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Continuous Monitoring of Cerebrospinal Fluid Oxygen Tension in Relation to Motor Evoked Potentials during Spinal Cord Ischemia in Pigs

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Background: **Perioperative assessment of spinal cord oxygenation might guide measures to prevent neurologic deficits secondary to ischemic or traumatic damage of the spinal cord. Although cerebrospinal fluid (CSF) partial pressure of oxygen (Po_2) measurement has been used to detect spinal cord ischemia (SCI), the diagnostic value and the temporal resolution of CSF Po_2 measurement compared with functional assessment of the spinal cord is unknown. This study compared CSF Po_2 with transcranial motor evoked potentials (tcMEPs) for detection of experimental SCI.**

Methods: **The aorta and segmental arteries were exposed in 10 sufentanil-ketamine–anesthetized pigs (weight, 40–50 kg). Myogenic tcMEPs were recorded from the upper and lower limbs, and continuous assessment of CSF Po_2 was provided by two Clark-type microcatheters inserted in the lumbar and thoracic intrathecal space. Graded lumbar SCI was produced by sequential clamping of segmental arteries. The relation between CSF Po_2 and tcMEP during graded SCI was determined using linear regression. Diagnostic characteristics of CSF Po_2 values for clinical SCI were determined using different cutoff points of CSF Po_2.**

Results: **Lumbar CSF Po_2 (baseline, 44 [interquartile range, 38–54] mmHg) decreased below 50% in all animals and was linearly related to loss of tcMEP amplitude in all animals. The median lumbar CSF Po_2 during reduction of tcMEP to less than 25% of baseline was 11 (4–29) mmHg, whereas thoracic CSF Po_2 remained constant (40 [28–50] mmHg). During absence of the tcMEP signal, lumbar CSF Po_2 was less than 20 mmHg in 80% of the animals. Optimal sensitivity and predictive values of CSF Po_2 measurement for SCI were in the range of 40–60% of baseline.**

Conclusions: **The data indicate that intrathecal Po_2 measurement is a sensitive monitoring technique to track real-time changes in local spinal cord oxygenation. Continuous monitoring of CSF Po_2 might be applied for evaluation of patients who are at risk for direct or secondary SCI.**

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EVALUATION of spinal cord integrity during aortic or spinal surgery aims to prevent functional deficit after prolonged periods of spinal cord ischemia (SCI). Myogenic transcranial motor evoked potentials (tcMEPs) allow fast and reliable assessment of the integrity of motor tract conduction.[1,2] However, the movement artifacts that are associated with partial neuromuscular blockade,[3] the delivery of high-voltage stimuli to the brain, and the complexity of the technique might hamper the use of tcMEP in neurosurgical and critical care environments. Continuous assessment of parenchymal oxygenation *via* implanted microprobes is used clinically to detect cerebral ischemia after traumatic brain injury,[4–6] but direct measurement of spinal cord tissue oxygenation is not feasible with the current technology. Changes in cerebrospinal fluid (CSF) partial pressure of oxygen (Po_2) values, which can be more readily assessed, seem to parallel neuronal tissue oxygenation,[4,7] and recently, intrathecal Po_2 reduction was reported to correlate with early ischemic neuronal changes after 1 h of incomplete SCI.[8]

The current study was designed to evaluate the temporal resolution of CSF Po_2 measurement with tcMEP during rapid changes in experimentally induced spinal cord hypoperfusion. Furthermore, to detect spinal cord hypoxia before irreversible neuronal damage has taken place, determination of the CSF Po_2 value that corresponds with motor tract dysfunction might contribute. Loss of tcMEP signals precedes irreversible damage during SCI.[9,10] Myogenic recorded tcMEPs are lost almost instantaneously after cross clamping of the thoracic aorta,[11,12] which correlates with a severe reduction of spinal cord blood flow.[9] Although CSF Po_2 measurement techniques have been applied in patients,[13] validation of CSF Po_2 with monitoring methods that directly measure neurophysiologic function has not been reported. The purpose of this study was to determine the agreement and correlation between local CSF Po_2 values and lower limb tcMEP during progressive SCI.

Materials and Methods

Animal care and experimental procedures were performed in compliance with the National Guidelines for Care of Laboratory Animals in The Netherlands. The study protocol was approved by the Animal Research Committee of the Academic Hospital at the University of

Amsterdam (Amsterdam, The Netherlands). Ten pigs weighing 47 ± 5 kg were included in the study.

Anesthesia

Premedication consisted of 15 mg/kg intramuscular ketamine. Anesthesia was induced with inhalation by mask of 2.0% isoflurane in a mixture of 50% O_2 in air. Two intravenous catheters (18 gauge) were placed in an ear vein, and normal saline was infused at a rate of 15 ml · kg^{-1} · h^{-1}. After induction of anesthesia, 15 μg/kg sufentanil and 2 μg/kg clonidine were given intravenously; isoflurane was discontinued; and anesthesia was maintained with a continuous infusion of ketamine (15 mg · kg^{-1} · h^{-1}), sufentanil (5 μg · kg^{-1} · h^{-1}), and clonidine (1 μg · kg^{-1} · h^{-1}). The tracheas were intubated, and animals were ventilated using intermittent positive-pressure ventilation. End-tidal carbon dioxide concentration was measured by a mainstream capnograph (Hewlett-Packard, Boebingen, Germany), and arterial carbon dioxide tension (Pa_{CO_2}) was maintained between 4.8 and 5.3 kPa (36–40 mmHg). Mean arterial pressure (MAP) was maintained between 60 and 70 mmHg. Adequacy of ventilation was confirmed by blood gas analysis at 37°C. The level of neuromuscular blockade was monitored electromyographically using a Datex Relaxograph (Datex, Helsinki, Finland), placed at the animal's wrist equivalent after stimulation of the median nerve. A closed-loop infusion system with pancuronium was used to maintain 40% relaxation as referenced to the control situation. Arterial blood pressure and central venous pressure were measured by means of pressure lines placed in the right femoral artery and the left cephalic vein, respectively. Oxygen saturation was continuously assessed by pulse oximetry. Nasopharyngeal temperature and urinary output were monitored throughout the experiment. Before the induction of ischemia and every 30 min during ischemic manipulations, arterial *p*H, arterial oxygen tension (Pa_{O_2}), Pa_{CO_2}, hemoglobin concentration, and hematocrit were measured.

Motor Evoked Potential Recording

Transcranial motor evoked potential stimuli were applied with a transcranial electrical stimulator (Digitimer D 185 cortical stimulator; Digitimer Ltd, Welwyn Garden City, United Kingdom) through four needle electrodes attached to the scalp. A train-of-four pulse with an interstimulus interval of 2 ms was distributed over the motor cortex *via* an anode located at the occiput and three interconnected cathodes placed behind the ears and in the soft palate. Compound muscle action potentials were recorded bilaterally from the skin over the upper limb triceps muscles and over the lower limb quadriceps muscles using adhesive gel Ag/AgCl electrodes. The signals were amplified 5,000–20,000 times (adjusted to obtain maximum vertical resolution) and filtered between 30 and 1,500 Hz using a 3-T PS-800 biologic amplifier (Twente Technology Transfer, Twente, The Netherlands). Stimulus intensity was adjusted to acquire maximal responses, and recording was performed 10% above the level that obtained maximal amplitude. Amplitude of the compound muscle action potentials was defined as the peak-to-peak distance in microvolts. A reduction of tcMEP amplitude on the muscle groups monitored to less than 25% of the baseline value was considered an indication of ischemic spinal cord dysfunction. Baseline tcMEPs were obtained during the surgical procedure by averaging 15 consecutive responses before the start of SCI induction. During the ischemic manipulations, tcMEPs were acquired every minute. Responses were displayed and stored on a MacIntosh Quadra computer (Apple Computer, Cupertino, CA) with 12-bit A/D conversion and acquisition software written in the LabVIEW programming environment (National Instruments, Austin, TX).[14]

Operative Procedure

The animals were placed on their right flank. Two laminectomies were performed at the L5 and Th9 level, with sufficient lateral extension to allow bilateral exposure of the local spinal roots. After minimal incision of the yellow ligament and the dura mater, two polarographic Clark-type microcatheters (LICOX P_{O_2} probe; GMS, Kiel, Germany) were carefully introduced into the subdural space and advanced in a cranioventral direction for approximately 3 cm, so that the tips of the probes were located over the ventral aspect of the spinal cord. Likewise, two temperature probes (LICOX temperature probe; GMS) were inserted and advanced in a position 1 cm cranial to the P_{O_2} probes. Finally, a 3-French catheter for CSF pressure measurement was inserted at the L5 level and advanced in a cranial direction for 5 cm. The catheters were carefully secured by closing the dura mater and yellow ligament with purse-string sutures, and the dorsal vertebral muscles were approximated.

Animals were then placed in the right decubitus position. The thoracoabdominal aorta, the segmental arteries, and the medial sacral artery were exposed by way of a left-sided thoracophrenic laparotomy. The group of vessels recruited for the induction of SCI consisted of all discernible segmental arteries and the medial sacral artery. At the end of the experiment, the interior of the aorta was inspected to determine whether all lumbar and intercostal segmental arteries had been identified.

Experimental Design

Fifteen minutes before the induction of lumbar SCI, baseline values for tcMEP and CSF P_{O_2} were obtained. Graded lumbar SCI was induced by sequential clamping of segmental arteries in a caudal-to-cranial direction, thus occluding the arteries that are most critical for the perfusion of the lumbar spinal enlargement at the beginning of the clamping sequence. A time interval of 5 min was applied between the clamping of two successive arteries. In pilot experiments, this period was sufficient for

CSF Po_2 values to equilibrate after clamping of an artery. After complete loss of the hind limb tcMEP signal, all clamps were released, and after 15 min of reperfusion, animals were euthanized.

Data Collection and Analysis

Analog signals of MAP, intracranial pressure, CSF Po_2, and CSF temperature were digitized every 3 s and stored on a personal computer with acquisition software written in the LabVIEW programming environment. Movement artifacts of the CSF Po_2 measurements caused by transcranial stimulation were filtered out during off-line analysis. All tcMEP and CSF Po_2 data were examined by an observer blinded to the experimental design using a replay module of the monitoring program, and recordings with poor signal quality were excluded from further analysis.

The statistical analysis was based on nine cases of graded SCI (325 tcMEP/CSF Po_2 pairs, with an average duration of 29 min [interquartile range, 27–36 min]). To examine the relation between CSF Po_2 and tcMEP, we performed a repeated-measures analysis of variance by fitting a linear mixed-effects regression model with tcMEP as the independent variable and CSF Po_2 as the dependent variable assuming a fixed correlation between repeated measures of the same animal (statistical package S-PLUS 2000; Insightful, Surrey, United Kingdom).[15] Basically, in this analysis, a separate linear regression line of CSF Po_2 on tcMEP for each animal was estimated with a different intercept for each animal but the same slope in all animals. To improve the fit of these regression lines, we allowed that the scatter around the regression lines also differed between animals; thus, we estimated a residual variance in each animal.

Individual receiver operating characteristic (ROC) curves were constructed to determine the accuracy of CSF Po_2 measurement to detect loss of tcMEP. A ROC curve is a graphic representation of the trade-off between false-positive and false-negative rates for every possible cutoff in a regression analysis of binary outcomes.[16] The graph plots the false-positive rate on the x-axis and the true-positive rate (1 − the false-negative rate) on the y-axis. The area under the ROC curve, which ranges between 0 and 1 (1 = optimal diagnostic accuracy), was presented. Sensitivity, specificity, and predictive values were calculated using standard equations.

Mean arterial pressure, CSF pressure, *p*H, Pao_2, $Paco_2$, hemoglobin concentration, and hematocrit are expressed as mean ± SD. Raw and relative (compared with baseline) tcMEP amplitudes, absolute CSF Po_2 values, and time are presented as medians (interquartile ranges). A *P* value of less than 0.05 was considered significant.

Results

Throughout the experiment, *p*H, $Paco_2$, Pao_2, hemoglobin concentration, and hematocrit were within normal limits in all animals. Individual MAP and CSF pressure values during three stages of graded SCI are shown in table 1. MAP values before and during SCI were 59 ± 4 and 58 ± 3 mmHg, respectively. During sequential clamping, CSF pressure was 7 ± 3 mmHg. Eight to 12 intercostal segmental arteries, 6 lumbar segmental arteries, and the medial sacral artery were identified. Complete loss of the hind limb tcMEP signal was established after sequential clamping of 8 ± 4 arteries.

Table 1. Individual MAP and CSFP Values during Gradual Loss of Spinal Cord Conduction

	MAP			CSFP		
Animal	Baseline, mmHg	MEP 25%, mmHg	No WF, mmHg	Baseline, mmHg	MEP 25%, mmHg	No WF, mmHg
1	63	57	57	12	12	12
2	58	56	53	6	4	4
3	57	61	66	10	10	10
4	60	59	60	6	5	5
5	55	60	60	6	6	6
6	64	59	60	5	5	5
7	59	54	55	5	5	5
8	51	52	53	6	6	6
9	63	66	58	8	10	10
10	61	61	61	5	4	4

Individual mean arterial pressures (MAPs) and cerebrospinal fluid pressures (CSFPs) during three stages of graded spinal cord ischemia, before and during spinal cord ischemia.

Baseline = just before clamping; MEP 25% = at the moment that motor evoked potential (MEP) was reduced to below 25% of baseline, being equal to clinical spinal cord ischemia; no WF = no waveform, complete absence of corticospinal conduction.

Reproducible tcMEPs were recorded in all animals, and the median amplitude before ischemic manipulations was 2,750 (1,320–3,865) μV. During sequential clamping of segmental arteries, tcMEPs were reduced to less than 25% of baseline value in all animals except one. In this animal, postmortem observation showed that two segmental arteries had not been identified during operation. This animal was not included in the analysis. In the other animals, postmortem observations showed that all arteries had been identified before experimental manipulations.

Figure 1 shows tcMEPs and CSF Po_2 for every successive clamping stage during graded SCI. Individual absolute CSF Po_2 values during four stages of graded SCI are shown in table 2. The period between the start of ischemic manipulations and the reduction of tcMEP signals to less than 25% was 24 (22–27) min. The local CSF Po_2 values during baseline recording were not different at the lumbar (44 [interquartile range, 38–54] mmHg) and the thoracic level (40 [28–50] mmHg). During absence of the tcMEP signal, CSF Po_2 was less than 20 mmHg in 80% of the animals. Median lumbar CSF Po_2 values when tcMEP was reduced to values less than 50, 25, and 0% of baseline were 25 (11–34), 11 (4–29), and 12 (2–17) mmHg, respectively.

Transcranial motor evoked potential reduction to below 25% was associated with a CSF Po_2 of 32% (9–54%)

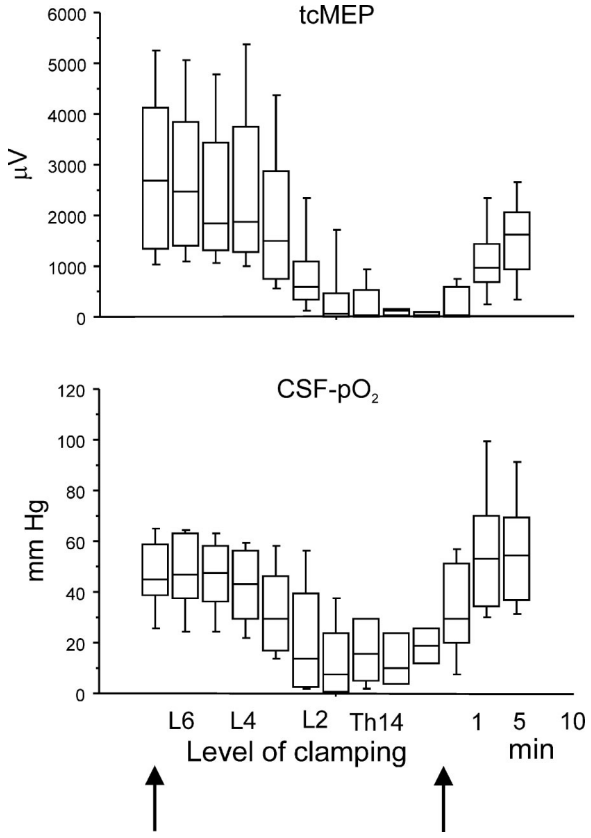

Fig. 1. Box-and-whisker plot of transcranial motor evoked potentials (tcMEPs) and cerebrospinal fluid (CSF) partial pressure of oxygen (Po_2) values (medians and interquartile ranges) during sequential clamping of segmental arteries and 10 min of reperfusion for all animals (n = 9). The *vertical arrow on the left* depicts the start of sequential segmental artery clamping; the *vertical arrow on the right* marks the onset of reperfusion. min = time in minutes during reperfusion.

compared with baseline at the lumbar level. In contrast, thoracic CSF Po_2 was 99% (84–106%) compared with baseline after the same tcMEP reduction. An original continuous registration of local oxygenation and tcMEP recording during graded SCI in one animal is shown in figure 2.

Relative values of both lumbar Po_2 and tcMEP were used for the statistical analysis because the variability of baseline tcMEP amplitudes did not allow for comparison of absolute values. On average, 1 percent point reduction of relative tcMEP was associated with 0.90 percent point reduction of CSF Po_2 (95% confidence interval, 0.85–0.94) with an average intercept of 12 percent points.

The area under the ROC curve was 1 for all animals except for animals 6 and 10, with respective areas of 0.942 and 0.923. This gives an average area under the ROC of 0.985. The validity of the CSF Po_2 monitoring results was further characterized with predictive values. Positive and especially negative monitoring results were most reliable in the range between 40 and 60% of CSF Po_2 cutoff points. Positive predictive values (proportion of true-positive observations within one animal) greater than 0.85 were observed in 50, 40, and 40% of all animals for the respective CSF Po_2 cutoff points of 40, 50, and 60%. Negative predictive values (proportion of true-negative observations within one animal) greater than 0.95 were observed in 90% of all animals for the same CSF Po_2 cutoff points.

Table 2. Individual CSF Po_2 Values during Gradual Loss of Spinal Cord Conduction

	Lumbar Segment				Thoracic Segment	
Animal	Baseline, mmHg	MEP 50%, mmHg	MEP 25%, mmHg	No WF, mmHg	Baseline, mmHg	MEP 25%, mmHg
1	55	35	21	15	56	55
2	53	62	38	23	48	37
3	41	16	4	1	28	28
4	22	14	7	2	51	60
5	30	1	0	0	23	23
6	56	25	27	29	49	64
8	55	32	11	12	26	22
9	43	34	34	13	40	35
10	44	2	2	2	40	42

Individual lumbar cerebrospinal fluid (CSF) partial pressure of oxygen (Po_2) values during four main stages of graded spinal cord ischemia, and thoracic CSF Po_2 before and during spinal cord ischemia.

Baseline = CSF Po_2 just before clamping; MEP 25% = CSF Po_2 at the moment that motor evoked potential (MEP) was reduced to below 25% of baseline, being equal to clinical spinal cord ischemia; MEP 50% = CSF Po_2 at the moment that was reduced to below 50% of its baseline value; no WF = no waveform, CSF Po_2 during complete absence of corticospinal conduction.

Discussion

In the current study, continuous measurement of lumbar CSF oxygenation correlated with the integrity of motor tract conduction during progressive SCI in pigs. In all animals, a similar linear relation was present between tcMEP and CSF Po_2. Furthermore, CSF Po_2 measurement showed a high sensitivity and specificity for clinical SCI. The predictive power of CSF Po_2 measurement for the detection of SCI was optimal between the relative cutoff points of 40 and 60% of CSF Po_2 baseline value.

Model

We opted to induce graded SCI by sequential clamping of segmental arteries in pigs. The spinal cord blood supply of this animal resembles that of humans because it comprises a plurisegmental segmental artery supply of a continuous anterior spinal artery, with the most vulnerable region regarding spinal cord blood flow located at the lower thoracic level.[17] Moreover, the same range of baseline CSF Po_2 values was described in the CSF in the lateral ventricles of pigs and humans.[4,18]

To evaluate the diagnostic accuracy of CSF Po_2 measurements, we opted to use tcMEP amplitude decrease as a functional criterion for SCI for several reasons. First, in contrast to most target areas of on-line brain tissue oxygenation measurements, functional evaluation of the

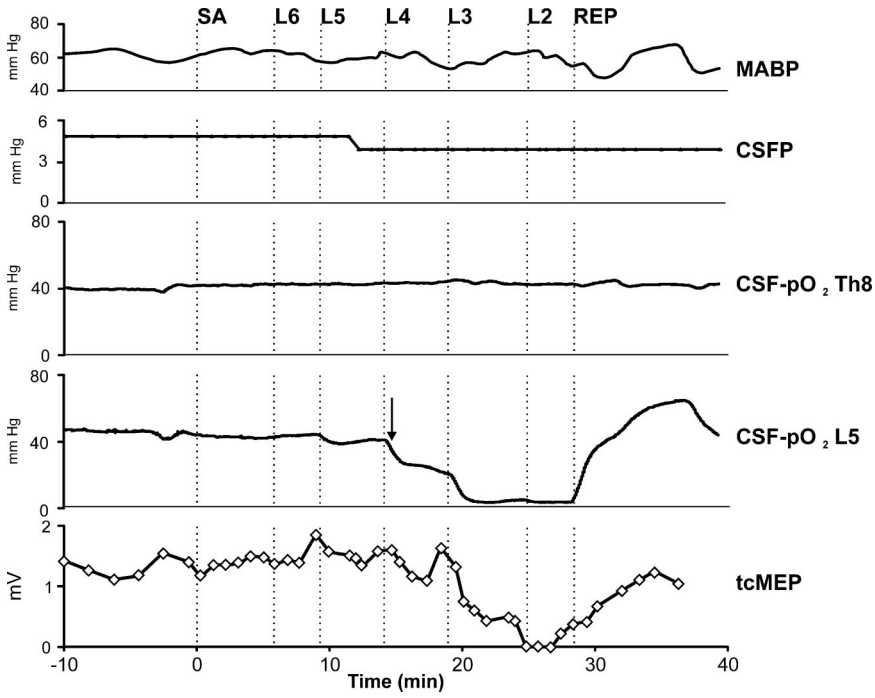

Fig. 2. Graph showing original continuous registration of five parameters in one animal. *Dashed vertical lines* represent the events of placing a clamp on the segmental artery indicated with sacral artery (SA), or the *x*th lumbar level. Note that reduction of lumbar cerebrospinal fluid (CSF) partial pressure of oxygen (Po_2) precedes the decline of transcranial motor evoked potentials (tcMEPs) (*arrow*). CSFP = cerebrospinal fluid pressure; MABP = mean arterial blood pressure; REP = reperfusion.

corticospinal motor pathways can be reliably conducted by the recording of myogenic tcMEPs.[2] Second, we recently showed that severe reduction of lumbar spinal cord blood flow corresponded with fast reduction of myogenic tcMEPs in a porcine model.[19] Third, after an ischemic episode of such severity that irreversible neuronal loss occurs, spinal cord blood flow or oxygenation may return to normal. Functional assessment by tcMEP might prevent such false-negative monitoring results. Fourth, in contrast to the recording of somatosensory evoked potentials, the monitoring of tcMEP seems to have good diagnostic properties for the detection of spinal cord motor pathway ischemia.[20,21] Therefore, tcMEP was used as the independent variable in the current study because this monitoring technique allows for direct functional assessment of the spinal cord.

Loss of tcMEP responses was defined as a reduction of tcMEP amplitude to less than 25% of the baseline value. A generally accepted criterion for SCI during evoked potentials monitoring of the somatosensory pathways is a decrease of amplitude to less than 50% of baseline or a 10% latency increase.[22] Our more restrictive criterion for spinal cord dysfunction was based on the larger amplitude variability of tcMEP signals compared with somatosensory evoked potentials.[23] Possibly, this amplitude variability depends on the partial muscle relaxation that is a minimal requirement for myogenic evoked potential recording.[3]

Partial Pressure of Oxygen

Progressive SCI was associated with a median decrease of CSF Po_2 to 32% of baseline, corresponding with absolute values between 9 and 27 mmHg. The observed decreases in CSF Po_2 are in agreement with previously reported data in animal models of SCI[8,24] and focal cerebral ischemia[25] and are also similar to transient decreases in brain tissue oxygenation during cerebrovascular occlusion in patients.[26] Moreover, CSF Po_2 values during complete abolishment of tcMEP were similar to earlier reports of intraspinal and surface Po_2 measurements after experimental aortic occlusion.[27]

The current baseline spinal CSF Po_2 values were approximately 20 mmHg lower than baseline values found in porcine ventricular CSF Po_2 at a Pao_2 of 100 mmHg, but they are consistent with values observed in the subarachnoidal space.[18] No significant change in thoracic CSF Po_2 was observed during ischemic manipulations, indicating that the spinal hypoxia that was induced with this model was restricted to the lumbar intumescence. Thoracic white matter tracts and motoneurons in the lumbar anterior horn might have a different sensitivity to signal transmission block during ischemia.[19] In the current study, we opted to confine ischemia to the lumbar spinal cord to relate fast synaptic conduction block of lumbar anterior horn motoneurons to local changes in CSF oxygenation. In theory, extension of the CSF Po_2 gradient along the rostrocaudal axis over time cannot be ruled out. However, we did not study the influence of a long duration of focal SCI on oxygenation of different levels in the intrathecal compartment.

Clinical Application

Local brain tissue oxygen monitoring is used in head-injured patients to detect and prevent the effects of cerebral ischemia.[4–6] Similarly, spinal cord tissue oxygen measurement could be useful to monitor intraoperative SCI or secondary ischemic episodes after acute

spinal cord injury. However, the vulnerability of the spinal cord to intraparenchymal probe placement limits the use of direct evaluation of spinal tissue oxygenation by the current devices. The strong relation between tcMEP and CSF Po_2 values, the high temporal resolution of the latter technique, and the diagnostic properties in relation to tcMEP recording might render spinal CSF Po_2 measurement a feasible, minimally invasive monitoring technique of spinal cord oxygenation in several surgical and critical care settings. In addition, CSF Po_2 monitoring does not carry the risk of sudden patient movements as introduced by tcMEP application.

Recently, intrathecal oxygenation was monitored to detect spinal cord ischemic dysfunction in patients undergoing aortic aneurysm resection.[13] Three measurements of CSF Po_2 were presented during ischemic manipulations: at baseline, 30 min after aortic clamping, and after 30 min reperfusion. The authors described a rapid decline of CSF Po_2 after aortic clamping. However, no conclusions could be drawn regarding the diagnostic accuracy and temporal resolution of the technique. Because false-negative monitoring results have devastating consequences for the patient, it is essential to determine the optimal test properties of CSF Po_2 measurement. The current data indicate the relevant pathophysiologic levels of CSF Po_2 that correspond with varying degrees of spinal cord dysfunction. This might contribute to the reliable detection of fast ischemic changes in the spinal cord before irreversible neuronal damage has occurred, in several pathologic and surgical conditions. The presence of residual flow during tcMEP loss, as measured with laser Doppler flowmetry, and radioactive microspheres[9,19] supports the idea that detection of SCI before actual damage has taken place is feasible. Moreover, neuronal loss and infarction seldom occur when the duration of SCI is less than 15 min.[10] However, clinical studies are needed to determine the critical threshold of CSF Po_2 as a function of the ischemic period in relation to neurologic outcome.

Conclusion

The data indicate that continuous Po_2 measurement in the spinal CSF might become a reliable and sensitive technique to detect real-time changes in local spinal cord oxygenation in patients who are at risk for direct or secondary SCI.

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