Changes in Plasma Homocyst(e)ine in the Acute Phase After Stroke

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Background and Purpose—Elevated plasma homocyst(e)ine \([\text{H(e)}]\) concentration has been associated with an increased risk of stroke. Although the literature suggests that \(\text{H(e)}\) increases from the acute to the convalescent phase after a stroke, it is not known whether \(\text{H(e)}\) changes within the acute period.

Methods—A prospective, multicenter study was conducted to examine changes in \(\text{H(e)}\) during the 2 weeks after an incident stroke. Blood samples were collected at days 1, 3, 5, 7, and between 10 and 14 days after the stroke.

Results—Seventy-six participants (51 men) were enrolled from 9 sites from February 1997 through June 1998. Mean age was 65.6 years, and subjects had at least two \(\text{H(e)}\) measurements. The estimated mean \(\text{H(e)}\) level at baseline was 11.3 ± 0.5 \(\mu\text{mol/L}\), which increased consistently to a mean of 12.0 ± 0.5, 12.4 ± 0.5, 13.3 ± 0.5, and 13.7 ± 0.7 \(\mu\text{mol/L}\) at days 3, 5, 7, and 10 to 14, respectively. The magnitude of the change in \(\text{H(e)}\) was not affected by age, sex, smoking status, alcohol use, history of hypertension or diabetes, or Rankin Scale Score.

Conclusions—These data suggest that the clinical interpretation of \(\text{H(e)}\) after stroke and the eligibility for clinical trials assessing treatment for elevated \(\text{H(e)}\) levels require an adjustment in time since stroke to properly interpret the observed \(\text{H(e)}\) levels. \(\text{Stroke. 2002;33:473-478.}\)

Key Words: homocyst(e)ine ■ stroke, acute ■ stroke, ischemic

_Homocyst(e)ine \([\text{H(e)}]\) is the demethylated product of the dietary amino acid methionine. Plasma or serum \(\text{H(e)}\) or total homocysteine (tHcy) refers to the sum of the sulfhydryl amino acid homocysteine and the homocysteinyl moieties of the disulfides homocystine and homocysteine-cysteine, whether free or bound to plasma proteins. Numerous case-control studies have shown an association between elevated \(\text{H(e)}\) level and stroke, but the results of the prospective studies are inconsistent, with most showing only a small or no association._

On the basis of these studies it has been postulated that an elevated \(\text{H(e)}\) level before stroke acts as a risk factor for the stroke. By design, in all of these case-control studies, stroke “cases” are identified first, and the assessment of \(\text{H(e)}\) levels follows the stroke. There is concern that the disease process may be what is altering the blood levels of \(\text{H(e)}\). That is, if stroke results in an increased \(\text{H(e)}\) level after the event, then the observed elevated poststroke levels among stroke “cases” may lead to misguided conclusions regarding the role of \(\text{H(e)}\) as a risk factor for the development of the stroke. It could be, as some suggest, that elevated \(\text{H(e)}\) is an acute-phase reactant and a consequence rather than a cause of the disease process.

Although \(\text{H(e)}\) levels have been shown to increase between the acute period and a convalescent period months after the stroke, there has not been a study of the changes in \(\text{H(e)}\) levels during the acute period after stroke. Acute changes have implications for both the clinical interpretation of \(\text{H(e)}\) levels and the design of clinical trials assessing the impact of treatments to lower \(\text{H(e)}\) levels. Folic acid with vitamins \(\text{B}_6\) and \(\text{B}_12\) has been shown to be effective in reducing elevated \(\text{H(e)}\) levels, but no randomized trials have yet been completed to determine whether lowering elevated \(\text{H(e)}\) levels will subsequently reduce stroke.

Secondary prevention trials are in progress. One of these, the Vitamin Intervention for Stroke Prevention (VISP) trial, limits enrollment to stroke patients whose \(\text{H(e)}\) exceeds a certain level and allows blood to be drawn up to 100 days after the stroke. However, the optimum lower time window to maximize the screened-to-eligible ratio is not known.

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A full list of collaborators is provided in the Appendix.

This article has been approved by the Executive and Publications Committees of the Vitamin Intervention for Stroke Prevention (VISP) study.

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_Stroke_ is available at [http://www.strokeaha.org](http://www.strokeaha.org)
The present study was designed to identify patterns of acute H(e) changes after cerebral infarction. A prospective, multicenter study of acute stroke patients was conducted to examine changes in plasma H(e) levels in the 2-week period after the stroke.

**Subjects and Methods**

Centers selected to participate in the main VISP trial in fall/winter 1996–1997 were invited to participate in this ancillary study. The protocol was approved by the institutional review boards of the 9 participating centers. The procedures followed were in accordance with institutional guidelines, and each study participant provided informed consent. vrouwen aged 40 to 85 inclusive who had a cerebral infarction within the previous 24 hours were eligible. Inclusion into the study required a clinical diagnosis of cerebral infarction, brain imaging (CT or MRI), and ability and willingness to give informed consent. Cerebral infarction was defined as an arterio-occlusive brain infarction characterized by the sudden onset of neurological deficit that persisted for a minimum of 24 hours or was associated with CT or MRI evidence of a previously undocumented infarction in the expected site of injury. Exclusion criteria were stroke caused by subarachnoid hemorrhage or hematoma, brain imaging (CT or MRI) showing a lesion other than infarction as cause of syndrome, or enrollment in a conflicting study. Patients were excluded if they had been on medications during the 7 days before the stroke that could have affected H(e), including multivitamins, niacin, methotrexate, tamoxifen, anticonvulsants, bile acid sequestrants, or nitrous oxide anesthesia.

Consecutive patients arriving at a study hospital with suspected stroke were screened for eligibility. For eligible patients, cooperation of the treating physician was sought, informed consent was obtained, and arrangements for additional blood draws were made by the neurologist investigator or study coordinator.

At the time of baseline blood draw, demographic information and stroke descriptors were obtained through patient interview, physician examination, and medical record review. History of hypertension, diabetes mellitus, and myocardial infarction (MI) were determined by asking the study participant if a physician ever told him/her that he/she had the condition. Participant self-report via interview or chart review determined race, current smoking status, regular multivitamin use, and alcohol use. Medication use and information on new stroke or coronary events were recorded during the 2-week study period.

Nonfasting blood draws were performed according to the following schedule: baseline (day 1) within 24 to 48 hours after onset of stroke symptoms, day 3, day 5, day 7, and 10 to 14 days after the stroke. Venous blood (4 mL in EDTA) was drawn and centrifuged within \( \frac{1}{2} \) hour at 3500 \( \times g \) for 15 minutes at 4°C. If centrifugation could not be done immediately, the blood was placed on ice until centrifuged, which was to be within 2 hours of collection. Plasma was then separated and aliquoted into a plastic tube and frozen at -70°C until shipped on dry ice to the Oregon Regional Primate Center for analysis. Total plasma H(e) was determined by high-performance liquid chromatography and electrochemical detection.13-14

Assays were run in duplicate and the results averaged. The analysis was repeated if duplicates differed by more than 10%. Daily standard curves bracketed the analyzed plasma. Current coefficients of variability are 4.33% and 6.28% for intra- and inter-runs, respectively. Although the protocol specified that the first blood draw was to take place 24 to 48 hours after the onset of stroke symptoms, 18 patients had their first blood draw before 24 hours (range, 37 minutes to 23 hours.) Although all records were reviewed to ensure the diagnosis of stroke rather than transient ischemic attack, special scrutiny was given to patients whose first blood sample was drawn before 24 hours. Subsequent blood draws also did not always conform to the precise date requirements, but as long as the blood draws for any individual patient were consecutive and within a “reasonable” range of the protocol requirement, the data were usable. All patients had at least 2 days between blood draws, and the time of the fifth (which was supposed to be between days 10 and 14) ranged from 8.8 to 16.2 days.

The primary analysis of interest was the change in H(e) over the five measurements. The approach in this report focused on the difference between the baseline and each of the four poststroke measurements as the primary measure of change: \( \Delta_{1} = H(e)_{day 1} - H(e)_{day 5} \), \( \Delta_{2} = H(e)_{day 5} - H(e)_{day 7} \), \( \Delta_{3} = H(e)_{day 7} - H(e)_{day 10} \), \( \Delta_{4} = H(e)_{day 10} - H(e)_{day 14} \). Estimates of these four changes were made using the mixed model approach of Laird and Ware,15 with an unrestricted variance and differences between time periods tested using linear contrasts. Calculations were performed using the SAS procedure PROC MIXED.16

The sample size calculation was based on a confidence interval for the anticipated change in H(e) levels. Using data from the VISP pilot study17 and including a Bonferroni adjustment for multiple comparisons, the study was planned for a sample size of 90 to estimate the change in H(e) level with a precision (95% confidence limits) of \( \pm 1.0 \) \( \mu \)mol/L.

**Results**

Nine centers enrolled participants into the study from February 1997 to June 1998. Seven centers stopped enrollment.

**TABLE 1. Patient Characteristics (n=76)**

<table>
<thead>
<tr>
<th>Mean age (range)</th>
<th>65.6 (39.5–85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>51 (67%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Black, not Hispanic</td>
<td>22 (29%)</td>
</tr>
<tr>
<td>White, not Hispanic</td>
<td>46 (61%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (4%)</td>
</tr>
<tr>
<td><strong>History of</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>51 (70%)</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>25 (33%)</td>
</tr>
<tr>
<td>Alcohol use*</td>
<td>32 (43%)</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>23 (30%)</td>
</tr>
<tr>
<td>Yes, quit &lt; 5 yr ago</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Yes, quit &gt;= 5 yr ago</td>
<td>23 (30%)</td>
</tr>
<tr>
<td>Yes, current smoker</td>
<td>21 (28%)</td>
</tr>
<tr>
<td><strong>Modified Rankin Scale</strong></td>
<td></td>
</tr>
<tr>
<td>0–No symptoms</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>1–No significant disability</td>
<td>17 (22%)</td>
</tr>
<tr>
<td>2–Slight disability</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>3–Moderate disability</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>4–Moderate-severe disability</td>
<td>18 (24%)</td>
</tr>
<tr>
<td>5–Severe disability</td>
<td>10 (13%)</td>
</tr>
<tr>
<td><strong>Ischemic stroke mechanism</strong></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic (nonlacunar but no clear cause)</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Large artery, severe stenosis, or occlusion</td>
<td>19 (25%)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Small-vessel/lacunar</td>
<td>25 (33%)</td>
</tr>
<tr>
<td>Insufficient data for subtyping</td>
<td>8 (11%)</td>
</tr>
</tbody>
</table>

*One patient with missing data.
†Three patients with missing data.
TABLE 2. Mean H(e) \(\mu\text{mol/L} \pm \text{SEM}\) by Time from Stroke, for All Subjects, and by Sex (Number of Participants)

<table>
<thead>
<tr>
<th>Time Period (mean)</th>
<th>24–48 Hours</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 10–14</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ((n=76))</td>
<td>11.3±0.5(76)</td>
<td>12.0±0.5 (72)</td>
<td>12.4±0.5 (65)</td>
<td>13.3±0.5 (59)</td>
<td>13.7±0.7 (59)</td>
</tr>
<tr>
<td>Male ((n=51))</td>
<td>11.5±0.6 (51)</td>
<td>12.0±0.6 (48)</td>
<td>12.8±0.6 (43)</td>
<td>13.5±0.7 (35)</td>
<td>14.4±0.8 (35)</td>
</tr>
<tr>
<td>Female ((n=25))</td>
<td>10.8±0.8 (25)</td>
<td>12.0±0.8 (24)</td>
<td>11.6±0.8 (22)</td>
<td>12.9±0.9 (24)</td>
<td>12.4±1.1 (24)</td>
</tr>
</tbody>
</table>

Discussion

The literature on serial measurements of H(e) concentrations after acute vascular events is sparse. Ours is one of the first studies with serial poststroke measurements during the acute phase of a stroke. It is also larger than studies of serial measurements after acute MI.18–21 This report provides evidence of a consistent pattern of increasing H(e) levels during the 2 weeks after a stroke, the rate of which was not affected by major stroke risk factors or stroke severity.

Two previous reports have looked at changes in H(e) from the acute to the convalescent phase of stroke. In both, plasma H(e) levels were lower in the acute phase than in the convalescent phase. Lindgren et al8 presented data on change in H(e) levels from the acute phase (mean 2 days after stroke) to the chronic phase (median 583 days after stroke) for 17 of 162 first-ever stroke patients, showing an increase in median H(e) level from 11.4 to 14.5 \(\text{mol/L}\). They found no correlation between homocyst(e)ine and time of blood sampling in the acute phase and concluded that the absence of a significant correlation implies that H(e) concentrations do not increase during the first 4 days after the stroke.5 Meiklejohn et al7 described changes in...
H(e) levels of 82 of 106 patients with cerebral infarction and transient ischemic attack from the acute phase (within 96 hours of onset) to the convalescent phase (within 68 to 270 days), with median H(e) increasing from 8.5 μmol/L to 10.1 μmol/L. Landgren et al.\(^\text{18}\) showed similar increases between the acute and convalescent periods in patients with MI, where H(e) levels of 53 patients with MI increased significantly from a mean (±SEM) of 13.1 (±4.6) μmol/L 24 to 36 hours after the onset of MI to 14.8 (±4.8) μmol/L 6 weeks after. However, in all of these studies there were only two H(e) measurements per participant, and none of these studies provided information on acute changes after stroke.

Although to our knowledge there are no studies examining changes in H(e) in the acute phase after stroke, there are 3 studies examining changes in H(e) in the acute phase after MI. Senaratne et al.\(^\text{19}\) measured H(e) within 48 to 72 hours of admission in 62 patients with acute MI and again at 6 weeks after discharge. The mean (±SEM) H(e) level during the acute phase was 13.6 (±0.98) μmol/L and decreased significantly to 12.1 (±1.01) μmol/L at 6 weeks. In a subgroup of 15 patients in whom H(e) levels were also measured on days 1 and 3, the mean H(e) level was significantly higher on day 3 (9.7±0.6 μmol/L) compared with day 1 (7.7±0.8 μmol/L).\(^\text{19}\)

In a small study, Egerton et al.\(^\text{20}\) reported on 10 patients with MI who completed blood draws for H(e) analysis at days 1, 3, 7, and 21, and at 6 months. Mean levels of total H(e) started at 12.9 μmol/L and increased at days 3 and 7, and then decreased at days 21 and 180. In a design similar to ours, Al-Obaidi et al.\(^\text{21}\) conducted a study of consecutive patients admitted with an acute MI or unstable angina pectoris, obtaining plasma samples for H(e) analyses at admission (within hours of the event), and at days 2, 7, 28, and 180. For the 22 participants with MI, the estimated median H(e) and 25th to 75th interquartile range (in parentheses) were as follows: 11.9 (10.7 to 12.6), 11.5 (9.1 to 13.4), 12.1 (11.4 to 14.1), 12.4 (11.1 to 14.4), and 12.1 (11.2 to 14.0) μmol/L at admission and at days 2, 7, 28, and 180, respectively. There was a decrease from admission to day 2 (4%) and a significant increase from day 2 to day 7 (2%). The results of these studies with repeat H(e) measures in the acute phase after MI showed increases in a brief period after MI, a finding that is similar to our observations during the acute phase after stroke.

It is tempting to assume that H(e) levels decreased in the acute phase after stroke and/or MI and subsequently recovered to pre-event levels in the convalescent period. However, because there were no H(e) measurements in these studies (or in our study) before the event, it is impossible to determine whether the pattern of changes in H(e) after the event is: (1) a decline immediately after the event followed by recovery in the early convalescent period, (2) no change or an increase immediately after the event, followed by a further increase in the convalescent period, (3) an artifact in the measurement of H(e) level due to a stress-related decrease in plasma albumin,\(^\text{8}\) or (4) an increase in poststroke elimination of thiols including H(e) due to poststroke increase in production of oxidative oxygen radicals.\(^\text{8}\)

The possibility that there may be an acute increase in H(e) levels after stroke has a profound impact on the interpretation of the literature establishing H(e) as a risk factor for stroke.

Several reports have reviewed the epidemiological evidence on elevated H(e) and stroke risk\(^\text{1–3,22–25}\) and have come to the same conclusion: numerous case-control studies have consistently found an association between moderately elevated H(e) and stroke risk, but the results of the few prospective studies are not as consistent. Results of new studies since these reviews were conducted still support this conclusion.\(^\text{4–6,26}\)

The case-control studies compared poststroke H(e) levels to levels from a stroke-free group. As such, much of the evidence of the association of H(e) and stroke risk is based on a comparison of H(e) levels after stroke to H(e) levels of controls. Our results suggest H(e) levels would be increased with blood collected later after the stroke. Therefore, the interpretation that a high H(e) level is a risk factor for stroke may be misleading; rather, it could be that the elevated H(e) is a consequence rather than a cause of the stroke.

Our findings also have substantial implications regarding the interpretation of H(e) levels after stroke. Because H(e) levels are consistently increasing during the acute phase, a specific H(e) level immediately after stroke must be interpreted in light of the time between the stroke and the H(e) assessment. The changing distribution of H(e) levels after stroke is shown in Figure 1 by the increases in the percentiles. Consider, for example, a hypothetical patient with a poststroke H(e) level of 13 μmol/L. If this assay were taken during the 24 to 48 hours after the stroke, the patient would be at the 79th percentile of all stroke patients and as such this H(e) level would be considered “high.” However, if the assay were taken at day 3, it would be at the 67th percentile of values; if at day 5, it would be at the 60th percentile; if at day 7, it would be at the 51st percentile; and if at 10 to 14 days, it would also be at the 51st percentile (the same by coincidence only). As such, an H(e) level of 13 μmol/L should be considered as “high” if taken at 24 to 48 hours after the stroke but would only be “average” if taken at 7 days or 10 to 14 days after the stroke. The implication of this observation is that the time between the stroke event and the blood draw to establish H(e) levels needs to be a critical part of the interpretation of the results.

There are several limitations of our report. Most notably, this report, like previous reports, does not have an assessment of H(e) level before the stroke. Even though the samples are collected soon after the event, there is still time for them to be affected by the stroke. In addition, our study would be strengthened by an assessment of H(e) levels after stroke and/or MI and subsequently recovered to pre-event levels. However, because there were no H(e) measurements in these studies (or in our study) before the event, it is impossible to determine whether the pattern of changes in H(e) after the event is: (1) a decline immediately after the event followed by recovery in the early convalescent period, (2) no change or an increase immediately after the event, followed by a further increase in the convalescent period, (3) an artifact in the measurement of H(e) level due to a stress-related decrease in plasma albumin,\(^\text{8}\) or (4) an increase in poststroke elimination of thiols including H(e) due to poststroke increase in production of oxidative oxygen radicals.\(^\text{8}\)

The possibility that there may be an acute increase in H(e) levels after stroke has a profound impact on the interpretation of the literature establishing H(e) as a risk factor for stroke.
2-week period. It is not unusual for an acute stroke patient to spend most of the first 24 hours recumbent in bed or on a gurney but to be mobilized after a few days. In general, recumbency and an increased venous return from the lower extremities increase plasma volume compared with sitting, and this relative increase in plasma volume would tend to decrease the concentration of plasma analytes, including H(e). It has been described that the plasma protein content is about 9% higher in the standing than in the supine position.27 Studies have shown that serum cholesterol is higher after standing and after diuretics because of hemoconcentration.28,29 Thus, it seems likely that hemodilution caused by recumbency soon after stroke may explain lower H(e) levels in the early phase, with recovery to what probably represents levels characteristic of the patient after a few days of mobilization.

Prandial status and dietary content may also alter H(e) levels.8,30–32 Subjects for whom the time since their last meal was longer tend to have higher H(e) levels.31 After acute stroke, patients may not be given food by mouth until a swallowing assessment is performed. It is likely that many of the baseline blood draws came from patients who had not eaten in the past 24 hours. Then, on days 3 and 5, many patients may have been on a restrictive (eg, low fat) hospital diet and by day 14, back on their usual home diet.

Our study shows that plasma H(e) levels increased with time from stroke. These data suggest that the clinical interpretation of H(e) after stroke, and the eligibility for clinical trials assessing treatment for elevated H(e) levels, require an adjustment for time since stroke to properly interpret the observed H(e) levels. The results may guide other H(e)-lowering trials in establishing time windows for obtaining baseline H(e) levels in the acute period after cerebral infarction.

Appendix

List of Participating Centers, Principal Investigators, and Study Coordinators (in order by number of patients enrolled [number in brackets], with personnel listed in the following order: principal investigator, research coordinator).

West LA VA Medical Center [31], Stanley Cohen, MD, Dana Carmody; State University of New York at Stony Brook [11], George C. Newman, MD, PhD, Giridhar Chintlapudi, MD; Roberts Research Institute [10], J. David Spence, MD, FRCPC, Leslie Paddock-Eliazi, Reg.N., CCRC; University of Texas Southwestern [8], D. Hal Unwin, MD, Jennifer Stanford, RN; St. Johns Mercy Medical Center [6], William Logan, MD, Sally Schroer, RN, BSN; California Pacific Medical Center [5], Philip Calanchini, MD, Pat Radosevich; Florida Neurovascular Research Institute [5], Efran Albakri, MD; Nathalie Chiasson, RN, University of California at Los Angeles [3], Jeffrey Saver, MD, Roy Sweeney, MD; University of Maryland at Baltimore [2], Steven J. Kittner, MD, MPH, Mary J. Sparks, RN, BSN.

Acknowledgments

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References


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