Review

Changes in ventilator settings and ventilation-induced lung injury in burn patients—A systematic review

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Objective: Ventilation strategies aiming at prevention of ventilator-induced lung injury (VILI), including low tidal volumes (VT) and use of positive end-expiratory pressures (PEEP) are increasingly used in critically ill patients. It is uncertain whether ventilation practices changed in a similar way in burn patients. Our objective was to describe applied ventilator settings and their relation to development of VILI in burn patients.

Data Sources: Systematic search of the literature in PubMed and EMBASE using MeSH, EMTREE terms and keywords referring to burn or inhalation injury and mechanical ventilation.

Study selection: Studies reporting ventilator settings in adult or pediatric burn or inhalation injury patients receiving mechanical ventilation during the ICU stay.

Data extraction: Two authors independently screened abstracts of identified studies for eligibility and performed data extraction.

Data synthesis: The search identified 35 eligible studies. VT declined from 14 ml/kg in studies performed before to around 8 ml/kg predicted body weight in studies performed after 2006. Low–PEEP levels (<10cmH2O) were reported in 70% of studies, with no changes over time. Peak inspiratory pressure (PIP) values above 35cmH2O were frequently reported.

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Nevertheless, 75% of the studies conducted in the last decade used limited maximum airway pressures (≤35 cmH₂O) compared to 45% of studies conducted prior to 2006. Occurrence of barotrauma, reported in 45% of the studies, ranged from 0 to 29%, and was more frequent in patients ventilated with higher compared to lower airway pressures.

Conclusion: This systematic review shows noticeable trends of ventilatory management in burn patients that mirrors those in critically ill non-burn patients. Variability in available ventilator data precluded us from drawing firm conclusions on the association between ventilator settings and the occurrence of VILI in burn patients.

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1. Introduction

Mechanical Ventilation (MV) is known to be lifesaving but can also lead to serious lung injury. To diminish this ventilator-induced lung injury (VILI), lung-protective MV strategies have become standard care in Intensive Care Unit (ICU) patients as was shown in two recent large international observational studies [1,2]. Ventilation strategies aiming at prevention of lung overdistention by use of low tidal volumes (VT) have been found to improve outcome of ICU patients with [3,4] and without acute respiratory distress syndrome (ARDS) [5,6]. Furthermore, increasing the level of positive end-expiratory pressure (PEEP), which might prevent atelectasis, also improved outcome of ICU patients with moderate and severe ARDS [7]. Whether PEEP benefits patients without ARDS is uncertain, as studies show contrasting results [7-9]. Nevertheless, a trend towards the use of higher levels of PEEP in ICU patients without ARDS is noticeable [2,10].

MV is often needed in burn patients. Up to 22% of burn patients are admitted to the ICU due to respiratory failure [11]. These patients may have an increased risk for VILI, especially if they suffered inhalation trauma [12,13]. Furthermore, an extensive systemic inflammatory response is induced by burn injuries in general, which increases oxygen consumption and CO₂ production and which may add to the development of ARDS [14].

Whether lung-protective MV is applied in burn ICU patients is unknown. There is no consensus on optimal MV in burn patients [15]. The aim of this systematic review was to investigate and describe changes in ventilation practice in burn patients over time. We also aimed to investigate the occurrence of VILI in ventilated burn patients. We hypothesized that, like in non-burn ICU patients, lung-protective MV is increasingly used in this patient population.

2. Methods

2.1. Search strategy

This systematic review was performed and reported in accordance with the PRISMA statement [16]. We conducted a systematic search of the literature in PubMed and EMBASE using MeSH, EMTREE terms and keywords referring to the patient population (‘burn’ or ‘smoke inhalation’) and intervention (‘mechanical ventilation’ or ‘artificial ventilation’). For details see Appendix 1 in Supplementary material.

2.2. Study selection

Studies in adult or pediatric burn and/or inhalation injury patients receiving mechanical ventilation during ICU stay...
were eligible for inclusion. Studies were included if they reported any of the following ventilator settings in the results: tidal volume ($V_t$), PEEP, maximum airway pressures (plateau pressures (Pplat) and peak pressure (Ppeak) or peak inspiratory pressure (PIP)) or FiO2. Searches were not limited by date or type of study. Studies in mixed populations (including also non-burn patients) were excluded if ventilation settings applied in the burn patients were not specified. We excluded case reports, manuscripts in languages other than English and papers of which full text was not available. All selected articles were cross-referenced for additional relevant material.

2.3. Data extraction

Two authors performed data extraction (GJG and SMvdH). Study characteristics including the year of publication, period of study conduct and study design, sample size and patient population were registered.

Our primary aim was to investigate and describe changes in ventilation practice in burn patients over time. Therefore, the following ventilator settings were our main parameters: $V_t$, PEEP, maximum airway pressures (PIP or Ppeak, and Pplat levels), FiO2 levels and ventilator modes. Also, data on type or timing of the applied ventilator settings were collected (e.g. specific time points; best or worst values; before or after an intervention). Our secondary aim was to provide an overview on the reported occurrence of the following forms of VILI: acute respiratory distress syndrome (ARDS), barotrauma or pulmonary atelectasis, according to the respective author’s definition. Additional collected data on clinical outcomes were duration of MV, length of ICU stay and mortality.

2.4. Data analysis

To assess changes over time in ventilation practices, we ordered studies chronologically based on the last year of study conduct. If the period in which the study was performed was not reported in the manuscript, we used the year in which the article was published. Studies were subdivided per decade in three groups (from 2016 to 2007, from 2006 to 1997 and studies conducted prior to 1997). Extracted ventilator data were subdivided as follows: a. $V_t$: Low <10 ml/kg, High ≥10 ml/kg, or milliliters only; b. FiO2: Low: ≤0.6, High: >0.6; c. PEEP: Low ≤10 cmH2O or High >10 ; d. PIF: Low: ≤35 cmH2O, High: >35 cmH2O and e. Pplat: Low ≤30 cmH2O, High: >30 cmH2O, f. ventilator mode: conventional or unconventional.

Conventional modes included assist controlled, pressure controlled, volume controlled, and synchronized intermittent mandatory ventilation modes. Unconventional modes included high frequency oscillatory ventilation, high frequency percussive ventilation, volume diffusive respirator, and synchronized bilateral ventilation.

Methodological quality of the non-randomized and randomized studies was assessed (by GJG and SMvdH) with use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and the Cochrane Collaboration’s tool for assessing risk of bias [17,18], see Appendix 2 in Supplementary material. Descriptive statistics were used to report the collected data.

3. Results

3.1. Search strategy and study selection

The search yielded 1260 potentially relevant publications of which 35 studies including 2196 burn patients met the inclusion criteria (Fig. 1, Table S1 in Appendix 1 in Supplementary material). Five studies compared MV strategies prospectively [19-23], of which three were randomized controlled trials [19,20,23]. Ventilation practices were the main topic of interest in 21 studies [19-39]. Methodological quality of the studies was low, with high risk of bias in most studies (Appendix 2 in Supplementary material).

3.2. Applied ventilator settings

Tidal volume was reported in ten studies and ranged from 6 to 16.8 ml/kg. In the last two decades, $V_t$ of around 8 ml/kg (ranging from 6 to 9 ml/kg) were reported [24-26,40,41], while $V_t$ of around 14 ml/kg (ranging from 14 to 16.8 ml/kg) were used in earlier years [24,34] (Tables 1; S3 and S4, Appendix 3 in Supplementary material; Fig. 2). Five studies did not specify which weight was used for calculation of the applied tidal volumes. The remaining studies reported tidal volumes in milliliters per kilogram of predictive body weight [20,40,42], ideal body weight [25] or preinjury weight [34] (Appendix 3, Table S3 in Supplementary material).

Applied PEEP levels were reported in 23 studies. Low PEEP levels (210 cmH2O) were reported in 70% of studies, with no changes over time [21-25,29,36-38,40-46]. Higher PEEP levels were described in 13 studies [24,29-33,36,37,42,44,45,47,48] (Tables 1; S3 and S4, Appendix 3 in Supplementary material). The majority of studies in which PEEP levels above 10 cmH20 were used, included patients with inhalational injury [30,30,31,32,33,36,37,42,47] and ARDS [30,30,31,32,33,47] (Table S5, Appendix 4 in Supplementary material). Plateau pressure levels were reported in three studies, ranging from 22 to 37 cmH2O (Table S3, Appendix 3 in Supplementary material). PIP values (reported in 25 studies) varied highly between studies, ranging from 16 to 95 cmH2O. Eighteen studies used PIP above the widely used maximum of 35 cmH2O [19,21,23,24,26-28,30,31,35-39,44,47,49] (Tables 1 and S4, Appendix 3 in Supplementary material). Extreme PIP values (>50 cmH2O) were reported in seven studies, all but one published before 2009 [24,36,36,37,38,39,44,49] (Table S3, Appendix 3 in Supplementary material). Moreover, 75% of the studies conducted in the last decade used limited maximum airway pressures (<35 cmH2O) compared to 45% of studies conducted prior to 2006. Studies conducted after 2007 reported FiO2 levels below 0.6 (Table S4, Appendix 3 in Supplementary material) while eight studies conducted prior to 2007 reported FiO2 levels above 0.6 in one or more study groups [27,29,30-32,36,37,47].

The used ventilator mode was specified in 18 studies (Appendix 3, Table S3 in Supplementary material). Conventional ventilation modes were compared to unconventional high frequency ventilation modes in 14 studies [19-23,26,28,30-33,36,37,39] (Table 1). The majority of those studies evaluated the use of unconventional high frequency modes of
ventilation, mainly as rescue therapy or as a potential lung protective ventilation strategy (Appendix 4, Table S5 in Supplementary material).

3.3. VILI

Occurrence of VILI was reported in 24 (69%) studies. The applied definitions for the reported forms of VILI varied highly between studies and over time. Ten studies reported the incidence of ARDS, which varied from 0 to 96% of the included patients. One retrospective study described significantly lower incidences of ARDS (11% vs 15%, $p=0.01$) and atelectasis (43% vs 58%, $p<0.001$) and a shorter duration of MV in patients ventilated with higher tidal volumes compared to patients ventilated with lower tidal volumes [24].

Barotrauma was reported in 16 studies, of which 12 evaluated the use of high frequency ventilation modes [19,20,22,23,26-28,30,31,33,36-38] (Table S5, Appendix 4 in Supplementary material). Barotrauma occurred in up to 29% of patients, and was more frequently reported in patients ventilated with higher compared to lower PIP levels (Tables 1 and S3, Appendix 3 in Supplementary material) [19,20,24,30,36]. Atelectasis was reported in three studies [24,33,45], all using PEEP levels of approximately 10 cm H$_2$O (Table S3, Appendix 3 in Supplementary material).

3.4. Clinical outcomes

Duration of MV, length of ICU stay and reported mortality are presented in Table S6, Appendix 5 in Supplementary material. Burn patients required MV for at least ten days in 17 out of 21 studies that provided data on the duration of ventilation. Four studies reported length of ICU stay, which ranged from 8 to 52 days. Mortality was reported in 28 studies, with mortality rates above 50% in 5 studies, and ranging from 20%-50% in 17 studies (Table S6, Appendix 5 in Supplementary material).

4. Discussion

This systematic review identified 35 studies that reported on method of MV used in burn and inhalation injury patients. The methodological quality of the studies was low and there was a large variation in details of MV reported. This hampered our systematic review and made it difficult to draw firm
conclusions. Nevertheless, we found a wide variation in MV practices, which reflects the lack of consensus on optimal MV management for burn patients. A trend towards the use of lung-protective MV can be seen, as studies conducted in the last decade reported the use of lower VT and lower maximum airway pressures. More frequent use of MV has been noticed in the same period, possibly for reasons other than respiratory failure [50]. The ventilatory settings included in this study might therefore be influenced by the lower values in patients not strictly needing MV for respiratory insufficiency.

Only 69% of the studies described VILI. Barotrauma was most frequently reported, in 46% of the included studies,
occurring in up to 49% of patients. Due to the scarcity and heterogeneity of available data, we were unable to determine an association between reported ventilation practice and the occurrence of VILI.

MV of burn patients can be challenging and is different from MV in general ICU patients. The often encountered hypermetabolic state with increased production of carbon dioxide requires large minute volumes to maintain acceptable pH. Moreover, decreased chest wall compliance due to edematous and eschar thickened chest walls [20,51] could hamper the use of lung-protective MV including low Vₚ and limited airway pressures [3], as it may impede burn patients to generate enough transpulmonary pressure to enable adequate ventilation [51,52]. Therefore, high airway pressures may not necessarily indicate lung overdistention in burn patients [52].

High FiO₂ levels, which may be temporarily necessary in case of carbon monoxide poisoning, may also cause lung injury, reabsorption atelectasis, and are associated with increased in-hospital mortality of critically ill patients [53,54]. Given these special features of MV in burn patients, it is currently unknown whether burn patients would benefit from lung-protective MV.

We found that over the last decades Vₚ declined from approximately 14 ml/kg to 8 ml/kg [20,24,26,41], which is similar to Vₚ sizes reported in non-burn critically ill patients [1,2,55]. Although low Vₚ sizes are lung-protective for the general ICU population, no reports of improved outcome of burn patients has been reported so far [20,24]. In contrast, in a retrospective study spanning three decades, Sousse et al. found that ventilation with high Vₚ (15 ± 3 ml/kg) was associated with a decrease in ventilator days, atelectasis and ARDS compared to ventilation with relatively low Vₚ (9 ± 3 ml/kg) [24]. Chung et al. conducted a RCT comparing low Vₚ ventilation with HFV [20], which was stopped early for safety reasons as significantly more patients in the low Vₚ arm failed to meet adequate oxygenation and ventilation goals [20].

Higher maximal airway pressures were associated with increased mortality in a recent international prospective cohort study in patients without ARDS [56], and worse outcomes in patients with ARDS [57,58]. Although the majority of the included studies used high airway pressures, limitation of airway pressure is increasingly being used. Indeed, five out of the seven studies that reported the use of low maximum airway pressures were conducted in the last decade [20,25,29,40,59].

The majority of studies reporting on ventilation strategies in burn patients described unconventional high frequency modes of ventilation. The underlying concept of high frequency ventilation (HFV) is the delivery of very low tidal volumes at high frequencies [60], supposedly allowing lower airway pressures [32]. In line herewith, lower maximum airway pressures and less barotrauma were reported in patients ventilated with HFV mode compared to conventional ventilation strategies [19,20,36,61]. Notably, there was a wide variation in applied conventional ventilator modes. This is in line with a recent survey on ventilator practice for burn patients which concluded that no particular mode of ventilation prevails in the management of burn patients [51].

We divided the ventilator data into ‘high’ and ‘low’ based on cutoffs previously used in the literature. Vₚ above 10 ml/kg are indeed frequently considered as high, whereas Vₚ below 10 ml/kg are generally considered as low to intermediate [1,56,62-66]. Maximum airway pressure has been used as surrogate to plateau pressures [56]. As previous consensus recommended plateau airway pressures below 35 cmH₂O [57,67,68], we chose a cutoff value of 35 cmH₂O for maximum airway pressure. Finally, to date, it is not clearly defined which PEEP levels are considered ‘adequate’ in critically ill patients and definitions of ‘high’ versus ‘low’ PEEP levels vary, ranging from 5 to 30 cmH₂O versus 0 to 10 cmH₂O [9].

The majority of the included studies used PEEP levels of up to 10 cmH₂O. Higher PEEP levels were mainly reported in patients ventilated with HFV modes [30-32,36,37], and in patients with inhalational injury [30-32,36,37,42,47] and ARDS [30-32,47]. Higher PEEP levels seem to be beneficial for general ICU patients with severe ARDS [7], and may be beneficial in burn patients with ARDS as well. Lung injury caused by severe inhalation injury frequently develops into ARDS [12]. Furthermore, major burn injury and inhalation injury are associated with the development of a type of lung injury that fits the description of ARDS [69]. It remains unclear whether the reported ARDS in the studies in this review was caused by the suffered injury, the applied ventilator settings, or if existing lung injury was aggravated by the applied ventilator settings, resulting in ARDS. Heterogeneity of patient populations, especially regarding the severity of burn injury, and in applied definitions of ARDS, may at least in part account for the high variation in the reported incidence of ARDS.

Driving pressure, an index for mechanical ventilation normalized to functional lung size, may be a better predictor for outcome of ARDS patients than Vₚ size [70]. Amato et al. demonstrated in general ICU patients that changes in ventilator settings were only beneficial if they were associated with decreases in driving pressure [70]. In our review, the available data did not allow a calculation of driving pressures.

4.1. Strengths and limitations

In this rigorously performed systematic review we summarized the available literature on mechanical ventilation in burn and inhalation injury ICU patients. By limiting the exclusion criteria, searching over a long period of time and combining data from pediatric and adult patients, we increased the available data. As some of the studies included mixed pediatric and adult patients we decided not to analyze ventilation data of adult and pediatric patients separately. We assessed the methodological quality of the studies and data of included studies were recorded by two independent authors. Limitations of our review include the differences in severity of burn injury and reported type and timing of available ventilator data. This hampered the comparability between studies. Furthermore, although VILI was reported in 69% of the included studies, differences in study designs, patient characteristics and applied definitions for the different forms of VILI, as well as the high number of potential confounders, precluded us from drawing firm conclusions on the association between the methods of MV and the occurrence of VILI.

5. Conclusion

This systematic review, which provides an overview of the existing literature on MV in burn patients, shows a high variety in
MV practices in this patient population, reflecting the lack of consensus regarding the optimal ventilation strategy. A trend towards implementation of lung protective MV is noticeable, however it remains unclear whether burn patients benefit from these strategies. The association between applied MV and the occurrence of VILI in burn patients remains to be determined. To gain further insight in current MV practice in burn injury patients we are currently performing a prospective observational international cohort study (trial registration: NCT02312869).

Conflict of interests

The authors declare that they have no conflict of interests.

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Authors' contributions

Contributed substantially to the conception and design of the study: Gerie J. Glas, Janneke Horn, Markus W. Hollmann, Benedikt Preckel, Marcus J. Schultz.

Contributed to the acquisition of data, or the analysis and interpretation of the data: Gerie J. Glas, Janneke Horn, Sophia M. van der Hoeven, Markus W. Hollmann, Barry Dixon, Nicole P. Juffermans, Paul Knape, Bert G. Loef, David P. Mackie, Manu Malbrain, Jan Muller, Auke C. Reidinga, Benedikt Preckel, Marcus J. Schultz.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.burns.2019.05.015.

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