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# Differential influence of arterial blood glucose on cerebral metabolism following severe traumatic brain injury

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**Abstract**

**Introduction**

Maintaining arterial blood glucose within tight limits is beneficial in critically ill patients. Upper and lower limits of detrimental blood glucose levels must be determined.

**Methods**

In 69 patients with severe traumatic brain injury (TBI), cerebral metabolism was monitored by assessing changes in arterial and jugular venous blood at normocarbia (paCO2 4.4-5.6 kPa), normoxia (paO2 9-20 kPa), stable hematocrit (27-36%), brain temperature 35-38 degreesC, and CPP 70-90 mmHg. This resulted in a total of 43,896 values for glucose uptake, lactate release, oxygen extraction ratio (OER), CO2 and HCO3 production, SjvO2, oxygen-glucose index (OGI), lactate-glucose index (LGI), and lactate-oxygen index (LOI). Arterial bood glucose concentration-dependent influence was determined retrospectively by assessing changes in these parameters within pre-defined blood glucose clusters, ranging from <4 to >9 mmol/l.

**Results**

Arterial blood glucose significantly influenced signs of cerebral metabolism reflected by increased cerebral glucose uptake, decreased cerebral lactate production, reduced oxygen consumption, negative LGI, and decreased cerebral CO2/HCO3 production at arterial blood glucose levels above 6-7 mmol/l compared to lower arterial blood glucose concentrations. At blood glucose >8 mmol/l signs of increased anaerobic glycolysis (OGI<6) supervened.

**Conclusions**

Maintaining arterial blood glucose levels between 6 and 8 mmol/l appears superior compared to lower and higher blood glucose concentrations in terms of stabilized cerebral metabolism. It appears that arterial blood glucose values <6 and >8 mmol/l should be avoided. Prospective analysis is required to determine the optimal arterial blood glucose target in patients suffering from severe TBI.

## Introduction

Traumatic brain injury (TBI) induces a plethora of structural and functional alterations which contribute to subsequent deterioration as observed under clinical and experimental conditions. These changes occuring in parallel and sequentially are associated with metabolic and energetic disturbances [1, 2], due to impaired perfusion [3], increased glycolysis [4] with increased lactate production [5], regionally altered glucose uptake [6] and impaired glucose metabolism due to changes in enzymatic and mitochondrial activity [6- 10], functional derangements as observed in cortical spreading depolarizations (CSD) [11], excitotoxicity with disturbed ionic homeostasis and activated intracellular destructive secondary cascades [12], and increased activity of neurons and astrocytes [13]. These changes are not only restricted to the area of impact but are also observed in areas distant to the primary impact corresponding to contre- coup lesions [14]. Apart from local alterations systemic influences as e.g., hypotension, hypoxia, and anemia are detrimental as cerebral oxygenation becomes insufficient. Consequently, induced pathologic alterations are aggravated. In addition to hypotension, hypoxia, and anemia, changes in blood glucose levels induce additional damage. In this context, hyperglycemia induces local acidosis [15, 16], induces oxidative stress, promotes edema formation, and impairs NO- mediated vasodilatation [17] and activates inflammation as reflected by increased leukocyte infiltration [18]. Hypoglycemia increases glutamate release [19], induces metabolic impairment [19], and promotes generation of CSD which, in turn, generates and aggravates exisiting edema [20].

In contemporary intensive care treatment of patients with severe TBI secondary brain damage must be avoided. In this context, hypo- as well as hyperglycemic episodes need to be prevented. While the upper limit of 10 mmol/l is well defined since hyperglycemia exceeding 10 mmol/l is associated with increased mortality [21] the lower acceptable limit void of any damaging effect is still unclear. As pointed out by Strong et al. blood glucose levels < 5 mmol/l increase the development of CSD [20]. In addition, maintaining blood glucose levels between 3.5 and 6.5 mmol/l increases frequency of hypoglycemic episodes [22- 27] and has been shown to induce metabolic impairment in brain injured patients [19]. Thus, it appears that arterial blood glucose levels between 5 and < 10 mmol/l could be more appropriate in terms of improved metabolic stability. The optimal limits, however, remain to be determined.

Intentionally lowering blood glucose levels and inducing hypoglycemia to investigate the impact of different arterial blood glucose levels on cerebral metabolism following severe TBI is unethical in humans. In this context, retrospective analysis in evaluating a

concentration- dependent impact of different arterial blood glucose concetrations on cerebral metabolism is helpful. For this, changes in various parameters of cerebral metabolism [jugular venous oxygen saturation ($SjvO_2$), oxygen- glucose index, lactate-oxygen index, lactate- glucose index, arterio- jugular venous glucose and lactate differences] were determined for pre- defined arterial blood glucose values in a total of 69 patients with severe TBI. In addition, *post hoc* analysis of influence of time, different lesions, side of jugular venous catheter insertion, and outcome was performed.

## Materials and Methods

Following approval by the local Ethics Committee which waived the need for written informed consent for this retrospective analysis, patient records from a total of 69 patients treated on our intensive care unit (ICU) from 2004 to 2006 were reviewed. All patients were required to have received a jugular venous catheter with a minimum monitoring time of 24 hours. Patients with severe injuries anticipated to succumb to their injuries within the first 24 hours were not considered for the present analysis. Barbiturates as well as propofol are known to dose- dependently suppress neuronal activity and cerebral metabolism [28]. To avoid difficult interpretation of the cerebral metabolic parameters due to differing depth of sedation only patients subjected to continuous infusion of fentanyl (Sintenyl®) and midazolam (Dormicum®) were investigated in the present study.

### Standardized treatment protocol

Following severe TBI intubated and ventilated patients were treated according to our standardized treatment protocol. Following CT diagnostic and surgical interventions including insertion of an ICP probe (Neurovent®, Raumedic AG, 95205 Münchberg, Germany) patients were transferred to our ICU. Continuous analgesia and sedation was controlled by BIS EEG (BIS VISTA™, Aspect Medical Systems, Inc., One Upland Road, Norwood, MA 02062) tapering drug dosage to maintain a BIS level between 20- 40. Norepinephrine, dobutamine, and volume (crystalloids and colloids) were administered to maintain CPP above 70 mmHg.

Sonographically guided insertion of a jugular bulb catheter in the larger internal jugular vein was performed within the first hour following admission to the ICU. In 88% of the investigated patients the right jugular vein was larger, irrespective of the type of lesion and predominant location of the brain lesions (table 1). Subsequent radiological control using conventional x- ray of the lateral aspect of the cervical spine and head revealed position of the tip of the jugular catheter. Whenever required the jugular catheter was repositioned with the tip of the catheter aimed at the caudal aspect of the mastoid process to avoid obstructing the jugular bulb and the sigmoid sinus. Thereafter, arterial and simultaneously drawn jugular venous blood samples were routinely investigated in 4- 6 hour intervals. This sampling frequency was the same for every day and every patient until removal of the jugular venous catheter. Arterial and jugular venous blood gas analyses using commercially available pre- heparinized syringes (*safe* PICO Aspirator, Radiometer, Copenhagen, Radiometer Medical ApS, Åkadevej 21, DK- 2700 Brønshøj, Denmark) were

performed using the ABL825 Flex Analyzer® (Radiometer Medical ApS, Åkadevej 21, DK-2700 Brønshøj, Denmark).

Differentiated CPP and ventilation management was guided by $SjvO_2$ maintaining $SjvO_2$ above 60%. Brain temperature was maintained between 35 and 36.0° C using cooling blankets or an intravenous cooling system (CoolGard3000®, Alsius®, 15770 Laguna Canyon Road, Suite 150, Irvine, CA 92618 USA).

Overall, treatment measures were adapted and tapered to primarily maintain ICP< 15 mmHg. Following optimization of therapeutic interventions an ICP < 20 mmHg was tolerated as long as CPP was maintained and cerebral metabolism was stable.

Patients received enteral nutrition via gastric or jejunal tube started within the first 12 hours. Administered calories were adapted according to indirect calorimetry performed twice weekly.

**Control and standardized management of arterial blood glucose concentrations**

Arterial blood glucose was controlled in 1- 4 hour intervals depending on the actual arterial blood glucose level determined in the arterial blood gas analysis. Arterial blood glucose target was set at 3.5- 6.5 mmol/l based on the findings by van den Berghe and colleagues [22- 24]. Arterial blood glucose was decreased by increasing insulin dose which was infused continuously. Arterial blood glucose was increased by decreasing infused insulin and by augmenting enteral nutrition. Glucose was not routinely infused as performed by van den Berghe and colleagues [22- 24] to prevent the risk of promoting brain edema formation. Transient glucose infusion was only considered in cases of severe hypoglycaemia (< 2 mmol/l) which occurred once in one patient.

**Calculated parameters of cerebral metabolism**

<u>Arterio- jugularvenous differences</u>

Uptake and release of glucose (glc) and lactate (lac) can be assessed by calculating corresponding arterio- jugularvenous differences (AJVD). While positive values reflect uptake, negative values unmask cerebral release:

1) AJVD glc= arterial glc- jugularvenous glc

2) AJVD lac= arterial lac- jugularvenous lac

<u>Cerebral arterio- jugularvenous difference in oxygen ($avDO_2$)</u>

$avDO_2$ was calculated based on the arterial and jugular venous oxygen content:

3) $avDO_2 = caO_2 - cjvO_2$

Arterial and jugular venous oxygen content were calculated based on hemoglobin (Hb) concentration and oxygen saturation in arterial ($SaO_2$) an jugular venous ($SjvO_2$) blood using the following equations:

4) $caO_2 = (1.34 \times Hb \times SaO_2) + (0.003 \times paO_2)$

5) $cjvO_2 = (1.34 \times Hb \times SjvO_2) + (0.003 \times pjvO_2)$

Oxygen extraction rate (OER)

OER was calculated based on the equation

6) $OER = (caO_2 - cjvO_2)/ caO_2$, expressed in%

Oxygen- glucose index (OGI)

OGI was calculated based on changes in $avDO_2$ and arterio- jugularvenous difference in glucose (AJVD glc):

7) $OGI = avDO_2/$ AJVD glc

During aerobic glycolysis approximately six molecules of oxygen are used to oxidate one molecule of glucose. Whenever glucose metabolism exceeds oxygen consumption, the calculated OGI will be < 6, thereby reflecting anaerobic glycolysis. An OGI > 6 indicates aerobic metabolism of substrates other than glucose, as e.g., lactate.

Lactate- glucose index (LGI)

LGI was calculated considering changes in arterio- jugularvenous difference in lactate (AJVD lac) and AJVD glc:

8) LGI= AJVD lac/ AJVD glc

LGI reflects generation of cerebral lactate from glucose. Increased cerebral lactate production results in negative LGI values while positive LGI reflects lactate uptake.

Lactate- oxygen index (LOI)

LOI was calculated using the following equation:

9) $LOI = AJVD\ lac/ avDO_2$

LOI can be used as a crude estimate for the extent of cerebral anaerobic metabolism relative to oxidative metabolism. In this context, lactate release results in negative LOI while lactate uptake is reflected by a positive LOI.

Arterio- jugularvenous difference in pH

AJVD pH can be used to assess dynamic changes. Less positive values unmask decreased release of $H^+$- ions, reduced production of $CO_2$ or sustained buffering of acidosis due to increased release of $HCO_3$.

10) AJVD pH= pHa- pHjv

Arterio- jugularvenous difference in $pCO_2$

Negative AJVD $pCO_2$ values represent increased cerebral production of $CO_2$. Less negative AJVD $pCO_2$ values unmask reduced release of $CO_2$.

11) AJVD $pCO_2$= $paCO_2$- $pjvCO_2$

Arterio- jugularvenous difference in $HCO_3$

Dynamic changes in AJVD $HCO_3$ reflect production of $HCO_3$ and intracerebral buffer capacity. In this context, negative AJVD $HCO_3$ represent increased $HCO_3$ production.

12) AJVD $HCO_3$= arterial $HCO_3$- jugularvenous $HCO_3$

Detailed evaluation

Pre- defined parameters (ICP, CPP, $paCO_2$, parameters of cerebral metabolism) were assessed for different arterial blood glucose values grouped in 1 mmol/l clusters ranging from < 4 to > 9 mmol/l.

Parameters of cerebral metabolism were investigated under conditions of normocarbia ($paCO_2$ 4.4- 5.6 kPa), normoxia ($paO_2$ 9- 20 kPa), and hematocrit between 27 and 36%. In addition, only values determined at a temperature between 35- 38°C and CPP between 70 and 90 mmHg were considered. This resulted in a total of 3'658 values per investigated parameter, representing 69% of all recorded time points. When considering the influence of arterial blood glucose clusters the remaining values per defined cluster were too small to allow meaningful statistical analysis.

Time dependency was determined by evaluating changes of the pre- defined paramaters within the arterial blood glucose clusters during the first, second, and third week.

Lesion- dependent influences were assessed by comparing the pre- defined parameters between lesion subtypes: isolated lesions vs. mixed lesions. A more detailed analysis was not possible due to a limited number of patients and samples per lesion subgroup.

Influence of outcome was determined by grouping the pre- defined parameters according to survivors and non- survivors.

Calculation of frequency of pathologic values allow to determine the impact of different arterial blood glucose clusters on cerebral brain metabolism. For this, frequency of $SjvO_2$< 60%, OGI< 6, negative LGI, negative LOI, and negative AJVD lactate levels reflecting increased cerebral oxygen consumption ($SjvO_2$, OER), anaerobic glycolysis (OGI), and lactate production (LGI, LOI, AJVD lactate) were assessed in pre- defined arterial blood glucose clusters.

**Statistical analysis**

Graphical and statistical analysis was performed using SigmaPlot®10.0 and SigmaStat®3.5, respectively. Changes over time and between groups were evaluated for statistically significant difference using the Mann Whitney rank sum test and ANOVA on ranks with post hoc all pairwise multiple comparison procedures (Dunn's test). Differences were rated significant with a $p < 0.05$.

## Results

Demographic data

Demographic data of the investigated 69 patients are given in table 1. These patients reflect the population of patients with severe TBI treated at our institution.

Number of determined values

Overall, a total of 3'658 arterial and corresponding jugular venous blood gas analyses were performed, resulting in a total of 43'896 values for the 12 pre- defined parameters (ICP, CPP, $paCO_2$, $SjvO_2$, OER, LOI, LGI, OGI, AJVD glc, AJVD lac, AJVD pH, AJVD $CO_2$, AJVD $HCO_3$).

According to the individual clinical courses, majority of values were determined in the first week (52%), followed by 39% in the second week and 9% in the third week. Thus, the strongest statistical power is found during the first two weeks.

Relative frequency of arterial blood glucose values

During weeks 1- 3, arterial blood glucose concentrations were predominantly measured between 5- 6 and 6- 7 mmol/l corresponding to the set blood glucose target of 3.5- 6.5 mmol/l (fig. 1). There was no significant difference between weeks 1- 3.

Glucose- dependent and time- dependent changes

Pre- defined arterial blood glucose clusters resulted in different numbers of values per cluster for the different parameters: < 4 mmol/l= 111, 4- 5 mmol/l= 543, 5- 6 mmol/l= 1385, 6- 7 mmol/l= 1005, 7- 8 mmol/l= 418, 8- 9 mmol/l= 134, > 9 mmol/l= 62 values.

Increasing arterial blood glucose was associated with a significantly increased cerebral glucose uptake reflected by a more positive AJVD glc (fig. 2). In parallel, lactate release was decreased revealed by a less negative AJVD lac approaching positive values (fig. 2). Significant increases were observed at arterial blood glucose levels between 8 and 9 mmol/l compared to arterial blood glucose < 8 mmol/l. There were no significant differences between the different weeks (week 1, 2, 3) (data not shown).

OER was significantly decreased reaching lowest values at blood glucose > 8 mmol/l (fig. 3). Changes in OER were reflected by increased $SjvO_2$ levels, respectively, reaching highest values at blood glucose > 8 mmol/l (fig. 3).

Calculated OGI was significantly decreased with increasing arterial blood glucose levels exceeding 8 mmol/l (fig. 4). There was no difference over time (data not shown).

Calculated LOI showed a trend towards elevated values with increasing arterial blood glucose levels. There was no difference over time (data not shown).
Calculated LGI approached positive values and was significantly increased with higher arterial blood glucose concentrations exceeding 8 mmol/l (fig. 5). There was no difference over time (data not shown).
Cerebral release/ production of $CO_2$ and $HCO_3$ was significantly reduced with arterial blood glucose exceeding 6 mmol/l (figs. 6 and 7). This was reflected by a smaller AJVD pH (data not shown).
With elevated arterial blood glucose levels, frequency of increased cerebral oxygen consumption ($SjvO_2$ < 60%) and cerebral lactate production (negative LGI values) were reduced (fig. 8). Rate of anaerobic glycoloysis (OGI< 6), however, was increased at higher arterial blood glucose levels (fig. 8).
Different blood glucose levels did not influence ICP and CPP values (data not shown).

Lesion- dependent changes

Pre- defined cerebral metabolic parameters as well as ICP and CPP were similar in patients with isolated lesions compared to mixed lesions (data not shown). There were no differences in type and extent of therapeutic measures.

Side- dependent changes

In the majority of the investigated patients (62/ 69 patients) the jugular venous catheter was inserted in the right jugular vein, irrespective of the type of lesion and the predominant side of the brain lesions (table 1) (right- sided brain lesions: 13/ 15 patients, left- sided brain lesions: 7/ 8 patients, bilateral brain lesions: 42/ 46 patients). In the remaining seven patients, the left jugular vein was canulated. There was no difference in brain metabolism between left- sided or right- sided cannulation. However, the low number of patients and uneven distribution within the different brain lesions do not allow statistical analysis .

Outcome- dependent changes

Investigated metabolic parameters could not differentiate non- surviving patients from surviving patients (data not shown).

## Discussion

Bed- side analysis of changes in arterial and jugular venous differences and their derived indices of cerebral metabolism differentiated less favorable from more favorable arterial blood glucose concentrations. Overall, cerebral metabolism appeared more stable as judged by increased glucose uptake, reduced cerebral lactate, $CO_2$ and $HCO_3$ production/ release, elevated $SjvO_2$, decreased OER, increased LOI, and elevated LGI with arterial blood glucose levels between 8 and 9 mmol/ l.

### Limitations of the study

The retrospective nature of the present analysis does not allow to clearly define dynamic processes induced by specific arterial blood glucose concentrations or induced therapeutic interventions as investigated changes were taken from the pooled data obtained in 69 patients with severe TBI. These pooled data consist of arterial and jugular venous blood samples which were drawn at fixed time intervals predominantly ranging from 4- 6 hours. These time intervals were independent from changes in arterial blood glucose values which might have occurred between these sampling intervals. A prospective study designed to specifically investigate the impact of dynamic changes by assessing alterations of cerebral metabolic parameters at pre- defined changes in arterial blood glucose levels is required to address this issue.

Calculated differences and indices of cerebral metabolism are widely accepted to gain insight in otherwise occult changes within the brain [7, 29- 33]. However, the low temporal and spatial resolution limit any detailed information concerning changes between the individual blood sampling time points and influences of injured vs. non- injured or lesser injured tissue since blood samples were drawn in 4- 6 hour intervals and jugular venous blood reflects global rather than local intracerebral changes. In this context it has been shown that $SjvO_2$ only partially reflects pathologic intracerebral alterations [34] which show a strong regional heterogeneity within peri-lesional tissue compared to lesions [35].

As observed in healthy volunteers magnetic resonance venography revealed a significant asymmetry in the venous blood flow form the superior sagittal sinus flow to one transverse sinus in 84% of the volunteers [36]. Based on a theoretical model this is accepted to result in an asymmetry in jugular venous oxygen saturation measurements in patients with a supratentorial lesion [36]. As shown by Metz and colleagues [37] monitoring of cerebral metabolism using bilateral jugular venous catheters is superior to the unilateral approach when searching for signs of posttraumatic cerebral ischemia due to insufficient CPP and hyperventilation. Nevertheless 87% of ischemic events were detected when monitoring

ipsilateral to the predominant lesion or the side with the predominant jugular venous outflow (in patients with diffuse brain injury). Thus, can expect to unmask pathologic alterations in the majority of our patients. The scientific superiority of bilateral cannulation of the jugular vein is off- set by the clinically relevant increased risk of bilateral thrombosis formation which could result in increased ICP due to reduced venous outflow.

While microdialysis [1, 2, 5, 16, 19, 38, 39], PET [4- 6, 39, 40], and SPECT [41] allow more detailed insight, these techniques are also confronted with specific limitations as e.g., high costs, decreased regional and temporal resolution, respectively.

Continuous arterial and jugular venous blood sampling with subsequent analysis of metabolic parameters would be helpful as described under experimental conditions [42]. For this, however, appropriate techniques have not yet been developed for the clinical application. Until then, easy and cheap analysis of intermittently drawn blood gases which is an integral part of contemporary intensive care treatment of critically ill patients is the only feasible approach applicable on any specialized ICU.

Glucose and cerebral metabolism

Glucose is the predominant fuel for energy consuming processes within the brain [32]. Glucose is mainly used by the $Na^+/ K^+$ ATPase which is indispendsable to maintain membrane stability and prevent functional as well as structural cell damage [43]. Various endothelial, glial, and neuronal glucose transporters with different transport characteristics guarantee sufficient glucose transport across the blood brain barrier (GLUT1) as well as glial (GLUT1, 5) and neuronal (GLUT3, 4, 6, 8) glucose uptake [13, 44]. In this context, the neuronal GLUT3 exhibits a lower $K_m$ (Michaelis constant) and a higher $V_{max}$ (maximal transport velocity) compared to the other glucose transporters: $K_m$= 1.4- 2.8 mmol/l [13, 44], $V_{max}$ 5- 34.6 nM/ $10^6$ cells/ min [13], resulting in a significantly higher affinity and transport capacity compared to e.g., GLUT1. These characteristics, in turn, guarantee adequate neuronal glucose utilization under conditions of decreased glucose supply. This is important since the ambient glucose levels within the neuronal environment is rather low ranging from 1- 2 mmol/l compared to normal blood glucose levels between 5 and 6 mmol/l. Thus, any decrease in arterial blood glucose in conjunction with impaired endothelial glucose transport due to reduced GLUT1 expression will endanger neuronal function and viability.

Following TBI, increased GLUT3 expression [45] guarantees neuronal glucose uptake while decreased GLUT1 expression [46] as found under experimental conditions limits endothelial glucose transport. Decreased GLUT1 expression in conjunction with reduced

blood glucose levels result in a concentration- dependent decrease in glucose flux which is mostly sustained at blood glucose levels below 3 mmol/l [47].

Under clinical conditions it is unclear which changes in presence and function of the different GLUT subtypes is prevalent. The arterial blood glucose concentration- dependent cerebral uptake of glucose as seen in the present study suggests that arterial blood glucose concentrations maintained below the optimal $K_m$ of the endothelial GLUT1, i.e., < 8 mmol/l [13, 44] will result in insufficient supply. This can be overcome by maintaining arterial blood glucose levels around 8 mmol/l as reflected by increased metabolic stability. This is in line with findings showing the impact of decreased glucose supply on posttraumatic functional disturbances following traumatic brain injury in terms of induced CSD [20], increased extracellular glutamate and elevated lactate/ pyruvate ratio [19]. As pointed out by Vespa and colleagues, cerebral oxygen consumption was decreased in patients with higher blood glucose concentrations (120- 150 vs. 90- 120 mg/ dl) [19]. This is also seen in the present patients. These findings strongly suggest that activation of glucose transporter systems influence cerebral oxygen consumption. As shown by Abate and coworkers [48] increased cerebral glucose consumption is associated with elevated oxygen extraction ratio (OER) while low cerebral glucose consumption results in decreased OER. Thus, the present data suggest that metabolic instability which can also occur independently from cerebral ischemia [2] can be influenced substantially by changing arterial blood glucose levels. Classically, OER has always been discussed in the context of altered cerebral perfusion due to hypotension and hyperventilation [49] as increased OER reflects insufficient cerebral perfusion. The present findings in conjunction with data published by Vespa and colleagues [19] and Abate and coworkers [45-48] suggest that changes in glucose metabolism substantially influence OER. Increased oxygen consumption resulting from energetic impairment (lactate production, elevated lactate/ pyruvate ratio) and neuronal excitation due to sustained glutamate release could increase cerebral perfusion to correct this oxygen and energy deficit. This, however, requires an intact coupling between metabolism and perfusion [50] which is known to be disturbed following severe TBI [34] and during sedation/ anesthesia [51]. Based on the facts that CPP was maintained above 70 mmHg and sedation was unchanged at all investigated time points of analysis- assuming sufficient regional cerebral perfusion and stable pharmacological coma- we speculate that metabolic impairment due to low arterial blood glucose levels was the driving force for the observed increase in OER at arterial blood glucose values < 7 mmol/ l coinciding with increased lactate and CO2 production, and lower LGI. However, the present data do not allow to reliably differentiate whether

metabolic impairment might aggravate edema formation resulting in microcirculatory deterioration which, in turn, increases OER. It also remains unclear whether the increased $CO_2$ production reflected by the negative AJVD $pCO_2$ counteracts perfusion- metabolism mismatch or contributes to ongoing metabolic impairment due to vessel dilation and subsequent sustained brain swelling with compression of the microcirculation. Further analysis including assessment of cerebral perfusion is warranted to determine the functional impact of the metabolic changes observed in the present retrospective analysis .

Signs of tissue acidosis and regulation of cerebral metabolism

Severe TBI induces brain tissue acidosis reflected by significantly decreased brain tissue pH inversely correlated with elevated brain lactate and $pCO_2$ during the first posttraumatic day [52]. Brain pH can either be determined directly by inserting specialized probes to measure pH or indirectly by measuring tissue $pCO_2$ and lactate. In addition, assessing changes in arterio- jugular venous differences in $pCO_2$ as reported by Chieregato and colleagues [33] or $HCO_3^-$ as performed in the present study can be used to indirectly determine changes in brain pH. Apart from insufficient cerebral perfusion and cerebral oxygenation [52] concomitant hyperglycemia has also been shown to aggravate TBI- and ischemia- induced brain tissue acidosis [53, 54]. Sustained cerebral $CO_2$ and $HCO_3^-$ production due to increased metabolism reflect underlying activation of various transporter systems and regulatory mechanisms. In this context, cerebral pH is regulated by $Na^+/H^+$ exchange, Na+- driven $Cl^-/ HCO_3^-$ exchange, $Na^+$-$HCO_3^-$ cotransport, and passive $Cl^-/ HCO_3^-$ exchange [55]. As unmasked by the present study, low arterial blood glucose levels < 8 mmol/l are also associated with sustained $CO_2$, $HCO_3^-$, and lactate production suggesting that inadequate glucose supply activates various transporter systems as e.g., the $Na^+/ K^+$ATPase and glucose transporters to meet increased metabolic and energetic demands resulting from e.g., sustained hypoglycemia- induced glutamate release [19] and subsequent glutamate- mediated increased cerebral glucose consumption [56].

Glucose and secondary cerebral damage

Any decrease in arterial glucose will impair cerebral glucose- dependent pathways, thereby resulting in disturbed metabolism as reflected by increased lactate/ pyruvate ratio [19]. This, in turn, can induce excitotoxic damage resulting in increased extracellular glutamate levels [19]. As shown by Shulman and colleagues [57] approximately 80% of cortical glucose consumption (in the rat brain) is driven by glutamate cycling. Thus, glutamate release due to reduced arterial blood glucose levels [19] increases cerebral

glucose utilization which cannot be met if arterial blood glucose remains low. This is of importance whenever glucose uptake, glucose metabolism, enzymatic function, local perfusion and local diffusion processes are disturbed. Together with these alterations reduced blood glucose can aggravate underlying brain damage. In this context, a decrease in blood glucose levels below 8 mmol/l was associated with a significant elevation in peri-ischemic cortical depolarizations [58] which coincided with metabolic impairment reflected by an increase in extracellular cerebral lactate and decrease in extracellular glucose measured by microdialysis [58]. The occurrence of cortical depolarizations was dramatically increased when blood glucose levels dropped below 6 mmol/l [58, 59]. Consequently, induction of CSD known to promote secondary damage can be avoided by maintaining arterial blood glucose above 5 mmol/l. As suggested by the present findings arterial blood glucose ranging from 7- 9 mmol/l appear more beneficial in terms of improved metabolic stability.

Which arterial blood glucose concentration is optimal following severe TBI?

Under conditions of relative cerebral glucose insufficiency due to increased cerebral glycolysis or absolute glucose insufficiency caused by systemic hypoglycemia, the brain can metabolize lactate, pyruvate, and keton bodies [13, 32]. However, lactate metabolism is less efficient than glycolysis and mitochondrial oxidative phosphorylation which result in higher ATP production compared to lactate degradation. Lactate metabolism includes energy- consuming shuttling processes to transport lactate from astrocytes to neurons for subsequent generation of pyruvate via lactate dehydrogenase and further processing in the citric acid cycle and mitochondrial respiratory chain [13]. While cerebral glycogen stores have been shown to exceed arterial blood glucose levels by a three- to fourfold during euglycemia in healthy controls [60], reflecting an additional valuable energetic reserve, it is unclear to which extent and for which duration glycogenolysis can fuel energy- requiring processes under pathologic conditions. As suggested by Otori and colleagues, increase in cerebral glycogen content following experimental TBI could serve as an endogenous source of metabolic energy [61]. Thus, a decrease in arterial blood glucose should trigger glycogenolysis to maintain extracellular glucose concentrations and avoid metabolic impairment. However, this does not seem to occur under clinical conditions since decreased blood glucose resulted in a significant reduction in extracellular glucose concentrations determined by microdialysis in TBI and epileptic patients [19, 62]. Hypoglycemia- induced impaired cerebral metabolism in terms of lactate production as observed in the present study and increased lactate/ pyruvate ratio [19] reflects a

subordinated importance of glycogen under these specific conditions to prevent energetic deterioration. Consequently, sufficient cerebral glucose supply must be guaranteed to prevent avoidable secondary brain damage.

As suggested by the present retrospective analysis, optimal arterial blood glucose levels range from 6 to 8 mmol/ l. With arterial blood glucose levels exceeding 8 mmol/ l differentiated metabolic pathways appear to be activated as reflected by decreased rate of increased oxygen consumption and reduced frequency of increased cerebral lactate production. At the same time, however, anaerobic glycolysis reflected by OGI values < 6 was increased. Apart from anaerobic metabolims which implies underlying ischemia or hypoxia it could be possible that non- oxidative metabolism resulting from mitochondrial damage and impaired oxidative phosphorylation despite sufficient perfusion and oxygen supply accounts for the observed decrease in OGI. This is in line with the pathophysiologic mechanism of destructive influence of elevated arterial blood glucose levels on mitochondria due to hyperglycemia- induced production of free oxygen radicals with subsequent impairment of oxidative phosphorylation as discussed by van den Berghe and colleagues [22- 24].

Taken together, arterial blood glucose levels between 6 and 8 mmol/ l could be an appropriate range for patients suffering from severe traumatic brain injury.

**Conclusions**

To avoid cerebral metabolic impairment and prevent secondary brain damage adequate blood glucose levels must be induced and maintained during the intensive care phase.

While substantial and reproducible evidence exists to avoid arterial blood glucose levels exceeding 10 mmol/l the optimal lower blood glucose level is less clear. The present results strongly suggest that arterial blood glucose concentrations < 6 mmol/l should be avoided and that optimal cerebral metabolic stability is found at arterial blood glucose levels around 8 mmol/l as reflected by increased cerebral glucose uptake, decreased cerebral lactate production, increased $SjvO_2$, as well as decreased cerebral oxygen extraction, $CO_2$ and $HCO_3$ production. The increased frequency of reduced oxygen-glucose index (OGI) below 6 at arterial blood glucose levels exceeding 8 mmol/ l appears to delineate the upper limit of acceptable arterial blood glucose levels.

Prospective studies are needed to define the optimal arterial blood glucose target in patients with severe traumatic brain injury.

***Key messages:***

- Changes in cerebral metabolism determined by analyzing jugular venous blood gases and calculating arterial- jugular venous differences of metabolic indices are significantly influenced by arterial blood glucose concentrations.
- Arterial blood glucose concentration- dependently improved cerebral metabolism reflected by elevated $SjvO_2$, increased cerebral glucose uptake, decreased cerebral lactate production, reduced $CO_2$ and $HCO_3^-$ production, and increased lactate- glucose index.
- Increased incidence in decreased oxygen- glucose index (OGI < 6) reflecting anaerobic glycolysis occurred at arteral blood glucose > 8 mmol/ l but was not associated with increased cerebral lactate production.
- Cerebral metabolic stability is reached at arterial blood glucose levels between 6 and 8 mmol/l.
- Arterial blood glucose concentrations < 6 and > 8 mmol/l should be avoided to prevent signs of worsened cerebral metabolism reflected by increased cerebral lactate production and anaerobic glycolysis, respectively.

**Abbreviations**

AJVD= arterio- jugular venous difference

CPP= cerebral perfusion pressure

ICP= intracranial pressure

ICU= intensive care unit

LGI= lactate- glucose index

LOI= lactate- oxygen index

OER= oxygen extraction ratio

OGI= oxygen- glucose index

TBI= traumatic brain injury

**Competing interests**

The authors declare that they have no competing interests.

**Author's contributions**

MH collected the majority of the data, drafted parts of the manuscript and performed graphical analysis. MB helped analyzing and interpreting the data and drafted parts of the manuscript. SL and JS were responsible for data collection and maintaining the data bank. SRC, MK, and RS helped analyzing and interpreting the data. JFS conceived the study design, collected parts of the data, performed graphical and statistical analysis, and drafted parts of the manuscript.

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**Table 1** Demographic data of 69 patients suffering from severe traumatic brain injury. (Abbreviations: GCS= Glasgow Coma Scale; ISS= injury severity score; TBI= traumatic brain injury; EDH= epidural hematoma; SDH= subdural hematoma; tSAH= traumatic subarachnoid hemorrhage; ICU= intensive care unit)

| Parameters | Median, range or % |
|---|---|
| **age [years]** | 38, 18- 65 |
| **gender** | 76% male |
| **initial GCS** | 11, 3- 15 |
| **ISS** | 34, 12- 54 |
| **isolated TBI** | 25% |
| **mortality [%]** | 26% |
| **Isolated lesions [%]** | 32% |
| **EDH** | 2% |
| **SDH** | 8% |
| **contusions** | 12% |
| **tSAH** | 4% |
| **edema** | 6% |
| **Mixed lesions [%]** | 68% |
| **Predominant side of brain lesion** | |
| **right** | 22% |
| **left** | 11% |
| **bilateral** | 67% |
| **Cannulation of right jugular vein** | |
| **right- sided lesions** | N= 13; 87% |
| **left- sided lesions** | N= 7; 88% |
| **bilateral lesions** | N= 42; 91% |
| **Length of ICU [days]** | |
| **survivors** | 16, 2- 52 |
| **deceased** | 10, 2- 43 |
| **Duration of jugular bulb [days]** | |
| **survivors** | 10, 2- 24 |
| **deceased** | 7, 2- 15 |

**Figure 1**

Changes in relative frequency of arterial blood glucose levels determined in pre- defined blood glucose clusters for the first 3 weeks determined in a total of 69 patients. Majority of arterial blood glucose values were found between 5- 6 and 6- 7 mmol/l which was similar at all investigated time points.

**Figure 2**

Changes in calculated arterial jugular venous differences in glucose (upper panel) and lactate (lower panel) for pre- defined arterial blood glucose clusters. Compared to low arterial blood glucose levels cerebral glucose uptake was significantly increased while cerebral lactate production was significantly decreased at arterial blood glucose concentrations between 7.5 and 8.5 mmol/l (*$p < 0.001$; ANOVA on ranks and post hoc Dunn's test). (Cerebral uptake is reflected by positive values while cerebral release is unmasked by negative values.)

**Figure 3**

Changes in $SjvO_2$ (white box plots) within pre- defined arterial blood glucose clusters was significantly increased at arterial blood glucose levels above 8 mmol/l compared to lower arterial blood glucose levels (*$p < 0.001$; ANOVA on ranks and post hoc Dunn's test).

Calculated oxygen extraction ratio (OER) (grey box plots) within pre- defined arterial blood glucose clusters was significantly decreased at arterial blood glucose levels above 8 mmol/l compared to lower arterial blood glucose levels (*$p < 0.001$; ANOVA on ranks and post hoc Dunn's test).

**Figure 4**

Oxygen- glucose index (OGI) was significantly increased compared to normal values reflected by the straight line at 6. With increasing arterial blood glucose concentrations OGI was significantly decreased compared to lower arterial blood glucose levels (*$p < 0.001$; ANOVA on ranks and post hoc Dunn's test).

**Figure 5**

Lactate- glucose- index (LGI) was significantly decreased compared to normal values. With arterial blood glucose levels exceeding 8 mmol/l, LGI was significantly increased reaching normal values (*$p < 0.001$; ANOVA on ranks and post hoc Dunn's test).

**Figure 6**

Calculated arterial jugular venous difference in $pCO_2$ ($AJVDpCO_2$) was significantly increased with arterial blood glucose concentrations exceeding 6 mmol/l compared to low arterial blood glucose levels (*p< 0.001; ANOVA on ranks and post hoc Dunn's test).

**Figure 7**

Calculated arterial jugular venous difference in $HCO_3^-$ ($AJVDHCO_3^-$) was significantly increased with arterial blood glucose concentrations exceeding 8 mmol/l compared to low arterial blood glucose levels (*p< 0.001; ANOVA on ranks and post hoc Dunn's test).

**Figure 8**

Calculation of frequency of pathologic values within pre- defined arterial blood glucose clusters for increased cerebral oxygen consumption ($SjvO_2$< 60%), sustained anaerobic glycolysis (OGI< 6), and increased cerebral lactate production (negative LGI). With elevated arterial blood glucose the rate of increased cerebral oxygen consumption ($SjvO_2$< 60%) was reduced which coincided with decreased rate of increased cerebral lactate production (negative LGI). However, frequency of anaerobic glycolysis (OGI< 6) was increased.

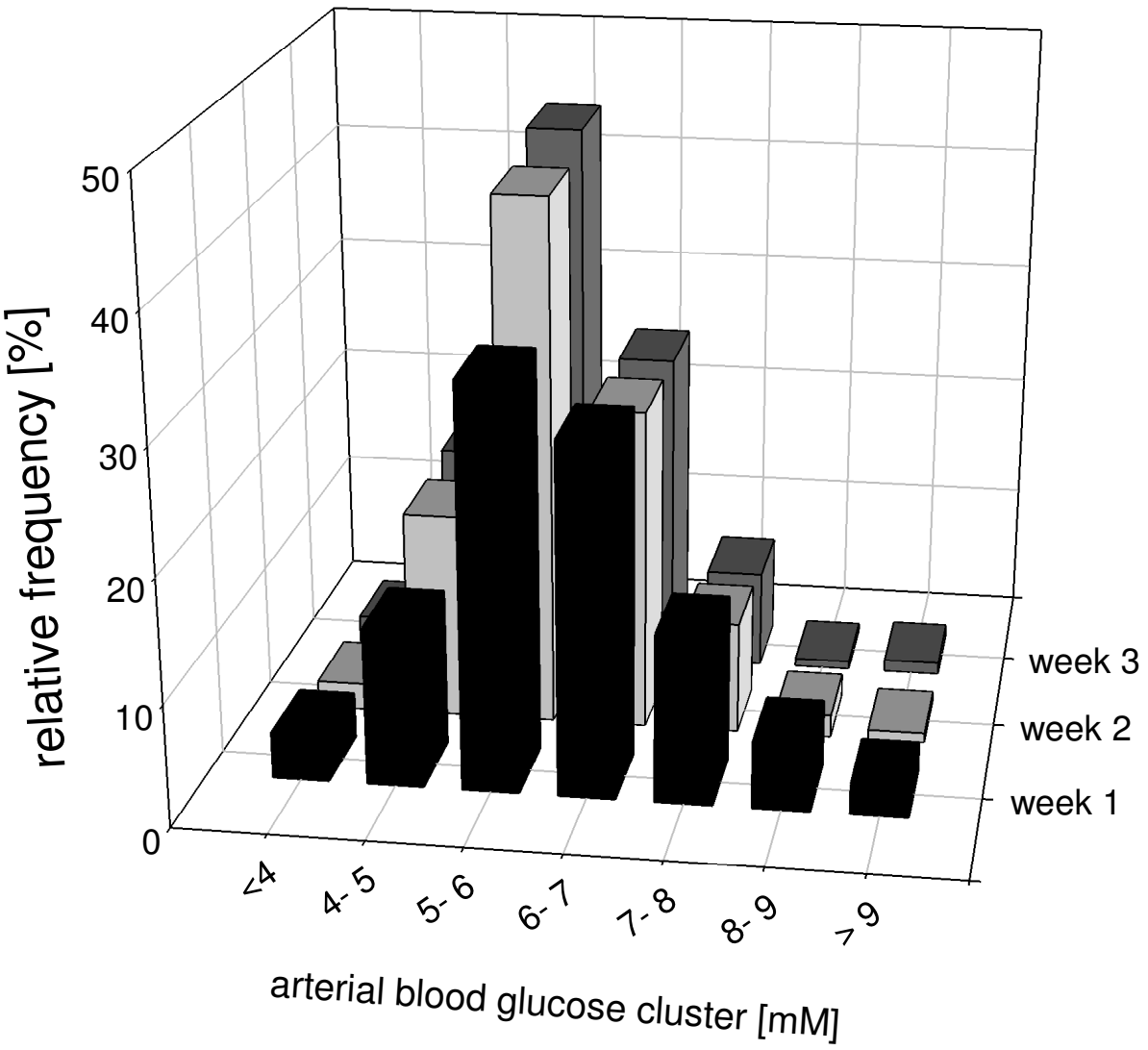


Fig. 1

Figure 1

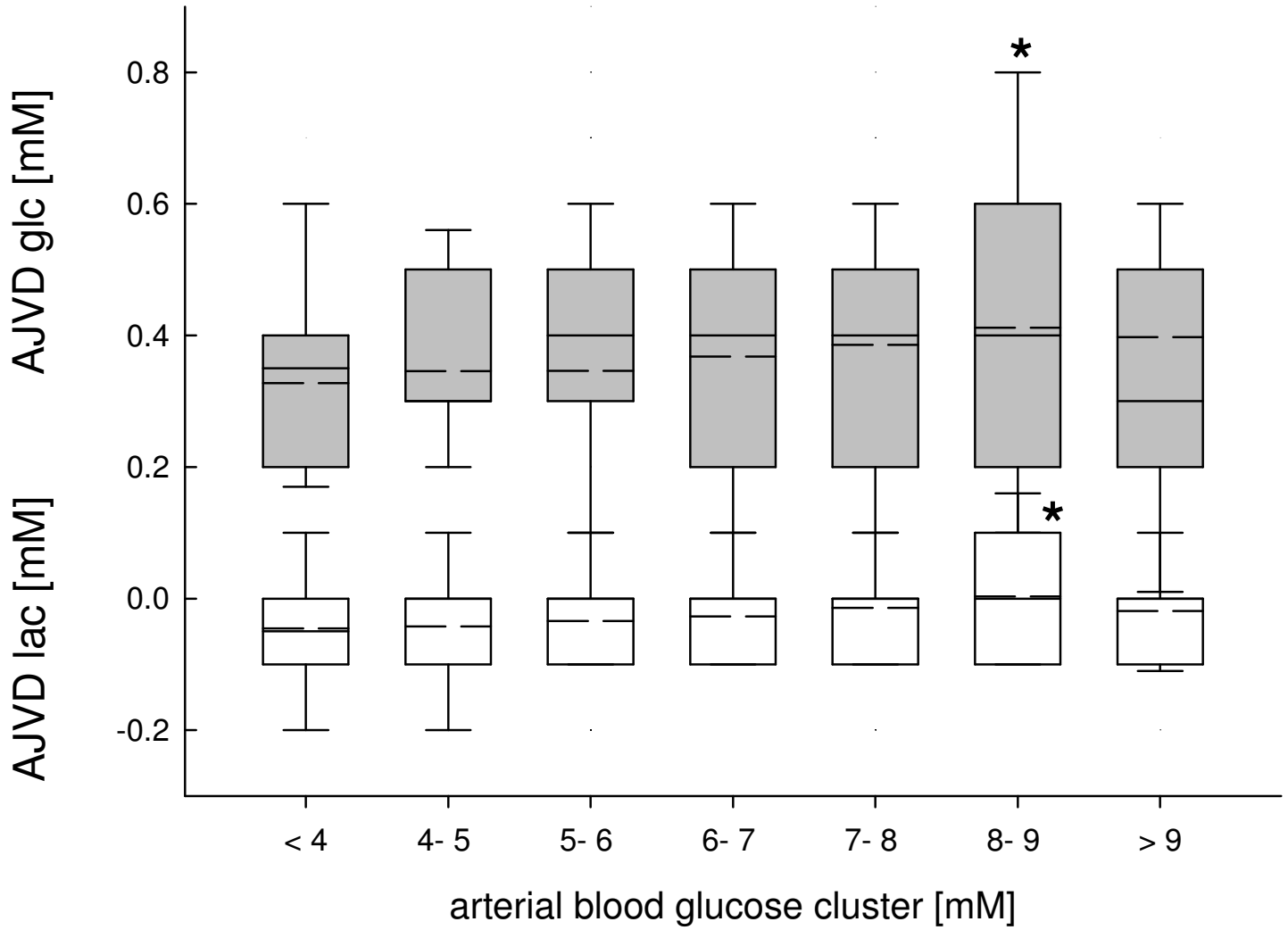


Fig. 2

Figure 2

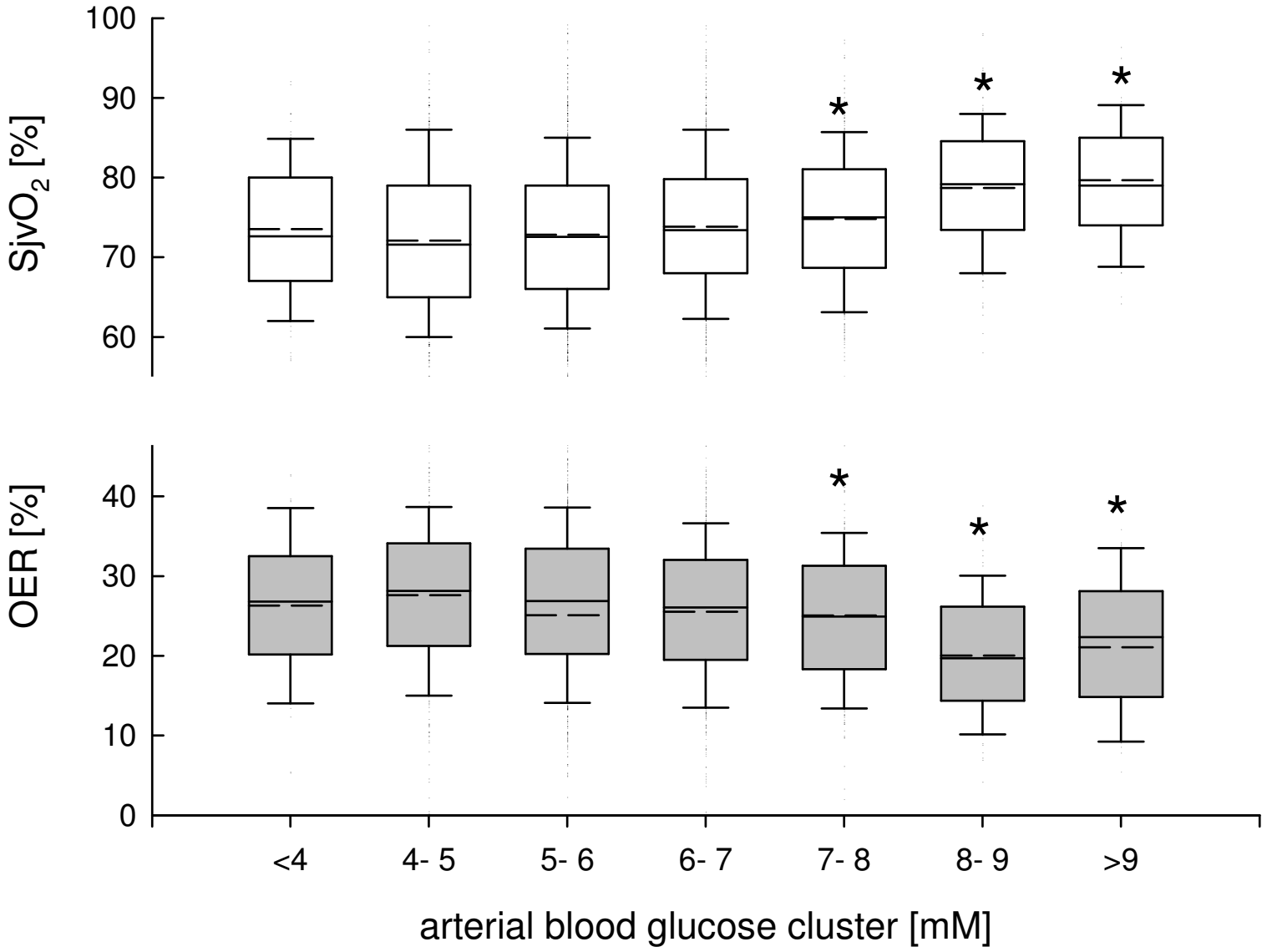


Fig. 3

Figure 3

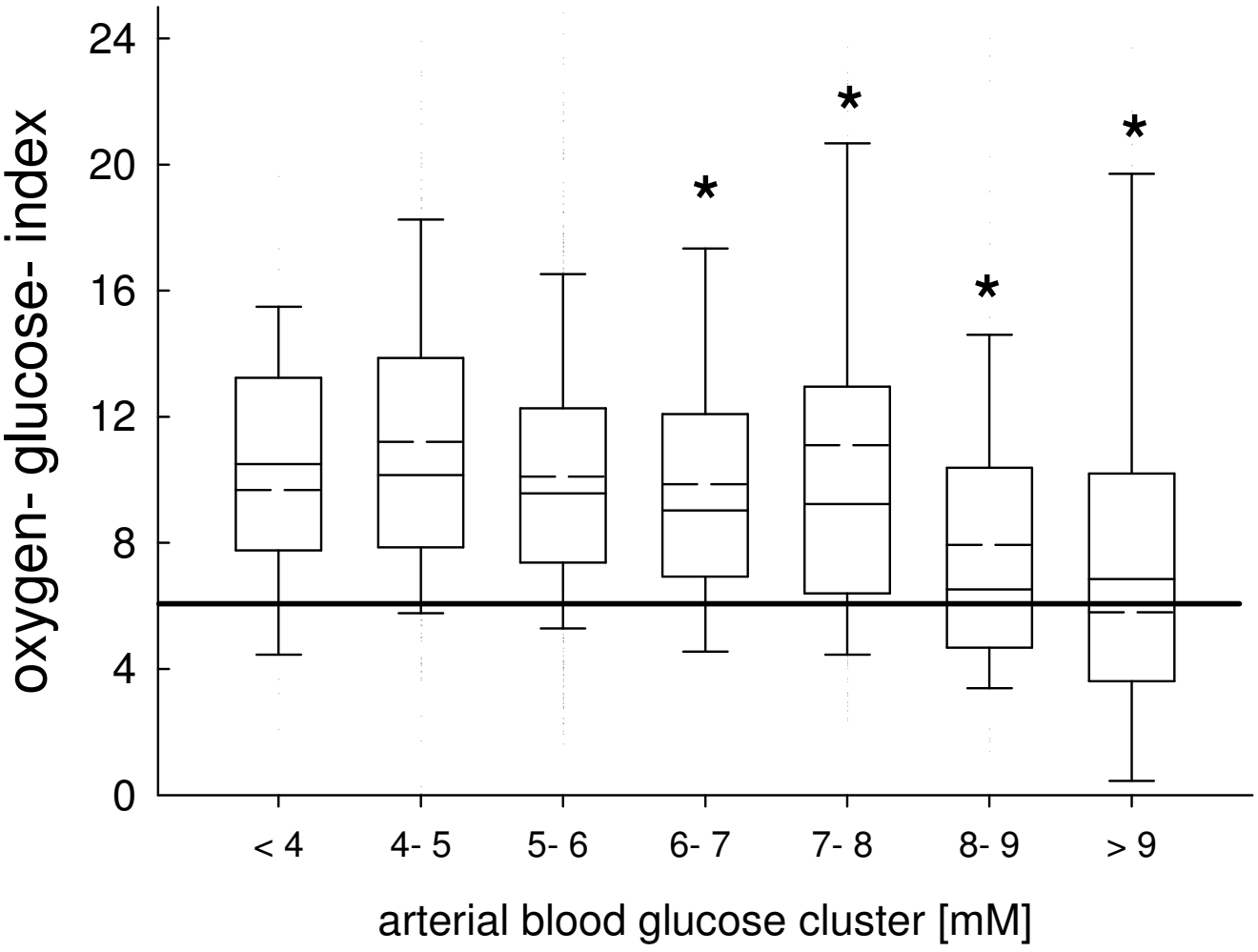


Fig. 4

Figure 4

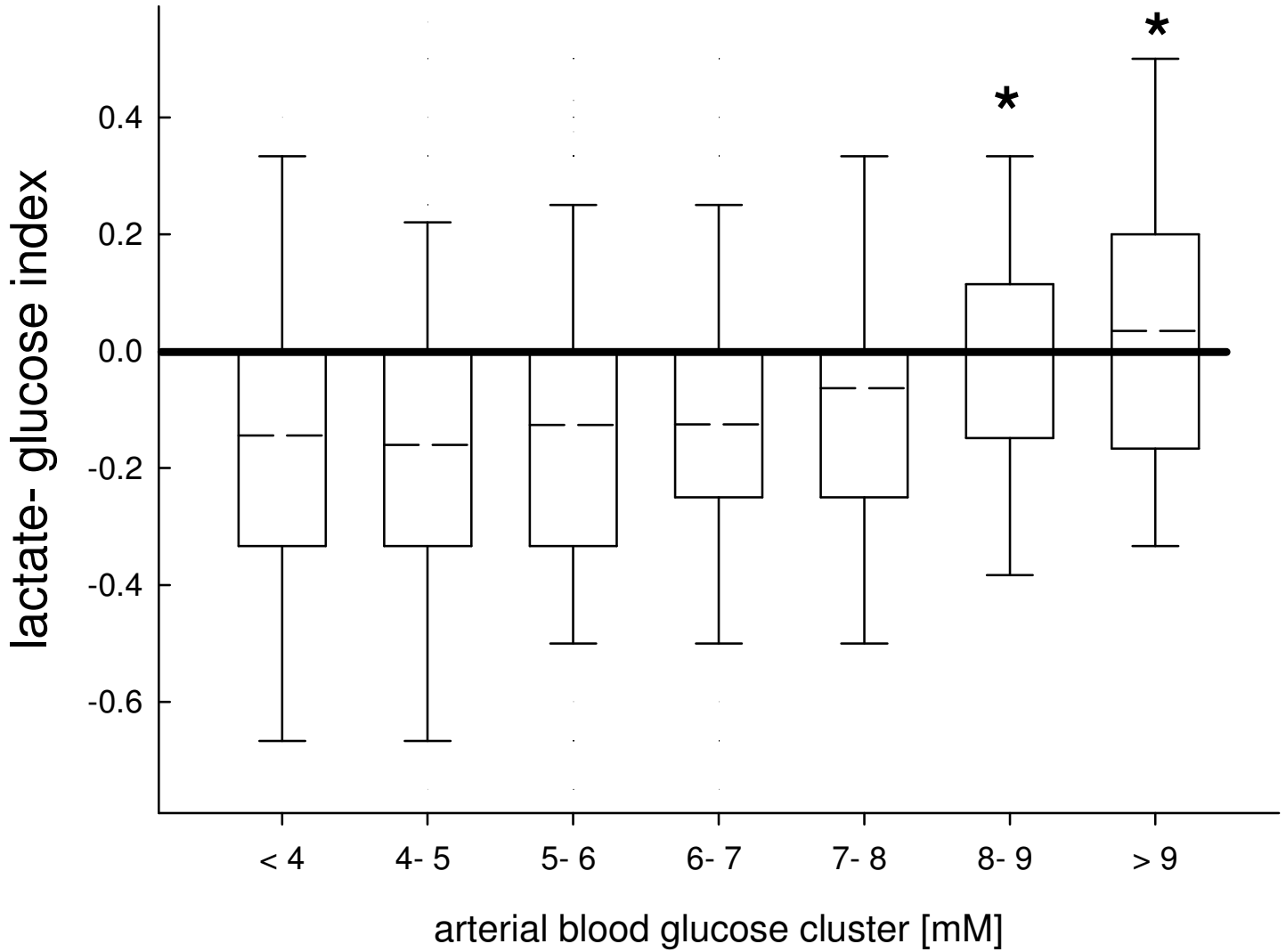


Fig. 5

Figure 5

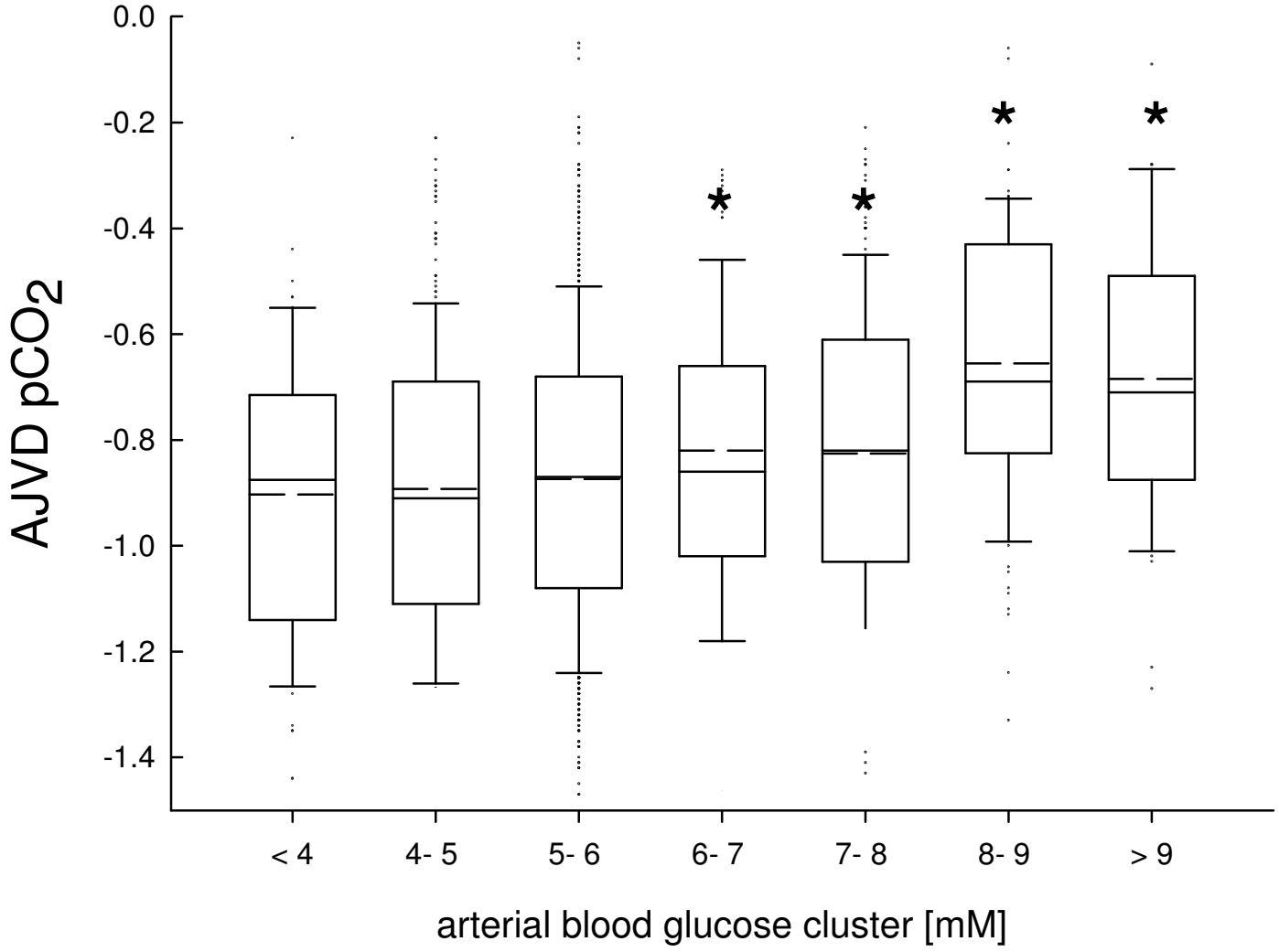


Fig. 6

Figure 6

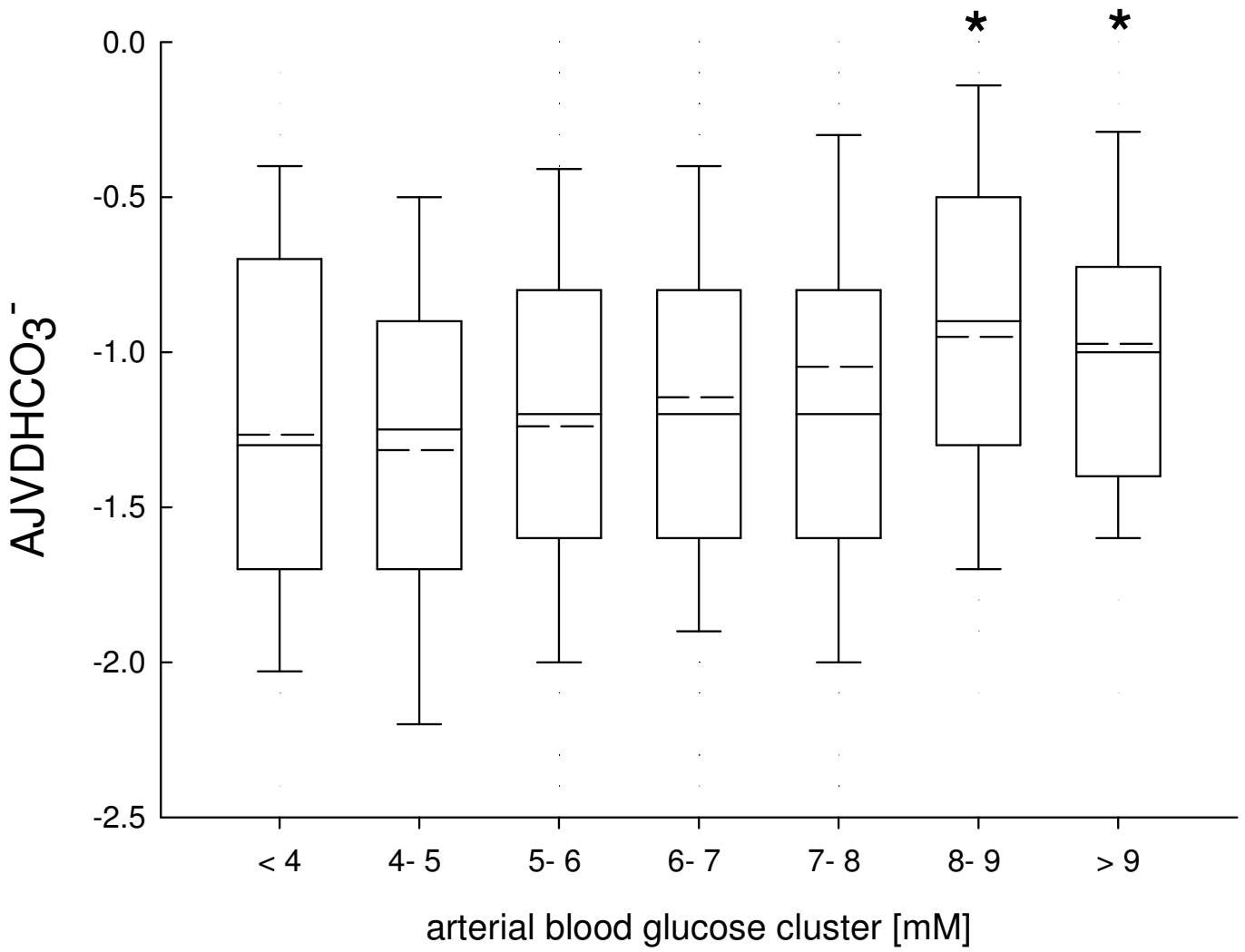


Fig. 7

Figure 7

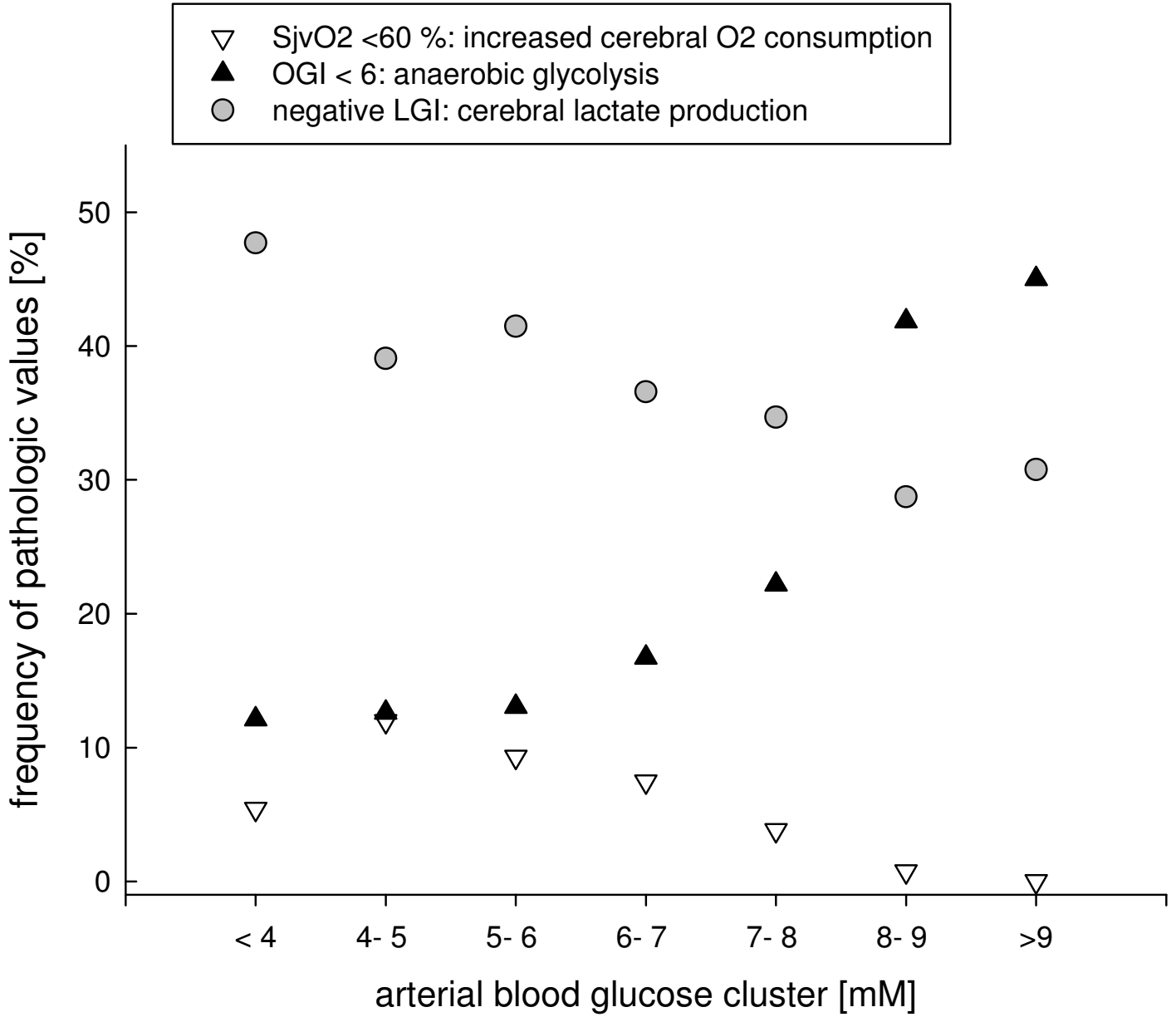


Fig. 8

Figure 8