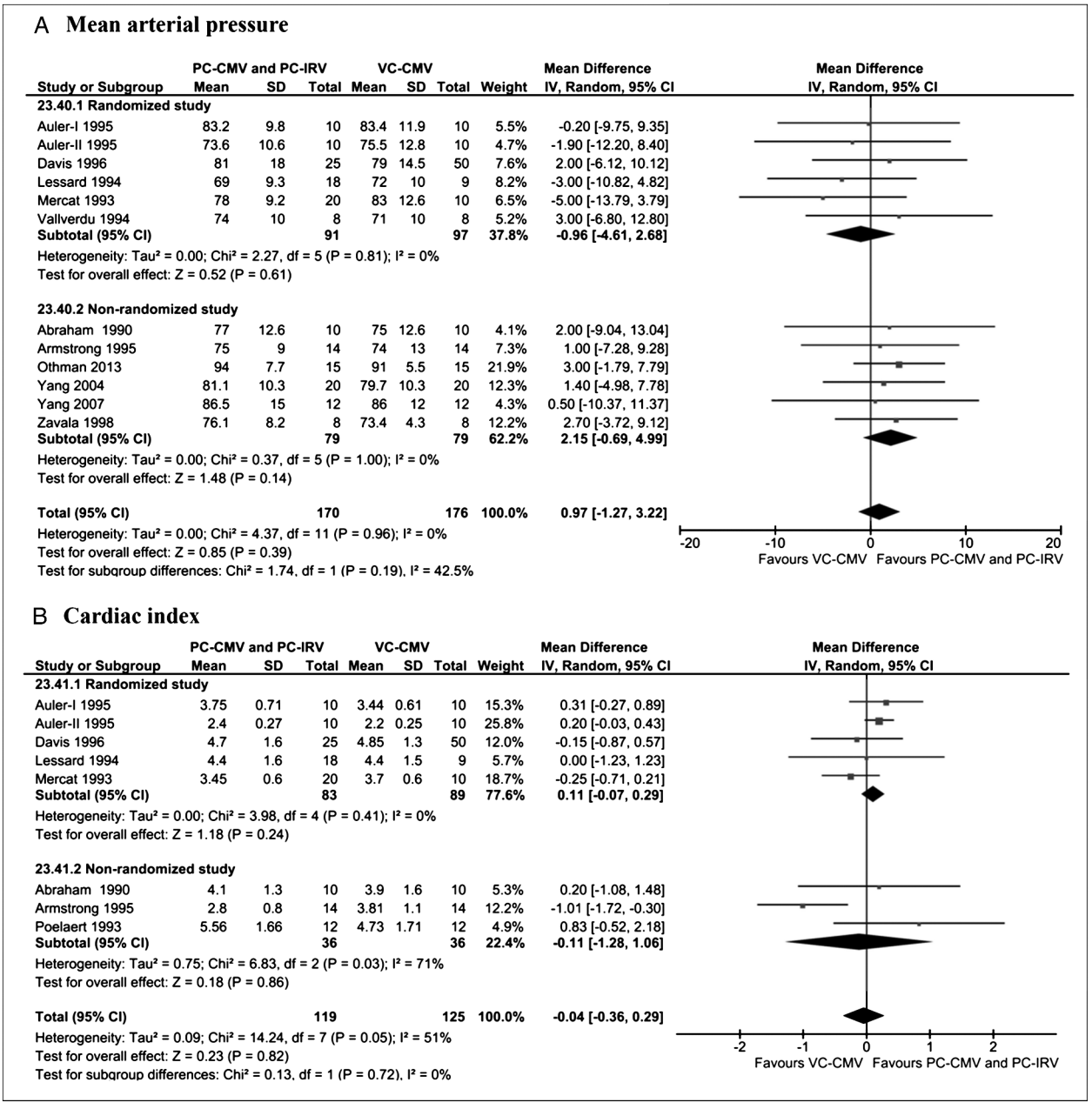

Figure 9 – *A, B, Hemodynamic parameters: mean arterial pressure (A) and cardiac index (B). See Figure 4 and 7 legends for expansion of abbreviations.*

Results

Using MEDLINE and EMBASE, 1,288 titles and abstracts were identified in the primary search. The CENTRAL database yielded 651 titles and abstracts in primary review. After elimination of duplicates, 815 articles remained (Fig 6). The characteristics of each trial are documented in Table 1.[10,32,39-41,44-47,50-74] In total, 880 patients from 34 studies were included, all having ARF, representing diverse medical and surgical populations. In total, 407 patients (46.2%) were documented as fulfilling ARDS criteria. Summaries of specific selection criteria, trial characteristics, and quality assessment are detailed in e-Appendix 1.

Outcomes

Respiratory System Mechanics: From the pooled analysis of PC-CMV and PC-IRV, no significant difference in Crs was found between modes (nine studies, n = 379 patients, mean difference of −0.9 mL/cm H_2O; 95% CI, −4.0, 2.2) (Fig 7). The same result was observed in the subgroups of PC-CMV, PC-IRV, ARDS, and non-ARDS (e-Fig 1).

Gas Exchange: P:F ratio in PC-CMV/PC-IRV was similar to VC-CMV (n = 120) with a mean difference of 11.2 mm Hg (95% CI, −11.1, 33.5) and no statistical significance (Fig 8A). This result was also consistent in subgroups of PC-CMV and PC-IRV, and in ARDS (e-Fig 2). No significant difference in $Paco_2$ was found between PC-CMV/PC-IRV and VC-CMV (Fig 8B) and also in the subgroups of PC-CMV, PC-IRV, and ARDS (e-Fig 3). For oxygenation index (a lower oxygenation index is more favorable), we included only three PC-IRV studies,[55,61,69] with 60 patients. The mean difference between PC-IRV and VC-CMV studies was 4.2 cm H_2O/mm Hg (95% CI, −0.8, 9.1), in favor of VC-CMV, but was nonsignificant (e-Fig 4).

Hemodynamic Parameters: There was no difference between PC-CMV/PC-IRV and VC-CMV regarding mean arterial pressure (346 patients) or cardiac index (244 patient) (Fig 9). Subgroup analysis of PC-CMV, PC-IRV, ARDS, and non-ARDS showed no difference between modes (e-Figs 5, 6).

Work of Breathing: We included five studies for work of breathing (n = 124). In pooled study, there was no significant difference between modes. In subgroup analysis, PCV showed a significant reduction of patient work of breathing when inspiratory flow rate was insufficient in VC-CMV, with a mean difference of −0.34 Joules/L (95% CI, −0.63, −0.04). However, PC-CMV did not demonstrate any benefit when inspiratory flow rate was the same as in VC-CMV (Fig 10).

Clinical Outcomes: No difference in ICU mortality (n = 221) was found between PC-CMV and VC-CMV. There was also no significant difference in ICU length of stay (n = 194) between the two modes (Fig 11).

Discussion

We could not demonstrate any systematic difference between PC-CMV or PC-IRV vs VC-CMV in terms of physiologic (Crs, gas exchange, and hemodynamics) or clinical outcomes (ICU mortality and length of stay). PC-CMV has a benefit in reducing patient work of breathing only when inspiratory flow rate is insufficiently set in VC-CMV. As previously discussed, this does not mean that the two modes are equivalent. The choice of the mode of ventilation in patients should be based on clinical context and individual adjustment of the setting by considering the important factors such as diagnosis, pattern of breathing (passive or active respiration), and patient-ventilator synchrony and on the clinician's priorities for the patient, such as lung protection vs comfort.

From a physiologic standpoint, PC-CMV could theoretically provide a different gas distribution than VC-CMV due to a decelerating flow pattern. However, we could not find any difference in P:F ratio between two modes. The calculated oxygenation index, if any different, tended to be worse with PC-IRV than VC-CMV. We think that these possible differences in ventilation distribution have probably no or very marginal consequences on gas exchange in most patients, provided the V_T is the same than in VC-CMV.

Physiologic knowledge tells us that possible differences between modes may be observed in case of acute changes in respiratory mechanics, in terms of lung protection, and regarding patient's comfort or work of breathing during assisted ("triggered") ventilation. Existing studies do not provide any data showing clinical differences but very few focused on these circumstances. Moreover, results may vary markedly with the precise settings of each of these modes, as shown by Cinnella et al.[32] Given the lack of details about actual ventilatory settings for clinical studies comparing PC-CMV and VC-CMV, it is not surprising that no differences were found in clinical outcomes.

Our study has strengths and weaknesses. We included all identified trials in critically ill patients, enhancing generalizability and optimizing pragmatism. We used a

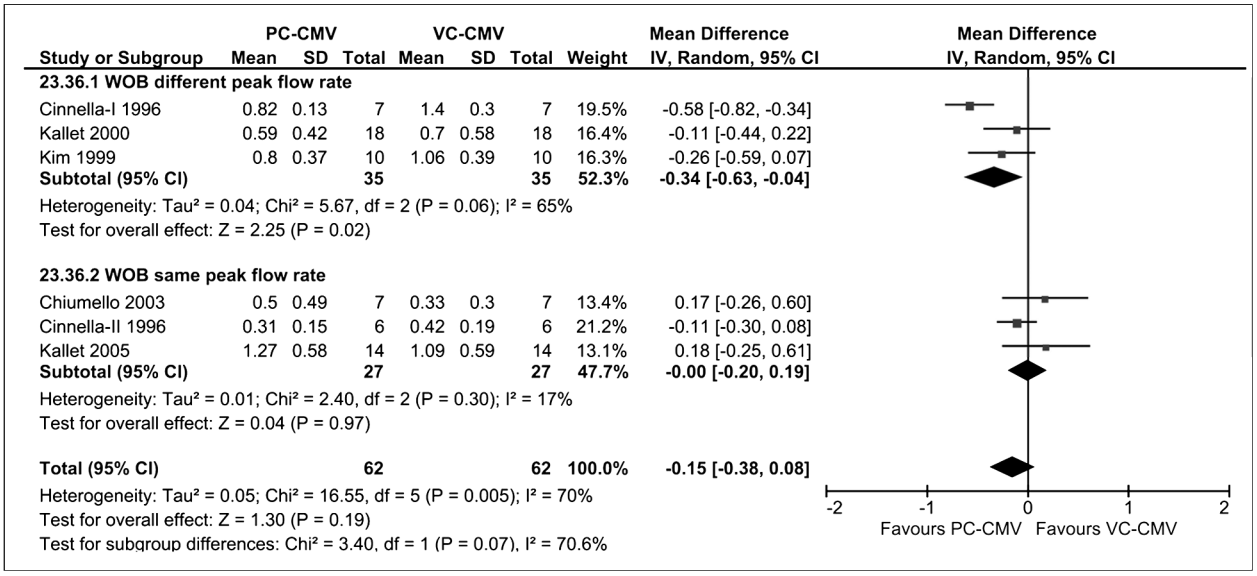

Figure 10 – *Patient work of breathing. WOB = work of breathing. See Figure 4 and 7 legends for expansion of other abbreviations.*

rigorous methodologic and physiologic quality assessment. Our results, however, show that many of the trials included are small, varying in study designs, with high heterogeneity in terms of quality. Physiologic quality assessment for inclusion into a meta-analysis has not been previously described. When including physiologic studies in meta-analysis, we believe that selecting the studies based on minimal physiologic requirements is necessary to make the aggregation of studies more meaningful and, therefore, to improve the overall quality of the analysis. To our knowledge, this study is also the first formal meta-analysis comparing these modes of ventilation regarding physiologic and clinical outcomes and using a physiologic approach for the selection of studies and the comparison of the outcomes.

Conclusions

In summary, this narrative review and meta-analysis provides a comprehensive, rigorous, and exhaustive inclusion of studies comparing PC-CMV and PC-IRV

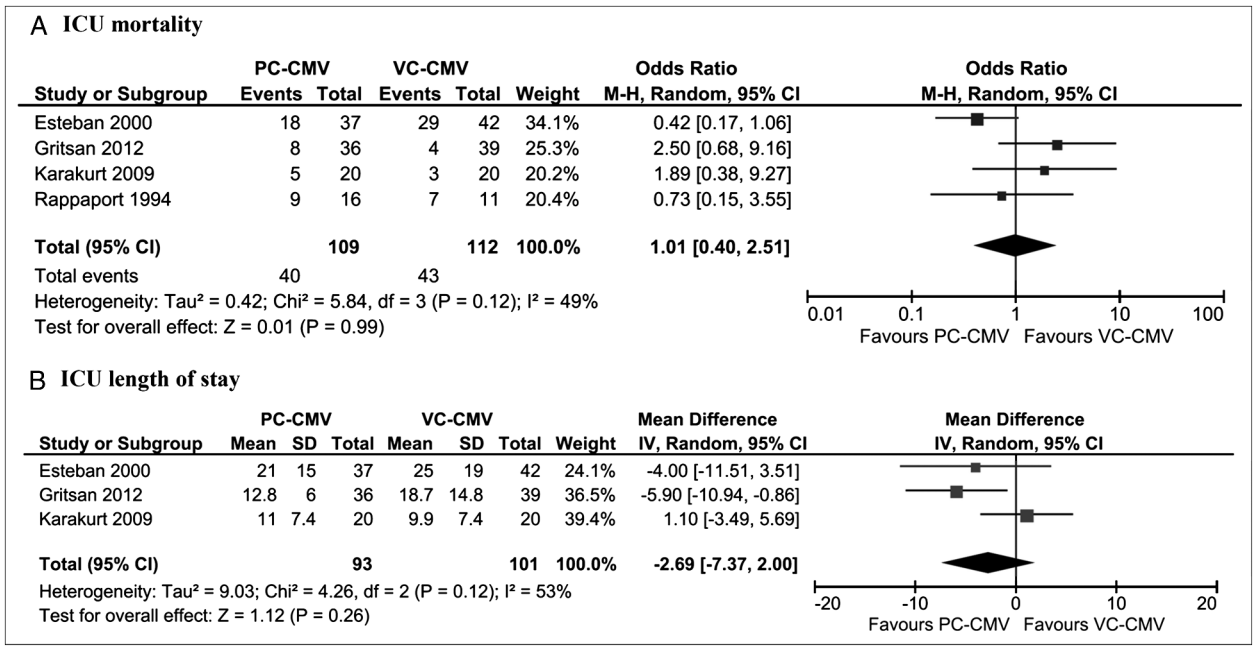

Figure 11 – *A, B, Clinical outcomes: ICU mortality (A) and ICU length of stay (B). M-H = Mantel-Haenszel. See Figure 4 and 7 legends for expansion of other abbreviations.*

to VC-CMV in critically ill patients with ARF in the context of an increasing use of pressure-targeted modes over the world. We could not find any significant differences between these modes in either physiologic or clinical outcomes, but included trials were small and varied considerably in quality. Our study may provide insights regarding the choice of ventilation of patients with ARF. Indeed, considering the working principles and the physiologic effects of the two types of breath, appropriately adjusting the ventilator settings regarding patient's individual characteristics may help to better ensure protective lung ventilation in some cases and to minimize work of breathing and improve comfort in others. We showed here that the overall outcome of ventilation will be unlikely influenced by simply using one breath type vs the other for all patients.

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Author contributions: L. B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. N. R. contributed to study conception, design, and selection, assessment of risk of bias and extraction, data analysis and interpretation, the draft of the manuscript, and critical revision and final approval of the manuscript; C. M. K. contributed to study conception and design, assessment of risk of bias and extraction, data analysis and interpretation, the draft of the manuscript, and critical revision and final approval of the manuscript; F. B. contributed to study selection, data interpretation, and critical revision and final approval of the manuscript; J. O. F. and J. M. contributed to data interpretation and critical revision and final approval of the manuscript; and L. B. contributed to the study conception and design, data interpretation, and critical revision and final approval of the manuscript.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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