Stress Hormone and Blood Glucose Response Following Acute Stroke in the Elderly

P.A. O'Neill, MD; I. Davies, PhD; K.J. Fullerton, MD; and D. Bennett, BSc

We studied the relation of reactive hyperglycemia, stress hormone response, and outcome in 23 consecutive elderly patients (median age 80 [range 75–92] years) following an acute first stroke. The median delay from the onset of the stroke to the first blood sample (day 0) was 9 (range 4–22) hours. Subsequent blood samples were taken, after fasting, for the determination of blood glucose, cortisol, catecholamine, insulin, C-peptide, glucagon, and lactate concentrations on days 1, 2, 3, 7, 14, 30, and 90. For all 23 patients, a significant relation was found between the blood glucose concentration and survival ($p=0.03$) and the blood glucose concentration decreased with time ($p<0.001$). There was also a significant relation between blood glucose concentration and outcome ($p=0.02$). For the 15 patients with complete data, the major determinants of the blood glucose concentration were the cortisol, insulin, and glucagon concentrations (all $p<0.001$), which accounted for 42% of the variance. When all the indexes were analyzed together by logistic regression, only the cortisol concentration was related to outcome ($p=0.02$). Hyperglycemia following a stroke probably reflects the intensity of the stress hormone response. We have confirmed that hyperglycemia is a predictor of outcome in persons with stroke. (Stroke 1991;22:842–847)

It is known that mortality following a stroke is increased by preexisting diabetes.1 A number of studies,1,2 but not all,3 have shown that even in the absence of diabetes, an initially high blood glucose concentration following a stroke is a predictor of poor outcome. In cats, glucose loading prior to middle cerebral artery occlusion increases infarct size,4 possibly due to anaerobic metabolism of glucose worsening the intracellular and extracellular acidosis.5 It has been suggested that similar effects occur in humans and that hyperglycemia following a stroke should be identified and treated vigorously.1

The high blood glucose concentration after a stroke is most likely related to the magnitude of the stress response6 but, unlike after a myocardial infarction, there have been only limited human studies examining changes in stress hormones after a stroke.8 Furthermore, measurements of stress hormone levels after a stroke have been confined to the immediate poststroke phase and have not been related to the blood glucose concentration.

We conducted a prospective study to confirm the relation of blood glucose concentration to outcome following an acute stroke, to measure the relative changes in stress hormone levels up to 3 months after the event, and to determine how these reflect blood glucose concentrations.

Subjects and Methods

Consecutive patients, admitted under the care of the geriatricians at the University Hospital of South Manchester, with a diagnosis of acute stroke were eligible for the study providing that the onset of symptoms could be accurately determined and that these had started <24 hours prior to the first blood sample's being taken. For the purpose of this study, stroke was defined as the acute onset of weakness including the arm, leg, or both that subsequently persisted for >24 hours. Patients were excluded if they were known to be diabetic or if they were receiving corticosteroid therapy. Informed written consent was obtained, and the study was approved by the ethical committee.

The patients were managed by the clinicians according to standard practices on the unit, including the use of computed tomography if considered appropriate. The clinicians were unaware of the results of the various measurements and assays. It is standard policy of the unit not to administer any specific therapies such as glycerol or mannitol to reduce brain edema.

Patients were followed up until death or 6 months following their stroke. They were assessed clinically.
at days 0, 1, and 7 and at 1, 3, and 6 months, including place of discharge and Barthel score for activities of daily living (ADL). The outcome for each patient was assigned as good, complete recovery or mild disability but regained independence in ADL (Barthel score of >10); or poor, dependent in ADL (Barthel score of ≤10); or dead. The subjects were also classified as alive or dead at 6 months.

A venous blood sample was taken on admission (day 0). All subsequent samples were taken, after fasting, at 8:30 AM through a cannula with the patient recumbent. On days 0, 1, 2, 3, 7, and 14, blood was taken for the determination of blood glucose, catecholamine (norepinephrine, epinephrine, and dopamine), cortisol, insulin, glucagon, C-peptide, and lactate concentrations. Blood glucose and cortisol concentrations were also measured at days 30 and 90. These latter two times were included because there is evidence that elderly patients have an abnormally persistent cortisol response following major stress.9

Catecholamine concentration was measured by high-performance liquid chromatography with electrochemical detection.10 Cortisol, insulin, glucagon, and plasma C-peptide concentrations were measured by radioimmunoassay (CIS Bioindustries, Gif-sur-Yvette, France). Lactate concentration was measured by a fully enzymatic method (Boehringer Mannheim UK, Lewes, UK).

Multiple stepwise regression was used to identify the independent combination of factors accounting for the maximum proportion of the variation in blood glucose levels. Logarithmic transformation was performed where necessary. Repeated-measures analysis of variance, together with Tukey’s critical range test, were used to determine time trends for each factor. The analysis was initially carried out on data from the 15 patients with complete data. A further analysis was then carried out using only the data for the first eight patients. There was a significant reduction in blood glucose concentration with time ($p<0.001$, Figure 1). For all 23 subjects there was a significant relation between average blood glucose concentration over the study period and outcome (Figure 1). In the poor outcome group the mean blood glucose concentration was 5.43 (95% CI 3.48–6.35) mmol/l and in the good outcome group it was 4.75 (95% CI 4.54–4.99) mmol/l ($p=0.02$). A similar relation was found when the 23 subjects were categorized as alive (mean blood glucose concentration 5.01 [95% CI 4.85–5.19] mmol/l) or dead (mean blood glucose concentration 5.67 [95% CI 5.11–6.46] mmol/l) at the end of the study period ($p=0.03$). There was also a significant time x outcome interaction.

Other than blood glucose concentration, none of the indexes measured showed a significant relation with time in the 15 patients with complete data (Table 2). In particular, the mean cortisol concentration, which was studied over 90 days, did not change significantly ($F_{1,8}=0.538, p=0.8$). However, the 95% CIs were wide for all measurements, reflecting a large between-subject variation (Figure 2). Throughout the study there was a significant correlation between plasma insulin and C-peptide levels ($r=0.76, p<0.001$).

When analyzed by outcome, high norepinephrine ($p=0.05$), cortisol ($p=0.04$), and glucagon ($p=0.02$) concentrations were related to poor outcome in the 15 patients with complete data (Table 2). When the subjects were grouped by survival, there were no
significant differences in hormone levels. The plasma cortisol concentration was higher in the patients who died, but only at the 10% level \((p=0.09)\).

Plasma cortisol \((p<0.001)\), insulin \((p<0.001)\), and glucagon \((p<0.001)\) concentrations were significantly related to the blood glucose concentration in the 15 patients with complete data. The variance accounted for by these three factors was 42%, with cortisol concentration being the major determinant, accounting for 20% of the variance. The regression equation was

\[
\text{InBG} = 0.60 - 0.062 \text{lnG} + 0.13 \text{lnI} + 0.15 \text{lnC}
\]

where In= natural logarithm, BG=blood glucose concentration +1, G=glucagon concentration +1, I=insulin concentration +5, and C=cortisol concentration +1. The standard errors for the regression coefficients were 0.19, 0.02, 0.02, and 0.03, respectively. No other factor was significantly related to the blood glucose concentration. For days 0 and 1 the insulin concentration accounted for 18.2% of the variance and the cortisol concentration 18.8%, giving a total of 37% \((p=0.002)\).

Using the day 0 values for the 15 patients with complete data in a logistic regression for concentrations of all hormones and blood glucose, only the cortisol concentration was independently related to outcome \((p=0.02)\); no factor reached significance as a predictor for survival. The blood glucose concentration was not a significant independent factor for either outcome or survival in this subset of the stroke patients.
TABLE 2. Concentrations of Glucose and Stress Hormones in Elderly Patients With Acute First Stroke

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Day after stroke</th>
<th>Mean</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/l)</td>
<td>0</td>
<td>5.64</td>
<td>4.71-7.54</td>
<td>4.50</td>
<td>3.97-5.31</td>
<td>4.33</td>
<td>3.85-5.03</td>
<td>4.85</td>
<td>4.21-5.90</td>
<td>4.45</td>
<td>3.86-5.38</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>6.25</td>
<td>5.43-7.61</td>
<td>5.32</td>
<td>4.78-6.08</td>
<td>5.16</td>
<td>4.67-5.85</td>
<td>5.27</td>
<td>4.67-6.17</td>
<td>5.05</td>
<td>4.40-6.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (nmol/l)</td>
<td>Good</td>
<td>0.68</td>
<td>0.32-1.90</td>
<td>0.48</td>
<td>0.49-1.65</td>
<td>0.67</td>
<td>-0.33-1.89</td>
<td>1.09</td>
<td>0.01-2.39</td>
<td>...</td>
<td>...</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1.87</td>
<td>1.11-2.72</td>
<td>2.08</td>
<td>1.30-2.96</td>
<td>2.38</td>
<td>1.57-3.30</td>
<td>1.77</td>
<td>0.95-2.71</td>
<td>...</td>
<td>...</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (nmol/l)</td>
<td>Good</td>
<td>0.54</td>
<td>0.10-1.11</td>
<td>1.79</td>
<td>1.14-2.50</td>
<td>1.09</td>
<td>0.51-1.73</td>
<td>0.75</td>
<td>0.20-1.35</td>
<td>...</td>
<td>...</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>0.90</td>
<td>0.56-1.27</td>
<td>0.94</td>
<td>0.59-1.31</td>
<td>0.75</td>
<td>0.41-1.10</td>
<td>0.95</td>
<td>0.56-1.36</td>
<td>...</td>
<td>...</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>Good</td>
<td>306.7</td>
<td>191.1-491.7</td>
<td>333.6</td>
<td>207.9-534.9</td>
<td>359.3</td>
<td>223.3-574.4</td>
<td>472.5</td>
<td>291.7-755.7</td>
<td>419.7</td>
<td>215.1-818.1</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>752.7</td>
<td>566.4-1000.2</td>
<td>654.2</td>
<td>492.2-869.4</td>
<td>551.8</td>
<td>415.1-733.4</td>
<td>611.2</td>
<td>437.8-853.1</td>
<td>424.8</td>
<td>246.1-732.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>Good</td>
<td>72.8</td>
<td>34.2-149.3</td>
<td>47.1</td>
<td>21.3-98.4</td>
<td>53.6</td>
<td>24.6-111.2</td>
<td>73.7</td>
<td>34.7-151.1</td>
<td>...</td>
<td>...</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>52.3</td>
<td>32.2-83.4</td>
<td>59.8</td>
<td>37.9-93.0</td>
<td>44.6</td>
<td>27.9-70.0</td>
<td>51.0</td>
<td>30.5-83.4</td>
<td>...</td>
<td>...</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon (pg/ml)</td>
<td>Good</td>
<td>44.8</td>
<td>18.8-104.8</td>
<td>31.2</td>
<td>12.9-73.4</td>
<td>36.8</td>
<td>15.4-86.3</td>
<td>43.8</td>
<td>18.4-102.5</td>
<td>...</td>
<td>...</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>52.4</td>
<td>31.2-87.4</td>
<td>65.6</td>
<td>38.2-112.0</td>
<td>78.8</td>
<td>47.1-131.1</td>
<td>63.4</td>
<td>35.8-111.5</td>
<td>...</td>
<td>...</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>Good</td>
<td>1.09</td>
<td>0.81-1.40</td>
<td>0.97</td>
<td>0.70-1.27</td>
<td>0.85</td>
<td>0.60-1.13</td>
<td>0.96</td>
<td>0.69-1.25</td>
<td>...</td>
<td>...</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1.29</td>
<td>1.10-1.48</td>
<td>1.32</td>
<td>1.13-1.51</td>
<td>1.06</td>
<td>0.89-1.24</td>
<td>1.13</td>
<td>0.93-1.33</td>
<td>...</td>
<td>...</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CI, confidence interval. Data for 15 patients.

Discussion

In stroke there have been no previous studies examining the relation of plasma glucose concentration to the stress hormone response. There is agreement, however, that preexisting diabetes increases the risk of having a stroke and increases the morbidity and mortality once a stroke occurs.6 Pulsinelli et al1 considered that in nondiabetics hyperglycemia following a stroke had an adverse effect due to anaerobic metabolism with consequent acidosis. On the other hand, a study of more than 1,400 patients could find no relation between a high blood sugar concentration and outcome after a stroke.11 The use of a random versus fasting blood sugar concentration also appears to influence the results.12 We found a clear difference in the fasting glucose levels between the good and poor outcome groups that persisted for up to 1 month, confirming the findings of Pulsinelli et al1 and others.2 The large proportion of our patients who had either died or were severely disabled at 6 months is consistent with the known consequences of stroke in an elderly population.13

The cause of the hyperglycemia is unclear. It might be due to the unmasking of a premorbid abnormal glucose tolerance.14,15 Power et al12 argued, however, that the relation between outcome and the fasting, rather than the random, blood sugar concentration pointed toward the hyperglycemia being a function of a stress response and not of preexisting glucose intolerance. In a large study, Woo et al16 found a greater relation between outcome and stress hyperglycemia in nondiabetics than in known or newly diagnosed diabetics. We did not find any relation between the glycosylated hemoglobin content and either the random or the first fasting blood sugar level. This militates against the differences being due to an undiagnosed diabetic state, although the relation between the glycosylated hemoglobin content and glucose tolerance in nondiabetics is unclear.17

We found that plasma norepinephrine, cortisol, and glucagon and blood glucose concentrations were related to outcome. Of the variables measured, the
major determinants of the blood sugar concentration were the cortisol, insulin, and glucagon concentrations. When analyzed separately, the relation of blood glucose concentration to outcome was significant, which was probably linked to its low variability. However, using logistic regression only the cortisol concentration was related to outcome; the blood glucose concentration was not significantly associated when analyzed in conjunction with the other indexes measured. The initial high variation found in concentrations of the other hormones may have masked other associations, though the variance did fall with time (Figure 2).

There is evidence that under other conditions stress hyperglycemia can occur secondary to alterations in circulating hormone levels. Oswald et al found that following acute myocardial infarction an increased plasma glucose concentration was related to a worse mortality rate. In their study the elevated glucose concentration was a reflection of an increased urinary output of catecholamines and a raised plasma cortisol concentration immediately following infarction. In patients suffering a cardiac arrest, higher blood sugar levels have been found in those in whom resuscitation was delayed or prolonged,2 suggesting that the elevated glucose concentration reflected the extent of cerebral damage rather than the cause. There are also parallels with severe head injury, where an elevated admission blood sugar concentration in the absence of diabetes was a significant predictor of outcome and was taken as evidence of a marked stress response.19 In stroke, studies have related a poor prognosis to a high plasma glucose concentration with an elevated plasma cortisol concentration.8,20

While there is apparently a link between the blood glucose and stress hormone levels in this study, there are other outstanding issues related to the magnitude of the stress response and the effect that an elevated blood glucose concentration has on neuronal damage. The first problem is to determine whether the magnitude of the stress response is related to the extent21 or the nature16 of the damage occurring in the brain. The second is whether high levels of blood sugar induce acidosis in the brain and exacerbate the damage to neurons.1 These issues are not mutually exclusive. There may be an element of positive feedback where the initial event is the occlusion and its sequel the stress response. However, unless the stress response (in the form of hyperglycemia) is rapidly brought under control, there may be a continuation of the damage because of a metabolic acidosis in the presence of a high blood sugar concentration. In the elderly, this may be worn down because the stress response may persist.9 In some animal models a glucose preload increases anoxic brain damage,12 although in other models it reduces the extent of cerebral infarction.22,24 However, these models are analogous to the diabetic patient, not the nondiabetic patient in whom a high blood glucose concentration develops after the insult.

In conclusion, our data support the view that hyperglycemia in nondiabetics is a marker of a worse prognosis following a stroke but that this probably reflects changes in the circulating levels of stress hormones, particularly cortisol, glucagon, and insulin. If this is the case, then vigorous treatment of the hyperglycemia as proposed by others1 might at best be expected to produce no favorable effect and cannot be recommended on the evidence of this study. Further studies would require more subjects and might concentrate on the wide variation in the stress hormone response we observed and how this relates to the age of the patient, the site of the stroke, and the pathology. The last variable may be of major importance because Woo et al16 reported that the increase in mortality associated with stress hyperglycemia was observed only following cerebral hemorrhage. Interventional studies of the value of hypoglycemic therapy during early stroke in nondiabetics would require much larger populations than that studied here. Because of the attendant risk of hypoglycemia, careful consideration needs to be given to the ethical and methodological problems before embarking on such a study.

Acknowledgments

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