Discontinuous versus Continuous Weaning in Stroke Patients

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Key Words

Stroke · Weaning · Adaptive support ventilation · Continuous · Discontinuous · T-piece-trial

Abstract

Background: An increasing number of stroke patients have to be supported by mechanical ventilation in intensive care units (ICU), with a relevant proportion of them requiring gradual withdrawal from a respirator. To date, weaning studies have focused merely on mixed patient groups, COPD patients or patients after cardiac surgery. Therefore, the best weaning strategy for stroke patients remains to be determined. **Methods:** Here, we designed a prospective randomized controlled study comparing adaptive support ventilation (ASV), a continuous weaning strategy, with biphasic positive airway pressure (BIPAP) in combination with spontaneous breathing trials, a discontinuous technique, in the treatment of stroke patients. The primary endpoint was the duration of the weaning process. **Results:** Only the 40 (out of 54) patients failing in an initial spontaneous breathing trial (T-piece test) were included into the study; the failure proportion is considerably larger compared to previous studies. Eligible patients were pseudo-randomly assigned to one of the two weaning groups. Both groups did not differ regarding age, gender, and severity of stroke. The results showed that the median weaning duration was 10.7 days ($\pm$ SD 7.0) in the discontinuous weaning group, and 8 days ($\pm$ SD 4.5) in the continuous weaning group ($p < 0.05$). **Conclusions:** To

the best of our knowledge, this is the first clinical study to show that continuous weaning is significantly more effective compared to discontinuous weaning in mechanically ventilated stroke patients. We suppose that the reason for the superiority of continuous weaning using ASV as well as the bad performance of our patients in the 2 h T-piece test is caused by the patients' compliance. Compared to patients on surgical and medical ICUs, neurological patients more often suffer from reduced vigilance, lack of adverse-effects reflexes, dysphagia, and cerebral dysfunction. Therefore, stroke patients may profit from a more gradual withdrawal of weaning.

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Introduction

Due to new treatment options for severe stroke such as decompressive surgery [1] or hypothermia [2], an increasing number of stroke patients are supported by mechanical ventilation on intensive care units (ICU). It is well known that weaning is problematic in about one fourth to one third of patients in heterogeneous collectives [3–6], usually due to unfavorable respiratory mechanics, residual disease processes, cardiac dysfunction, respiratory muscle weakness, high secretion volumes, or altered mental state [7]. As a consequence, weaning time amounts to 40%

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of the duration of mechanical ventilation [8]. Since an undue prolongation of mechanical ventilation is associated with both an increased risk of infectious complications [9] and a higher overall mortality rate [3, 10], quick and reliable weaning is of paramount importance. So far, studies investigating different weaning strategies have either included heterogeneous patient groups [5, 11–13] or focused on patients with pulmonary disease [11, 14] or patients following cardiac surgery [15, 16]. Moreover, neurologic patients are known to require long ventilation durations and to feature high rates of tracheotomy and mortality compared to non-neurologic patients [17, 18].

Interestingly, specific weaning studies have not yet been performed at neurological ICUs, and previous ventilation studies did not focus on the increasing number of ventilated stroke patients. These patients are characterized by a high prevalence of cardiac dysfunction, chronic obstructive lung disease [19, 20] and, in up to 21% of cases, features acute pulmonary complications due to aspiration pneumonia as a complication of dysphagia [21, 22]. Additionally, severely affected stroke patients usually suffer from reduced vigilance, aphasia, neglect, or delirium [23], all of which may severely impair their compliance with the weaning procedure. Finally, Vallerdu and coworkers noted that in artificially ventilated neurological patients the ability to cough and clear respiratory secretions was significantly more impaired than in groups of patients with COPD or acute respiratory failure [24]. Taken together, one may assume that in stroke patients there is a plethora of both disease-specific and more general obstacles that prevent a successful weaning process.

Based on these considerations, we designed a prospective randomized study comparing two fundamentally different weaning strategies in a collective of ventilated stroke patients. We contrasted biphasic positive airway pressure (BIPAP) with intermittent periods of spontaneous breathing, a discontinuous weaning strategy, which has proven to be the most successful technique in the large study on a mixed group of patients by Esteban et al. [5], with a continuous weaning approach being based on the relatively new tool of adaptive support ventilation (ASV). This technique has limited ventilator settings, needs fewer ventilator adjustments [25], and adjusts to the mechanics of patients' lungs [26]. Therefore, from initial support up to weaning, a sole mode can be used [26]. Due to its smooth and very gradual withdrawal of ventilation, ASV seems to be a reasonable weaning method for difficult-to-wean stroke patients. We hypothesized that continuous weaning using ASV is superior to conventional discontinuous weaning using BIPAP plus spontaneous breathing in ventilated stroke patients.

Methods

Patients

We included patients with ischemic and hemorrhagic stroke, who were consecutively recruited over an 18 months period at the neurological ICU of a university hospital in Germany. The stroke diagnosis was confirmed by either computed tomography or magnetic resonance imaging. Further inclusion criteria were artificial ventilation for more than 24 h, failure in the 2 h spontaneous breathing trial, and dilatational tracheotomy prior to the weaning process. Exclusion criteria were fatal prognosis and cancer.

The following data were collected: anthropometrics, type and localization of stroke, National Institutes of Health – Stroke Scale (NIH-SS) and the Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) scores [27] at admission in our hospital, duration of ICU length of stay, duration of ventilation before weaning onset, and duration of weaning. APACHE II scores were estimated within 24 h after ICU admission (table 1). The study was carried out in line with ethical principles and approved by the Hospital Ethics Committee. After written informed consent was obtained from the patient (or a legal representative where the patient's communication ability was impaired), each participant was pseudo-randomly assigned to either continuous or discontinuous weaning. Pseudo-randomization was performed directly after patients failed the T-piece-test according to patients' age, gender, and initial NIH-SS with the goal to achieve comparable group means for these parameters.

T-Piece Test

The T-piece test was performed as previously published [24, 28, 29]. It evaluates the ability of the patient to sustain spontaneous breathing during disconnection from the ventilator with supply of supplemental oxygen and humidification of gas on a T-piece for a maximum of 2 h. The trial was attempted when (1) the patients showed improvement or resolution of the underlying cause of respiratory failure, and (2) the attending physician agreed that the patient was ready to be weaned from the ventilator. In addition, the following criteria were required: (1) body temperature $<38.5^{\circ}\text{C}$, (2) hemoglobin $>8\text{ mg/dl}$, (3) appropriate cardiovascular pharmacologic therapy, (4) relief from sedation, and (5) correction of electrolyte disorders. The following respiratory criteria were required to start the weaning procedure: (1) arterial oxygen saturation $\geq 95\%$, (2) $\text{PaO}_2 >60\text{ mm Hg}$, (3) an inspired oxygen fraction $\leq 40\%$, (4) PEEP level $\leq 8\text{ cm H}_2\text{O}$, (5) maximal inspiratory pressure $\leq 25\text{ cm H}_2\text{O}$, (6) breathing frequency $\leq 30/\text{min}$, and (7) vital capacity $\geq 10\text{ ml/kg}$ of body weight.

The T-piece test was considered unsuccessful if the patient showed any sign of poor clinical tolerance: (1) breathing frequency $>35/\text{min}$, (2) arterial oxygen saturation $<90\%$, (3) heart rate $>140/\text{min}$ or sustained increase or decrease by $\geq 20\%$, (4) systolic blood pressure of $>200\text{ mm Hg}$ or $<80\text{ mm Hg}$ or an increase by 20% or more, (5) arterial $\text{PO}_2 <50\text{ mm Hg}$, (6) arterial pH ≤ 7.30 , and (7) when agitation, anxiety, constrained vigilance, or diaphoresis was present. Arterial blood gas tensions were measured (ABL 800flex, Radiometer, Copenhagen, Denmark) 20 min after onset, and at the end of the 2 h period, and at any moment when clinically required. When no signs of poor clinical tolerance appeared the patient passed the T-piece trial and was not included in the study. Contrariwise, the T-piece trial was considered failed and the patient was randomly assigned to receive either continuous or discontinuous weaning (fig. 1).

Fig. 1. Course of attribution for stroke patients.

Table 1. Patient characteristics and prognostic factors

Patient characteristics	Group of patients with continuous weaning (n = 19)	Group of patients with discontinuous weaning (n = 20)	p value
Age, years, mean $\pm$ SD	67.1 $\pm$ 13.6	62.7 $\pm$ 14.6	0.343
Men, n (%)	13 (68)	13 (65)	1
NIH-SS on admission, mean $\pm$ SD	12.69 $\pm$ 4.4	11.15 $\pm$ 5.3	0.449
APACHE II on admission, mean $\pm$ SD	14.2 $\pm$ 5.9	12.7 $\pm$ 5.2	0.417
Cardiovascular risk factors, n (%)			
Hypertension	12 (63)	13 (65)	1
Diabetes mellitus	3 (16)	4 (20)	1
Coronary heart disease	5 (26)	7 (35)	0.731
Atrial fibrillation	8 (42)	9 (45)	1
Smoking	2 (11)	3 (15)	1
Etiology, n (%)			
Bleeding	6 (32)	3 (15)	0.273
Atherothrombotic	4 (21)	1 (5)	0.182
Embolic	9 (47.4)	10 (50)	1
Other etiology	3 (16)	2 (10)	0.661
Undetermined etiology	1 (5)	1 (5)	1
Treatment, n (%)			
Intra-arterial thrombolysis and/or thrombectomy	5 (26)	7 (35)	0.731
Intravenous thrombolysis	1 (5)	2 (10)	1
Decompressive surgery	8 (42)	7 (35)	0.748
Reason for failure of the spontaneous weaning test, n (%)			
Tachypnoe	10 (53)	10 (50)	1
Hypoxaemia	6 (32)	6 (30)	1
Agitation	2 (11)	2 (10)	1
Tachycardia	1 (5)	1 (5)	1
Duration of ventilation before beginning weaning	7.74 (4.7)	8.35 (3.6)	0.649

Categorical variables are compared using the Chi-square test. Depending on the scale level of the outcome, groups were compared either by parametric unpaired t-test or by non-parametric Mann-Whitney U test. Data are presented as means $\pm$ SD.

NIH-SS = Stroke Scale of the National Institute of Health.

Fig. 2. Example of discontinuous weaning for one patient. Over the first five days, the duration of the spontaneous weaning trials could be increased. On the fifth day, weaning had to be interrupted due to poor clinical tolerance. In the following days, the phases of spontaneous breathing could be extended. The patient was successfully weaned at the ninth day of the study.

Weaning Protocols

Intermittent Trials of Spontaneous Breathing (Discontinuous Weaning)

BIPAP ventilation is a mode with pressure-regulated, volume-controlled ventilation, during which spontaneous ventilation can be achieved at any point in the mechanical ventilation-cycle-inspiration or -expiration [30, 31]. The durations of the high- and low-pressure phases as well as the corresponding pressure levels can be adjusted independently [32]. Additionally, BIPAP allows unrestricted spontaneous breathing and by this reduces sedation and promotes weaning. The ventilator maintains a pre-set pressure even when the patient breathes spontaneously. By intermittent release and reapplication of this pressure the tidal volume is generated [33].

Airway pressures were adjusted to deliver a tidal volume of 6–8 ml/kg predicted body weight. An inspiration:expiration ratio of 1:2 was chosen. Respiratory rate was adjusted to achieve normocapnia. A continuous positive airway pressure of ≤ 8 cm H₂O was permitted.

For discontinuous weaning, BIPAP ventilation was used in combination with spontaneous breathing trials. During the ventilation periods, patients were ventilated with an EVITA dura 2 ventilator (Dräger Medical AG, Lübeck, Germany). For the spontaneous breathing trials, patients were disconnected from the ventilator and allowed to breathe spontaneously through a T-tube circuit. These spontaneous trials were performed if arterial pCO₂ was >38 mm Hg and <50 mm Hg, and if no sign of poor clinical tolerance as described earlier was observed. Each spontaneous breathing interval was controlled 10 min later by arterial blood gas tension. The duration of these trials was gradually increased, and they were attempted at least twice a day. Between the spontaneous trials, BIPAP ventilation was provided for at least 1 h [5]. Patients were classified as successfully weaned when they were able to breathe spontaneously through the T-tube for 24 h (fig. 2).

Adaptive Support Ventilation (Continuous Weaning)

ASV is a mode with mandatory minute ventilation, where the optimal combination of respiratory rate and tidal volume is calculated by the respirator based on the Otis equation [34], which was first described in 2001 [16, 35]. The target minute ventilation for the individual patient is calculated based on ideal body weight and estimated pulmonary death space. Actual target ventilation can be adjusted by changing the percentage of the initially calculated target for the patient. To achieve the target tidal volume, the ventilator delivers pressure-controlled breaths by adjusting the inspiratory pressure. If the patient breathes spontaneously, ASV changes to pressure support to reach target tidal volume and delivers additional pressure-controlled breaths if the respiratory rate of the patient is below the target rate [36, 37]. By this, stable minute ventilation and a very low work of breathing can be achieved [38, 39].

Patients weaned by means of ASV were ventilated with a Hamilton Gallileo ventilator (Heinen und Löwenstein GmbH und Co. KG, Bad Ems, Germany). The initial support was chosen as 180–220% of min ventilation and an oxygen-inspired fraction of $\leq 40\%$. Support was adjusted by 20%-steps depending on the arterial blood gas tension results: if arterial pCO₂ was >40 mm Hg and <48 mm Hg, and no signs of poor clinical tolerance as described earlier appeared, percent minute ventilation was decreased by 20%. If arterial pCO₂ was <38 mm Hg or >50 mm Hg, percent minute ventilation was increased by 20%. Each change in the settings of the ventilator was controlled 10 min later by arterial blood gas tension. When patients achieved a support of 80%, they were disconnected from the respirator. Being part of the group of discontinuously weaned patients, they were classified as successfully weaned when they were able to breathe spontaneously through the T-tube for 24 h (fig. 3).

Statistical Analysis

Patients were pseudo-randomly assigned to one of the two weaning groups (continuous or discontinuous weaning). Depending on the scale level of the outcome, groups were compared either by parametric unpaired t-test or by non-parametric Mann-Whitney-U test. The Kaplan-Meier estimator was used to determine the duration over which the patients had to be weaned from respiration. The comparison between groups was made using the log-rank-test. A p value of 0.05 was considered significance limit. Statistical analysis was performed with IBM-SPSS-Statistics 18 (SPSS Inc., Chicago, Ill., USA).

Results

During the study period, 54 patients fulfilled the inclusion criteria and performed the 2 h trial of spontaneous breathing. This trial was successfully completed by 14 patients. The most frequent reason for failure was tachypnoea (50%), followed by hypoxemia (30%), agitation (10%), and tachycardia (10%). The remaining 40 patients were randomly assigned to the two weaning groups. One patient in the continuous weaning group died during the weaning process due to neurological complications and was excluded from further calculations. Both weaning

Fig. 3. Example of continuous weaning for one patient. Over the first four days, the percentage of minute ventilation could be continuously decreased. On the fifth day, weaning had to be interrupted, and the percentage of minute ventilation had to be adapted to 160% due to bad blood gas samples. In the following days, ventilation support could be further decreased, and the patient was weaned on the ninth day.

Table 2. Results of the spontaneous weaning trail and outcome variables

	Group of patients with continuous weaning (n = 19)	Group of patients with discontinuous weaning (n = 20)	p value
ICU length of stay in days, SD	23.2 (7.0)	26.25 (10.7)	0.26
Duration of weaning in days, SD	8.0 (4.5)	10.7 (7.0)	0.05
Complications			
Ventilation associated			
Pneumonia, n (%)	7 (37)	7 (35)	1
Urinary tract infection, n (%)	1 (5)	1 (5)	1

Categorical variables are compared using the Chi-square test, ICU length of stay and duration of weaning are compared using the log-rank test.

groups were well matched with respect to age, gender, and severity of stroke. They were also comparable regarding underlying disease, reason for intubation, reason for failure of T-piece test, and the indication for mechanical ventilation. Groups did not differ regarding the duration of ventilation before the onset of weaning, the overall duration of ICU length of stay, and the initial NIH-SS and the APACHE II scores ($p > 0.05$) (table 1).

Weaning took 3–25 days in the discontinuous weaning group (mean 10.7 days; SD 7.0) and 3–20 days in the continuous weaning group (mean 8.0 days; SD 4.5). The mean weaning time from mechanical ventilation was significantly longer in the discontinuous than in the continuous weaning group (log-rank-test: $p < 0.05$) (fig. 4).

Seven patients in the continuous weaning group and 6 patients in the discontinuous weaning group developed

a ventilation-associated pneumonia (VAP) and required antibiotic therapy during the weaning process. In those patients, weaning from mechanical ventilation took significantly longer compared to patients without VAP ($p < 0.001$). One patient in each group needed antibiotic therapy due to a urinary tract infection during the weaning process (table 2). Weaning was not prolonged in these two patients (5 respectively 4 days of weaning). No correlation was found between age and weaning duration ($p > 0.05$).

Discussion

In the present study, we compared continuous vs. discontinuous weaning strategies in a group of patients with acute hemorrhagic or ischemic stroke requiring artificial

Fig. 4. Kaplan-Meier-graph showing the percentage of ventilated patients in the continuous (blue line) and discontinuous (red dashed line) weaning groups for each day following weaning onset ($p < 0.05$).

ventilation. This study yielded two main findings. First, a high proportion (74%) of stroke patients in need of mechanical ventilation profited from a stepwise separation from the ventilator. Second, ASV, a form of continuous weaning, was more effective and significantly faster than discontinuous weaning via BIPAP in combination with spontaneous breathing. To the best of our knowledge, this is the first study to compare different weaning strategies in ventilated stroke patients.

One study could show that a spontaneous breathing trial over 2 h is not superior to a spontaneous breathing trail of only 30 min [40]. Due to the numerous problems of ventilated stroke patients, we decided to choose the more conservative spontaneous breathing trail of 2 h to reduce the reintubation rate. Noteworthy is the fact that in the current study only 26% of the patients could be taken off the respirator as soon as no medical indication for further ventilation was present. This proportion is considerably lower compared to what was found in previous studies with other patient groups. In the largest weaning study to date that employed a mixed medical-surgical collective of 546 patients, 76% of the participants were successful in spontaneous weaning [5]. In a similar study with a mixed group of 456 patients, Brochard and coworkers could also show primarily successful spontaneous weaning also in 76% of the patients [4]. In COPD patient samples, fewer subjects could be weaned sponta-

neously. After at least 24 h of mechanical ventilation, 54% of the patients could be taken off the respiration in the first attempt [8]. After at least 15 days of mechanical ventilation, a spontaneous breathing trial was successful in 31% of COPD patients [11]. In COPD patients, lung function is the limiting factor that leads to a reduced spontaneous weaning rate. In the current study, 50% of patients failed in the T-piece test due to tachypnoea without substantial changes of blood gases. Pulmonary insufficiency, documented as hypoxemia, was the reason for failure in only 30% of patients. We therefore conclude that compliance with the spontaneous breathing trial is one critical feature characterizing our patient collective. Based on previous findings reporting that 105 out of 589 extubated patients had a preextubation respiratory rate >30 breaths/min [41], one might suppose that spontaneous breathing would have principally been possible in some of our patients. However, due to obvious vegetative stress and the patients' impaired insight into the actual clinical condition, such a procedure seems questionable in stroke patients.

The second main finding of our study suggests that continuous weaning using ASV leads to a faster weaning of stroke patients compared to discontinuous weaning using alternating phases of BIPAP and spontaneous breathing. Previous studies with mixed surgical-medical collectives comparing different weaning strategies revealed the superiority of intermittent trials of spontaneous breathing compared to both intermittent mandatory ventilation and pressure-support ventilation [5], while Brochard and coworkers showed that Pressure Support Ventilation (PSV) with reduction of pressure support twice a day led to significantly shorter weaning duration compared to intermittent t-tests or Synchronized Intermittent Mandatory Ventilation (SIMV) [4].

In long-term ventilated COPD patients, discontinuous weaning and decreasing levels of PSV were equipotent [11], while in shorter-term ventilated COPD patients decreasing support of PSV was even superior to discontinuous weaning [8]. Altogether, the results of prior weaning studies with mixed patient groups and studies with chronic pulmonary disease patients are inconsistent. While the largest study demonstrated the superiority of discontinuous weaning [5], studies on pulmonary ill subjects showed faster weaning using PSV [8, 11].

ASV, a novel closed loop mechanical ventilation strategy, has already demonstrated its efficiency and safety [42, 43]. Promising weaning results were found in different groups of patients. It could be shown that ASV

is not inferior to conventional ventilation modes [25, 44], and that it even led to shorter ventilation times in both patients after cardiac surgery [15, 16, 45] and COPD patients [46]. First results even demonstrated a weaning success rate of nearly 50% in chronically ventilated patients using ASV as the sole mode [47]. In that study, a mixed group of 27 medical and neurologic patients was included. Each patient was mechanically ventilated for at least 3 months and had at least one failed weaning attempt. ASV support was reduced weekly, until patients could be disconnected from the respirator. Twelve out of 27 patients could be weaned within two months. Little is known about weaning with ASV mode in patients with cerebral injury. In a small collective of 12 brain injured patients, ASV mode provided normoventilation in 8 patients. In the remaining 4 patients, hyperventilation with CO₂ decrease due to brainstem irritation occurred [48]. The big advantage of ASV is the patients' ability to decide how much support is needed at any time of artificial ventilation. In our study we wanted to compare the standard weaning method for discontinuous weaning with this new continuous method. With an average of 9 days, weaning took longer in the current study than in the previous study by Esteban and coworkers, who reported a mean weaning duration of 4 days [5]. The list of factors that can lead to weaning failure and prolonged weaning in surgical and medical patients is very long [49]. In neurologic patients, reduced vigilance, lack of defense reflexes, dysphagia, and cerebral dysfunction are observed regularly. Further complications including aphasia, neglect, delirium [23], critical-illness-polyneuropathy, critical-illness-myopathy, and neuropsychiatric symptoms [50] prolong the weaning duration in neurologic patients. Additionally, patients with hemorrhagic or ischemic stroke that need mechanical ventilation are mainly elderly and present with complications such as cardiac dysfunction and chronic and acute pulmonary complications [19–22]. All these factors may help to explain the worse weaning compliance of stroke patients compared to surgical or medical patients.

The question arises why continuous weaning using ASV is superior to conventional discontinuous weaning in stroke patients. We suppose that this is mainly caused by patients' compliance. As mentioned earlier, neurologic patients more often suffer from reduced vigilance, lack of defense reflexes, dysphagia, and cerebral dysfunction compared to patients on surgical and medical ICUs. Therefore, stroke patients seem to profit from a more gradual withdrawal of weaning, where the stepwise re-

duction of ventilator support is not really noticeable by patients.

In accordance with previous observations [51, 52], the risk for VAP was directly proportional to weaning duration. In the present data, six (respectively seven) patients in each group developed a VAP requiring antibiotic treatment. Weaning was significantly prolonged in those patients. Additionally, one patient per group suffered from urinary tract infection without any effect on weaning duration. Altogether, there were no statistically significant differences in complication rates between the continuous vs. discontinuous weaning groups.

Limitations

The small sample size is the main limitation of the present study. This might also explain the missing correlation between age and duration of weaning. Additionally, no conclusions can be drawn regarding concurrent continuous weaning modes. In future studies, different continuous and discontinuous weaning modes should be compared in larger collectives of stroke patients, and additional predictors for weaning success should be observed in more detail. Additionally, different continuous weaning modes like slow reduction of pressure support and ASV should be compared. Nevertheless, the present study gives a first insight into the weaning of the difficult-to-wean group of ventilated stroke patients.

Summary

Our study is, to our knowledge, the first to evaluate the effectiveness of different weaning modes in mechanically ventilated stroke patients. Compared to surgical and medical ICU patients, stroke patients more often fail in a spontaneous breathing trial after long-term ventilation and therefore profit from a stepwise separation from the ventilator. In these cases, continuous weaning using adaptive support ventilation offers a benefit, crystallizing in the reduced duration of mechanical ventilation and weaning times.

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