Hypoglycemia aggravates critical illness induced neurocognitive dysfunction

Running title: Hypoglycemia and neurocognitive dysfunction in ICU

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**Objective:** Tight glycemic control in critically ill patients (TGC) is associated with an increased risk of hypoglycemia. Whether those short episodes of hypoglycemia are associated with adverse morbidity and mortality is a matter of discussion. Using a case control study design we investigated whether hypoglycemia under TGC causes permanent neurocognitive dysfunction in patients surviving critical illness.

**Research Design and Methods:** From our patient data management system we identified adult survivors treated for more than 72 hours in our surgical intensive care unit (ICU) between 2004 and 2007 (n=4635) without a history of neurocognitive dysfunction or structural brain abnormalities who experienced at least one episode of hypoglycemia during treatment (“hypo-group“) (n=37). For each hypo-patient one patient stringently matched for demographic and disease related data was identified as control. We performed a battery of neuropsychological tests investigating 5 areas of cognitive functioning in both groups at least one year after ICU-discharge. Test results were compared to data from healthy controls and between groups.

**Results:** Critical illness caused neurocognitive dysfunction in all tested domains in both groups. The dysfunction was aggravated in hypo-patients in one domain, namely that of visuospatial skills (p<0.01). Besides hypoglycemia, both hyperglycemia (r= -0.322; p=0.005) and fluctuations of blood glucose (r= -0.309; p=0.008) were associated with worse test results in this domain.

**Conclusions:** Hypoglycemia was found to aggravate critical illness induced neurocognitive dysfunction to a limited but significant extend, however, an impact of hyperglycemia and fluctuations of blood glucose on neurocognitive function cannot be excluded.
Since the concept of tight glycemic control (TGC) was introduced in critical care medicine in 2001 (1), its implementation in daily clinical practice is subject of a vivid discussion. Several single-center trials in different patient populations largely confirmed the clinical benefits, at least when patients were treated for a few days or longer in an intensive care unit (ICU) (2). Numerous studies have suggested plausible mechanisms behind the clinical benefits (3). However, a recent multi-center trial failed to confirm the strict blood glucose (BG) targets (4) and two multi center-trials have been stopped preliminary because of a high incidence of hypoglycemic episodes (5).

Indeed, hypoglycemia appears as the major side effect of any effort to regulate blood glucose levels with insulin, whatever the BG levels aimed for (2). Although numerous algorithms are available to minimise this risk (6), the fear of hypoglycemia-induced mortality and permanent disability largely impedes the implementation of TGC in daily routine. Scientific evidence supporting the common notion that hypoglycemia is responsible for an increased mortality and profound permanent neurocognitive dysfunction rather than it being just a marker of severity of illness is poor and controversial however. Efforts to substantiate any evidence are based on post hoc analyses, since confirmation from prospective randomised controlled trials is precluded for obvious ethical reasons. Some studies imply that any mortality benefits of TGC might be outweighed when the incidence of hypoglycemia is very high (7), however, other analyses revealed conflicting results in this respect (8). Besides direct effects on mortality, neuroglycopenia might cause neuronal damage and, at least subtle, permanent neurocognitive impairment that potentially affects life-quality after discharge.

From diabetes mellitus it is known that neuroglycopenia might have a permanent effect on neurocognitive function, at least when it occurs repetitively. Since diabetes mellitus and critical illness induced dysregulations of glucose homeostasis represent substantially different entities, it is inappropriate to extrapolate these data to the ICU population. Cognitive impairment is a relevant problem of patients surviving critical illness in general (9). Currently, there are no data available on the specific impact of hypoglycemic events during treatment in ICU on long term neurocognitive function.

Using a case control design, we investigated whether hypoglycemic episodes under TGC induce or aggravate permanent neurocognitive deficits in patients surviving critical illness.

**RESEARCH DESIGN AND METHODS**

The work was approved by the local ethics committee, written informed consent was obtained from all patients prior to neurocognitive testing. The protocol was registered with clinicaltrials.gov (NCT00662922).

**Patients.** All patients in the surgical ICU of our university hospital are treated according to our institutional TGC-protocol (anologue to (1)) aiming for BG between 80 and 110 mg/dl using insulin infusions as necessary. BG was measured in full blood drawn from an arterial line with an ABL-blood gas analyzer (glucose oxidase method with amperometric reading, range 7-540 mg/dl, coefficient of variance <10% for lower detection limit, Radiometer, Copenhagen, Denmark). Quality checks of the device were performed according to the instruction manual.

We identified all patients who suffered from at least one episode of hypoglycemia (BG 40 mg/dl or below) (labelled “hypo-group”) between January 1st 2004 and December 31st 2007 from our patient data management
system. Patients were selected to undergo a battery of validated neuropsychological tests that was designed to assess a full range of cognitive functions (Table 1) at least one year after discharge from the unit. To diagnose patients with manifest neurological deficits, a short neurological examination was performed (sensory and motor responses, reflexes including Babinski’s sign, examination of posture and movements). We included all patients aged between 18 and 80 years upon admission that were treated for at least 72 hours in ICU. We excluded patients who did not survive until scheduled time-point of testing, or had a medical history or medical condition potentially biasing neurocognitive testing, such as neurocognitive, neurodegenerative (Alzheimer’s or Parkinson’s disease) or psychiatric disorders (drug abuse, depression and schizophrenia and the use of respective medication), severe liver disease (ammonia three times the upper limit of normal or CHILD C liver insufficiency), or end stage kidney failure. Patients after neurotrauma, intracranial haemorrhage, stroke, intracranial surgery and other structural brain lesions were also excluded.

For each hypo-patient a matching partner (“control-group”) without any hypoglycemic event meeting the same in- and exclusion criteria was identified from the database according to strict demographic and illness related matching criteria (Table 2). We recorded and calculated duration (time from last BG above hypoglycemia threshold before, to first BG above 40 mg/dl after a hypoglycemic reading), number and severity of hypoglycemia (minimum BG during treatment), mean BG over the whole ICU stay, mean morning BG, maximum BG, deltaBG (difference between the minimum BG and maximum BG within 6 hours following hypoglycemia) and the difference between minimum and maximum BG during ICU treatment.

**Neuropsychological assessment.** One investigator unaware of the allocation of the patients conducted the neuropsychological tests. Test results were primarily analyzed by the same investigator, supervised by an experienced clinical neuropsychologist. Performances in 5 major areas of cognitive functioning were evaluated. Cognitive domains and their particular tests are listed in Table 1. Concerning the Rey Osterrieth Complex Figure Test (ROCFT), we also calculated the relative difference between both test results since results of delayed recall performance can be influenced by an impairment of initial copying. Additionally, test results from patients were compared to published normative data for age, sex and educational level. A detailed description of each test can be found in Lezak et al. (10).

**Statistical Analyses.** Data were tested for normal distribution with the Shapiro-Wilk Test. To determine meaningful composite scores of cognitive domains we performed a principal component analysis (PCA) using the single test results, followed by an oblique (Oblimin with Kaiser-normalization) rotation. The same test was not included in more than one composite score. The resulting 5 factors of the principal component analysis were z-transformed (mean score of 0 and standard deviation of 1). For timed tests, the sign of the z-score was reversed so that improved performance resulted in a higher score in all tests.

Primary analysis assessed differences in neurocognitive test results between groups with either paired t-test or Mann-Whitney-U test as appropriate. Secondary analyses were carried out to test the relation of hypoglycemia severity, length of hypoglycemic episode and the number of hypoglycemic events to neurocognitive scores and whether maximum glucose values, deltaBG or the difference between minimum and maximum BG were associated with worse test results by means of Pearson's
correlation. Test results of the ICU patients were compared to published normative data for age, sex and educational level. Differences were expressed semi quantitatively as “normal”, “close below average” or “far below average”, respectively. Test results are given as mean ± SD. A two tailed p-value <0.05 was considered significant. All data were analysed using SPSS Statistics 15.0.

RESULTS
4635 Patients were treated in our ICU in the study period for more than 72 hours, 193 of whom experienced at least one episode of hypoglycemia (4.2%). 37 hypo-patients met inclusion criteria, fulfilled no exclusion criteria and for each one matching control partner could be identified (Figure 1). Demographic data were as follows given as mean (standard error): 44 male, 30 female, age 66.3 (1.3) years, Simplified Acute Physiology Score (SAPS) 39 (2.3), length of stay on ICU 15.2 (1.6) days, 32% had diabetes mellitus. Admission BG (167.8 ±7.8 versus 167.0±8.3 mg/dl p=0.941), mean morning BG (131.7±3.0 versus 126.5±2.6 mg/dl p=0.196) and mean BG (139.0±3.0 versus 137.1±2.5 p=0.644) did not differ between groups. Mean maximum BG was significantly higher in the hypo-group as in the control-group (297.8±14.9 versus 249.8 ±10.7 mg/dl p=0.017). Demographic data did not differ between groups, as patients were matched accordingly. None of the patients revealed manifest neurological deficits in the neurological examination. Neurocognitive tests in both patient groups showed impaired neurocognitive function in several domains as compared to age matched healthy controls (Table 1). Analyses of differences between both patient groups in the 5 neurocognitive domains revealed solely a significant impairment of visuospatial skills in the hypo- compared to the control-group (p=0.001). Within the single subtests, results of both copy (p=0.007) and delayed recall (p=0.002) of the ROCFT were lower in the hypo- as compared to the control-group. The relative difference between copy and delayed recall also significantly differed between both groups (hypos < controls; p=0.043). Results of all other tests did not differ between groups (Table 1).

Solely within the hypoglycemic group, the maximum BG and the difference between minimum and maximum BG serving as rough surrogates for the quality of glycemic control during ICU treatment were negatively correlated with visual-spatial processing parameters. Neither the number nor the duration of hypoglycemic episodes showed a significant correlation. Severity of hypoglycemia was also not significantly associated with visuospatial performance, but did show a negative trend (Table 3). In the control group, no correlations between parameters of glycemic control and the performance in the neurocognitive tests were found.

DISCUSSION
In the current case control study we found that patients who experienced one or more hypoglycemic events during ICU treatment showed an aggravation of critical illness induced neurocognitive dysfunction compared to patients who did not experience hypoglycemia. Both groups showed significant neurocognitive dysfunctions in all domains compared to healthy controls, but hypo-patients had an additional deficit in visuospatial skills. Since tests were done at least one year after ICU discharge, these impairments must be considered long-term if not permanent. Former studies investigating the consequences of hypoglycemia under TGC in the critically ill have revealed conflicting results (7,8), however, they have been
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primarily focused on mortality and gross somatic morbidity. Data on the positive effects of TGC on mortality from prior trials could not be confirmed by the recent multi-centre trial (NICE-SUGAR) [4] that investigated the impact of a strict versus a more liberal TGC protocol. NICE-SUGAR revealed a higher mortality in the strict TGC group. The high incidence of hypoglycemia in the strict TGC-group might be considered one possible explanation for this controversy. Alike, from mathematical modelling Krinsley concluded that negative effects of hypoglycemia might outweigh any benefits on mortality and gross morbidity when they occur in a critical incidence [7]. Our study focuses on ICU survivors and is thus the first to explore the long term effects of hypoglycemia under TGC during ICU treatment on subtle neuropsychological function. With the employed test battery we largely confirm and complement prior studies (9) demonstrating neurocognitive impairment in the tested domains in both critically ill patient groups as compared to age, gender and educational level matched healthy controls. Furthermore, we could show that in patients surviving ICU without primary brain damage and pre-existing neurocognitive deficits, critical illness induced deficits of complex neurocognitive functions might be aggravated by even a single episode of hypoglycemia, in particular visuoconstructive performance as well as figural and spatial aspects of nonverbal memory. Although the aggravation appears minor at first view and is restricted to one single domain, the impairment of visual-spatial processing might have a relevant impact on overall daily functioning (11). It could be associated with the evolution of further cognitive decline over time (12), and, thus, have a significant impact on patients’ quality of life.

Recent studies have indicated that an impairment of visuoconstructive skills and both figural and spatial aspects of nonverbal memory are associated with temporal and hippocampal dysfunction (13). Neuroimaging has demonstrated that not all neurons and brain regions are equally sensitive to hypoglycemic injury, but that there appears to be a selective vulnerability of especially those hippocampal and/or temporal neurons, followed by neurons in the basal ganglia (14, 15). Although the reported abnormalities could be transient and reversible by glucose infusion, several studies in both animals and humans have consistently demonstrated hypoglycemia induced permanent neuronal damage in regions of the hippocampus, especially in the dentate gyrus (16, 17). Although most biochemical studies have focused on cell death, more recent studies indicate that mild, recurrent hypoglycemia can cause synaptic dysfunction even in the absence of neuronal death, particularly in hippocampal neurons (18). Repeated episodes of even moderate hypoglycemia in diabetic patients have been reported as being associated with a decline of intelligence quotient, persistent cognitive impairment and other long-term effects such as mood changes and affected general well-being (19, 20); however, since conflicting results have been published assigning hypoglycemia the sole cause of these findings is debatable. Some of the divergent results may be due to methodical issues with regards to the determination of cognitive function; other negative studies may not have been sufficiently long to detect a significant effect. On the other hand, the associations between intellectual disadvantage and episodes of hypoglycemia might exist simply because patients manage their insulin treatment less accurate. It is thus difficult to differentiate between effects of hypoglycemia and modest glycemic control comprising hyperglycemia, hypoglycemia and BG fluctuations. To conclude from clinical trials that persistent neurocognitive impairment in diabetics is exclusively a consequence of (repeated)
episodes of hypoglycemia is plausible but not imperative. Moreover, the underlying pathogenetic mechanisms of the long-term cognitive deficits remain largely unclear, some findings indicate that dopaminergic functional disturbance in the hippocampus (21), changes in brain glucose transporters or astrocyte-neuron interactions may play a major role (14). The agreement between neurocognitive test results, their probable functional and structural neuroanatomic correlates and the specific vulnerability of (para-)hippocampal neuron populations to hypoglycemic damage is striking however. Current data suggests that a great portion of ICU survivors in general develops persistent cognitive impairment (9, 22); we also found neurocognitive impairment in various domains in both our patient groups compared to published normative data. Since critical ill patients per se seem to be at risk for neural damage, one might speculate that critical illness can induce a specific vulnerability of neurons to glucose deprivation. Our data show that hypoglycemic events under TGC aggravate this critical illness induced neurocognitive deficits, but that this is limited to one neurocognitive domain. Notwithstanding stringent matching criteria for demographic and severity of illness data including mean BG we cannot completely exclude confounders. Our groups differ in mean maximum and minimum glucose, suggesting that the hypo-group experienced a worse quality of BG control with more variability. Solely within the hypo-group we found a significant association of hyperglycemia and the difference between lowest and highest BG with declined visuospatial skills, whereas for quantity and duration of hypoglycemic episodes no such correlation was found. No correlations at all were found in our control group. Indeed, previous work showed that hyperglycemia in diabetes mellitus too is associated with adverse effects on the brain (23), neurocognitive impairment and affected general well being (19). Not only hypoglycemia but also hyperglycemia, glucose fluctuations and their treatments thus might have an impact on cognitive function of ICU survivors. Moreover, neural death is aggravated when glucose concentrations rise rapidly and hyperglycemia occurs after hypoglycemia (“glucose reperfusion injury” (24)). Notably, critically ill patients reveal increased insulin levels and insulin has also been reported to accelerate neural cell death in the hippocampus during low glucose levels suggesting that insulin might have a double-edged effect on neuron death dependent on glucose concentration (25). Our findings are in accordance with these data. Since exclusively in the hypo-group a correlation of hyperglycemia and a surrogate parameter of the quality of glycemic control with neurocognitive dysfunction was found, we cannot rule out those parameters as relevant confounders of our findings. However, our hypothesis and design only allow to draw a causal link between hypoglycemia and neurocognitive impairment. It is undue to conclude causality between maximum BG or glucose fluctuations from our data, we solely can allude to an association. To unequivocally prove a causal relation between hypoglycemia and neurocognitive dysfunction, a prospective, randomised controlled trial would be required, but, self-evident, ethical considerations preclude this approach. We thus have to rely on the available data from post-hoc analysis with its limitations. Another limitation is the absence of brain imaging in all patients. Significant structural brain lesions are unlikely however, since none of the patients revealed manifest neurological deficits during the study period. However, subtle structural cerebral lesions can not completely be excluded.

In conclusion, neurocognitive dysfunction is common in patients surviving critical illness. Patients who experienced a hypoglycemic
event during ICU treatment show a significant additional impairment in the visuospatial domain compared to patients who did not. In those patients, hyperglycemia and fluctuations of BG levels were also associated with long-term visuospatial dysfunction and might thus confound this conclusion. Every effort should be put in implementing effective BG-control algorithms, largely avoiding hypo- and hyperglycemia as well as large fluctuations of BG.

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| Cognitive domain and tests | Hypo-group | Control-group |
|---------------------------|------------|--------------|
| **Dementia screening**    | Score      | Evaluation | z-scores | Score | Evaluation | z-scores | p     |
| Mini-Mental State Examination | 0.006     | close below average | -0.003   | 0.969  | close below average | -0.003   | 0.909  |
| Boston Naming Test        | 13.8       | normal      | -0.039   | -0.045 | 0.774      |          |        |
| **Attention and working memory** | -0.039   | normal      | -0.039   | -0.045 | 0.774      |          |        |
| Nuernberg Gerontopsychological Inventory | -2.084 | close below average | -2.084   | 0.001  | close below average | -2.084   | 0.001  |
| - Digit Symbol Substitution | 30.0 (56.7) | normal | 31.1 (60.7) | normal | 0.770      |          |        |
| - Color-Word-Interference Task (reading) | 39.8(10.2) | far below average | 40.0 (12.5) | far below average | 0.861  |          |        |
| - Color-Word-Interference Task (colour naming) | 53.3 (28.4) | close below average | 52.8 (26.6) | close below average | 0.608  |          |        |
| Wechsler Memory Scale-Revised | -0.001   | normal      | -0.007   | 0.991  | close below average | -0.007   | 0.991  |
| - Digit Span Forward      | 11.6 (51.7) | normal | 12.6(54.4) | normal | 0.156      |          |        |
| - Digit Span Backward     | 10.7 (40.6) | close below average | 11.6 (42.0) | close below average | 0.892  |          |        |
| Trail-making test [A]     | 60.1 (13.9) | far below average | 59.6 (13.0) | far below average | 0.270  |          |        |
| **Executive function**    | -0.027     | close below average | -0.027   | 0.000  | close below average | -0.027   | 0.000  |
| Color-Word-Interference Task (interference) | 17.5 (47.9) | normal | 19.5 (51.3) | normal | 0.421      |          |        |
| Regensburg Word Fluency Test (letter fluency) (‘S’) | 14.2 (28.4) | close below average | 14.2 (28.4) | close below average | 1.000  |          |        |
| Trail-making test [B]     | 117.0 (27.8) | close below average | 110.8 (25.6) | close below average | 0.792  |          |        |
| **Visuospatial skills**   | -2.084     | close below average | -2.084   | 0.001  | close below average | -2.084   | 0.001  |
| Rey-Osterrieth-Complex-Figure Test | 20.4       | close below average | 24.7     | 0.007  | close below average | 24.7     | 0.007  |
| - Copy                    | 9.4 (22.8) | close below average | 14.5 (29.9) | close below average | 0.002  |          |        |
| - Delayed recall          | -54.3 %    | close below average | -41.9 % (4.2) | close below average | 0.043  |          |        |
| **Verbal learning and memory** | -0.027   | close below average | -0.027   | 0.000  | close below average | -0.027   | 0.000  |
| Auditory-Verbal-Learning Test [German] | 4.9 (30.2) | close below average | 5.5 (38.4) | close below average | 0.503  |          |        |
| - Recall trial 1          | 10.7 (31.1) | close below average | 10.5 (28.8) | close below average | 0.543  |          |        |
| - Total trials 1 to 5     | -54.3 %    | close below average | -41.9 % (4.2) | close below average | 0.043  |          |        |
| - Delayed recall          | 8.5 (13.8) | far below average | 9.0 (15.0) | far below average | 0.240  |          |        |
| Recognition (True Positives – False Positives) | 10.9 (30.5) | close below average | 10.9 (30.5) | close below average | 1.000  |          |        |
Table 2: Matching-criteria.

**Demography**

|   |   |
|---|---|
| a) | Sex | male - female |
| b) | Age (classified in groups) | <40; 41-60; 61-75; >75 years |
| c) | Simplified Acute Physiology Score | <7; 8-14; >14 |
|    | (max. SAPS, classified in groups) |   |
| d) | Year of ICU-treatment |   |

**Disease related Criteria**

|   |   |
|---|---|
| e) | Type of surgery | elective surgery – emergency surgery |
| f) | Cardiopulmonary Resuscitation (CPR) | yes - no |
| g) | Type 1 or type 2 diabetes | yes - no |
| h) | Length of stay in ICU * |   |
| i) | Mean morning blood glucose * |   |
| j) | Duration of sedation (classified in groups) | <3 days; 3-7 days; 1-2 weeks; > 2 weeks |
| k) | Respiratory failure † | >300; 200-300; <200 |
|    | (classified by Horrowitz Index in groups) |   |
| l) | Cardiovascular failure † | Catecholamine therapy: yes – no |
|    | Mechanical assist device: yes - no |   |
| m) | Renal failure † | Hemodialysis of any kind: yes – no |
|    | Classified by RIFLE-Criteria |   |
| n) | Hepatic failure (classified by laboratory liver-testing, classified in 4 groups) | All values <2.5 ULN, one value 2.5-5 ULN, one value >5 ULN, all values > 5 ULN |
| o) | Medication | Steroids: yes - no |
|    | Immunesuppressants: yes - no |   |

*smallest possible difference, † at time of hypoglycemia ±3 days, ULN: upper limit of normal
Table 3: Correlation of the parameters of glycemic control with ROCFT results in the hypo-group.

| Parameters of glycemic control                  | r    | p-values |
|------------------------------------------------|------|----------|
| Mean moring BG                                 | -0.055 | 0.747    |
| Mean BG                                        | 0.116  | 0.494    |
| Number of hypoglycemias                        | -0.097 | 0.414    |
| Duration of hypoglycemias                      | -0.293 | 0.154    |
| Maximum BG during treatment                    | -0.322 | 0.005    |
| Minimum BG during treatment                    | -0.299 | 0.072    |
| Difference maximum/minimum BG                 | -0.309 | 0.001    |
| deltaBG                                        | 0.052  | 0.765    |

BG: blood glucose

Figure 1: Flow chart patient inclusion in the hypo-group.
193 patients with hypoglycaemia

138 did not meet inclusion criteria for testing

55 patients

4 died after discharge

51 patients

6 no matching partner found

45 patients

8 patients were not traceable or refused consent

37 patients tested and analyzed