CONSIDERABLE INFORMATION NOW EXISTS on the neurochemical effects of severe insulin-induced hypoglycemia, as well as on the brain damage which may be incurred as a result of the hypoglycemia. Observations in man, and in animal experiments, demonstrate that stupor and coma, or their EEG equivalents, are accompanied by a reduced cerebral glucose utilization, at an unchanged or only slightly reduced oxygen consumption. Subsequent experimental studies gave detailed information on endogenous substrates utilized by the glucose-deprived (for literature, see Siesjo and Agardh). These studies also showed that cessation of spontaneous EEG activity ("isoelectricity") occurs pari passu with deterioration of cerebral energy state, eg, with reduction in phosphocreatine (PCr) and ATP concentrations, and corresponding increases in ADP and AMP concentrations. The energy failure also leads to loss of ion homeostasis, since massive cellular efflux of K+ and uptake of Ca2+ are observed.

Several observations suggest that hypoglycemia does not normally encroach upon cellular oxygen supply. Thus, studies designed to provide information on oxygen and glucose utilization (see above) showed that cerebral blood flow (CBF) is well maintained. Subsequent autoradiographic CBF measurements corroborated these observations. In fact, these studies showed that if blood pressure is maintained at values of 140-160 mm Hg, CBF is generally increased, in many structures to 200-300% of control. Furthermore, analysis of neurochemical variables suggest that cellular redox systems are oxidized during hypoglycemia.

All these studies allowed tight control of physiological variables such as blood pressure and arterial oxygenation. This has neither been the case in clinical material which has documented neuronal necrosis as a result of hypoglycemia, nor in earlier experimental studies confirming the clinical observations. Indeed, hypotension and/or hypoxia as contributing causes seemed likely. Thus, hypoglycemic and ischemic brain damage were considered identical, and hypotension was assumed to exacerbate hypoglycemic brain damage. Hypoglycemia was thought to be a form of hypoxia.

The advent of a physiologically controlled animal model which allows the delivery of purely hypoglycemic insults, followed by long term survival, has brought new information on the density and distribution of hypoglycemic neuronal necrosis. It has been shown that neuronal necrosis does not occur unless the EEG becomes isoelectric, suggesting that energy failure and loss of ion homeostasis are prerequisites for damage to be incurred. Furthermore, a comparison between hypoglycemic and ischemic insults in the same species demonstrates that the distribution of neuronal necrosis is not identical in the two conditions.

Although these results demonstrate that hypoglycemic brain damage can be incurred in the absence of cellular hypoxia, they do not provide an answer to the
important question of whether arterial hypotension will aggravate hypoglycemic brain damage. Some recent results provide hints that this could be the case. Thus, experiments on cerebral acid-base regulation in severe hypocapnia (PaCO2, 15 mm Hg) showed that moderate hypotension further aggravated the deterioration of cerebral energy state, caused by hypoglycemia. Finally, it could be shown that vascular autoregulation was lost during hypoglycemia, and that even relatively moderate reductions in blood pressure could severely reduce local CBF.

With this background, we wished to test the hypothesis that hypoglycemic brain damage, defined as neuronal necrosis, is exacerbated by hypotension. Seven groups of animals were studied. In three, the influence of hypotension during hypoglycemia on the cortical energy state was investigated. To that end, blood pressure was held at 160, 100, and 80 mm Hg in three separate groups, during a 30 min period of isoelectricity, and labile phosphates were analyzed in neocortical tissue. In four groups, rats were subjected to a standard hypoglycemic insult at varying blood pressures, and were then allowed to recover one week before perfusion fixation, followed by quantitative histopathological examination.

Materials and Methods

Seventy six male Wistar rats weighing 290–345 g were used (Møllergaard Breeding Center, Copenhagen). The animals for the metabolite series were divided into groups with high (group A, about 140 mm Hg), medium (group B, 100 mm Hg), and low (group C, 80 mm Hg) blood pressures (table 1). At each pressure, brains were frozen in situ for metabolite measurements after 5 and after 30 min isoelectricity. Normoglycemic control brains were similarly analyzed at 140–160 mm Hg and 100 mm Hg.

The animals for the histopathology series were also divided into high (D), medium (E), and low pressure (F) groups (table 1). However, to ensure that the high pressure group had high cerebral perfusion rates, the animals were regulated to a pressure of at least 140 mm Hg. Furthermore, to ensure that the low pressure animals had enhanced deterioration of cerebral energy state, they were kept at a blood pressure of 60 mm Hg during the period of isoelectricity.

A seventh series (G) was also examined by quantitative histopathology. Here the blood pressure was held at 140 to 160 mm Hg during the isoelectric period, but was lowered to 60 mm Hg in the recovery period.

A previous publication describes more completely the model used. Briefly, the rats were fasted overnight with free access to tap water. The next day, they were given 9–21 I.U./kg of regular insulin (Actrapid, Novo Industri A/S, Copenhagen), immersed in 3% halothane, intubated, and mechanically ventilated with 0.8% halothane in a 2:1 N2O:O2 mixture. Two tail veins, and the tail artery were then cannulated, and continuous paralysis maintained via an i.v. infusion of suxamethonium. A bipolar interhemispheric electroencephalogram (EEG) was continuously monitored. The halothane was discontinued, the animals were

### Table 1 Physiologic Parameters During Hypoglycemia

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of animals</th>
<th>MABP (mm Hg)</th>
<th>Temp (°C)</th>
<th>PO2 (mm Hg)</th>
<th>PCO2 (mm Hg)</th>
<th>pH</th>
<th>Blood glucose (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1*</td>
<td>8</td>
<td>136 ± 9</td>
<td>37.0 ± 0.6</td>
<td>103 ± 11</td>
<td>35.4 ± 1.2</td>
<td>7.35 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>Control 2*</td>
<td>6</td>
<td>96 ± 8</td>
<td>37.2 ± 0.5</td>
<td>97 ± 8</td>
<td>32.9 ± 1.5</td>
<td>7.39 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>A 5'</td>
<td>6</td>
<td>143 ± 6</td>
<td>37.0 ± 0.2</td>
<td>100 ± 9</td>
<td>32.0 ± 1.6</td>
<td>7.34 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>A 30'</td>
<td>6</td>
<td>142 ± 4</td>
<td>37.0 ± 0.3</td>
<td>101 ± 7</td>
<td>34.5 ± 3.0</td>
<td>7.34 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>B 5'</td>
<td>6</td>
<td>101 ± 2</td>
<td>36.8 ± 0.4</td>
<td>108 ± 10</td>
<td>30.5 ± 10.4</td>
<td>7.36 ± 0.17</td>
<td></td>
</tr>
<tr>
<td>B 30'</td>
<td>4</td>
<td>101 ± 6</td>
<td>37.0 ± 0.3</td>
<td>110 ± 20</td>
<td>32.9 ± 2.1</td>
<td>7.31 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>C 5'</td>
<td>6</td>
<td>80 ± 0</td>
<td>36.9 ± 0.3</td>
<td>106 ± 9</td>
<td>37.1 ± 4.4</td>
<td>7.29 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>C 30'</td>
<td>8</td>
<td>79 ± 2</td>
<td>37.0 ± 0.3</td>
<td>105 ± 5</td>
<td>32.0 ± 2.7</td>
<td>7.29 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>6</td>
<td>159 ± 12</td>
<td>37.3 ± 0.3</td>
<td>93 ± 24</td>
<td>37.2 ± 4.4</td>
<td>7.38 ± 0.05</td>
<td>0.53 ± 0.17</td>
</tr>
<tr>
<td>E</td>
<td>8</td>
<td>104 ± 2</td>
<td>37.3 ± 0.2</td>
<td>105 ± 10</td>
<td>35.7 ± 2</td>
<td>7.37 ± 0.05</td>
<td>0.41 ± 0.15</td>
</tr>
<tr>
<td>F</td>
<td>6</td>
<td>60 ± 2</td>
<td>37.3 ± 0.2</td>
<td>94 ± 6</td>
<td>33.8 ± 3</td>
<td>7.41 ± 0.06</td>
<td>0.35 ± 0.09</td>
</tr>
<tr>
<td>G</td>
<td>6</td>
<td>63 ± 6†</td>
<td>37.5 ± 0.4</td>
<td>109 ± 9</td>
<td>37.4 ± 4</td>
<td>7.38 ± 0.06</td>
<td>0.31 ± 0.12</td>
</tr>
</tbody>
</table>

The values are taken at the end of the given EEG isoelectric period.
All values are given as mean ± standard deviation.
*Control 1 denotes a normoglycemic group with spontaneous blood pressure of 140 to 160 mm Hg. Control 2 denotes a normoglycemic group exsanguinated to a blood pressure of 100 mm Hg.
Group A: High BP, metabolite analysis.
Group B: Medium BP, metabolite analysis.
Group C: Low BP, metabolite analysis.
Group D: High BP, histologic analysis.
Group E: Medium BP, histologic analysis.
Group F: Low BP, histologic analysis.
Group G: Low BP in recovery only, histologic analysis.
Mean arterial blood pressure in the first 30 min of recovery.
Different Blood Pressures During the Hypoglycemic Period

**TABLE 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Glucose</th>
<th>PCr</th>
<th>ATP</th>
<th>ADP</th>
<th>AMP</th>
<th>Energy charge</th>
<th>Lactate</th>
<th>Pyruvate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.25 ± 0.39</td>
<td>4.46 ± 0.18</td>
<td>2.83 ± 0.04</td>
<td>0.275 ± 0.008</td>
<td>0.066 ± 0.012</td>
<td>0.937 ± 0.003</td>
<td>1.51 ± 0.11</td>
<td>0.108 ± 0.007</td>
</tr>
<tr>
<td>A (BP 140)</td>
<td>0.07 ± 0.03</td>
<td>0.57 ± 0.11</td>
<td>0.81 ± 0.11</td>
<td>0.915 ± 0.091</td>
<td>0.447 ± 0.025</td>
<td>0.580 ± 0.026</td>
<td>0.41 ± 0.09</td>
<td>0.036 ± 0.002</td>
</tr>
<tr>
<td>B (BP 100)</td>
<td>0.14 ± 0.11</td>
<td>0.50 ± 0.08</td>
<td>0.72 ± 0.14</td>
<td>0.821 ± 0.075</td>
<td>0.575 ± 0.056</td>
<td>0.532 ± 0.027</td>
<td>0.38 ± 0.08</td>
<td>0.019 ± 0.005</td>
</tr>
<tr>
<td>C (BP 80)</td>
<td>0.03 ± 0.01</td>
<td>0.22 ± 0.05</td>
<td>0.36 ± 0.05</td>
<td>0.724 ± 0.028</td>
<td>0.768 ± 0.027</td>
<td>0.370 ± 0.021</td>
<td>0.33 ± 0.04</td>
<td>0.022 ± 0.002</td>
</tr>
</tbody>
</table>

The values are given in μmol g⁻¹ wet weight and represent means ± standard error of the mean.

ventilated on a 2:1 N₂O:O₂ mixture, and a flat EEG ("isoelectricity") was awaited.

During isoelectricity, blood pressure was held at the desired level through controlled exsanguination and re-infusion of blood. The actual blood pressures throughout the period of isoelectricity are given in figure 1 for the histopathology series D to F. The temperature, arterial PO₂, PCO₂, and pH were maintained within the physiological range.

The animals in which the energy metabolites were studied had a funnel fitted onto the skull. The brain was then frozen in situ according to Pontén et al. After removal of the brain from the skull it was kept at −80°C until analyzed. Fragments weighing approximately 25 mg were dissected from the parietal cortex at −20°C, and were extracted in HCl-methanol and subsequently in perchloric acid at ± 0°C. After neutralization, the metabolites were determined fluorometrically. The conditions for the anlayses have been previously described.

After thirty minutes of EEG isoelectricity the animals in the histopathology series were recovered with a infusion of 0.2 ml of 50% glucose, given by hand over one minute. A 50% glucose infusion was then tapered over the ensuing hours, and substituted with 25% glucose in Krebs-Henseleit solution overnight, in order to maintain a plasma glucose of between 5 and 10 mM/l. Following extubation, usually one to three hours after glucose induced recovery, blood glucose, blood gases and pH were checked finally in the awake, conscious animal before removal of the tail catheters. The animals were weighed and examined daily, and were allowed to survive one week. They were sacrificed by perfusion fixation with 4% phosphate buffered formaldehyde under 1% halothane anesthesia. The brains were left in situ at 4°C and were removed the following day. After processing in graded ethanol and xylol, they were embedded in paraffin and sub-sion sectioned at 8 μm.

Sections were double stained with acid fuchsin and cresyl violet, and the number of acidophilic neurons was assessed by direct visual counting of sections at standardized control levels of the brain.

The crude damage index (CDI) was generated as follows: For the caudate nucleus, subiculum, CA1 pyramidal neurons, and dentate granule neurons, the following numbers were assigned for the per cent neuronal necrosis: <10% = 1, 10–50% = 2, and 50–100% = 3. For the cerebral cortex, 10 to 100 necrotic neurons per section was assigned the number 1, 100 to 1000 the number 2, and >1000 the number 3. These integers were added to produce the CDI for each brain.

### Results

Physiologic parameters during EEG isoelectricity are shown in table 1. All animals were normothermic and normoxic, and their PCO₂ and pH values showed little deviation from control. Results from the metabolite series demonstrate that mean arterial blood pressure was kept constant between the 5th and the 30th minute. Corresponding blood pressure data from the histology series are shown in figure 1. The blood pressure in the recovery period in the post-insult hypotension group was comparable to that shown during isoelectricity in the low blood pressure group, i.e. roughly 60 mm Hg.

1. **Cerebral Metabolites**

Cerebral metabolic changes were similar after 5 and 30 min of isoelectricity, demonstrating that a new steady state is reached soon after cessation of EEG activity. Due to this constancy, we will discuss the 30 min data only. Furthermore, since the hypotensive control animals had values identical to normotensive ones, only the latter are shown in table 2, which gives tissue metabolites. In all isoelectric animals, tissue glucose concentrations were very low. In the normotensive group, PCr and ATP concentrations decreased to about 10% and about 25% of control, respectively, with corresponding increases in ADP and AMP concentrations. As expected, lactate and pyruvate concentrations were reduced.

---

**Figure 1. Blood pressure as a function of duration of isoelectricity for each group. All values are ± standard deviation.**
HYPOTENSION AND HYPOGLYCEMIA/Auer et al

1. Hypertension and Hypoglycemia

The results of table 2 demonstrate that hypotension further reduced PCr and ATP concentrations, as well as the calculated adenylate energy charge, as defined by Atkinson. The cortical energy charge during hypoglycemia was 0.58 at a blood pressure of 140 mm Hg, 0.53 at 100 mm Hg, and sank to 0.37 at 80 mm Hg. In order to illustrate the pressure-dependent deterioration of cerebral energy state, individual values for ATP and energy charge were plotted against blood pressure (fig. 2). The results demonstrate a significant correlation (p < 0.01). At a blood pressure of 80 mm Hg, PCr and ATP concentrations were reduced to 5 and 10% of control respectively.

2. Histopathology

The density of neuronal necrosis was determined by direct visual cell counts in each of the major brain regions. The data are summarized in table 3. As the results demonstrate, no effect of hypotension in enhancing neuronal necrosis was seen. The results obtained in the group maintained hypotensive for 30 min in the immediate recovery period were likewise negative.

Figure 3 plots the crude damage index, derived from the number of necrotic neurons in each brain region (see Material and Methods) against the blood pressure. It is apparent that there was considerable variation in brain damage within each group, but the degree of damage was unchanged by lowering the blood pressure to either 100 mm Hg or 60 mm Hg.

Not only the density of brain damage, but also the distribution of hypoglycemic brain damage was unaltered by lowering the blood pressure to 100 or to 60 mm Hg. Affected areas included the dentate gyrus (fig. 4), the cerebral cortex (fig. 5) and septal nuclei (fig. 6) in a pattern identical to that seen after hypoglycemia at a blood pressure of 160 mm Hg. Thus, the crest and the external blade of the dentate gyrus were affected first. The superficial cerebral cortical layers showed the most damage, with a superficial to deep gradient seen.

The cerebellum was affected near the foramina of Luschka, with numerous necrotic Purkinje cells seen.

![Figure 4. Histologic appearance of hippocampal damage, one week after 30 min of hypoglycemic isoelectricity complicated by hypotension to 60 mm Hg. The distribution is identical to that seen after hypoglycemic isoelectricity accompanied by a BP of 100 or 160. There is neuronal necrosis at the crest and external blade of the dentate gyrus (D), and in the CA1 pyramidal cells (CA1), especially medially near the subiculum (S). Acid fuchsir/Cresyl violet. Bar = 200 μm.](image)
over the hemispheres in some animals (not shown). Infarction was never seen.

No features regarding the distribution of neuronal necrosis serve to distinguish the brain damage observed in the present study from that previously reported in normotensive hypoglycemia.31 However, due to the marked regional differences in the degree of remaining autoregulation, special attention was focussed on certain brain regions histologically. The cingulate gyrus is known to have an ischemic flow rate during hypotensive hypoglycemia as studied here,15 and increased neuronal necrosis might therefore be expected in this region. However, the cingulate gyrus showed sparing, rather than enhancement of neuronal necrosis (fig. 5), a distribution pattern also seen in hypoglycemia at normal blood pressure levels.31

In contrast to the cingulate gyrus, the septal nuclei show relative preservation of autoregulation, and hence blood flow, in the range of blood pressures tested.15 They might therefore be expected to show sparing, if blood flow factors are operant in causing neuronal necrosis in hypoglycemia. Nevertheless, the septal nuclei demonstrated selective neuronal necrosis histologically (fig. 6).

Discussion

Hypotension has long been assumed to exacerbate hypoglycemic brain damage.28,29 The present experiments were designed to test this hypothesis, and are based on an animal model which allows tight control of physiologic parameters, as well as long term survival. The former was considered necessary to unequivocally dissect out cause and effect relationships between the physiologic and metabolic data during and after the insult, and the consequent neuronal damage. The latter was deemed necessary to allow for the unequivocal signs of neuronal necrosis to develop.

The results demonstrate a very marked dichotomy and are somewhat surprising. The metabolic part of this study showed enhanced deterioration of the cere-
bral energy state when low blood pressure accompa-
nied hypoglycemia. However, there was no effect of
hypotension to 60 mm Hg, either during or after the
period of isoelectric EEG, on either the density or the
distribution of hypoglycemic neuronal necrosis.

As stated in the introduction, results obtained in
severely hypoglycemic animals demonstrated a relation-
ship between blood pressure and the adenylate energy
charge of neocortical tissue, suggesting that even mod-
erate hypotension will aggravate the deterioration of
cellular energy metabolism during hypoglycemia. 
Results obtained with measurements of extracellular
K+ activity were in line with this conclusion. These
results, and those showing regional loss of vascular
autoregulation in many brain structures during hypo-
glycemia, suggest that hypotension during hypogly-
cemia leads to a reduction in flow rate from hyper-
emic levels which are of sufficient magnitude to
further reduce glucose delivery to the substrate-de-
prived cells. The present results indicate that these
events do not increase neuronal necrosis.

It is of considerable interest that a reduction of ATP
concentration to 0.36 ± 0.05 mol·g⁻¹ of tissue, as
occurred in the group C, did not aggravate hypoglycemic
neuronal necrosis. In fact, since the histopathol-
y group F had an even lower blood pressure (60 mm
Hg) than the metabolite group C (80 mm Hg), it would
seem that a more severe reduction of ATP concentra-
tion causes no aggravation of the neuronal death. The
results suggest that the events which lead to hypogly-
cemic neuronal necrosis occur already at a normal or
reduced blood pressure, and are not dependent on
blood flow. Such events include a reduction of ATP
concentration to about 25% of control, marked in-
creases in ammonia concentrations, aspartate and in
free fatty acid concentrations, and extensive depolarization
of cells with release of K+. These are reductions of extra-
cellular Ca²⁺ concentration to very low levels, prob-
ably because of influx into cells.

It now seems established that hypoglycemia leads to
neuronal necrosis with a different distribution in the
rat that observed in ischemia. The ischemic pat-
tern of distribution shows involvement of the middle
cortical layers, uniform involvement of the CA1 py-
ramidal cell band of the hippocampus, but conspicuous
sparring of the dentate gyrus until damage is very
severe.

The hypoglycemic pattern of distribution involves an
affection of the superficial layers of neocortical
cells, medial CA1 pyramidal cells of the hippocampus,
and heavy affection of cells at the crest of the dentate
gyrus, the conspicuous relationship of neuronal necro-
sis to tissue fluid and CSF pathways suggesting the
participation of a fluid-borne toxin. Dark neurons are
seen acutely, and acidophilic neurons subsequently, in
all these brain regions. Although the dark neurons
may potentially recover, the acidophilic neurons are
established as necrotic by their mitochondrial floccu-
lent densities and absent cell membranes, and by their
subsequent removal from the tissue. It is this acido-
philic neuronal necrosis which was quantitated at one
week survival in the present study, rather than acute,
potentially reversible neuronal changes.

Since the distribution of neuronal necrosis is not the
same in ischemia and hypoglycemia, it is possible to
distinguish hypoglycemic and ischemic patterns of
brain damage. Lowering the blood pressure during,
and after the period of hypoglycemic isoelectricity
might theoretically have given rise to an ischemic pat-
tern of brain damage, a hypoglycemic pattern of brain
damage, or even a combination of the two. It is of
interest that hypotension did not alter the pattern of
distribution of neuronal necrosis from one typical of
hypoglycemia to one more characteristic of ischemia.

Since the density of hypoglycemic brain damage was
also unaffected by hypotension, one may conclude that
formation of the hypothetical toxin is not enhanced
when ATP concentrations are further reduced.

Infarction was not seen in the present study. Pan-
necrosis of all cell types of the CNS, comprising brain
infarction, has been linked to lactic acid produc-
tion. In hypoglycemia, lactic acid formation is im-
possible due to glucose deficiency. Since the addition
of hypotension to hypoglycemia actually caused isch-
emic blood flow rates in areas such as the cingulate
cortex, and since such areas were relatively spared of
damage, the present results may be construed as dem-
onstrating that profound hypoglycemia actually pro-
tects against infarction.

Acknowledgments

The authors appreciate the technical assistance of Helène Wilhelm-
son, Karin Hansson, Kerstin Beirup, Lille-Mor Lindeström, Marianne
Forssén, and Maud Salomonsson, and the secretarial skill of Donna
Wilson in typing the manuscript.

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# Appendix

## Hypotension and Hypoglycemia

Data available on request

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Caud</th>
<th>Dent</th>
<th>CA1</th>
<th>Sub</th>
<th>II-III</th>
<th>IV-VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 I.U./kg</td>
<td>108 cells</td>
<td>0 cells</td>
<td>47%</td>
<td>85%</td>
<td>2.8%</td>
<td>0.85%</td>
</tr>
<tr>
<td>11 I.U./kg</td>
<td>85 cells</td>
<td>0 cells</td>
<td>36%</td>
<td>94%</td>
<td>3.5%</td>
<td>0.55%</td>
</tr>
<tr>
<td>10 I.U./kg</td>
<td>70 cells</td>
<td>0 cells</td>
<td>88%</td>
<td>55%</td>
<td>16%</td>
<td>58%</td>
</tr>
<tr>
<td>9 I.U./kg</td>
<td>624 cells</td>
<td>9 cells</td>
<td>86%</td>
<td>91%</td>
<td>19%</td>
<td>49%</td>
</tr>
<tr>
<td>8 I.U./kg</td>
<td>70 cells</td>
<td>3 cells</td>
<td>58%</td>
<td>67%</td>
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<td>21%</td>
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<tr>
<td>7 I.U./kg</td>
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<td>36%</td>
<td>97%</td>
<td>28%</td>
<td>37%</td>
</tr>
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<td>6 I.U./kg</td>
<td>104 cells</td>
<td>4 cells</td>
<td>55%</td>
<td>97%</td>
<td>28%</td>
<td>37%</td>
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<tr>
<td>5 I.U./kg</td>
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<td>78%</td>
<td>80%</td>
<td>15%</td>
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</tr>
<tr>
<td>4 I.U./kg</td>
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<td>3 I.U./kg</td>
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<td>89%</td>
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<tr>
<td>2 I.U./kg</td>
<td>129 cells</td>
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<td>98%</td>
<td>90%</td>
<td>9%</td>
<td>0.51%</td>
</tr>
<tr>
<td>1 I.U./kg</td>
<td>6 cells</td>
<td>0 cells</td>
<td>71%</td>
<td>68%</td>
<td>6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>10 I.U./kg</td>
<td>10 cells</td>
<td>0 cells</td>
<td>76%</td>
<td>66%</td>
<td>6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>5 I.U./kg</td>
<td>58 cells</td>
<td>0 cells</td>
<td>85%</td>
<td>73%</td>
<td>48%</td>
<td>8.2%</td>
</tr>
<tr>
<td>5 I.U./kg</td>
<td>2 cells</td>
<td>0 cells</td>
<td>89%</td>
<td>11%</td>
<td>8.2%</td>
<td>1.3%</td>
</tr>
<tr>
<td>4 I.U./kg</td>
<td>24 cells</td>
<td>0 cells</td>
<td>90%</td>
<td>52%</td>
<td>12%</td>
<td>0.35%</td>
</tr>
<tr>
<td>3 I.U./kg</td>
<td>16 cells</td>
<td>0 cells</td>
<td>90%</td>
<td>56%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>2 I.U./kg</td>
<td>76 cells</td>
<td>3 cells</td>
<td>98%</td>
<td>91%</td>
<td>8%</td>
<td>0.65%</td>
</tr>
<tr>
<td>1 I.U./kg</td>
<td>76 cells</td>
<td>3 cells</td>
<td>98%</td>
<td>98%</td>
<td>9%</td>
<td>0.51%</td>
</tr>
<tr>
<td>10 I.U./kg</td>
<td>2 cells</td>
<td>0 cells</td>
<td>99%</td>
<td>90%</td>
<td>9%</td>
<td>0.51%</td>
</tr>
<tr>
<td>5 I.U./kg</td>
<td>7 cells</td>
<td>0 cells</td>
<td>99%</td>
<td>96%</td>
<td>9%</td>
<td>0.51%</td>
</tr>
<tr>
<td>4 I.U./kg</td>
<td>6 cells</td>
<td>0 cells</td>
<td>99%</td>
<td>95%</td>
<td>9%</td>
<td>0.51%</td>
</tr>
<tr>
<td>3 I.U./kg</td>
<td>5 cells</td>
<td>0 cells</td>
<td>98%</td>
<td>92%</td>
<td>9%</td>
<td>0.51%</td>
</tr>
<tr>
<td>2 I.U./kg</td>
<td>4 cells</td>
<td>0 cells</td>
<td>98%</td>
<td>92%</td>
<td>9%</td>
<td>0.51%</td>
</tr>
<tr>
<td>1 I.U./kg</td>
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<td>98%</td>
<td>92%</td>
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<td>0.51%</td>
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<td>10 I.U./kg</td>
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<td>98%</td>
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<td>5 I.U./kg</td>
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<td>0.51%</td>
</tr>
</tbody>
</table>
Hypotension as a complication of hypoglycemia leads to enhanced energy failure but no increase in neuronal necrosis.

R N Auer, P Hall, M Ingvar and B K Siesjo

_Stroke_. 1986;17:442-449
doi: 10.1161/01.STR.17.3.442

_Stroke_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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