Xenon Attenuates Cerebral Damage after Ischemia in Pigs

Michael Schmidt, M.D.,* Thomas Marx, M.D.,† Egon Glöggli,‡ Helmut Reinelt, M.D.,* Uwe Schirmer, M.D.§

Background: Cerebral blood flow may be compromised in a variety of clinical situations (e.g., stroke, trauma, cardiac arrest) and surgical procedures (e.g., intracerebral aneurysm clipping, aortic arch surgery). The induced cerebral cell injury results in neurologic deficit and permanent loss of neurocognitive function. Xenon is described as an effective neuroprotectant in both in vivo and in vitro models of acute neuronal injury. In the variety of clinical indications, the need for neuroprotection is described best for cardiac patients. Ischemic cerebral complications represent the leading cause of morbidity after cardiac operations. The reported incidence of perioperative stroke as a major neurologic complication varies from 0.4 to 5.4%, and in-hospital neuropsychological dysfunction as a minor neurologic problem occurs in 25–79% of the cases. The underlying pathology consists of a variety of mechanisms, e.g., hemodynamic fluctuations, cerebral embolization of atherosclerotic plaque, air, fat and platelet aggregates caused by cardiopulmonary bypass and surgical procedure. These mechanisms induce an imbalanced state of oxygen supply and demand causing major (type I, fatal cerebral injury and nonfatal strokes) and minor (type II, new deterioration in intellectual function or new onset of seizures) neurologic complications.

One of every $10 spent on surgical treatment of coronary disease is related to a complication in the United States. As compared with patients without adverse neurologic outcome, type I neurologic complications are responsible for an additional $10,266 per patient in in-hospital boarding costs, and type II events are responsible for an additional $6,150 per patient. When one applies these estimates to the 800,000 patients per year who undergo coronary surgery throughout the world, the additional in-hospital cost is approximately $400 million annually. The expense of long-term out-of-hospital medical and rehabilitative services probably results in additional expenditure of some $2 billion to $4 billion annually.

With the growing awareness of their social and economic importance, increasing attention is being given to neuroprotective strategies, not only in cardiac anesthesia.

The neuroprotective effect of xenon is thought to involve blockade of the N-methyl-D-aspartate subtype of the glutamate receptor as a key step in the cascade of neuronal damage. With almost ideal characteristics as a safe anesthetic combined with data suggesting a role for xenon in neuroprotection, the current study was designed to determine whether xenon would attenuate cardiac arrest–induced brain injury in pigs. This model for transient cessation of cerebral perfusion with a certain time onset and offset was chosen because the common pathophysiologic mechanism of all clinical situations of inadequate cerebral perfusion leading to cerebral damage is deprivation of oxygen or glucose or both to the brain. Because depletion of intrinsic central nervous system energy stores occurs within 2–4 min of anoxia, we imitated this clinically relevant situation in our experimental model and investigated the effect on cerebral microdialysis results during inhalation of xenon as compared with total intravenous anesthesia (TIVA).

Materials and Methods

After approval by the local animal care committee (Rezirkunpräsidium Tübingen, Tübingen, Baden-Württem-
dose of 4 mg/kg azaperone (Stresnil®; Janssen Pharma-
water. Before induction of anesthesia, a premedication
animals were fastened overnight with free access to
approved veterinary surgeon.
240 min (fig. 1). Each experiment was supervised by an
achieved. All parameters were investigated for a time of
defibrillation was not successful, further CPR was per-
odular fibrillation was terminated by electrical defibrillation. If
defibrillation was not successful, further CPR was per-
formed until return of spontaneous circulation could be
achieved. All parameters were investigated for a time of
240 min (fig. 1). Each experiment was supervised by an
approved veterinary surgeon.

Anesthesia
The animals were cared and handled in accordance
with the US National Institutes of Health guidelines. The
animals were fastened overnight with free access to
water. Before induction of anesthesia, a premedication
dose of 4 mg/kg azaperone (Stresnil®; Janssen Pharma-
ceutica, Neuss, Germany) and 0.1 mg/kg atropine
(Braun, Melsungen, Germany) was administered intra-
vascularly. An ear vein was punctured, an intravenous
line was placed, and anesthesia was induced with a bolus
dose of 10 mg/kg body weight of pentobarbital (Nem-
butal®; Sanofi CEVA, Munich, Germany). Analgesia was
achieved by an intravenous dose of 0.01 mg/kg bu-
prenorphine (Temgesic®; Boehringer Mannheim, Mann-
heim, Germany). Neuromuscular relaxation was ex-
vided by a single dose of 0.1 mg/kg pancuronium
bromide (pancuronium duplex curamed; CuraMED
Pharma GmbH, Karlsruhe, Germany). After the trachea
was intubated anesthesia was maintained with a con-
stant infusion of 0.2 mg · kg⁻¹ · min⁻¹ pentobarbital and
0.008 μg · kg⁻¹ · min⁻¹ buprenorphine.
Lactated Ringer’s solution was infused at a rate of
8 ml · kg⁻¹ · h⁻¹ with an infusion pump (Infusomat;
Braun).

Body temperature (blood temperature) was recorded
from the thermistor of the pulmonary artery catheter and
was maintained constant using a heating blanket.
The level of anesthesia was assessed using a spectral
edge frequency 95 (SEF₉₅) electroencephalographic
monitor. SEF₉₅ levels of approximately 8 were regarded
to be sufficient, and no reactions to ventilation or surgi-
cal manipulation were observed. During instrumentation
of the animals (phase 1) controlled ventilation was per-
formed using room air. Intermittent positive-pressure
ventilation was performed in a partial rebreathing sys-
tem (Draeger Cicero; Draegerwerk Luebeck, Germany),
which was calibrated for xenon by the manufacturer.
The fresh gas flow was set to 1 l/min. The ventilation
volume was adjusted to achieve normocapnia according
to blood gas analysis. During phase 2 of anesthesia,
xenon (75%) in oxygen (25%) or air in oxygen (25%) was
added to the inspiratory gas mixture according to ran-
donization. To compensate the higher uptake of xenon
immediately after application, the flow was increased to
6 l/min during the first 5 min. Xenon was supplied in a
purity of 99.9999% by Linde (Linde-Gas Therapeutics,
Lidingö, Sweden).

To exclude other known additional influences of neu-
roprotection in our experiment, the body temperature
of the animals was kept constant, and no hypothermia
occurred. For the same reason, the coadministered in-
travenous anesthesia was reduced in the xenon group
during inhalation of xenon to maintain comparable
depth of anesthesia in both groups by means of SEF₉₅
during investigation time.

Study Protocol
In phase 1 of the experiment, multiple catheters were
inserted for hemodynamic monitoring. A Swan-Ganz
catheter was placed into the right vena subclavia and, by
a femoral cut down, a 7-French arterial line was inserted
in the descending aorta for monitoring of blood pressure
and withdrawal of blood samples. All catheters were
flushed with physiologic saline at a rate of 3 ml/h (Intra-
flow; Abbott Laboratories, Wiesbaden, Germany).
By two parietal drill holes in the skull, a subdural ICP
probe (Camino catheter/Ventrix Monitor; NeuroCare
Group, San Diego, CA), a cerebral microdialysis catheter
(Cerebral Microdialysis AB, Solna, Sweden) and a tem-
perature-adjusted brain ptio₂ probe (Gesellschaft für
medizinische Sondentechnik, GMS, Kiel, Germany) were
placed in the brain. After completion of surgery 5,000 U
heparin was administered to prevent clot formation.
The animals were left without any stimulus for 60 min of
hemodynamic renormalization.
After this first period, during phase 2, the investigation
anesthetic procedure (xenon or TIVA) was conducted
according to the randomization list. The animals were
assigned to two groups to receive anesthesia with either
gxenon (75%) in oxygen (25%) or TIVA combined with air
in oxygen (25%) ventilation 15 min before cardiac arrest.
Ventricular fibrillation (t₀) was induced by electrical defibrilation
by an alternating current (60 Hz, 20 V). After cardiac arrest of
Fig. 1. Study design with 4 min of cardiac arrest, 1 min of
closed-chest cardiopulmonary resuscitation (CPR), and 240 min
of investigation. ROSC = return of spontaneous circulation.

4 min, closed-chest CPR with application of vasopressin (20 U) was performed for 1 min, and ventricular fibrillation was terminated by electrical defibrillation. If defibrillation was not successful, CPR was continued until return of spontaneous circulation could be achieved. The study parameters were investigated for 240 min. All parameters were measured simultaneously every 30 min. After investigation, all animals were killed during general anesthesia. Four animals had to be excluded from the study because of septic or resuscitation complications.

**Measurements**

For electroencephalographic monitoring, we used a bispectral electroencephalographic monitor A 2000® (Aspect Medical Systems Inc., Natick, MA) and an SEF electroencephalographic monitor (IXP 1; Datex-Ohmeda, Helsinki, Finland). Inspiratory and expiratory oxygen and carbon dioxide concentrations were measured simultaneously (Draeger Cicero). Inspiratory and expiratory xenon concentrations were measured by mass spectrometry (Xenotec 2000; Leybold, Cologne, Germany). Simultaneously, blood gas analysis was performed with a blood gas analyzer in combination with a hemoximeter (ABL 700/OSM 3, Radiometer, Copenhagen, Denmark), which was calibrated for porcine blood. Mean arterial blood pressure, heart rate, central venous pressure, and pulmonary arterial pressure were measured using a Datex CS/3 monitor (Datex-Engstrom, Helsinki, Finland). All parameters were measured simultaneously every 30 min. Cardiac output was measured continuously with a Vigilance Monitor (Baxter Healthcare, Irvine, CA).

**ICP, CMD, and Brain ptiO2 Measurements**

For ICP measurement, a subdural intracranial pressure monitoring system (Camino catheter/Ventrix Monitor) was inserted in subdural position via a drill hole. The catheter was secured with a tight Camino bolt system at the insertion site corresponding to the parietal lobe of the cerebrum. The following system specifications of the Camino system are given by the manufacturer: accuracy ±10%, zero point drift 2 mmHg in 24 h, and time constant less than 50 ms for increasing or decreasing pressure. Before each investigation, the accuracy of the system was tested in a water bath.

Via the same way a cerebral microdialysis catheter (CMA; Cerebral Microdialysis AB) was placed in the brain. In approximately 2 cm distance, a temperature-adjusted brain ptiO2 probe (Gesellschaft für medizinische Sondentechnik) was inserted into the brain by a second drill hole.

The difference between mean arterial blood pressure and ICP was used to calculate cranial perfusion pressure.

Cerebral microdialysis was used in our study as an *in vivo* approach to cerebral cell metabolism and integrity. Microdialysis has been used for many years to investigate alterations in the neurochemical milieu of experimental animals. More recently, this technique has been used in humans with different indications, including patients with Parkinson disease, subarachnoid hemorrhage, and head injury. Increases of microdialysate lactate and excitatory amino acids have been described in head injury patients experiencing clinical and physiologic deterioration. In several human studies, ischemia in cerebral vascular surgery has led immediately to characteristic changes in the extracellular fluid, which are measurable by microdialysis. It is concluded that microdialysis is a sensitive method of detecting intraoperative changes in cerebral metabolism. These alterations reflect changes in the composition of the extracellular fluid of the brain in the vicinity of the microdialysis probe. Such measurements provide fundamental insights into the cellular and molecular events of underlying diseases and also in action and possible side effects of anesthetics. Glutamate, lactate, pyruvate, and glycerol in the dialysate were measured by an automated spectrophotometric kinetic enzymatic analyzer (CMA 600; Cerebral Microdialysis AB).

**Technical Aspects**

We used microdialysis with a CMA70 catheter, perfused by a precision microdialysis-pump using disposable precision syringes. The flow rate of the lactated Ringer’s solution used in our study was low (0.3 µl/min), to reach high concentrations of analytes in the dialysate. The 10-mm dialysis membrane of the CMA70 brain catheter used in this study gives approximately 80% of the concentration in the extracellular fluid. The 30-mm dialysis membrane would make it possible to reach close to 100% recovery but could not be implanted because of anatomical reasons in the pig brain. The dialysate was collected in microvials designed for low evaporation and minute volumes. Glucose as the energy source of the brain was measured systemically in the arterial blood to monitor normoglycemia.

As in other microdialysis studies investigating acute pathologic processes, we choose to perform our experiment on the same day as implantation of the microdialysis probe after allowing tissue recovery for a short term of 2 h. Grabb *et al.* raise concerns about the use of chronically implanted microdialysis probes because the tissue surrounding chronically implanted probes exhibited a high degree of inflammation and fibrin deposits were substantial. Both *in vitro* and *in vivo* tests revealed a diffusional barrier in chronically implanted probes after 24 h as compared with probes implanted acutely for 2 h.

**Statistical Analysis**

Values are expressed as mean ± SD. Statistical analysis was conducted using the Sigma Stat and Sigma Plot software package (Jandel, Hamburg, Germany). To compare the effect of treatment within one group, repeated-measurements analysis of variance was used. In normally...
distributed data, analysis of variance was used to determine differences between three groups at the same points of observation. In non-normally distributed data, the Kruskal-Wallis analysis of variance on ranks was used. Sigma Stat uses the Kolmogorov-Smirnov normality test. For the interpretation of the glycerol results, area under curve procedures were calculated. Statistical significance was considered to be at the $P < 0.05$ level.

**Results**

As a result of cardiac arrest and failure of cerebral perfusion for 4 min, brain ptiO$_2$ decreases from normal values (xenon group, 11.5 mmHg vs. control group, 12.5 mmHg) to critical values (fig. 2). Corresponding to that pathology, electroencephalographic activity demonstrated as SEF$_95$ is depressed as sign of reduced electrical activity (fig. 3). Resuscitation time including closed-chest CPR until return of spontaneous circulation was not significant different for the xenon group versus the control group (3 vs. 2.5 min). After return of spontaneous circulation, return of spontaneous circulation brain ptiO$_2$ increased significantly over time up to supranormal values for both groups (fig. 4). As compared with control, there were higher brain ptiO$_2$ levels for the xenon group, but the differences did not reach significance.

Systemic perfusion expressed as continuous cardiac output did not change over the investigation period of 240 min for either group (table 1).

Blood gas determination values were not different for the two groups and are given in table 2.

During reperfusion time, there was a significant increase in ICP for both groups, but there was no significant difference between the groups (table 1).

In cerebral microdialysis results, there were no significant differences in glutamate between the groups (fig. 5).

Lactate concentrations increased significantly after 60 min in both groups as compared with t0 but returned earlier toward normal values (t150) in the xenon group. Lactate concentrations remained increased until the end of investigation at t240 for the control group (fig. 6).

Correspondingly, the lactate/pyruvate ratio reached a pathologic peak after 60 min reperfusion time, with ratios of 33 for the xenon group and 39 for the control group, respectively. During the investigation time of 240

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**Fig. 2.** Brain tissue partial oxygen pressure (ptiO$_2$) at baseline (t0) and after cardiac arrest until return of spontaneous circulation for xenon and total intravenous anesthesia groups. Box plot with median, 25th–75th percentiles (box), and 5th–95th percentiles (whiskers). No significant differences between the groups. CPR = cardiopulmonary resuscitation.

**Fig. 3.** Electroencephalogram, spectral edge frequency 95% at baseline (t0) and after cardiac arrest until return of spontaneous circulation for xenon and total intravenous anesthesia groups. Box plot with median, 25th–75th percentiles (box), and 5th–95th percentiles (whiskers). CPR = cardiopulmonary resuscitation.

**Fig. 4.** Brain tissue partial oxygen pressure after return of spontaneous circulation for xenon and total intravenous anesthesia groups. Box plot with median, 25th–75th percentiles (box), and 5th–95th percentiles (whiskers). No significant differences between the groups; * significant difference as compared with t0 for xenon group; + significant difference as compared with t0 for control group.
Table 1. Continuous Cardiac Output and Intracranial Pressure Values for Xenon and Control Groups

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Xenon</th>
<th>Control</th>
<th>Xenon</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>6.3 ± 1.5</td>
<td>6.7 ± 1.1</td>
<td>15 ± 6</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>130</td>
<td>5.4 ± 2.2</td>
<td>4.5 ± 1.5</td>
<td>16 ± 3</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>160</td>
<td>4.0 ± 1.2</td>
<td>3.8 ± 1.2</td>
<td>17 ± 4</td>
<td>19 ± 5†</td>
</tr>
<tr>
<td>190</td>
<td>3.7 ± 1.0</td>
<td>3.6 ± 1.3</td>
<td>19 ± 6†</td>
<td>20 ± 5†</td>
</tr>
<tr>
<td>120</td>
<td>3.5 ± 0.9</td>
<td>3.9 ± 1.5</td>
<td>20 ± 6†</td>
<td>21 ± 5†</td>
</tr>
<tr>
<td>150</td>
<td>3.4 ± 0.8</td>
<td>3.9 ± 1.4</td>
<td>20 ± 5</td>
<td>20 ± 4†</td>
</tr>
<tr>
<td>180</td>
<td>3.5 ± 0.7</td>
<td>3.9 ± 1.3</td>
<td>21 ± 6†</td>
<td>21 ± 5†</td>
</tr>
<tr>
<td>120</td>
<td>3.6 ± 0.7</td>
<td>3.8 ± 1.7</td>
<td>22 ± 6†</td>
<td>21 ± 6†</td>
</tr>
<tr>
<td>240</td>
<td>3.6 ± 0.7</td>
<td>4.1 ± 0.7</td>
<td>23 ± 6†</td>
<td>21 ± 6†</td>
</tr>
</tbody>
</table>

No significant differences between the groups and intracranial pressure (ICP) for xenon and total intravenous anesthesia groups.

* Significant difference as compared with t0 for xenon group. † Significant difference as compared with t0 for control group.

CO = cardiac output.

Discussion

Xenon (75%) provided hemodynamic stable anesthesia without disturbance of the cerebral cell metabolism equal to TIVA at a comparable depth of anesthesia. This is the first study to evaluate whether xenon (75%) also provides a neuroprotective effect to attenuate brain injury in vivo after transient cerebral ischemia due to cardiac arrest. As a major result of this study, during reperfusion, brain injury is smaller for the xenon group as compared with TIVA determined by means of CMD.

Table 2. Blood Gas Analysis Results for Xenon and Control Groups

<table>
<thead>
<tr>
<th>Time</th>
<th>Xenon</th>
<th>Control</th>
<th>Xenon</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH</td>
<td></td>
<td>pH</td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>7.48 ± 0.04</td>
<td>7.39 ± 0.08</td>
<td>7.43 ± 0.05</td>
<td>7.44 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Pco₂, mmHg</td>
<td>39 ± 4</td>
<td>44 ± 4</td>
<td>41 ± 5</td>
</tr>
<tr>
<td></td>
<td>Po₂, mmHg</td>
<td>106 ± 16</td>
<td>97 ± 16</td>
<td>107 ± 26</td>
</tr>
<tr>
<td></td>
<td>BE, mm</td>
<td>6.9 ± 1.8</td>
<td>1.1 ± 2.2</td>
<td>2.8 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin, g/dl</td>
<td>8.6 ± 1.4</td>
<td>10.1 ± 0.9</td>
<td>10.3 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>Glucose, mm</td>
<td>9.5 ± 5.8</td>
<td>17.4 ± 8.7</td>
<td>16.6 ± 7.5</td>
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<tr>
<td></td>
<td>Lactate, mm</td>
<td>1.6 ± 0.6</td>
<td>4.0 ± 1.4</td>
<td>3.0 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Sao₂, %</td>
<td>102 ± 1</td>
<td>99 ± 3</td>
<td>100 ± 2</td>
</tr>
<tr>
<td></td>
<td>Cto₂, vol%</td>
<td>12.0 ± 1.9</td>
<td>14.1 ± 1.3</td>
<td>14.3 ± 0.7</td>
</tr>
</tbody>
</table>

Control

<table>
<thead>
<tr>
<th>Time</th>
<th>pH</th>
<th></th>
<th>pH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>7.48 ± 0.06</td>
<td>7.39 ± 0.08</td>
<td>7.44 ± 0.05</td>
<td>7.47 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Pco₂, mmHg</td>
<td>38 ± 4</td>
<td>41 ± 4</td>
<td>40 ± 5</td>
</tr>
<tr>
<td></td>
<td>Po₂, mmHg</td>
<td>101 ± 20</td>
<td>124 ± 86</td>
<td>129 ± 75</td>
</tr>
<tr>
<td></td>
<td>BE, mm</td>
<td>7.3 ± 0.9</td>
<td>2.4 ± 3.0</td>
<td>3.5 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin, g/dl</td>
<td>9.7 ± 1.1</td>
<td>10.9 ± 1.2</td>
<td>10.4 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>Glucose, mm</td>
<td>8.5 ± 2.4</td>
<td>16.2 ± 6.3</td>
<td>15.0 ± 6.6</td>
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<td></td>
<td>Lactate, mm</td>
<td>1.3 ± 0.3</td>
<td>4.1 ± 1.8</td>
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<tr>
<td></td>
<td>Sao₂, %</td>
<td>99 ± 8</td>
<td>98 ± 4</td>
<td>100 ± 1</td>
</tr>
<tr>
<td></td>
<td>Cto₂, vol%</td>
<td>13.3 ± 1.3</td>
<td>15.0 ± 1.8</td>
<td>14.7 ± 1.6</td>
</tr>
</tbody>
</table>

BE = base excess; Cto₂ = oxygen content; Pco₂ = arterial carbon dioxide tension; Po₂ = arterial oxygen tension; Sao₂ = oxygen saturation.
General Aspects

The cardiac arrest model was chosen to induce transient general cerebral ischemia with a definite time of a complete arrest in cerebral perfusion until consecutive return of spontaneous circulation. In other pig models using catheter-induced regional ischemia, an uncertain amount of collateral/residual perfusion was described in sequential multitracer positron emission tomography scanning the middle cerebral artery after occlusion.24 After cessation of cerebral perfusion due to cardiac arrest, brain ptiO2 values decreased to critical values below 5 mmHg,25 and electrical activity of the brain (SEF95) was flattened as described previously during brief cardiac arrest in humans.26,27 We chose to administer 75% xenon as the maximum concentration accepted for safe use of xenon. However, this is certainly a sub–minimal alveolar concentration (MAC) in pigs. Until now, there has only been one publication in which the MAC (claw clamp) in pigs was calculated as 119%.28 How the MAC (claw clamp) in pigs is related to the MAC (skin incision) in humans is not clear. The MAC xenon in humans has been reported previously as 71%.29

Cerebral Microdialysis

Following the heterogeneous approach using microdialysis monitoring for ischemic cerebral deterioration in intensive care patients published by Nilsson et al.,30 we investigated the same parameters in pigs after cardiac arrest and consecutive ischemia of the brain with critical brain ptiO2 values31 assigned to two groups to receive either xenon (75%) in oxygen (25%) or TIVA–oxygen (25%) anesthesia, respectively.

Fig. 6. Lactate values, cerebral microdialysis for xenon and total intravenous anesthesia groups. Box plot with median, 25th–75th percentiles (box), and 5th–95th percentiles (whiskers). No significant differences between the groups; * significant difference as compared with t0 for xenon group; + significant difference as compared with t0 for control group.

Fig. 7. Lactate/pyruvate ratios, cerebral microdialysis for xenon and total intravenous anesthesia groups. Box plot with median, 25th–75th percentiles (box), and 5th–95th percentiles (whiskers). No significant differences between the groups.

Fig. 8. Glycerol values (μM/l) as area under the curve, cerebral microdialysis for xenon and total intravenous anesthesia groups. Significant difference between the groups.

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Glutamate as a marker for cytotoxicity in brain tissue, lactate and pyruvate as markers for ischemia/anaerobic glycolysis and hypoglycemia in central nervous tissues, and glycerol as a marker for cell membrane damage are studied in cortical brain tissue.

Lactate and the lactate/pyruvate ratio is related to the extent of glycolysis and anaerobic metabolism. Pyruvate production is reduced relatively during ischemia, which causes an increase in the lactate/pyruvate ratio. A ratio of approximately 20 or lower is regarded as safe, reflecting a balanced redox state of the cells without energy disturbances due to ischemia.32

In our study, after cardiac arrest, critical low brain PtO2 levels were induced in both groups, and a significantly higher lactate production due to anaerobic glycolysis was observed. However, lactate production renormalized earlier in the xenon group as compared with control.

As described by Persson and Hillered,32 the reliability of neurochemical monitoring with microdialysis increases when pairs of substances, which behave in antidromic ways in pathologic situations, are compared. Such a ratio can help to compensate for changes in vivo recovery and for glial reaction around the microdialysis probe.

Our results revealed in both groups a pathologic increase of the lactate/pyruvate ratio after 60 min reperfusion time with ratios of up to 33 for the xenon group and 39 for the control group, respectively.

Increased release of the excitotoxic amino acid glutamate is considered an important cause of brain damage after ischemia. Kanthan et al.33 described a dramatic increase in the levels of extracellular glutamate with ischemia in acute focal ischemia in a human brain model. Intracerebral microdialysis was conducted in five patients who underwent resection of the temporal lobe for intractable epilepsy. Surgical excision leads to an acute ischemic state of the resected brain. In this model, the changes in human extracellular fluid during acute focal ischemic conditions were studied. Extracellular glutamate concentrations were 15–30 μM/l in the preischemic samples. This increased to 380.69 ± 42.14 μM/l with partial (incomplete) ischemia and reached a peak of 1,781.67 ± 292.34 μM/l (>100-fold) with total isolation of the temporal pole (complete ischemia).

These human preischemic data are in accord with our animal glutamate data for the xenon (13.03 ± 10.12 μM/l) and for the control group (19.18 ± 16.14 μM/l). In contrast to complete ischemia due to isolation of parts of the brain, glutamate values in our study after 4 min of cardiac arrest and return of spontaneous circulation did not show this dramatic 100-fold increase.

Glycolysis has emerged as a compound signaling cellular damage. Glycerol is an integral part of the hydrophilic portion of the bilayer of glycerophosphate and fatty acids, which constitute most cell membranes. Massive increases in extracellular glycerol are seen during ischemia in human as well as animal brains. It seems conceivable that the influx of calcium, caused by energy failure, activates phospholipids that start the decomposition of cell membranes.34

In a study by Marklund et al.,35 using the weight-drop technique, degradation of membrane phospholipids was induced in artificially ventilated rats. The trauma caused a significant, 8-fold increase of dialysate glycerol in the injured cortex, with a peak concentration in the second 10-min fraction after trauma. Hillered et al.36 describe a 15-fold increase of glycerol values in acute human brain injury. The results support the concept that phospholipid degradation occurs early after injury and that interstitial glycerol, harvested by microdialysis, may be useful as a marker allowing in vivo monitoring of phospholipid breakdown.

In our study, glycerol as a damage marker of cerebral cells increased significantly at 60 min after cessation of cerebral perfusion but did not reveal significant differences for the xenon group versus control as far as the primary lesion due to cardiac arrest is concerned. The primary lesion seems to be independent from the anesthetic procedure used in our experiment. However, in the second phase of the glycerol curve after the peak at 90 min after cardiac arrest, the glycerol values for xenon are significant lower and renormalize faster during reperfusion as compared with control.

The different underlying mechanisms of neuroprotection using xenon are still under discussion. In a rat study by Ma et al.,10 describing xenon to attenuate CPB-induced adverse neurocognitive outcome, the authors suggest a neuroprotective effect of xenon via an N-methyl-D-aspartate receptor antagonism.

Also, an increased cerebral blood flow as demonstrated in own studies using the microspheres method37 could contribute to faster brain tissue recovery during xenon inhalation and could reduce reperfusion damage after return of spontaneous circulation on a comparable level of ICP.

As another approach, hypoxia-induced neuronal damage and glutamate release were investigated by Petzelt et al.,11 in an N2 or a xenon atmosphere for embryonic rat cortical neurons. Cellular damage and glutamate overrelease were observed in N2-treated cells, whereas xenon protected the cells from the hypoxic injury. The protective effect of xenon was strongly reduced by preincubating neurons with a calcium chelator, indicating a role for calcium in this process. The results demonstrate the neuroprotective properties of xenon, suggest a relation between the prevention of neurotransmitter release in a hypoxic situation and neuroprotection, and present evidence that such neuroprotection may be based on yet other xenon-dependent mechanisms.11

The relation between neurotransmitter release in a hypoxic situation and neuroprotection by xenon remains uncertain also in the current study, because no difference was found between groups for glutamate release and the primary injury was equivalent in both groups. An explana-
tion might be the relatively long harvesting time of CMD (20 min) due to low pump flow rates in favor of high recovery rates such that short-acting increases of analytes such as glutamate might be missed.

**Intracranial Pressure**

Another point of interest for a potential new neuroprotective agent is its influence on intracranial pressure. Besides the CMD results, another important result of this study is the fact that xenon does not increase ICP more than TIVA during cerebral ischemia. As described by Sanders et al., promising neuroprotective agents that increase ICP have a limited role in clinical practice.

Xenon may represent a new neuroprotective agent in animal in vivo and in vitro studies besides being a safe anesthetic as shown in a large number of patients with promising clinical features such as rapid induction and emergence (fast tracking) combined with almost no influence on the cardiovascular system. 39–41 These are interesting properties of xenon for clinical anesthesia as well as for intensive care, but further investigation is necessary to show a neuroprotective effect of xenon in humans, particularly in cardiac and neurosurgery procedures with temporary hypoperfusion and ischemic episodes.

In conclusion, our cerebral microdialysis results demonstrate that xenon induces a differential neurochemical benefit in cerebral cell damage and metabolism as compared with TIVA in vivo during cerebral reperfusion after cardiac arrest in a pig model.

**References**


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