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Clinical Guideline for Treating Acute Respiratory Insufficiency with Invasive Ventilation and Extracorporeal Membrane Oxygenation: Evidence-Based Recommendations for Choosing Modes and Setting Parameters of Mechanical Ventilation

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Keywords
Acute respiratory failure · Acute respiratory distress syndrome · Mechanical ventilation · Invasive ventilation · Ventilation mode · Ventilation parameter setting

Abstract
For patients with acute respiratory insufficiency, mechanical ("invasive") ventilation is a fundamental therapeutic measure to ensure sufficient gas exchange. Despite decades of strong research efforts, central questions on mechanical ventilation therapy are still answered incompletely. Therefore, many different ventilation modes and settings have been used in daily clinical practice without scientifically sound bases. At the same time, implementation of the few evidence-based therapeutic concepts (e.g., "lung protective ventilation") into clinical practice is still insufficient. The aim of our guideline project "Mechanical ventilation and extracorporeal gas exchange in acute respiratory insufficiency" was to develop an evidence-based decision aid for treating patients with and on mechanical ventilation. It covers the whole pathway of invasively ventilated patients (including indications of mechanical ventilation, ventilator settings, additional and rescue therapies, and liberation from mechanical ventilation). To assess the quality of scientific evidence and subsequently derive recommendations, we applied the Grading of Recommendations, Assessment, Development and Evaluation method. For the first time, using this globally accepted methodological standard, our guideline contains recommendations on mechanical ventilation therapy not only for acute respiratory distress syndrome patients but also for all types of acute respiratory insufficiency. This review presents the two main chapters of the guideline on choosing the mode of mechanical ventilation and setting its parameters. The guideline group aimed that – by thorough implementation of the recommendations – critical care teams may further improve the quality of care for patients suffering from acute respiratory insufficiency. By identifying relevant gaps of scientific evidence, the guideline group intended to support the development of important research projects.

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Introduction and Methodology

Mechanical ("invasive") ventilation via endotracheal tube or tracheal cannula is an essential therapy for patients with acute respiratory insufficiency.

Despite a large number of studies on mechanical ventilation, there has been a lack of a comprehensive clinical treatment guideline based on systematic literature research and evaluation. In 2017, one international ATS/ERS practice guideline as well as one multi-disciplinary guideline from 21 scientific societies from Germany, Switzerland, and Austria – both on mechanical ventilation – were published [1, 2]. Both guidelines were developed according to the internationally accepted Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method based on systematic literature search and assessment [3]. While the ATS/ERS statement focused on 6 specific therapeutic questions (tidal volume, PEEP-level, prone positioning, high-frequency oscillation ventilation (HFOV), recruitment maneuvers, and vvECMO) regarding only patients with acute respiratory distress syndrome (ARDS), the multidisciplinary evidence- and consensus-based (= S3) guideline from the German-speaking countries developed a comprehensive clinical practice guideline reflecting the entire therapeutic pathway of patients with acute respiratory insufficiency treated in an intensive care unit.

The current practice of care of mechanically ventilated patients is inhomogeneous: some simple, scientifically proven, and mortality lowering measures as limiting tidal volume and peak inspiratory pressure are clinically applied in only about two-third of the patients with ARDS [4]. At the same time, technically improved extracorporeal gas exchange devices are used more frequently and in part uncritically without sufficient scientific evidence of a beneficial effect for those patients [5].

The aim of this S3 guideline is to provide an evidence-based source of information and decision support on the clinical issues associated with mechanical ventilation and extracorporeal gas exchange in patients with acute respiratory insufficiency. The structure of the guideline follows the typical clinical pathway in an intensive care unit. Indications of and, if necessary, alternatives to mechanical ventilation, choice of ventilation modes, setting the parameters of mechanical ventilation, adjunctive measures, procedure for refractory hypoxemia, as well as weaning and follow-up care after mechanical ventilation are discussed successively.

In this summary, we present the recommendations of this guideline on ventilation mode and setting the parameters of mechanical ventilation. Their implementation in daily clinical practice should generate suitable benefit for the critical ill patient or hinder further harm, at least. The complete version in German language [6] is available at (http://www.awmf.org/leitlinien/detail/ll/001-021.html).

The guideline group was methodically supported by representatives of the AWMF and consisted of 59 mandate holders from 21 scientific societies from Germany, Austria, and Switzerland including representatives of all disciplines and professions of the ICU team as well as patient representatives (Table 1). During the 4-year developmental period of the guidelines, the group members made statements on possible conflicts of interest, which were evaluated. In the event of relevant conflicts of interest, the members abstained from voting on the respective recommendations. A detailed description of conflicts of interest rules is provided in the guideline report.

Methodologically, the guidelines follow the approach of the international GRADE working group [3].

Initially, clinically relevant questions were developed according to the Patient-Intervention-Control-Outcome structure. This was followed by systematic literature research in Medline (via PubMed), Embase, Cochrane, and the Guidelines International Network and National Guideline Clearing House databases.

The literature was selected according to predefined criteria, the selected studies were sorted according to the study type, and a full-text database comprising approximately 3,500 studies was created.

At first, national and international guidelines were examined for content and quality. Relevant recommendations of current, high-quality guidelines were adopted. Thereafter, current meta-analyses and systematic reviews were analyzed for content and quality; the methodological quality was critically appraised by external methodologists with statistical expertise on the basis of the criteria of the Scottish Intercollegiate Guidelines Network. In the absence of adoptable meta-analyses, the analysis and evaluation of RCTs and – only in case of missing high quality RCTs – studies of lower evidence quality were carried out and documented in evidence tables. Finally, the body of evidence for each question was summarized in an evidence profile and evaluated qualitatively according to the GRADE criteria (Table 2). Evidence quality was provided in 5 categories (Table 2).

The guideline recommendations are based on a total of 297 evaluated guidelines and studies, details can be found in the evidence reports of the guideline [7–9].

For content and strength of recommendation *(StoRe)*, the benefits and risks of a specific therapy were evaluated

Table 1. The guideline group

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Participating scientific societies	*Guideline supervision*
Main issuing society:	(AWMF) Association of the Medical Scientific Societies in Germany
(DGAI) German Society for Anesthesiology and Intensive Care Medicine	(DGNI) German Society for Neurointensive Care and Emergency Medicine
Participating societies and organizations:	
(DIVI) German Interdisciplinary Association for Intensive Care and Emergency Medicine	(DGKJ) German Society for Pediatrics and AdolescentMedicine
(SGI) Swiss Society for Intensive Care Medicine	(DGNPI) German Society for Neonatology and Pediatric Intensive Care Medicine
(ÖGARI) Austrian Society for Anesthesiology, Resuscitation, and Intensive Care Medicine	(DGG) German Geriatric Society
(DGIM) German Society for Internal Medicine	(DGPalliativmedizin) German Society for Palliative Care
(DGP) German Society for Pulmonology and Respiratory Medicine	(DGHM) German Society for Hygiene and Microbiology
(DGK) German Society for Cardiology and Cardiovascular Research	(DGF) German Society for Specialized Nursing and Auxiliary Services
(DGIIN) German Society for Intensive Care Medicine and Emergency Medicine in Internal Medicine	(ZVK) German Physiotherapy Association – Central Association of Physiotherapists
(DGCH) German Surgical Society	(DGfK) German Society for Cardiotechnology
(DGTHG) German Society for Thoracic, Cardiac, and Vascular Surgery	German Sepsis Aid
(DGNC) German Society for Neurosurgery	(BDO) German National Association of Organ Transplant Recipients
(DGN) German Neurological Society	

Table 2. Quality of evidence and strength of recommendation (GRADE Approach)

Quality of evidence	
symbol	assessment
++++	*Quality of Evidence: high* Description "[...] Further studies are very unlikely to change confidence of the guideline group in the estimate of effect [...]"
+++	*Quality of Evidence: moderate* Description "[...] Higher-quality studies may influence the confidence of the guideline group in the estimated effect or may change the estimate [...]"
++	*Quality of Evidence: low* Description "[...] Higher-quality studies are likely to influence the confidence of the guideline group in the estimated effect or to change the estimate [...]"
+	*Quality of Evidence: very low* Description "[...] There remains a high level of uncertainty about the estimated effect […]"
Expert consensus	*No relevant evidence available*
Strength of recommendation	
assigned wording	explanation
"[...] we recommend [...]" "[...] we recommend, not to [...]"	*Strong recommendation for/against* Description: "[…] strong confidence in the relation between desired and undesired effects or strong predominance of benefits or risks […]"
"[...] we suggest [...]" "[...] we suggest, not to [...]"	*Weak recommendation for/against* Description: "[…] weak confidence in the relation between desired and undesired effects or weak predominance of benefits or risks […]"
"[…] we cannot give any recommendation […]"	*No recommendation* Description: "[…] no confidence in the relation between desired and undesired effects or no predominance of benefits or risks […]"

on this evidence basis and categorized into 3 categories (Table 2). Clinical experience, patient preferences, and an assessment of mandatory resources were also taken into account. The strength of each recommendation is therefore not only bound to the previously assessed quality of the underlying evidence, but also on clinical judgement.

The members of the guideline group had to vote for or against the recommendations individually and in a second stage as their role of mandate holders of 1 of the 21 scientific societies.

The following results section describes the main results of the guideline. In full, these results are comprehensively described in the extended version of the guideline in German language [6]. Due to the close relation of our manuscript to the original full version of the guideline, parts of the guideline's text may resemble the original wording without being marked as quotations.

Results

We present here not all, but key recommendations for choosing the ventilation mode and setting the parameters of mechanical ventilation, of which the guideline group expects suitable benefit, or – at least – the avoidance of harm for the patient if implemented in clinical practice. Furthermore, we present recommendations whose contents deviate from current clinical practice or are still discussed controversially among clinicians.

Table 3. Modes of mechanical ventilation

Modes of mechanical ventilation			
subgroup	technical description	abbreviation	control/targeting
Modes of controlled ventilation			
	Volume-controlled ventilation	VCV	Set-point targeting: application of volume-controlled ventilation target: tidal volume
	Pressure-controlled ventilation	PCV	Set-point targeting: application of pressure-controlled ventilation target: inspiratory pressure
	Pressure-regulated volume control	PRVC	Set-point + adaptive: volume-controlled ventilation with adaptive pressure changes
Modes of ventilation supporting spontaneous breathing			
Tidal volume support	Assist-control ventilation	A/C	Set-point targeting: application of (patient-triggered) volume-controlled ventilation on the basis of set target variables
	Pressure-support ventilation-assisted spontaneous breathing	PSV ASB	Set-point targeting: spontaneous breathing is assisted by a set amount of pressure support
	Variable pressure support	noisy PSV	Set-point targeting: automatic variation of the level of pressure support
Minute volume support	Volume-controlled synchronized intermittent mandatory ventilation	VC-SIMV	Automatic adaptation of peak inspiratory pressure to ensure a target tidal volume, time-controlled intermittent mandatory inspiration to ensure set minute volume
	Pressure-controlled ventilation enabling spontaneous breathing in inspiration and expiration, for example, biphasic positive airway pressure (BIPAP), airway pressure release ventilation (APRV); synonyms, DuoPAP, BI-LEVEL, BI-VENT, etc.	APRV BIPAP	Set-point targeting: time-regulated, pressure-controlled ventilation enabling spontaneous breathing during inspiration and expiration
	Pressure-controlled synchronized intermittent mandatory ventilation	PC-SIMV	Automatic adaptation of the tidal volume to ensure a target airway pressure, time-controlled intermittent mandatory inspiration to ensure set minute volume
Adaptive support	Adaptive support ventilation	ASV	Adaptive targeting or optimal targeting: variable pressure-controlled or pressure-supported ventilation depending on pulmonary mechanics and the work of breathing
	Intellivent-ASV	Intellivent-ASV	Adaptive targeting or intelligent targeting: combination of ASV with additional treatment approaches
	Neurally adjusted ventilatory assist	NAVA	Adaptive targeting or servo-targeting: ventilation pressure proportional to respiratory effort, measured by the electrical activity of the diaphragm
	SmartCare/PS	SmartCare/PS	Automatic adaptation of pressure support to keep the patient within a target comfort zone
	Proportional assist ventilation und proportional assist ventilation plus Synonym: proportional pressure support, PPS	PAV und PAV+	Automatic adaptation of the level of support and the performance of the ventilator according to demand or respiratory effort
Hybrid modes of ventilation			
For example, intermittent mandatory ventilation with pressure-support ventilation (IMV + PSV), intermittent mandatory ventilation with automatic tube compensation (IMV + ATC), biphasic positive airway pressure with pressure-support ventilation (BIPAP + PSV), biphasic positive airway pressure with automatic tube compensation (BIPAP + ATC), pressure-support ventilation with automatic tube compensation (PSV + ATC), and proportional assist ventilation with automatic tube compensation (PAV + ATC).			
Special modes of ventilation			
	High-frequency oscillation ventilation	HFOV	High-frequency, constant-volume maintenance of a continually high airway pressure

Can We Define Acute Respiratory Insufficiency?

Acute respiratory insufficiency is not defined uniformly. The central symptom of the conscious patient is shortness of breath, but impaired consciousness is also an important clinical sign. Hypoxemia, hypercapnia, and mixed forms can be distinguished by blood gas analysis, but general threshold values are missing. In clinical practice, patients are mechanically ventilated due to the clinical judgment of the treatment team.

Therefore, the guideline's recommendations should always be applied *whenever the treatment team assumes that mechanical ventilation or extracorporeal procedures have to be performed* on a patient due to acute hypoxemic/hypercapnic respiratory insufficiency.

For the clinical entity of ARDS, we applied the Berlin definition [10].

Choosing the Ventilation Mode

How Can Ventilation Modes Be Categorized?

The most important ventilation modes currently used in clinical routine have been categorized according to their capability of enabling and supporting spontaneous breathing efforts of the patient (Table 3). Thereby, the guideline group simplified the comprehensive taxonomic approach to mechanical ventilation developed by Chatburn et al. [11]. Despite the wide variety of ventilation modes available, only a limited number is regularly used in daily clinical practice. With controlled ventilation, the ventilator takes over the entire work of breathing ("controlled ventilation modes"). If only part of the work of breathing is performed by the ventilator and the patient is not only allowed to breathe spontaneously but also is at least in part supported by the ventilator while breathing spontaneously this is called "assisted" ventilation. In many different modes, spontaneous breathing of the patient is possible and supported ("Ventilation modes that support spontaneous breathing"). A distinction is made between tidal volume-supporting ventilation modes (equal support of each breath), minute volume-supporting ventilation modes (intermittent mandatory breath strokes independent of individual inspiratory efforts), and adaptive ventilation modes (strength of support depending on the inspiratory effort of the patient). Combinations of these procedures we called hybrid ventilation modes.

Should We Allow Spontaneous Breathing in Mechanically Ventilated Patients with Acute Respiratory Insufficiency?

When choosing the ventilation mode, it must be determined if the patient should be allowed to breath spontaneously while being mechanically ventilated. Need for deep sedation is associated with increased long-term mortality; therefore, a patient who is as less sedated as possible (and therefore usually having a higher amount of spontaneous breathing effort) is always a rational target for sedation [12]. Further, a number of smaller RCTs on patients with trauma-associated or mild-moderate ARDS showed beneficial effects (improvement of oxygenation, lower level of sedation needed, etc.) of early spontaneous breathing assisted by different ventilation modes, but there is still no sufficient data demonstrating positive effects on ICU- or in-hospital mortality [13–16]. Thus, for all mechanically ventilated patients with acute respiratory insufficiency (except severe ARDS), we suggest using an assisted ventilation mode to enable spontaneous breathing early (<48 h after intubation) (QE: +, StoRe: weak). In patients in whom spontaneous breathing activity has to be avoided due to the underlying medical condition (e.g., increased intracranial pressure), the benefit and risk of assisted ventilation have to be assessed individually.

In patients with severe ARDS, a significant reduction in 28-day mortality was achieved by applying neuromuscular blockade to prevent spontaneous breathing (cisatracurium 23.7% [95% CI 18.1–30.5] vs. control 33.3% [95% CI 26.5–40.9]) [17]. Due to the limited methodological quality of the trial (insufficient statistical power for primary outcome, unusual low PEEP levels, usage of cisatracurium in control group, etc.) and the risk of too deep sedation for patients with severe ARDS, we cannot currently neither recommend for nor against allowing spontaneous breathing within the first 48 h of mechanical ventilation (no recommendation). The ROSE trial, published after completion of the guideline, showed no effects of early neuromuscular blockade in patients with ARDS, but gives no further information about the question of benefits and risks of spontaneous breathing in severe ARDS [18].

Should We Prefer Pressure – or Volume-Controlled Ventilation if Controlled Ventilation Is Necessary?

Ventilation modes for controlled ventilation are generally divided into pressure-controlled ventilation (PCV) and volume-controlled ventilation (VCV). Roughly, for VCV, a fix tidal volume is applied regardless of the generated peak inspiratory pressure, while for PCV, a fix peak

inspiratory pressure is applied regardless of the generated tidal volume. In the foretimes of intensive care, it was hypothesized that VCV might generate higher inspiratory pressure and therefore more ventilator-induced lung injury. At least in Europe, PCV was widely accepted as the appropriate controlled ventilation mode for patients with acute respiratory insufficiency.

In a recent major meta-analysis, pressure-controlled ventilation did not reduce hospital mortality (nor 28 days mortality) compared to volume-controlled ventilation [19]. ICU mortality in patients with PCV was slightly reduced in comparison to VCV (relative risk 0.84, 95% CI 0.71–0.99, 1,062 patients, 2 studies). Neither incidence of barotrauma (relative risk 1.24, 95% CI 0.87–1.77, 1,062 patients, 2 studies) nor duration of invasive ventilation was positively affected by PCV. Data on incidence of organ failure and duration of ICU and hospital stay were rejected by the authors of the meta-analysis since they were not interpretable due to poor quality. The overall quality of evidence for the central critical outcome parameter "mortality" was considered to be moderate due to a lack of precision. The quality of data on barotrauma was assessed as low due to lack of precision and clinical heterogeneity of the methodology (use of recruitment maneuvers only in the treatment group PCV). Based on this meta-analysis including all major RCTs, patients with acute respiratory insufficiency can be ventilated using either PCV or VCV. We cannot give any recommendations for or against either of the 2 controlled ventilation modes (QE: +++, no recommendation).

Is There Any Benefit Using Tidal-Volume-Supporting Ventilation Modes?

Apart from 2 individual studies [20, 21] showing some improvement in gas exchange under pressure-support ventilation compared to controlled ventilation, only pathophysiological considerations (e.g., avoiding inactivation atrophy of the respiratory muscles) argue for the use of PSV instead of controlled ventilation. Hence, despite the widespread use of tidal volume supporting ventilation modes, we cannot give evidence-based recommendations for or against it as the ventilation mode in mechanically ventilated patients with acute respiratory insufficiency due to a lack of clinical data on benefit and risk.

Nevertheless, refer to the following paragraph on minute-volume-supporting ventilation modes in accordance with the initial weak recommendation in favor of the early use of an assisted ventilation mode in patients with acute respiratory failure to enable early spontaneous breathing (excepting severe ARDS).

Is There Any Advantage for Our Patients Using Minute-Volume-Assisted Ventilation Modes?

While one of the first widely used ventilation modes for minute volume-assisted ventilation was SIMV (synchronized intermittent mandatory ventilation), which is still widely used, there is now a large number of related modern ventilation modes (e.g., airway pressure release ventilation, biphasic positive airway pressure [BIPAP], BiVent, etc.) switching between 2 different pressure levels using demand valves to enable spontaneous breathing at each phase of the respiratory cycle. We generally use the term airway pressure release ventilation/BIPAP for all variants of pressure-controlled ventilation with the possibility of spontaneous breathing in the inspiration and expiration phases.

Larger randomized controlled trials on minute volume-assisted ventilation modes enabling spontaneous breathing in patients with ARDS are lacking. Hence, recommendations are based on small randomized [15] and observational studies in heterogeneous patient cohorts [22]. The positive effects of minute volume-assisted ventilation modes on oxygenation and systemic blood flow have been well documented in numerous experimental and some small clinical studies [23, 24] and suggested that early spontaneous breathing might be allowed. In addition, there are some benefits, which might be induced by allowing spontaneous breathing activities: A reduced need for sedation with fewer hemodynamic side effects, supposedly less delirious states and cognitive dysfunction and more alert, spontaneously breathing patients that might be mobilized earlier to counteract muscular inactivity atrophy. Keeping in mind the low quality of the underlying evidence due to the lack of large RCTs and the methodological heterogeneity of the studies, the following recommendation was given: Weighing the potential clinical benefits and the lack of evidence for relevant harm, we suggest to consider the use of pressure-controlled ventilation with the possibility of spontaneous breathing in the inspiratory and expiratory phases in patients without severe ARDS. Further, the individual patients particular medical conditions (e.g., increased ICP) should be considered as contraindication for spontaneous breathing (QoE: ++, StoRe: weak).

Should We Use Adaptive Ventilation Modes in Patients with Acute Respiratory Insufficiency?

The basic principle of these modes is the intra- and interindividual adaptation of ventilatory support to the actual needs of the individual patient. The increasing degree of automation enables the processing of protocols by the

ventilator, aiming on the de-escalation of the ventilation or weaning of the patient. For patients with acute respiratory insufficiency, there is currently no available data demonstrating a clear survival benefit from the use of adaptive ventilation modes. In a number of studies investigating different modes (Adaptive Support Ventilation, Neurally Adjusted Ventilator Assist, SmartCare/PS, Proportional Assist Ventilation etc.), the main proven clinical benefits have been observed in the improved synchronization of patient and ventilator (e.g., [25, 26]). This currently might be of clinical importance in hypercapnic patients, in whom a significant improved synchronization of patient and ventilator can be achieved. The main disadvantage of adaptive ventilation is that these algorithms do not ensure the application of low tidal volumes and can result in tidal volumes that significantly exceed 6 mL/kg. Therefore, we cannot give any recommendation on the use of adaptive ventilation modes for ARDS patients. For patients suffering primary hypercapnic respiratory insufficiency, we suggest to consider using adaptive ventilation modes to improve the interaction between patient and ventilator and to increase patient comfort while closely monitoring for avoidable intensity of ventilation (QeE: +, StoRe: weak).

Should We Use Hybrid Ventilation Modes in Mechanically Ventilated Patients?

Hybrid ventilation modes combine assisted ventilation that supports tidal volume with assisted ventilation that supports minute volume in many different combinations and under many different names (IMV + PSV, IMV + ATC, Intermittent Mandatory Release Ventilation, BIPAP + PSV, BIPAP + ATC, PSV + ATC, and Proportional Assist Ventilation + ATC). The aim of hybrid ventilation methods is to combine the beneficial characteristics of the different ventilation modes in 1 single mode for the patient.

Until now for hybrid ventilation modes, their advantage with regard to clinically relevant outcome parameters for patients with acute respiratory insufficiency has not been investigated by high-quality controlled trials. Due to the lack of comparative clinical data, the guideline group is currently unable to make an evidence-based recommendation for or against the use of hybrid ventilation modes.

Should We Use HFOV to Treat Patients Suffering from Severe ARDS?

HFOV generates a continuous high airway pressure (PAW) and thus elevated transpulmonary pressure (TPP) in an open ventilation system using high gas flow, which theoretically should lead to an improved alveolar recruitment. High-frequency vibrations of the gas flow, induced by the ventilator, ensure gas exchange without significantly increasing the PAW or PTP and, probably, the consecutive decreased ventilator-induced lung injury.

After earlier trials showed improvements in oxygenation in patients with severe ARDS treated with HFOV [27], the newest 2 large RCTs showed no differences in 30-day survival [28] , or an increased hospital mortality (HFOV 47% vs. control 35%) [29] using HFOV. As expected, subsequent meta-analyses showed no reduction in 30-day or in-hospital mortality and in some cases less ventilator free days and an increased length of intensive care stay for the use of HFOV in predominantly adult (>18 years) patients with moderate and severe ARDS (PaO2/FIO2 <200) [30, 31].

To avoid harm to the patients, we recommend not to use HFOV in patients with ARDS (QoE: ++++, StoRe: strong).

How to Set the Ventilator

Which PEEP-Level Should Be Chosen for Patients with ARDS?

PEEP is thought to counteract a reduction in functional residual capacity by keeping alveoli open and therefore avoiding formation of atelectases. PEEP application is intended to improve oxygenation. By increasing intrathoracic pressure und diminishing venous blood flow into the thorax, its application goes not without risks for some patients (i.e., hyperinflation of localized lung areas, dropping cardiac output, or increasing intracerebral pressure).

Hence, the PEEP-level has to be adjusted according to patient's respiratory condition while considering potential side effects on other organs.

For patients with ARDS, different methods of setting PEEP have been suggested, including imaging technologies (e.g., computed tomography [32] or bedside electrical impedance tomography [EIT] [33]), bedside measurements of respiratory pressure-volume-curves, or serial blood gas analysis. In contrast, setting of PEEP according to ventilator protocol cards of the ARDS network [34] is probably the easiest way in clinical practice, but it leaves completely aside the individual respiratory condition of the patient treated.

The original ARDS network ventilator protocol cards presented 2 PEEP tables (lower PEEP/higher FiO2 and higher PEEP/lower FiO2), in which different PEEP levels are proposed to be applied depending on the FiO2. The

high PEEP/lower FiO2 table presented here was used in the ALVEOLI study [35] before protocol adjustment to even higher PEEP values.

The following aspects speak in favor of applying higher PEEP levels:

- proven reduction in ARDS mortality using higher PEEP levels combined with low tidal volumes compared to traditional ventilation demonstrated in several RCTs and subsequent meta-analyses [36, 37].
- observed reduction in ICU and hospital mortality of patients with severe ARDS using higher PEEP levels compared to lower PEEP levels while maintaining protective tidal volumes in both groups [38].
- no significant negative effects (no differences in signs of barotrauma) [36–38].

Weighing the evidence for benefits and risks the guideline group strongly recommends the use of a higher PEEP level for all ARDS patients (QoE:++++, StoRe: strong). Taking into account its simplicity and easy implementation, we suggest setting PEEP levels according to the ARDS network ventilator protocol cards (QoE: ++, StoRe: weak).

Which Level of PEEP Should Be Used in Mechanically Ventilated Patients without ARDS?

For mechanically ventilated patients without ARDS, there is no evidence of positive effects on survival, ICU length of stay, or ventilator free days, if these patients were ventilated with a higher PEEP, but ventilation with a PEEP of ≥5 cm H_2O showed better oxygenation and lung compliance and no relevant risks if compared to ZEEP [39]. The guideline group recommends the general use a PEEP of ≥5 cm H_2O in mechanically ventilated patients without respiratory failure in intensive care (QoE: +, StoRe: strong).

Which Level of PEEP Should Be Used in Patients Suffering Acute Hypercapnic Respiratory Insufficiency?

In chronic obstructive pulmonary disease, progressive airway obstruction causes expiratory trapped air due to the inability to exhale completely. The resulting intrinsic PEEP adds to the inspiratory resistance and increases the inspiratory respiratory work of the patient. For mechanically ventilated, spontaneously breathing patients the increased inspiratory workload translates into an increased inspiratory work on the ventilator. Therefore, in these patients, the application of the correct level of external PEEP can reduce the increased inspiratory trigger work caused by intrinsic PEEP and prevent respiratory collapse during forced expiration. In contrast, if the externally applied PEEP is too high, it will become an expiration obstacle and increase the work of breathing additionally.

There are no randomized controlled trials available investigating the effect of externally applied PEEP in mechanically ventilated patients with acute hypercapnic respiratory insufficiency in terms of survival and quality of life as well as ventilator-free days nor ICU-length of stay. The 2016 guideline of the British Thoracic Society on hypercapnic respiratory failure, based on evidence of low quality (case–control studies, physiological outcome parameters), concludes that an externally applied PEEP should not exceed 12 cm H_2O in patients with hypercapnic respiratory failure [40].

A Brazilian clinical experts guideline from 2014 suggests the use of an external PEEP of 3–5 cm H_2O for invasive ventilation of patients with acute bronchial asthma, whereas in patients with exacerbated chronic obstructive pulmonary disease, the external PEEP can be adjusted depending on the change in the exhaled tidal volume: the externally applied PEEP can be increased until the PEEP-induced increase in the exhaled tidal volume turns into a decrease. For assisted spontaneous breathing, the Brazilian guideline recommends an external PEEP at a level of approximately 85% of the intrinsic PEEP, but the difficulty of measuring the intrinsic PEEP while breathing spontaneously is not further discussed. Without any data from prospective controlled clinical trials, this statement has only a level of an expert recommendation.

Due to the lack of clinical data on critical outcome parameters, our recommendation to adjust the PEEP in acute hypercapnic respiratory insufficiency is based on pathophysiological considerations of respiratory mechanics (breathing work, triggering, etc.) and follows the expert recommendation of the Brazilian guideline.

Thus, in mechanically ventilated patients with acute hypercapnic respiratory insufficiency, we suggest using extrinsic PEEP up to 85% of intrinsic PEEP (QoE: – [expert recommendation], StoRe: weak).

Can We Define a Goal for Setting FiO2?

There are neither high-quality trials showing evidence of toxicity of high oxygen concentrations in adult patients with lung failure nor any controlled studies showing a causal relationship between FiO2 and mortality or other relevant outcome data. In an observational study, hyperoxia was associated with increased mortality [41]. Further, in 2 smaller RCTs, no increased mortality or organ failure rate was observed in mechanically ventilated patients with restrictive FiO2 settings [42, 43].

Due to the low quality of evidence, we suggest as an expert consensus to adjust the FiO2 during mechanical ventilation in order to achieve a SaO2 of 90–94% or a PaO2 of 60–80 mm Hg (8.0–11.7 kPa). The guideline group recommends SaO2 of 90% as the lower limit of SaO2, since the actual measured saturation was higher than 90% in many studies, even though a range of SaO2 of 88–92% was stated in the study protocol in individual cases.

The guideline group primarily recommends the use of arterial saturation or arterial partial pressure due to potential difficulties in peripheral measurement with a pulse oximeter. If the measured peripheral saturation matches the arterial saturation, it can also be used.

Should the Tidal Volume Be Limited in Mechanically Ventilated Patients with ARDS?

During positive pressure invasive ventilation, the lung inflation is associated with a cyclically increased intrapulmonary pressure and thereby cyclically increased transpulmonary pressure (TPP). The cyclic increase in TPP causes a certain amount of distension and elongation of the lung parenchyma. Levels of lung distension exceeding the elastic capacity of the lung causes direct and indirect pulmonary damage (ventilator-associated lung injury) and are suspected to result in progression of multiple organ failure in ARDS patients [44, 45].

Meta-analyses [37, 46] comparing RCTs with low VT or low end-inspiratory pressures (PEI) <30 cm H_2O (resulting in VT <7 mL/kg standard body weight [SBW]) versus observed VT 10–15 mL/kg SBW with and without change of PEEP showed reductions in hospital mortality in patients with ARDS, which was even more prominent if low VT and higher PEEP-levels were combined. The quality of evidence is moderate due to heterogeneity of the study data.

Considering the documented benefits and no further evidence of harm, the guideline group recommends mechanical ventilation with a tidal volume VT ≤6 mL/kg SBW for patients with ARDS (QoE: +++, StoRe: strong).

Mechanical ventilation using low tidal-volume strategy may lead to significant hypercapnia in certain patients. If hypercapnia has to be avoided in individual treatment settings (e.g., intracranial hypertension, severe pulmonary hypertension, acute right heart failure), a thorough weighing of benefits and risks for the individual patient is necessary.

Should the Tidal Volume Be Limited in Mechanically Ventilated Patients without ARDS?

The adverse effects of mechanical ventilation on lung parenchyma and other organs are not limited to patients with ARDS, since the same pathophysiological phenomena (cyclic hyperinflation) can occur in a healthy lung.

A meta-analysis from 15 trials demonstrated a reduced length of mechanical ventilation and lower risk for postoperative pulmonary complication rates using smaller VTs (6–8 mL/kg SBW) in patients without ARDS receiving mechanical ventilation during surgery or in ICU [47].

Therefore, the guideline group recommends invasive ventilation of patients without ARDS with a VT of 6–8 mL/kg standard KG (QoE: +++; StoRe: strong).

Exceptions from this recommendation are in line with those discussed in the previous section.

Is There Any Upper Limit for Peak Inspiratory Pressure?

The terms respiratory peak pressure, PEI, and peak inspiratory pressure are used to describe types of the highest inspiratory pressures depending on the actual mode of mechanical ventilation. Volume-controlled ventilation with constant inspiratory flow results in a peak airway pressure (Ppeak) higher and earlier in the inspiratory cycle than the PEI. PEI is measured at the end of the inspiratory cycle. In pressure-controlled modes, an inspiratory airway pressure (Pinsp) is usually given, which is roughly equivalent to the PEI. The driving pressure (ΔP) is the difference between PEI and PEEP and thus the driving force for lung inflation during inspiration.

Application of high inspiratory pressures during mechanical ventilation might induce hyperinflation of the lung parenchyma (barotrauma). Thus, limitation of inspiratory respiratory pressure to prevent barotrauma is part of lung-protective ventilation strategies. However, Pinsp is only one of several parameters, which can be adapted to prevent barotrauma. Depending on the focus of the ventilation strategy, end-inspiratory or peak inspiratory pressures may be just the result of the PEEP-levels or tidal volumes applied to a respiratory system with a reduced compliance.

In a high-quality Cochrane meta-analysis, the effect of lung-protective ventilation in patients with ARDS was analyzed. An absolute reduction of mortality about 10% was observed only in the combined data of 3 studies (n = 1,009 patients) in which the inspiratory pressure of the control group was above 31 cm H_2O [46]. Neither data from the individual RCTs nor from combined meta-analysis showed if the reduction of peak inspiratory pressure or the limitation of tidal volume was primary related to the observed mortality reduction.

According to the evidence, we recommend limiting end-inspiratory airway pressure in patients with ARDS to ≤30 cm H_2O (QoE: +++, StoRe: strong).

For other groups of patients with acute respiratory insufficiency no prospective multi-center RCTs exist. Since data on patients with ARDS showed no evidence of harm, the guideline group suggests limiting endinspiratory airway pressure in patients with acute respiratory insufficiency to ≤30 cm H_2O (QoE: +++, StoRe: weak).

Should We Aim on a Certain Driving Pressure Limit?

The correlation of driving pressure (ΔP) and mortality was investigated in a retrospective analysis of data from several prospective randomized controlled studies [48]. Ventilatory parameters of a total of 3,562 mechanically ventilated patients were analyzed retrospectively and showed that an increased driving pressure in ARDS patients was associated with an increased mortality. This correlation was independent of different PEEP levels and observable at different PEI levels. A large-scale observational study in ARDS patients and an individual patient data analysis of patients with ARDS treated with ECMO reported similar correlations of driving pressure and hospital mortality [49, 50].

Since underlying data are either observational or derived retrospectively, the evidence we ground our recommendation on is weak: We suggest to limit the driving pressure level 15 cm H_2O if possible (QoE: +, StoRe: weak).

Exceptions: In obese patients or patients with increased intra-abdominal pressure, a higher PEI may be necessary. There are no prospective randomized studies that prove the safety of such an approach.

How Should the Ratio of Inspiration to Expiration Time Be Adjusted in Acute Hypoxemic Respiratory Failure?

Under the conditions of controlled ventilation, the inspiration (I) and expiration (E) times and the I:E ratio are specified by the ventilator settings. The setting of I:E ratio depends on the underlying cause of respiratory failure. In acute hypoxemic respiratory failure with reduced compliance, collapsed lung areas and reduced functional residual capacity, prolonging inspiration time while shortening expiration time might increase intrinsic PEEP and may contribute to an improvement in alveolar recruitment and oxygenation [51, 52].

Controlled trials on inversed ratio ventilation (I:E >1) mainly investigated direct effects on surrogate parameters (e.g., pulmonary gas exchange and respiratory mechanics). Without stratification of severity of ARDS and by not using lung-protective ventilation no solid assessment of benefits and risks is possible from data provided by these trials. Those older studies make it difficult to assess a possible treatment benefit.

However, measuring intrinsic PEEP (induced by I:E > 1) is difficult and imprecise; therefore, application of external PEEP with an I:E ≤1 will result in better-defined, constant, and controllable pressure levels. Furthermore, negative effects of inconstant intrinsic PEEP on barotrauma and VILI are unknown.

Due to lack of sound evidence of effects of different I:E, as an expert consensus, we suggest mechanical ventilation using a prolonged I:E ratio (1:1.5 to 1:1) for patients with acute hypoxemic respiratory failure (QoE: –, StoRe: weak); we give a weak recommendation against the use of inverse ventilation (I:E >1) (QoE: ++, StoRe: weak).

How Should the Relation of Inspiration to Expiration Time Be Adjusted in Acute Hypercapnic Respiratory Insufficiency?

In acute hypercapnic respiratory failure, limitations or truncation of expiratory flow causes pulmonary hyperinflation and intrinsic PEEP, which can be prevented or at least ameliorated by extending expiratory flow time [53]. In contrast to this neat pathophysiological concept, we did not find any high-quality prospective clinical study investigating the influence of different I:E ratios in patients with acute hypercapnic respiratory insufficiency. The members of the guideline group could only give recommendations on an expert consensus level based on theoretical considerations and clinical experiences.

Based on these, we assume that mechanically ventilated patients with acute hypercapnic respiratory failure might benefit from a prolonged expiratory time.

When adjusting the inspiratory to expiratory time ratio (I:E), we recommend taking into account the characteristics of the pressure and flow curves displayed by the ventilator (QoE: –, StoRe: strong).

We suggest to adjust the I:E ratio in mechanically ventilated patients with hypercapnic respiratory insufficiency with signs of expiratory flow limitation to achieve the longest possible expiratory phase while simultaneously maintaining a sufficient tidal and respiratory minute volume (QoE: –, StoRe: weak).

Which Respiratory Rate Is to Be Set in Mechanically Ventilated Patients?

There are no RCTs available answering the question of the optimal ventilation frequency in ARDS. The ARDS-Network trial protocol is frequently cited, although the

trial does not provide information to evaluate optimal frequency or possible effects on clinically relevant outcome or surrogate parameters [54]. In the large observational LUNG-SAFE trial with 2377 ARDS patients – besides other factors – low-frequency ventilation was associated with increased survival [50]. In sum, without existing sound data, we cannot give any recommendation on the setting of respiratory rate in mechanically ventilated patients with acute respiratory insufficiency.

Which Monitoring Should Be Used Treating Patients on Mechanical Ventilation?

Patients who require invasive ventilation due to acute respiratory insufficiency are considered at high-risk for life-threatening state of illness. Monitoring ventilatory settings and resulting parameters as well as oxygenation and CO_2 elimination are considered obligatory. In addition, the extrapulmonary effects of mechanical ventilation should be monitored additionally. Naturally, the same principles apply for patients treated with ECMO, who are even more complex and must be monitored carefully, extensively, and thoroughly.

On expert consensus level, we recommend as minimal monitoring for patients with acute respiratory failure continuous pulse oximetry, continuous ECG, and continuous blood pressure measurements (QoE: –, StoRe: strong).

There are no sound data on the benefit/risk ratio of a definite frequency of arterial blood gas analyses in patients with acute respiratory insufficiency. While repetitive arterial blood gas analyses provide robust data on oxygenation and CO_2 – elimination, the cumulative blood loss, and the prolonged arterial vascular access can cause relevant harm to the patient.

We recommend regularly repeated monitoring of arterial blood gases in mechanically ventilated patients (QoE: –, StoRe: strong).

The term "regular" cannot be defined here more precisely on scientific bases. The frequency of regular arterial blood gas analyses should in any case be individually adapted to the clinical situation and potential therapeutic decision based on the analysis.

Furthermore, likewise without reasonable data, the guideline group comes to the conclusion that in ventilated patients with acute respiratory insufficiency it is essential to monitor the ventilation parameters for reasons of patient safety.

For mechanically ventilated patients with acute respiratory insufficiency, we recommend continuous monitoring of the ventilatory parameters (airway pressures, tidal volume, I:E ratio, respiratory rate, flow time curves) (QoE: –, StoRe: strong).

When and How Should We Use Capnometry and Capnography in Mechanically Ventilated Patients?

In capnometry, the carbon dioxide partial pressure in the breathing gas is determined by infrared spectrometry using the main or bypass flow method. The additional graphic representation is called capnography. The accuracy of the measurement is 5%. In patients with acute respiratory insufficiency and ARDS as well as patients with pulmonary embolism, however, it should be noted that increased ventilation perfusion mismatch might result in a large difference between the end-expiratory and arterial CO_2 partial pressure.

Several clinical practice guidelines recommend capnography/capnometry to confirm the endotracheal tube position after intubation and during mechanical ventilation for reasons of patient safety. Our guideline group followed those recommendations:

We recommend to apply capnometry or capnography during intubation to verify endotracheal tube position (QoE: ++, StoRe: strong).

We suggest using capnometry or capnography to monitor mechanical ventilation (QoE: ++, StoRe: weak).

A monitoring procedure per se cannot improve the outcome of patients, a treatment algorithms based on the results of a monitoring procedure might be able to improve outcome.

Should We Use a Pulmonary-Artery Catheter or Transpulmonary Thermodilution in Patients with Acute Respiratory Insufficiency?

Several studies on the use of the pulmonary artery catheter in ARDS patients did not show any beneficial effects [55–57] on clinically relevant outcome parameters. The International Guidelines for the Treatment of Severe Sepsis and Septic Shock strongly discourage routine use of the pulmonary arterial catheter in patients with sepsis-induced ARDS. The use should be limited to selected patients and it should be taken strict care to ensure correct interpretation of the measured items [58].

A prospective randomized trial investigating the benefit of volume and catecholamine therapy guided by transpulmonary thermodilution in patients with septic shock and/or ARDS was discontinued early for futility [59].

In the absence of evidence for benefits of the general use of pulmonary artery catheter or transpulmonary thermodilution in patients with acute respiratory insufficien-

cy and in consideration of potential harm of the invasive procedure, the guideline group agrees with the recommendation of the SSC Guideline Committees [58]. In the subgroup of patients with right ventricular dysfunction or acute pulmonary or coronary artery disease, therapy might be accompanied by the use of a pulmonary arterial catheter or echocardiography.

We recommend against the routine use of pulmonary artery catheter in patients with acute respiratory insufficiency (QoE: +++, StoRe: strong).

We suggest that in patients with acute respiratory insufficiency and signs of right ventricular dysfunction the use of a pulmonary arterial catheter or echocardiography should be considered to control therapy (QoE: –, StoRe: weak).

Are There Any Other Beneficial Methods of Monitoring for Mechanically Ventilated Patients?

A large number of other monitoring methods exist providing additional information for the treatment patients with acute respiratory insufficiency. A systematic literature search on the different types of monitoring focusing on outcome parameters relevant for this guideline was not performed since we expected only a very small amount of clinically relevant literature.

In general, no recommendations for routine application can be given for any method, since there are still insufficient outcome data to rely on.

Transpulmonary thermodilution enables the determination of intrapulmonary blood volume and extravascular lung water. The pulmonary vascular permeability index can also be calculated. Extravascular lung water correlates with the extent of pulmonary edema and therefore might be possible to discriminate patients with ARDS or cardiac pulmonary edema from patients with atelectasis or pleural effusion [60].

EIT is an imaging technique based on repetitive measurement of the electrical conductivity of biological tissues. Electrodes placed around the chest can detect and visualize intrathoracic impedance changes during the respiratory cycle, which strongly correlate with changes in regional pulmonary ventilation. The effect of mechanical ventilation, recruitment maneuvers, and changes in PEEP and tidal volume as well as body positioning on the distribution of pulmonary ventilation in patients with acute respiratory insufficiency was demonstrated by EIT [61]. However, uniformly defined standards of measurement as well as data analysis and interpretation are necessary in order to further investigate the implication of EIT in the treatment of patients with acute respiratory insufficiency [62, 63].

Conclusion

This clinical practice guideline, developed by representatives of all relevant different disciplines and professions involved in the treatment of mechanically ventilated patients with acute respiratory insufficiency and by patient representatives, is intended to provide a source of information and an aid for decision-making for the main therapeutic questions in mechanical ventilation in patients with acute respiratory insufficiency. Following the GRADE approach of systematic literature search and quality assessment of the data, always considering needs and interests of the patients, the guideline group weighed up benefits and risks to finally give recommendations for or against many different therapeutic strategies.

This review focused on the core of mechanical ventilation therapy: choosing ventilation mode and setting parameters of mechanical ventilation.

After having indicated the need for mechanical ventilation for a patient, the central initial question to answer before choosing a ventilation mode is whether the patient should be allowed to breathe spontaneously or not. For most patients with acute respiratory insufficiency, breathing spontaneously in lightly sedated state as soon as possible after initiation of mechanical ventilation is crucial step to successful weaning, but some exceptions have to be considered carefully. Until now, no single mode of mechanical ventilation was shown to be superior to others, but there is growing evidence that modes enabling spontaneous ventilation during the complete respiratory cycle are beneficial. Two central issues on mechanical ventilation in patients with ARDS should be emphasized here:

First, the concept of neuromuscular blockade and controlled ventilation during the early severe ARDS is under an ongoing scientific debate and high-quality multicenter trials to confirm or disprove the data of the initial landmark study were awaited after the publication of the guideline. Recently, the ROSE trial was published, which showed no benefits for early neuromuscular blockade in ARDS, but from the data published in the ROSE trial it is not clear to which degree patients in the group without neuromuscular blockade were breathing spontaneously [18].

Second, HFOV is the only mode of mechanical ventilation for which the evidence published showed possible harm without detectable benefit; therefore, a strong recommendation against the use was made.

Quality of evidence for different settings on the ventilator was much higher. Hence, the guideline group gave

strong recommendations for lung-protective ventilator setting of patient-adapted individual higher PEEP, a tidal volume limited to 6–8 mL/kg, and an upper airway pressure level kept below 30 cm H_2O for most of the patients with acute respiratory insufficiency. All 3 parameters were in general automatically recorded by modern patient data management systems. Adaption of the 3 recommendations in clinical practice can therefore be used as an indicator of quality of care.

Finally, the guideline group defined important research questions in order to close the gaps of scientific knowledge on mechanical ventilation for the benefit of our future patients. From the guideline group's perspective, strong confirmative data are needed on the impact of allowing or even augmenting early spontaneous breathing in mechanically ventilated patients, especially in patients with ARDS. Furthermore, it has to be clarified, whether certain adaptive ventilation modes, that is, enabling automatically ventilator support to be individualized to the patient's actual needs, are beneficial.

The next review of the guideline is scheduled in 2022. The authors of this review are deeply grateful to all members of the guideline group, who, through their voluntary work over a period of 4 years, made it possible to finally successfully complete this guideline project.

Statement of Ethics

The authors have no ethical conflicts to disclose.

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Author Contributions

F.F., S.L., O.M., S.W.-C., M.N., and U.K. are the members of the guideline coordination group. F.F. and S.L. contributed equally to conception and writing of the manuscript. O.M., M.N., S.W.-C., and U.K. revisited and corrected the manuscript. Table 1 shows the composition of the entire guideline group, showing the contributions of the different members. According to consensus guideline statute all members marked with an asterisk (*) are collaborative authors of the guideline's content and thereby collaborative authors of this manuscript.

Guideline Group

"Guideline Invasive Ventilation and Extracorporeal Gas Exchange in Acute Respiratory Insufficiency" AWMF Reg.Nr. 001-21: Table 1.

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