Association of hyperglycemia and computed tomographic perfusion deficits in patients who underwent endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion

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Association of hyperglycemia and computed tomographic perfusion deficits in patients who underwent endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion: A subgroup analysis of a randomized phase 3 trial (MR CLEAN)


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ABSTRACT

Introduction: Hyperglycemia is highly prevalent in patients with acute ischemic stroke and is associated with increased risk of symptomatic intracranial hemorrhage, larger infarct size and unfavorable outcome. Furthermore, glucose may modify the effect of endovascular treatment (EVT) in patients with ischemic stroke. Hyperglycemia might lead to accelerated conversion of penumbra into infarct core. However, it remains uncertain whether hyperglycemia on admission is associated with the size of penumbra or infarct core in acute ischemic stroke. In this study, we aimed to assess the association between hyperglycemia and Computed Tomographic Perfusion (CTP) derived parameters in patients who underwent EVT for acute ischemic stroke.

Methods: We used data from the MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). Hyperglycemia was defined as admission serum glucose of $>7.8$ mmol/L. Dichotomized and quantiles of glucose levels were related to size of core, penumbra and core-penumbra ratio. Hypoperfused area is mean transient time 45% higher than that of the contralateral hemisphere. Core is the area with cerebral blood volume of $<2$ mL/100 g and penumbra is the area with cerebral blood volume $>2$ mL/100 g. Core-penumbra ratio is the ischemic core divided by the total volume of hypoperfused tissue (core plus penumabra) multiplied by 100. Adjustments were made for age, sex, NIHSS on admission, onset-imaging time and diabetes mellitus.

Results: Hundred seventy-three patients were included. Median glucose level on admission was 6.5 mmol/L (IQR 5.8-7.5 mmol/L) and thirty-five patients (20%) were hyperglycemic. Median core volume was 33.3 mL (IQR 13.6-62.4 mL), median core volume was 80.2 mL (IQR 36.3-123.5 mL) and median core-penumbra ratio was 28.5% (IQR 18.6-45.8%). Patients with hyperglycemia on admission had larger core volumes and core-penumbra ratio than normoglycemic patients with a regression coefficient of 15.1 (95% confidence interval (CI), 1.8 to 28.3) and 11.5 (95% confidence interval (CI), 3.4 to 19.7) respectively.

Conclusion: Hyperglycemia on admission was associated with larger ischemic core volume and larger core-penumbra ratio in patients with acute ischemic stroke who underwent endovascular treatment.

* Corresponding author at: Department: Neurology, Institute/University/Hospital: Medisch Spectrum Twente, Street Name & Number: Koningsplein 1, Enschede, Overijssel 7512 KZ, the Netherlands.
E-mail address: c.kersten@mst.nl (C.J.B.A. Kersten).

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1. Introduction

Hyperglycemia on admission is common in acute ischemic stroke [1–3]. Increased glucose levels have been associated with a higher risk of symptomatic intracerebral hemorrhage and unfavorable outcome after both treatment with intravenous rt-PA and endovascular treatment (EVT) [4–9]. Moreover, a recent meta-analysis found that serum glucose levels modifies the effect of EVT in patients with ischemic stroke due to large vessel occlusion (LVO) of the anterior circulation [4]. The treatment effect is doubled in patients with glucose values on admission between 5.0 and 5.5 mmol/L.

Following arterial occlusion, ischemia initially is most severe in the ischemic core tissue, an area in which irreversible cellular deterioration develops quickly. The penumbra is brain tissue surrounding the ischemic core in which perfusion is disturbed. This tissue is metabolically compromised but potentially salvageable due to collateral circulation [7,16,11]. Without reperfusion, parts of the penumbra converts into irreversible ischemic core. Hyperglycemia adversely affects this process by activation of coagulation, reduction of the fibrinolytic activity of alteplase, altered blood brain barrier permeability, increased post-ischemic inflammatory response and lactate formation with cortical acidosis [1,2,8,10–16]. However, the association of hyperglycemia on admission with the estimated size of infarct core and penumbra has not been clearly demonstrated in patients with acute ischemic stroke who undergo EVT.

Nowadays, CT perfusion (CTP) can be used to estimate ischemic core and penumbra [17]. It is used to support the clinical decision-making in patients with acute ischemic stroke presenting beyond the standard window for reperfusion therapy. As patients with hyperglycemia have a less favorable outcome, the ratio between core volume and penumbra might differ between patients with normoglycemia and hyperglycemia. In this study, we aimed to assess the association between hyperglycemia and CTP derived parameters in patients who underwent EVT for acute ischemic stroke using CTP data of the MR CLEAN trial [18].

2. Methods

2.1. Patient selection

All patients who were enrolled in the MR CLEAN trial and of whom CTP data and admission serum glucose levels were available, were included in the present study. The study protocol of the MR CLEAN trial has been described in detail previously [18]. Briefly, MR CLEAN was a randomized controlled trial that assessed the effect of EVT versus standard care in patients with acute ischemic stroke. Patients were 18 years of age or over and stroke was caused by a large vessel occlusion of the anterior circulation. Endovascular treatment had to be initiated within six hours after stroke onset and patients or their legal representatives signed informed consent. The study protocol was approved by the medical ethics committee and the institutional research board.

Exclusion criteria were CTP data with severe motion artefacts, intravascular contrast volume which was insufficient, incorrect timing of image acquisition after injection of contrast and truncation of the venous output or arterial input curves.

2.2. CTP analyses

CTP data were analyzed by a trained observer. The procedure has been described previously [17]. Brain CT perfusion software (Philips Intellispace, version 7.0) was used. The pre-processing steps included filtering, (3D) registration and segmentation of brain tissue. Definition of ischemic core was a mean transient time (MTT) 45% higher than that of the contralateral hemisphere (relative MTT of >1.45) and cerebral blood volume (CBV) of <2 mL/100 g. Ischemic penumbra was defined as relative MTT of >1.45 and CBV >2 mL/100 g. Additionally to these volumes, also the core-penumbra ratio was calculated by dividing the ischemic core volume by the total volume of hypoperfused tissue (which consists of the ischemic core plus penumbra) multiplied by 100.

2.3. Glucose assessment

Serum glucose levels of included patients were assessed on admission to the emergency department, before EVT. Patients with glucose levels >22 mmol/L were excluded in accordance with exclusion criteria from the MR CLEAN trial.

Hyperglycemia was defined as blood glucose levels of 7.8 mmol/L or over [19].

2.4. Outcome measures

Primary outcome measures were ischemic core and penumbra volumes in millilitres (mL) and the ratio between ischemic core to the total volume of hypoperfused tissue (core-penumbra ratio).

Secondary outcome measures include functional outcome assessed by modified Rankin Scale (mRS score) at 90 days. Favorable outcome was defined as a score on the mRS of 0 to 2.

2.5. Statistical analysis

Patient characteristics were compared between patients with and without hyperglycemia on admission. Categorical variables were studied with chi-square test. Continuous variables were analyzed using unpaired t-test when they are normally distributed. If not normally distributed a Mann-Whitney U test was used. Normality of data was visually inspected. Variables were indicated statistically significant when p < 0.05.

Hyperglycemia and glucose levels on admission were related to primary outcome measures with univariable linear regression. Based on comparable literature, adjustments were made for age, sex, NIHSS on admission, onset-imaging time and diabetes mellitus with multivariable linear regression analyses. In addition, admission glucose levels were subdivided in quartiles and were related to the primary outcome measures. The association between patients with hyperglycemia and outcome at 3 months was expressed as odds ratios (OR) with corresponding confidence intervals. Adjustments were made for age, sex, baseline NIHSS, onset-imaging time and EVT using multivariate logistic regression.

Statistical analyses were performed using SPSS statistics software version 15.

3. Results

Five hundred patients were included in the MR CLEAN trial of whom 333 (67%) underwent CTP. In 64 of these patients no source image data were available. Other patients were excluded because of motion artefacts (n = 28), incorrectly time started of acquisition (n = 14), truncation of the venous output curve or arterial input curve (n = 50) and insufficient intravascular contrast (n = 2). In two patients glucose on admission was unknown. This left 173 patients for the analyses. Median glucose on admission was 6.5 mmol/L (IQR 5.8–7.5 mmol/L). Thirty-five patients (20%) were hyperglycemic on admission. Hyperglycemic patients more often had known diabetes mellitus. Other patient characteristics were comparable between the hyperglycemic and normoglycemic group. Patient characteristics are shown in Table 1.

In the included patients CTP showed a median core volume of 33.3 mL (IQR 13.6–62.4 mL) and a median penumbra volume of 80.2 mL (IQR 36.3–123.5 mL); median core–penumbra ratio was 28.5% (IQR 18.6–45.8%). Median core volume was larger in hyperglycemic patients than in normoglycemic patients, 37.3 mL (IQR 13.7–71.3 mL) versus 27.1 mL (IQR 10.8–51.7 mL; p = 0.03). Median penumbra volume was smaller in the hyperglycemic group than in the normoglycemic group.
respectively 57.2 mL (IQR 32.9–107.7 mL) and 89.4 mL (47.7–131.3 mL), \(p = 0.06\). Median core-penumbra ratio was increased in the hyperglycemic group compared with the normoglycemic group, respectively 43% (IQR 13–58%) and 23% (IQR 10–41%); \(p = 0.02\). Adjusting for potential confounders did not change the association between hyperglycemia on the one hand, and core volume and core-penumbra ratio on the other (Table 2).

After dividing admission glucose into quartiles of \(<5 \text{ mmol/L}, 5–7 \text{ mmol/L}, 7–9 \text{ mmol/L} \) and \(>9 \text{ mmol/L}\), the relation between admission glucose and core volume seems U-shaped (Fig. 1). Corresponding results were observed for core-penumbra ratio with median percentages of 31%; 22% 38% and 33% respectively \(p = 0.03\). In this analysis median penumbral volumes per quartile were 92.2 mL; 80.2 mL; 81.9 mL and 81.5 mL respectively \(p = 0.95\).

Sixteen patients (46%) with hyperglycemia had unfavorable functional outcome, compared with 71 patients (51%) in the normoglycemic group. After adjusting for confounders, hyperglycemia was not associated with unfavorable outcome with aOR of 1.18 (95%-CI 0.53–2.76).

### 4. Discussion

We found that patients with acute ischemic stroke due to LVO of the anterior circulation imaged with CTP within six hours of symptom onset and hyperglycemia on admission had a significant larger ischemic core volume and core-penumbra ratio. Moreover, hyperglycemia tended to be associated with a smaller penumbra volume. Serum glucose levels on admission seems to have a U-shaped relationship with larger ischemic core volume, larger core-penumbra ratio and smaller ischemic penumbra volume when glucose levels of \(<5 \text{ and } >7 \text{ mmol/L}\) are compared to serum glucose levels between 5 and 7 mmol/L.

#### Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Hyperglycemia (n=35)</th>
<th>Normoglycemia (n=138)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>60 (14)</td>
<td>64 (12)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>22 (63)</td>
<td>69 (50)</td>
<td>0.17</td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>18 (13–19)</td>
<td>17 (14–21)</td>
<td>0.49</td>
</tr>
<tr>
<td>Current smoker N, (%)</td>
<td>8 (23)</td>
<td>44 (32)</td>
<td>0.03</td>
</tr>
<tr>
<td>Known diabetes mellitus, N (%)</td>
<td>7 (20)</td>
<td>6 (4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Dyslipidemia, N (%)</td>
<td>10 (29)</td>
<td>29 (21)</td>
<td>0.33</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>18 (51)</td>
<td>50 (36)</td>
<td>0.10</td>
</tr>
<tr>
<td>Glucose on admission, mean (IQR)</td>
<td>9.1 (8.5–10.4)</td>
<td>6.2 (5.7–6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD)</td>
<td>143 (18)</td>
<td>139 (20)</td>
<td>0.29</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD)</td>
<td>81 (12)</td>
<td>78 (11)</td>
<td>0.22</td>
</tr>
<tr>
<td>Onset-imaging time in minutes, median (IQR)</td>
<td>195 (105–256)</td>
<td>176 (110–245)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

#### Table 2

<table>
<thead>
<tr>
<th>Association between hyperglycemia and CT-perfusion derived parameters.</th>
<th>Core volume (mL)</th>
<th>Penumbra volume (mL)</th>
<th>Core-penumbra ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>13.8 (3.8–27.6)</td>
<td>-17.5 (-9.6–4.6)</td>
<td>10.5 (1.7–19.3)</td>
</tr>
<tr>
<td>Hyperglycemia * (%)</td>
<td>15.1 (6.3–28.3)</td>
<td>-16.3 (-9.6–6.2)</td>
<td>11.5 (3.4–19.7)</td>
</tr>
</tbody>
</table>

* adjusted for age, sex, NIHSS on admission, onset-imaging time and previously known diabetes mellitus.

In line with our results, a study of 317 patients with ischemic stroke with confirmed intracranial arterial occlusion of the anterior circulation found (close to) significant smaller penumbral volume and smaller penumbral percentages in patients with hyperglycemia on admission [5]. However, they did not find an association between hyperglycemia and ischemic core volumes. Possible explanations might be a more limited time interval between symptom onset and admission in this study (mean interval of 84 and 78 min respectively in the hyperglycemic and normoglycemic group), and a different cut-off level of hyperglycemia (\(>7 \text{ mmol/L}\), in contrast to ours \(>7.8 \text{ mmol/L}\)). In addition, perfusion mismatch was one of the inclusion criteria for EVT. During our study period, CTP was not a standard procedure in acute ischemic stroke patients. CTP was included as an additional parameter in some affiliated centers. It is possible that larger core volumes were excluded in this study because patients were not eligible for EVT.

Another study with a smaller sample size of 80 ischemic stroke patients, showed no significant differences in core volume and ratio of infarct core to penumbra deficit between patients with hyperglycemia and normoglycemia [20]. This study included all patients with a diagnosis of acute non-lacunar ischemic stroke of the anterior circulation, whereas our study population consists of only patients with an intracranial large vessel occlusion of the anterior circulation.

Regarding our results, previous studies found that larger core volumes could be explained by the reduced recoverability of penumbral tissue due to effects of hyperglycemia [2,7,11,21–23]. There are several mechanisms through which elevated glucose concentrations can exacerbate cell injury in the penumbra. This includes activation of coagulation, reduction of the fibrinolytic activity of alteplase and altered blood brain barrier permeability resulting in brain edema formation [2,9,12]. Furthermore, impaired cerebrovascular reactivity in the microvasculature, impairment of nitric oxide (NO) availability, endothelium–dependent vasodilatation and an increased post-ischemic inflammatory response are described [1,8,13–16]. Additionally, delivery of oxygen and glucose is disrupted during occlusion of an arterial vessel, leading to greatly reduced ATP production. To meet energy requirement without sufficient oxygen, glucose is metabolised anaerobically with lactate formation. This causes increased cortical acidosis with exacerbation of ischemic brain injury [10,11]. These processes may have an important role in the conversion of penumbra into irreversible core [2,7,11,21–23].

Both diabetes mellitus and stress hyperglycemia are associated with worse functional outcome after acute ischemic stroke [24]. However, stress hyperglycemia seems to particularly affect infarct volume and functional outcome in patients without known diabetes mellitus [24,25]. Through habituation, chronic hyperglycemia may have a neuroprotective role in stress hyperglycemia during acute ischemic stroke. However, this mechanism is not clearly understood. In our study, diabetes mellitus does not affect the association between hyperglycemia and larger core volume and larger core-penumbra ratio. In this case, it would be of interest to know whether the glucoses of our patients are fasting glucose values. However, 147 patients (85%) of patients included in our study were last seen well between 06.00 a.m. and 09.00 p.m. It can be assumed that a small proportion of these have fasting glucose values. Therefore, relevant statements cannot be made on this
small number of patients. The proportion of patients with previously known diabetes mellitus ($n = 13$) was also too small to perform further analyses to explore effects of modified glucose metabolism in these patients.

It remains uncertain whether actively lowering glucose levels results in better outcome in patients with acute stroke. Several randomized controlled trials assessed the effect of lowering glucose levels in the acute phase of stroke [26–30]. In addition to these studies, a recent systematic review did not demonstrate a significant difference in functional outcome or death between the group who underwent intensive glucose lowering and those with regular treatment [31]. None of the studies focused on patients who underwent recanalization treatment. Restitution of blood flow within the first few hours after stroke onset can (partially) prohibit that penumbral tissue is being converted in irreversible core [10]. This relationship is “time dependent”. While arterial occlusion exceeds three hours, many cells are compromised at the time of reperfusion, resulting in less residual capacity of penumbral tissue [10,11]. Only one study assessed the effects of glucose reduction in the very early phase of acute stroke [26]. This study was hampered by the heterogeneity of the population and failure to realise target recruitment and target glucose levels in the intervention group.

Moreover, it is unknown what the optimal glucose target should be. The American and European Stroke Association advice to achieve blood glucose levels in a range of 7.8 mmol/L and 10 mmol/L [19,32]. A recent meta-analysis, which also includes data of our study population, showed the most favorable effect of EVT when using a cut-off for hyperglycemia of 5.5 mmol/L [4]. Our results show a U-shaped relationship between glucose levels and core volume of which glucose levels between 5.0 and 7.0 mmol/L seems to be most favorable. Therefore, more insight into the evolution of glucose values and the extend and duration of hyperglycemia during acute ischemic stroke might be important.

Some limitations have to be discussed. MR CLEAN was a multicenter study, as a result imaging data were acquired with different CT-scans and protocols. Considering CTP was no part of standard work-up of acute ischemic stroke patients and due exclusion of poorly assessable CTPs, only data from a small subgroup of the MR CLEAN population were available. Thirty-five patients of this subgroup were hyperglycemic on admission, so analysis are based on a small amount of patients. Probably because of this, in contrast to previous studies, we found no association between hyperglycemia and unfavorable outcome [4,5].

In conclusion, we found an association between hyperglycemia and larger ischemic core volumes and larger core-penumbra ratio in patients with acute ischemic stroke due to large vessel occlusion of the anterior circulation. Further studies are needed to assess if lowering glucose levels in patients with acute ischemic stroke and hyperglycemia who underwent endovascular treatment results in smaller core volumes on CTP and possibly also into better functional outcome.

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Author contributions
C.J.B.A. Kersten: Writing original draft.
H.M. den Hertog and A.A.M. Zandbergen: Supervision.
M. Haalboom: Formal analysis.

Declaration of Competing Interest
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2022.120333.

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