Influence of Positive End-Expiratory Pressure on Intracranial Pressure and Cerebral Perfusion Pressure in Patients With Acute Stroke

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Background and Purpose—We undertook this study to evaluate the influence of positive end-expiratory pressure (PEEP) on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in patients with acute stroke.

Methods—A total of 20 ventilated patients of a neurological intensive care unit were examined under a protocol entailing variation of PEEP to 4, 8, 12, and 4 mm Hg; mean arterial blood pressure (MAP), ICP, heart rate, and mean velocity of the middle cerebral arteries (V_m MCA) were recorded.

Results—CPP significantly changed depending on the various PEEP levels. No significant differences in remaining parameters were evident. Three distinct reaction patterns of the parameters monitored were observed: (1) All parameters remained stable through the various PEEP levels (15 patients, 40 examinations). (2) Increase in PEEP resulted in a significant decrease of MAP, while V_m MCA remained unchanged, indicating an intact cerebral autoregulation. A slight (statistically insignificant) increase in ICP, which was significantly related to the MAP changes, was evident (7 patients, 16 examinations). (3) Increase in PEEP resulted in a decrease of MAP and V_m MCA; ICP remained unchanged or demonstrated a slight decline (3 patients, 6 examinations).

Conclusions—PEEP increase up to 12 mm Hg does not significantly influence ICP. The observed marked changes in CPP are mediated through the MAP. Thus, PEEP application should be safe, provided that MAP is maintained. (Stroke. 2001;32:2088-2092.)

Key Words: stroke, acute ■ treatment outcome

According to a recent study, 10% of unselected stroke patients require mechanical ventilation during their hospital stay.1 This percentage would probably be higher in neurological intensive care units applying specific treatment techniques such as hemicraniectomy or hypothermia. Thus far, no study has evaluated the optimal ventilation mode for patients with acute stroke. This issue is particularly relevant for stroke patients with elevated intracranial pressure (ICP) who develop severe pneumonia or respiratory distress syndrome. Although higher levels of positive end-expiratory pressure (PEEP) improve oxygenation by preventing atelectasis, increasing the pulmonary functional residual capacity and reducing pulmonal shunting, the influence of PEEP on ICP remains uncertain.

We undertook this study to evaluate the effect of PEEP on ICP, cerebral perfusion pressure (CPP), and flow velocities of the middle cerebral arteries (MCAs) in patients with acute stroke.

Subjects and Methods
A total of 20 patients (11 men and 9 women; age, 49±12 years; age range, 30 to 72 years) were enrolled in this study; their clinical details, including diagnosis and specific treatment, are listed in the Table. All patients were sedated with midazolam or propofol at the time of the study; fentanyl was used for analgesia. Patients lay in the 30° head-up position. Most patients had suffered an acute ischemic stroke (n=16); of these, 9 underwent hemicraniectomy, while 6 were treated with moderate hypothermia (33°C) according to our institutional protocol. Patients examined during hypothermia were additionally receiving vecuronium or atracurium for neuromuscular blockade. The same ventilator type was used for all patients enrolled in this study (Servo Ventilator 300, Siemens). All patients were ventilated with the use of a volume-controlled, pressure-regulated mode and an inspiratory/expiratory ratio of 1:2.

This study was performed according to ethical committee standards, and all data were analyzed without patient identification. Enrollment criteria were (1) invasive ICP measurement, (2) initial PEEP ≤4 mm Hg, (3) maximal inspiratory pressure <25 mm Hg, (4) no history of severe cardiopulmonary disease, and (5) at least unilateral temporal bone window adequate for transcranial Doppler examination. According to the protocol, the examination was to be discontinued and the PEEP returned to initial values if a sustained (>30 seconds) drop of CPP <65 mm Hg occurred. This, however, was not the case in any patient during the study. Most (17/20) patients received catecholamines via continuous infusion at the time of examination. This did not constitute an exclusion criterion for this study, provided that their dosage was kept unchanged throughout the monitoring period. Eight patients were also treated with intermittent boluses of mannitol (0.5 g/kg), glycerin (maximum 100 g/d), or combined 10% hydroxyethyl starch and 7.2% saline infusion (100 mEq/L).
affected side. Therefore, only V_m values derived from the MCA of 20 cases, mostly because of permanent MCA occlusion on the sweep speed, 5 seconds. Bilateral monitoring was only feasible in 5 follows: power, 110 to 150 mW; sample volume, 5 to 8 mm; and frequency of 100 Hz. Settings of the Doppler machine were as the MCA (V_m MCA) was registered online with a data acquisition device to minimize movement artifacts. Peak mean flow velocity of 52 to 58 mm and continuously insonated with the 2-MHz transducer(s) of a pulsed-wave ultrasound machine (Multi-Dop X-4, DWL). Thus, flow velocities of the MCA, ICP, MAP, and ECG sensors were always inserted ipsilateral to the affected hemisphere.

Arterial MAP was invasively monitored via a catheter inserted in the radial artery. ICP was monitored with the use of either parenchymal (Codmann [Codman microsensor, Johnson & Johnson], n=9, or Spiegelberg III [Spiegelberg pneumatic transducer, Spiegelberg AG], n=4) or ventricular (n=7) catheters. Parenchymal ICP sensors were always inserted ipsilateral to the affected hemisphere. MAP, ECG, and ICP curves were exported to the Doppler machine as analog data with the use of a commercially available interface (Siemens). Thus, flow velocities of the MCA, ICP, MAP, and ECG curves were simultaneously recorded in real time. Subsequently, all data were exported in ASCII format on a beat-to-beat basis for later evaluation. CPP was calculated as MAP minus ICP (mm Hg).

During each monitoring session, PEEP levels were successively changed to 4, 8, 12, and 4 mm Hg and kept stable for 5 minutes for each level. The time required for stabilization of functional residual capacity and arterial oxygenation after changing PEEP level was previously reported to be as short as 15 to 30 seconds. Therefore, 5-minute interval used for each PEEP level appears appropriate. Inspiratory pressure was adjusted accordingly to ensure that the tidal volume remained unchanged. Respiratory rate was not changed throughout the study. The number of monitoring sessions per patient varied between 2 and 7 (Table), depending on length of ventilation. ICP, MAP, V_m MCA, and heart rate (HR) values for each PEEP level were calculated by averaging the values acquired over the last minute of this level.

Results from each examination were only included in the final evaluation if the values obtained during the last PEEP level were within ±20% of the values obtained during the initial PEEP level; otherwise, it was assumed that the observed changes were not (or not solely) influenced by the changes in PEEP, and the results were discarded. This was the case in 2 of 64 (3.1%) examinations in our study. Nominal data were expressed as mean±SD. Nonnormally distributed data were expressed as median and 95% CI and compared with the Mann-Whitney U test. Potential differences in ICP, MAP, CPP, V_m MCA, and HR depending on the PEEP level were tested with the Kruskal-Wallis test. Correlation of nonparametric data was examined with the Spearman rank test. Statistical analysis was repeated with patients divided into 2 categories, depending on their initial ICP (≥15, <15 mm Hg). Significance was declared at the P<0.05 level.

Results
Median initial ICP was 11.5 mm Hg (95% CI, 9.9 to 13.2 mm Hg) (minimum, 1; maximum, 29 mm Hg); ICP was normal (<15 mm Hg) in 37 (60%) and elevated in 25 examinations (40%) (14 and 9 patients, respectively; numbers do not add up because the ICP of 3 patients was <15 mm Hg during the first examination and >15 mm Hg on the subse-
Figure 1. Median values and 95% CI of ICP, MAP, and CPP of 20 patients (62 examinations) during the various PEEP stages. *P<0.05, **P<0.005; all other differences were statistically not significant.

quent examinations). Median values and 95% CI of ICP, MAP, and CPP values from all examined patients, depending on the different PEEP levels, are displayed in Figure 1. No significant changes in median ICP or MAP were evident depending on PEEP (P=0.9 and P=0.2, respectively, Kruskal-Wallis). Median CPP values significantly differed depending on PEEP (P=0.02, Kruskal-Wallis; for comparisons between single values, see Figure 1). When PEEP was changed from 4 to 8 mm Hg, CPP decreased in 44 of 62 examinations (71%). This decrease corresponded to a median of 4.7% (95% CI, 3.4% to 6.5%) of the initial value (maximal decrease, 18.3% of the initial value). When PEEP was subsequently increased to 12 mm Hg, CPP decreased further. This decrease corresponded to a median of 6.7% (95% CI, 4.7% to 9.7%) of the initial value (maximal decrease, 33.8% of the initial value). When PEEP was returned to 4 mm Hg, CPP returned to baseline values (Figure 1). Vm MCA and HR remained unchanged throughout the study (P=1 and P=0.9, respectively, Kruskal-Wallis). No changes in arterial oxygen or carbon dioxide tension were observed during any examination. Separate analysis of patients with normal ICP and patients with increased ICP disclosed the same results as the initial analysis.

Three distinct reaction patterns of the parameters monitored were evident when the values of each individual patient were analyzed. In the first group (15 patients, 43 examinations), the different PEEP stages did not influence MAP (MAP within 90% to 110% of baseline values throughout each examination). No changes in ICP, Vm MCA, and CPP were evident in these patients (P>0.9, Kruskal-Wallis). Median initial ICP was 12.4 mm Hg (95% CI, 10.4 to 14.7 mm Hg) (minimum, 1; maximum, 29; elevated in 18 of 40 cases).

In the second group (7 patients, 16 examinations; Figure 2), increase of PEEP to 8 and 12 mm Hg resulted in significant decreases of MAP (MAP <90% of the baseline value), followed by a reincrease to baseline values when PEEP was reset at 4 mm Hg (P<0.0001, Kruskal-Wallis; for individual comparisons, see Figure 2). At the same time, Vm MCA remained unchanged during the complete monitoring period (P=0.7, Kruskal-Wallis), indicating that cerebral autoregulation was intact. ICP increased while PEEP was 8 and 12 mm Hg compared with PEEP of 4 mm Hg, but this difference did not reach statistical significance (P=0.7, Kruskal-Wallis; Figure 2). The maximal ICP increase was 22% and 35% under PEEP of 8 and 12 mm Hg, respectively, compared with baseline values. Linear regression analysis revealed a significant relation between the decline of MAP and the increase of ICP values (r²=0.75, P<0.0001, Spearman’s rank test). Changes in CPP depending on the different PEEP stages were significant (P<0.01, Kruskal-Wallis; for differences between single values, see Figure 2).

In the third group, consisting of 3 patients and a total of 6 examinations, increase of PEEP to 8 and 12 mm Hg also resulted in a drop in MAP (MAP <90% of the baseline value). In contrast to the second group, however, a similar drop was observed for Vm MCA. A weak but significant correlation between the changes in MAP and the changes in Vm MCA was evident (r²=0.49, Sₚ=2.8, P=0.01, Spearman’s rank test); these observations indicate that cerebral autoregulation in these patients was impaired. Either no changes or a slight decrease in ICP was noted. Because of the limited number of observations and the high data variation, no further statistical analysis was performed in this group. Results from a single examination of 1 of these patients are displayed in Figure 3. All 3 patients with this pattern had suffered an ischemic infarct, involving the complete territory of the right MCA, and underwent hemicraniectomy 1 to 2 days before their first examination.

Significant differences in CVP were evident when patients in whom no MAP decline was observed under higher PEEP levels (group 1) were compared with remaining patients (groups 2 and 3, 12.5 [95% CI, 11 to 15] versus 9.5 [95% CI, 7.5 to 11.5], respectively; P=0.01, Mann-Whitney).

Discussion

The influence of PEEP on ICP in patients with acute stroke has not been previously examined. Existing data were derived from animal models or patients with severe head injury.

Figure 2. Median values and 95% CI of ICP, MAP, and Vm MCA of 7 patients (16 examinations) with intact cerebral autoregulation during the various PEEP stages. *P<0.01, **P<0.001, §P<0.0001; all other differences were statistically not significant.
Huseby et al\textsuperscript{3} observed a significant decline in MAP, together with an ICP increase in a dog model under application of PEEP levels ranging from 0 to 20 cm H\textsubscript{2}O; these changes were less pronounced in the presence of intracranial hypertension. Aidinis et al\textsuperscript{4} reported ICP increases $>15$ cm H\textsubscript{2}O in 8 of 15 cats during application of graded PEEP levels (5 to 15 cm H\textsubscript{2}O) in a model of intracranial hypertension. Doblar et al\textsuperscript{5} observed significant decreases of MAP and CVP associated with a significant increase in cerebrospinal fluid pressure at a PEEP level of 15 cm H\textsubscript{2}O in healthy, mechanically ventilated goats. These effects could be counteracted by increasing initial CVP with mannitol. Feldman et al\textsuperscript{6} recently reported that intracranial compensatory reserves are significantly decreased in the presence of 10 cm H\textsubscript{2}O PEEP compared with 0 cm H\textsubscript{2}O PEEP in a rabbit model of space-occupying intracranial lesion. Thus, the results of several animal models unanimously argue for an increase in ICP under various PEEP levels. Most studies in head-injured patients also demonstrated ICP increases when PEEP was applied.\textsuperscript{7–10} These changes were again less pronounced in patients with high baseline ICP\textsuperscript{10} and appeared to be related to systemic hemodynamic effects of PEEP.\textsuperscript{8} Their magnitude considerably varied in the different studies: some reported significant impairment of CPP\textsuperscript{7,9} while others merely noted clinically insignificant ICP and CPP changes.\textsuperscript{8,10} Frost,\textsuperscript{11} on the other hand, failed to observe an ICP increase even under PEEP levels of 40 cm H\textsubscript{2}O in the absence of changes in cardiac output or blood pressure.

To date, no such studies have been conducted in patients with acute stroke. The fact that stroke victims constitute a significant proportion of patients in neurological intensive care units, together with the introduction of treatment options such as hypothermia, which not only necessitates mechanical ventilation but are also commonly associated with pulmonary infections,\textsuperscript{12} highlights the need for optimizing ventilation techniques in those patients. Because intracranial hypertension represents a major cause of mortality in acute stroke, similar to patients with acute brain injury, the safety of PEEP application represents an important issue.

Theoretically, increase of PEEP should result in an ICP increase through (1) the increased spinal pressure, reducing cerebrospinal fluid outflow; (2) the increased CVP, reducing cerebral venous outflow; and (3) the decline in MAP, resulting in cerebral vasodilation. One of the major findings of this study was that the reduction of cerebral venous or cerebrospinal fluid outflow does not influence the ICP, since we failed to observe any ICP changes in the 33 examinations in which PEEP variations did not affect MAP. This finding could be due to the fact that the patients were nursed in a position of 30° head elevation, which prevents the transmission of intrathoracic pressure to the intracranial contents through the collapse of the jugular veins, as was previously demonstrated in animal studies\textsuperscript{\textsuperscript{13}} and in neurosurgical patients.\textsuperscript{14} Drainage of cerebral veins through the vertebral plexus, which has been shown to play a major role in the erect position\textsuperscript{15} and is independent of the intrathoracic pressure, could also provide a possible explanation for this finding. In the presence of an intact cerebral autoregulation, decrease in MAP did indeed result in ICP elevations, although these were not significant and probably of limited clinical value.

Our results demonstrate that application of PEEP is only problematic because of its potential influence on MAP and therefore on CPP. The magnitude of CPP changes observed in this study suggests that this effect could be of major importance; nevertheless, these changes were mainly seen in association with lower CVP values. It thus appears reasonable to suggest that raising the CVP, as long as this is tolerated by the individual patient, should reduce the influence of PEEP on the CPP. The observation that increasing the PEEP level in stroke patients is safe as long as the MAP remains stable is of particular importance, since MAP monitoring is common practice, while ICP monitoring is applied in a minority of patients, even in neurological intensive care units.

Cerebral autoregulation could only be assessed in the 10 of 20 patients in whom the changes in PEEP level also resulted in MAP changes. Interestingly, all 3 patients diagnosed with an impaired autoregulation had suffered a right MCA infarction and undergone hemicraniectomy. On the contrary, cerebral autoregulation was found to be intact in the 3 patients with left MCA infarction treated with moderate hypothermia who demonstrated MAP changes. All patients treated with hypothermia were examined while their core temperature was 33°C to 34°C. Data from animal experiments suggest that hypothermia can enhance contractility of cerebral arteries.\textsuperscript{16} The influence of hypothermia on cerebral autoregulation has not been previously assessed, however. Our limited number of observations prohibits any statements on this matter.

The fact that examined patients were receiving a variety of vasoactive substances constitutes an obvious limitation of this study. Additionally, it was not possible to perform the same number of examinations in all patients. Furthermore, cerebral autoregulation was assessed on the healthy instead of the affected side, mainly because of permanent MCA occlusion. This is probably the reason that this was found to be impaired in only 3 of 10 patients. Still, we believe that these limitations constitute problems that can hardly be overcome in the clinical situation. ICP was &ge;15 mm Hg in 8 patients and 26 recordings in this study; ICP values between 20 and 30 mm Hg were only observed during 9 recordings in 3 patients. Thus, our results cannot be extrapolated to patients with high ICP values; further studies are necessary to evaluate the influence of PEEP in this group.

Figure 3. ICP, MAP, and $V_{m}$ MCA during the various PEEP stages in a patient with impaired cerebral autoregulation.

In conclusion, this article provides the first report of the influence of PEEP on ICP and CPP in patients with acute...
stroke. Our results suggest that PEEP levels up to 12 mm Hg result in negligible increases in ICP through decreased cerebral venous or liquor outflow. The observed marked changes in CPP are mediated through the MAP, both directly and (provided that the cerebral autoregulation is intact) indirectly through increases in ICP caused by cerebral vasodilation.

References
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