Cognitive Changes after Saline or Plasmalyte Infusion in Healthy Volunteers

A Multiple Blinded, Randomized, Cross-over Trial


ABSTRACT

Background: In an incidental finding, during a study of plasma chemistry after crystalloid infusion, participants reported subjective cognitive changes, particularly slower thinking, after saline but not Hartmann’s (Ringer’s lactate) solution. The authors tested the hypothesis that saline infusion would produce greater adverse cognitive changes than Plasmalyte infusion.

Methods: The authors conducted a randomized, cross-over, multiple blinded study of healthy adult volunteers. On separate days, participants received 30 ml/kg over 1 h of either 0.9% saline or Plasmalyte with the order randomly allocated. Plasma chemistry was tested on venous samples. As part of a battery of cognitive tests our primary endpoint was the reaction time index after infusion.

Results: The authors studied 25 participants. Plasma chloride was greater after saline than after Plasmalyte: mean difference 5.4 mM (95% CI, 4.1–6.6 mM; P < 0.001). Saline was also associated with greater metabolic acidosis: base-excess 2.5 mM more negative (95% CI, 1.9–3.0 mM more negative; P < 0.001). There was no evidence of a difference in the reaction time index between the two interventions: mean reaction time index 394 ms (SD, 72) after saline versus 385 ms (SD, 55) after Plasmalyte. Difference: saline 9 ms slower (95% CI, 30 ms slower to 12 ms faster; P = 0.39). There were minimal differences in the other cognitive and mood tests.

Conclusions: Despite expected differences in plasma chemistry, the authors found that measures of cognition did not differ, despite expected differences in plasma chemistry.

VER the last 100 yr, normal saline (154 mM sodium chloride) has been the most widely used intravenous fluid in the perioperative setting.1–3 Alternative solutions with lower chloride concentrations are available, including...
Hartmann’s solution (Ringer's lactate) and Plasmalyte (table 1). Normal saline administration is associated with hyperchloremic metabolic acidosis. 1, 4–8 Saline infusion has also been associated with decreased renal function, abdominal pain, and altered cognition. 6, 9 These physiological changes may be associated with hyperchloremia, or acidosis, or both. Despite these associations, saline continues to be the most widely used fluid worldwide. 2

Cognition refers to the mental processes involved in gaining knowledge and comprehension, including thinking, knowing, remembering, judging, and problem solving. 10 These are higher-level functions of the brain and encompass language, imagination, perception, and planning. Altered cognition after saline infusion was an incidental finding in a study of plasma chemistry, comparing saline with Hartmann’s solution in healthy volunteers. 11 Limitations of that study included lack of formal cognitive testing and large volumes of administered fluid, leading to physical discomfort in participants. Although there are studies examining other adverse associations of saline compared with Plasmalyte, 1 to our knowledge, there are no published studies of cognitive changes after administration of Plasmalyte solution, which has a lower chloride concentration than Hartmann’s solution, and therefore, a greater difference from saline.

We conducted a cross-over study in healthy volunteers to test the hypothesis that saline produces greater adverse cognitive changes than Plasmalyte, in particular, slower cognition. We also examined plasma chemistry, particularly plasma chloride concentration, pH, and base-excess after infusions of both these solutions.

Materials and Methods
We conducted a blinded, randomized, cross-over trial in healthy volunteers. The Human Research Ethics Committee at Austin Health (Melbourne, Victoria, Australia) approved this study (approval number: H2011/04213). The study was also registered with The University of Melbourne, Psychological Sciences Human Ethics Advisory Group (Melbourne, Victoria, Australia), and the Australian and New Zealand Clinical Trials Registry (ACTRN1261100124932). Participants gave written informed consent. Participants were healthy adults not requiring any daily medication other than the contraceptive pill. Exclusion criteria included: (1) pregnancy, (2) age less than 18 or more than 60 yr, (3) body mass index more than 35 kg/m², (4) heart disease (cardiac failure, ischemia, or treated arrhythmias), (5) intellectual disability, (6) history of psychiatric illness, and (7) previous allergic reaction to the study solutions.

Cognitive Testing
We used a battery of cognitive tests chosen for their sensitivity to detect subtle disturbances of general cognitive function, such as those after a first seizure in adulthood. 12 The tests targeted markers of general (but subtle) cognitive disturbance, such as information processing speed and reaction time under varying levels of stimulus complexity and decision-making load. These objective measures were complemented by subjective measures of cognition and mood, given the only previous report of cognitive change after fluid infusion 11 was based on anecdotal subjective reports of individuals. Our primary endpoint was the reaction time index, which is an objective measure of attentional processing that is sensitive to general cognitive dysfunction, as previously shown by our research. 12, 13 The task consists of four levels that measure the time a participant requires to respond to visual stimuli under 12 conditions that increase in stimulus complexity (table 2). The first level measures general psychomotor speed, while each subsequent level introduces greater processing demands, by requiring the participant to maintain or shift attention to selected stimuli, or to inhibit a certain response (higher-level executive control). The task was created using the program E-prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA), and was administered on a laptop computer with a 13.3-inch screen, running Windows 7 operating system (Microsoft, Seattle, WA), with a 2.53 GHz processor.

Secondary outcomes included a well-established measure of attention and speed, the Processing Speed Index of the Wechsler Adult Intelligence Scale Version 3 (WAIS-III-PSI) 14 comprising Digit Symbol-Coding and Symbol Search subtests. The WAIS-III-PSI allows comparison with a population mean of 100 and a SD of 15. 14 We also measured subjective physical and cognitive symptoms by asking two qualitative questions: (1) “Have you noticed any new physical symptoms during the infusion, and if so, what?”, and (2) “Have you noticed any changes in your thinking during

Table 1. Concentration of Ions in Intravenous Fluids

<table>
<thead>
<tr>
<th>Strong Ion (mEq/l)</th>
<th>Hartmann’s</th>
<th>Ringer’s Lactate</th>
<th>Plasmalyte</th>
<th>Normal Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (Na⁺)</td>
<td>129</td>
<td>130</td>
<td>140</td>
<td>154</td>
</tr>
<tr>
<td>Chloride (Cl⁻)</td>
<td>109</td>
<td>109</td>
<td>98</td>
<td>154</td>
</tr>
<tr>
<td>Potassium (K⁺)</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Calcium (Ca²⁺)</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium (Mg²⁺)</td>
<td>0</td>
<td>0</td>
<td>3.0</td>
<td>0</td>
</tr>
<tr>
<td>Acetate, mEq/l</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Gluconate, mEq/l</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Lactate, mEq/l</td>
<td>29</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Anesthesiology 2013; 119:569-75 571

Table 2. Reaction Time Index

<table>
<thead>
<tr>
<th>Task</th>
<th>Stimuli</th>
<th>Instructions</th>
<th>Conditions</th>
<th>Trials</th>
<th>Constructs Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Simple reaction time</td>
<td>Repeated presentations of the letter “A”</td>
<td>Press the “0” key in response to the letter</td>
<td>1</td>
<td>5 practice 40 trials</td>
<td>Psychomotor speed</td>
</tr>
<tr>
<td>2. Choice reaction time (a)</td>
<td>Letters with a curved part (e.g., R, U), and letters constructed with all straight lines (e.g., L, V)</td>
<td>Press “0” in response to a letter with a curved part and “1” in response to a letter with only straight lines</td>
<td>1</td>
<td>10 practice 40 trials</td>
<td>Psychomotor speed and perceptual discrimination</td>
</tr>
<tr>
<td>3. Choice reaction time (b)</td>
<td>Strings of 1, 2, 4, or 8 letters, which included a letter with a curved part (e.g., LMRE) or letters made of straight lines only (e.g., TKLV)</td>
<td>Press “0” in response to a letter with a curved part and “1” in response to letters with all straight lines</td>
<td>8</td>
<td>8 practice 120 trials</td>
<td>Psychomotor speed and increasingly complex perceptual discrimination</td>
</tr>
<tr>
<td>4. Go-no-go reaction time</td>
<td>A random sequence of red and green lights. To ensure greater difficulty for inhibiting responses, “go” responses (70%) outweighed “no go” responses (30%) in each condition</td>
<td>Condition 1: press “0” in response to a green light. Do not respond to a red light. Condition 2: press “0” in response to a red light. Do not respond to a green light</td>
<td>2</td>
<td>No practice 200 trials</td>
<td>Psychomotor speed and cognitive inhibition</td>
</tr>
</tbody>
</table>


the infusion, and if so, what?” The first question aimed to detect any patterns of physical symptoms, such as bloating.11 The second question formed part of the assessment of subjective cognition, which is a person’s own perception of cognitive change, and supplements objective cognitive testing by standardized neuropsychological tests. These qualitative questions were included because comprehensive assessment of cognition requires assessing both subjective and objective facets that represent different aspects of cognition and are not strongly correlated.15,16

We used the AB Neuropsychological Assessment Schedule to quantitatively assess cognitive complaints across the following domains: fatigue, slowing, memory, concentration, language, and motor skills on a 4-point scale of whether a particular cognitive difficulty has been “not a problem”, “a mild problem”, “a moderate problem”, or “a serious problem.”17 The total AB Neuropsychological Assessment Schedule score was obtained by summing scores across these domains and reflects both the number and severity of cognitive complaints perceived by the patient.

Finally, we assessed mood using the Profile of Mood States, allowing us to explore the effects of mood on objective and subjective cognition. Mood is associated with subjective cognition12,16 and compromises speed of information processing, the key outcome variable of the study.18–20 The Profile of Mood States calculates a total score derived from the subscales: tension, depression, anger, vigor, fatigue, and confusion.

Procedure

This study was conducted between May and September 2011. Participants were recruited by word of mouth from staff in perioperative services at the Austin hospital; a large, University-affiliated, metropolitan hospital in Melbourne, Australia. Participants attended on 2 separate days, which were 6 days at the least, but less than 30 days apart. Participants fasted for 2 h before both study visits, however, oral intake was not controlled before this time. On arrival, we encouraged participants to empty their bladders to avoid discomfort during the study. Participants were weighed on a validated scale to calculate the volume of fluid to be infused. Participants then had a 20-gauge intravenous cannula placed in a cubital fossa vein. Tourniquets were in place for all blood sampling: 5 ml of blood was taken and discarded, followed by 2.0 ml for clinical chemistry in a heparinized blood gas syringe. Clinical chemistry was analyzed by a clinical blood gas machine before and after infusion (ABL 800; Radiometer, Copenhagen, Denmark). The principal plasma clinical chemistry variables were pH, standard base-excess, bicarbonate, and chloride. The machine also reported: hemoglobin, glucose, ionized calcium, potassium and lactate, in addition cooximetry variables.

The only cognitive testing before fluid infusion was a baseline reaction time index. Participants then received 30 ml/kg of 0.9% saline (Baxter Healthcare, Toongabbie, NSW, Australia), or 30 ml/kg of Plasmalyte (Baxter Healthcare; table 1), from room temperature operating room stock. Fluid was
infused via volumetric pumps (Alaris GP; Cardinal Health, Seven Hills, NSW, Australia) for more than 1 h via the cubital fossa cannula. Participants were randomly assigned to receive either saline at the first visit and Plasmalyte at the second visit, or vice versa, according to a computer-generated table of random numbers without blocking, stratification, or other restrictions. Participants were seated and provided with magazines during infusion. At the end of the procedure the infusion line was disconnected, and after 2 min further venous blood was sampled from the 20-gauge cannula and the clinical chemistry repeated. Participants then performed the entire battery of cognitive testing. The cannula was removed after cognitive testing.

**Blinding**

The randomization code was stored separately from the rest of the study data. Fifty opaque envelopes were prepared by an independent person and marked participant 1A and participant 1B right up to participant 25A and participant 25B, with envelope 1A containing details of the fluid to be received during the first period for participant 1 and 1B the second period, with each participant receiving one infusion of each fluid type (Plasmalyte or saline). The allocation was concealed at multiple levels: participant, cognitive tester, and data analyst. Infusions were prepared and masked with opaque bags. Infusions were prepared and connected by unblinded medical members of the team (Drs. Story, Teoh, or Weinberg).

**Sample Size Calculation**

We used commercial software (PASS, NCSS; LLC, Kaysville, UT) to calculate the required sample size for this cross-over study. We assumed that the postinfusion reaction time index would be 500 ms after Plasmalyte, with a SD of 100 ms as seen previously in a similar setting. We hypothesized that the reaction time index would increase to at least 600 ms after saline, which would be a clinically important difference that we proposed would be associated with the reaction time index and plasma chloride concentration and base-excess after infusion. Differences in plasma chemistry between the two groups were compared using paired t tests. We proposed that clinically important absolute values for plasma pH were 7.30 and −3.0 mM for base-excess, and reported the number of participants with measurements below (more abnormal) these values by treatment group. We used two-tail hypothesis testing and considered a P value less than 0.05 as significant. Data were analyzed using Stata version 12 software (StataCorp, College Station, TX) and GraphPad Prism version 5 software (GraphPad Software, San Diego, CA). This study is reported in accordance with the CONSORT guidelines.

**Results**

We studied 25 healthy participants (table 3) with all of them completing both interventions. At baseline, before infusion, clinical chemistry variables were similar in both interventions (table 4 and figs. 1 and 2). At the end of the saline infusion, plasma chemistry was consistent with greater hyperchloremic metabolic acidosis and acidemia, than that after Plasmalyte infusion (table 4 and figs. 1 and 2). In particular, plasma chloride concentration was 5.4 mM greater (95% CI, 4.1–6.6 mM greater; P < 0.001) and base-excess was 2.5 mM more negative (95% CI, 1.9–3.0 mM more negative; P < 0.001) after saline rather than Plasmalyte infusion.

At baseline, the reaction time index was similar between the saline and Plasmalyte interventions (fig. 3). Although there was a decrease in the reaction time index postinfusion compared with baseline after both interventions (potentially due to a learning effect), there was no evidence of a difference in reaction time index between the two interventions. After saline, the mean reaction time index was 394 (SD, 72) ms, and after Plasmalyte was 385 (SD: 55) ms: mean difference saline 9 ms slower (95% CI, 30 ms slower to 12 ms faster, P = 0.39; P = 0.71 with nonparametric testing). This corresponds to a mean increase in reaction time of 2.3% after saline when compared with that after Plasmalyte. There was evidence of a learning effect from the first to second days (period effect) for the reaction time index: 54 ms faster on day two (95% CI, 23–86 ms faster). However, when the comparison between interventions was adjusted for the period effect, there was little difference in the unadjusted results: saline was 15 ms slower (95% CI, 41 ms slower to 12 ms faster; P = 0.28).

After infusion, there was minimal correlation between plasma chloride and reaction time index (Pearson r = −0.13; P = 0.38) and a mild, nonsignificant, correlation.
between base-excess and reaction time index (Pearson r = 0.27; P = 0.06). Of note, three participants had a pH less than 7.30 (2 after Plasmalyte and 1 after saline) and three had a base-excess less than −3.0 mM (1 after Plasmalyte and 2 after saline). Plasma glucose was very similar at the end of infusion in both groups: 5.0 mM (Range 4.1–5.6 mM) after saline and 5.1 mM (range: 4.0–5.8 mM) after Plasmalyte.

There was also little evidence of differences in the other cognitive or mood tests between the two interventions (table 5). The reporting of physical symptoms between the two treatment groups was similar. The most frequent symptom was that of feeling cold, which was reported by 11 participants during the saline intervention, and ten participants during the Plasmalyte intervention. None reported of bloating during either intervention, and one participant reported abdominal pain after Plasmalyte. On questioning, 15 participants reported subjective cognitive changes after Plasmalyte compared with 12 after saline (P = 0.57); 8 participants reported cognitive changes following both infusions, and 6 did not report subjective cognitive changes during either intervention.

### Discussion

We conducted a cross-over randomized study in healthy volunteers to test the hypothesis that saline produces greater adverse cognitive changes than Plasmalyte, particularly slower cognition. Contrary to our hypothesis, we found little evidence of differences in cognitive testing after saline and Plasmalyte infusions. This was despite marked differences in plasma chemistry after the two infusions, in particular hyperchloremic metabolic acidosis and acidemia after saline infusion.

The primary endpoint was the reaction time index after infusion.12,13 A longer reaction time index reflected slower cognition. The reaction time index after infusions was about 400 ms (fig. 3), with no apparent difference after saline compared with Plasmalyte. Of note, even the upper limit of a 30 ms increase (7% relative increase) for saline was much less than our proposed important difference of 100 ms or 20% relative increase. We used a battery of other quantitative and qualitative cognitive tests, but found little evidence of differences in any of the outcomes after Plasmalyte and saline. Of interest, the WAIS-III score of 112 during both interventions was slightly above the population mean of 100.14 These findings are in contrast with the marked differences in plasma chemistry that we found and that we proposed would be associated with adverse cognitive effects after saline infusion. Few of the absolute pH and base-excess values were, however, clinically important in either intervention. Further, there was little correlation between reaction time index and plasma chloride concentration or base-excess.

Our cognitive findings contrast with the study of Williams et al.,11 which is the only previous study reporting cognitive changes after fluid infusions. Their study examined the plasma osmolality effects of saline and Hartmann’s (Ringer’s lactate) solution11 and found an incidental association between saline infusion and subjective cognitive changes. The study did not aim to compare cognition. During the saline intervention, however, 13 of 18 volunteers reported cognitive changes. None of the volunteers reported these cognitive changes following Hartmann. The reported cognitive problems were highly specific: “a perceived difficulty in abstract thinking, such as mental arithmetic, reading medical journals, or replying to anaesthetist board questions.” These reported cognitive problems are not typical of those encountered in routine clinical practice.10

One possible limitation of the current study is the wide variety of tests that we could have used to detect the type

### Table 4. Summary of Plasma pH and Bicarbonate

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Saline Mean (SD)</th>
<th>Plasmalyte Mean (SD)</th>
<th>Postinfusion</th>
<th>Saline Mean (SD)</th>
<th>Plasmalyte Mean (SD)</th>
<th>Difference Postinfusion</th>
<th>Plasmalyte vs. Saline Mean difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td></td>
<td>7.36 (0.03)</td>
<td>7.36 (0.02)</td>
<td></td>
<td>7.33 (0.03)</td>
<td>7.36 (0.02)</td>
<td></td>
<td>0.03 (0.01–0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bicarbonate, mM</td>
<td></td>
<td>27.2 (2.7)</td>
<td>27.7 (2.5)</td>
<td></td>
<td>24.7 (2.0)</td>
<td>27.2 (1.8)</td>
<td></td>
<td>2.2 (1.7–2.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
of cognitive problems reported by Williams et al.\textsuperscript{11} There is currently no agreed set of tests for the study we conducted.\textsuperscript{10} We tested cognition with a battery of neuropsychological tests, using the reaction time index as our primary measure of cognition because it is sensitive to subtle changes in cognition, such as those following a first seizure in adulthood.\textsuperscript{12} Cognitive studies of patients after anesthesia have used different batteries of tests to look at different aspects of postoperative cognitive dysfunction including attentional problems.\textsuperscript{22} Although there are no other studies of cognition after fluid infusions, there is a limited number of studies of cognition and dehydration in healthy volunteers, which show inconsistent results both within, and between the different batteries of tests used.\textsuperscript{23} We had a consistent finding of no effects from fluid intervention across our battery of tests that measured similar cognitive processes in the dehydration studies.\textsuperscript{23}

One potential explanation for the difference in findings between our study and Williams et al.\textsuperscript{11} is that they administered 50 ml/kg of saline and Hartmann’s solution over 1 h, whereas we used 30 ml/kg of saline and Plasmalyte (table 1). Direct clinical chemistry comparison between the two studies is limited, however, because Williams et al. did not report chloride or base-excess. At the end of infusion, the plasma pH in the Williams study was 7.44 in the Hartmann intervention and 7.38 in the saline intervention (difference 0.06), whereas in our study the plasma pH was 7.36 in the Plasmalyte intervention and 7.33 in the saline intervention (difference of 0.03). Whether this difference in pH could explain differences in cognitive results is unclear. Further, the chemistry of Hartmann’s solution differs from Plasmalyte (table 1), with Hartmann having lactate instead of acetate and gluconate, and more chloride than Plasmalyte. However, the sodium and chloride concentrations in Plasmalyte more closely resemble plasma than Hartmann. It is possible, but unlikely, that these formulation differences could account for the differences in study findings.

As anticipated, in our study with smaller infused volumes than the Williams study,\textsuperscript{10} none of the participants reported bloating and only one reported abdominal pain. In the Williams study,\textsuperscript{10} all participants reported bloating after both solutions and most reported abdominal discomfort after saline. Bloating and discomfort in the Williams study may have affected cognition either directly, or indirectly through mood changes,\textsuperscript{16} although this was not measured in the Williams study. Using the Profile of Mood State, we did not find differences in mood after both the infusions in the current study. During each intervention, however, about half the patients reported feeling cold during the infusion. Although it is unclear whether feeling cold biased the postinfusion cognitive results, we consider this unlikely.

Our study has several other limitations. First, this is a small study of young, healthy volunteers. This restricts extrapolating our results to patients undergoing surgery and anesthesia, particularly when there is the combination of increased metabolic acidosis, surgical stress, hemorrhage, and hemodynamic instability in older, and more sick patients.\textsuperscript{24} However, conducting a randomized study of cognition after saline or Plasmalyte during surgery would be very difficult, given the large number of confounding factors during the perioperative period.\textsuperscript{22} Second, saline was associated with a clinically relevant but mild metabolic acidosis, and mild acidemia, so our results may not reflect the possible cognitive effects of more severe metabolic acidosis with more severe acidemia. Third, our study compared saline and Plasmalyte, which may limit extending our results to other fluid formulations, such as lactate- and bicarbonate-based solutions.\textsuperscript{4} Fourth, we did not provide training to minimize learning effects, however,
the learning effects between study days did not appear to have much effect on the results, presumably due to randomization. Fifth, we cannot exclude cognitive effects of the intervention, which may have developed in the hours after testing.

Understanding the risks and benefits of fluid therapy is an important part of perioperative medicine.2 We found that, despite important differences in plasma chemistry, saline was not associated with deterioration in cognitive testing compared with Plasmalyte when infused into healthy volunteers. Although saline is associated with important adverse effects, including renal impairment and increased transfusion requirements,1 in addition to, at times severe, hyperchloremic metabolic acidosis,4–6–8 we cannot conclude that altered cognition is one of those adverse effects.

The authors thank Christine Wu, Medical Student, and Claire Pollock, R.N., Cert. Avd. Nursing, P.G.Dip. Nursing Sci., Anaesthesia Resource Nurse; Austin Hospital, Melbourne, Victoria, Australia.

References

Table 5. Summary of Secondary Cognitive Outcomes after Infusion

<table>
<thead>
<tr>
<th></th>
<th>Saline Mean (SD)</th>
<th>Plasmalyte Mean (SD)</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-psi</td>
<td>112 (11.9)</td>
<td>112 (12.8)</td>
<td>0.2 (−4.4 to 3.9)</td>
<td>0.91</td>
</tr>
<tr>
<td>ABNAS</td>
<td>6.0 (7.1)</td>
<td>5.7 (6.3)</td>
<td>0.3 (−4.6 to 3.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>POMS</td>
<td>24.6 (13.9)</td>
<td>22.6 (11.8)</td>
<td>2.0 (−9.0 to 5.0)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

ABNAS = AB Neuropsychological Assessment Schedule; POMS = Profile of Mood States; WAIS-PSI = Wechsler Adult Intelligence Scale Version 3 Processing Speed Index.