Serum Calcium as Prognosticator in Ischemic Stroke

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Background and Purpose—Calcium (Ca\(^{2+}\)) plays a role in the cellular and molecular pathways of ischemic neuronal death. We evaluated the impact of both early and delayed Ca\(^{2+}\) levels on clinical outcomes from acute ischemic stroke.

Methods—The relations between blood calcium level obtained early (<4.5 hours), and delayed (72 to 96 hours) after ischemic stroke onset versus clinical outcomes were analyzed in 826 subjects enrolled in an international trial in the Virtual International Stroke Trials Archive. Subjects were categorized into Ca\(^{2+}\) quartiles. Outcome measures analyzed included baseline and 72- to 96-hour stroke severity, as well as 3-month functional and global disability scales. The independent effect of calcium on outcome was evaluated by median and logistic regression analysis.

Results—Six hundred and fifty-nine (80%) of the trial subjects had complete baseline data including Ca\(^{2+}\) levels. Bivariately, the highest delayed Ca\(^{2+}\) quartile (versus lowest) was associated with lesser stroke severity and better 3-month functional and independence scale outcomes (all \(P<0.001\)), but no significant outcome differences were noted among early Ca\(^{2+}\) levels. In multivariable analysis, delayed Ca\(^{2+}\) in the highest quartile (versus lowest quartile) was associated with greater 3-month independence score on the Barthel Index scale (76.9 versus 55.4, \(P=0.006\)). No other significant outcome differences were noted between highest and lowest quartiles for both early and delayed Ca\(^{2+}\) quartiles.

Conclusions—Elevated 72- to 96-hour serum Ca\(^{2+}\) levels independently predict greater independence 3 months after ischemic stroke, but very early serum Ca\(^{2+}\) appear not to have any prognostic significance. (Stroke. 2008;39:2231-2236.)

Key Words: acute care ■ acute stroke ■ cerebrovascular disease ■ outcomes ■ prognosis ■ stroke ■ stroke care

Given the immense burden that ischemic stroke exerts, the need to develop more precise estimates of a stroke survivor’s prognosis remains an important goal. Ischemic neuronal death engages several terminal pathways including the loss of ionic homeostasis.\(^{1}\) Calcium (Ca\(^{2+}\)) ions play a physiological role in the multiple pathomechanisms of cerebral ischemia.\(^{2}\) Cell calcium metabolism during and immediately after a transient period of ischemia influences the cascade of events that leads to subsequent neuronal injury.\(^{1}\) For instance, ischemia/hypoxia triggers rapid translocation of Ca\(^{2+}\) from extracellular to intracellular spaces of cerebral tissues.\(^{3,4}\) Awareness of the participation of Ca\(^{2+}\) in the ischemic cascade has led to the development of several potential neuroprotective agents designed to modify the role of this ion in acute focal brain injury.\(^{5}\)

Ca\(^{2+}\) has also been studied with regard to its relationship with stroke risk factors and stroke incidence.\(^{6}\) High dietary intake of Ca\(^{2+}\) has been associated with reduced risk of stroke.\(^{6}\) To our knowledge very few attempts have been made to investigate the impact of serum Ca\(^{2+}\) level on clinical outcomes after ischemic stroke.\(^{7-9}\) A recent study suggested that calcium levels obtained within 24 hours of stroke onset are associated with better hospital discharge clinical outcomes.\(^{9}\) However, this finding requires confirmation and it remains unclear as to whether timing of calcium level is of prognostic significance. In this study we aimed to compare the impact of very early versus delayed calcium levels on clinical outcomes after acute ischemic stroke.

Methods
We reviewed data from the modified Repinotan–Randomized Exposure Controlled Trial (mRECT) trial, for this analysis.\(^{10}\) Data from this trial was contributed to the Virtual International Stroke Trials Archive, a vast resource of stroke patient data collated for anonymized analysis and hypothesis testing.\(^{11}\) The methods and results of the mRECT trial have already been described.\(^{10}\) In brief, mRECT was a double-blind, placebo-controlled, parallel group, international multicenter study to evaluate the efficacy, safety, tolerability, and pharmacokinetic/pharmacodynamic effects of a targeted exposure of...
intravenous repinotan, a serotonin agonist (5HT1A receptor subtype). A total of 681 patients with an ischemic thromboembolic hemispheric stroke were randomized 1:1, to placebo or repinotan. Subjects had to have a National Institute of Health Stroke Scale (NIHSS) score of 8 to 23 with a motor deficit ≥2, to be eligible for participation in mRECT. Patients with CT evidence of major early infarction involving more than one-third of the middle cerebral artery territory, primary intracerebral hemorrhage, a baseline Rankin score ≥2, systolic blood pressure ≥210 or <110 mm Hg, diastolic blood pressure >110 or <60 mm Hg, myocardial infarction within 3 months of enrollment, or who had unstable supraventricular and/or ventricular arrhythmia, severe conduction defect (AV-block grades 2 and 3), bradycardia, or uncompensated heart failure, were excluded.

For enrolled mRECT patients, study drug infusion had to be initiated within 4.5 hours from the onset of ischemic symptoms. Recombinant tissue plasminogen activator was permitted as standard medication. The primary intention-to-treat outcome was a Barthe Index score >85 at 3 months post-treatment. Repinotan failed to show clinical benefit, because there was no statistically significant difference between the treatment arms with regard to the primary outcome.10

For the purpose of this analysis, repinotan and placebo groups were combined given the lack of difference in efficacy between them. However, a separate analysis was also performed to assess any potential differences in Ca²⁺ serum levels between repinotan versus placebo-treated subjects at various study time points. Prespecified outcome measures to be evaluated in relation to very early calcium level (obtained within 4.5 hours after stroke onset) and delayed calcium level (obtained at 72 to 96 hours after stroke onset) included the following: (1) Stroke Severity on Admission (median NIHSS Score); (2) Stroke Severity at 72 to 96 hours (median NIHSS Score); (3) Neurological Improvement ΔNIHSS (median baseline NIHSS Score to median NIHSS Score at 72 to 96 hours); (4) Global Rankin Scale Score; (5) Functional Activity at 72 to 96 hours (median Barthel Index Score); (6) Global Disability at 72 to 96 hours (median Barthel Index Score); (7) Functional Activity at 3 months (modified Rankin Scale Score ≥2).

Statistical Analyses
Serum Ca²⁺ level was collapsed into quartiles (see cutpoints in tables below), for both early and 72- to 96-hour measures. These quartile versions were used as predictor variables in modeling. Tables and χ² tests were used to investigate bivariate relationships between the 2 calcium quartile measures and demographic or outcome measures that were categorical or collapsed into categories. Next descriptive statistics and Kruskal-Wallis rank sum tests were used to investigate bivariate relationships between the calcium quartiles and continuous measures. In addition, Pearson correlations were computed among the several continuous measures, including uncollapsed calcium levels. Multivariable analyses were conducted (with Stata 9.1), using median regression for continuous measures, logistic regression for dichotomous measures, and ordinal logistic regression for measures collapsed into 3 categories. To evaluate the role of possible confounding factors, other potential determinants of incident stroke severity and outcome were also analyzed and so each model included one of the sets of calcium quartiles plus other covariates, including age,11 history of atrial fibrillation,12 history of stroke,13,14 admission temperature,16 admission glucose,17–18 admission systolic blood pressure,21 Potential baseline covariate predictors of functional activity and global disability at 72 to 96 hours and at 3 months included all the aforementioned potential determinants of stroke severity as well as admission NIHSS score.22 Statistical tests were made to check whether the coefficients for the calcium quartiles were simultaneously significant.

To evaluate the role of albumin-adjusted Ca²⁺, serum Ca²⁺ was adjusted by serum albumin using the formula: Corrected Calcium = serum calcium +0.8 (4 – serum albumin).18 These adjustments were made for both early and delayed Ca²⁺ levels, matching Ca²⁺ and albumin on time.

Results
Of 826 ischemic stroke subjects enrolled in the trial, 659 (80%) had complete baseline data including very early calcium levels. Table 1 shows a breakdown of salient baseline demographic and clinical variables by very early Ca²⁺ level. There were no significant differences in demographic and clinical factors by Ca²⁺ quartile. A comparison of serum Ca²⁺ at baseline, 24 hours and 72 hours, as well as change from baseline at 24 and 72 hours, between placebo versus repinotan groups did not reveal any statistically significant differences.

Table 2 displays the results of the bivariate analyses evaluating early and delayed Ca²⁺ levels versus the prespecified clinical outcomes. There were no significant differences with regard to the clinical outcomes studied among quartiles of early Ca²⁺ (Table 2). Also no significant improvements in median 72- to 96-hour NIHSS scores from baseline (ΔNIHSS) were noted among Ca²⁺ quartiles (Table 2). For delayed Ca²⁺, those in the highest quartile had significantly lesser 72- to 96-hour stroke severity, greater 72- to 96-hour independence, and better 72- to 96-hour functional activity than those in the lowest quartile (Table 2). Three-month independence and functional activity outcomes were also significantly better in the highest delayed Ca²⁺ quartile when compared to the lowest quartile.

Results of the correlation analyses showed early Ca²⁺ correlated weakly with baseline NIHSS score (r = −0.05, P = 0.21); 72- to 96-hour NIHSS score (r = −0.10, P = 0.01); ΔNIHSS (72- to 96-hour NIHSS score–baseline NIHSS score score, r = −0.09, P = 0.04); and 72- to 96-hour Barthel Index score (r = 0.11, P = 0.008). Delayed Ca²⁺ showed stronger correlations with baseline NIHSS score (r = −0.2, P = 0.0001); 72- to 96-hour NIHSS score (r = −0.3, P < 0.0001); ΔNIHSS (72- to 96-hour NIHSS score–baseline NIHSS score, r = −0.2, P = 0.0001); and with Barthel Index score (r = 0.3, P < 0.0001). Early Ca²⁺ and delayed Ca²⁺ had a correlation of 0.4 (P < 0.0001), whereas baseline NIHSS score and 72-hour NIHSS score had a correlation of 0.5 (P < 0.0001).

Table 3 shows the multivariable analysis results for baseline and 72- to 96-hour clinical outcomes comparing trends across early and delayed Ca²⁺ quartiles. Those in the highest delayed calcium quartile had significantly better Barthel Index scores and greater improvements in ΔNIHSS than those in the lowest quartile. Results of the multivariable analyses for the 3-month independence and functional activity outcomes are shown in Table 4. After adjusting for prespecified covariates those in the highest delayed Ca²⁺ quartile had significantly better median Barthel index scores than the lowest quartile (Table 4). For the early Ca²⁺ quartiles there was a significant difference across quartiles but not in a linear fashion with the greatest difference being between the first and second quartiles (Table 4). There were no significant differences in the likelihood of a poor functional outcome among early Ca²⁺ quartiles following multivariable analyses, and although the highest delayed Ca²⁺ quartile had less of a likelihood of a poor functional outcome compared to the lowest delayed Ca²⁺ quartile this difference did not reach statistical significance (Table 4). Using the formula noted
above we examined the influence of early and delayed albumin-corrected Ca\textsuperscript{2+} levels on the prespecified clinical outcomes, and did not find any significant differences in outcomes among albumin corrected Ca\textsuperscript{2+} quartiles with regard to the 3-month end points (data not shown). Furthermore, there were no correlations between baseline albumin levels and the 72-hour and 3-month clinical outcomes (data not shown), but there was a weak correlation of baseline albumin with baseline NIHSS score (0.0889, $P=0.02$).

**Discussion**

Our analysis suggests that elevated serum calcium levels obtained at 72 to 96 hours after ischemic stroke onset are associated with higher 3-month functional independence scores. Furthermore, higher serum calcium levels at 72 to 96 hours after the index stroke showed a clear pattern of association with better functional activity at 3 months, but this relationship did not reach statistical significance. Associating elevated calcium levels with better clinical outcomes after ischemic stroke has been shown in 2 prior single-center studies,\textsuperscript{7,9} but our study provided the added advantages of investigating this issue within the rigorous procedures of a clinical trial, including subjects from multiple sites from around the world, evaluating the impact of very early calcium levels after ischemic stroke, and examining an outcome time point (3 months postevent) frequently studied in acute stroke clinical trials. The 2 prior studies which looked at the prognostic significance of calcium levels after ischemic stroke found better hospital discharge functional outcomes in those with elevated admission Ca\textsuperscript{2+} levels,\textsuperscript{9} and a significant reduction in Ca\textsuperscript{2+} level in patients who died during hospitalization compared with survivors.\textsuperscript{7} Our study, however, suggests that timing is particularly important because we found that serum calcium levels drawn early (within 4.5 hours of ischemic stroke ictus) were not of any prognostic significance.

Clarifying the exact pathophysiological mechanism that may underlie these clinical observations has been challeng-
ing, especially because it is unclear whether serum Ca\(^{2+}\) level exerts a primary effect on ischemic stroke, or if it reflects a secondary epiphenomenon of ischemic stroke severity.\(^9\) However, our study’s findings of prognostic significance for delayed rather than early Ca\(^{2+}\) suggests that the truth may be closer to the latter. Animal studies have shown that Ca\(^{2+}\) movement from serum to brain occurs primarily via the choroid plexuses,\(^1\) and when neurons (and/or glia) are exposed to lipid peroxidation, their intracellular structures lose their protection from the extracellular space and a Ca\(^{2+}\) sink is created. As a result more calcium is extracted from the blood into the brain. In order to pull Ca\(^{2+}\) from the serum, the gradient must be sufficient to reduce the content of Ca\(^{2+}\) in the serum.\(^1\) It is thought that total neuronal cell Ca\(^{2+}\) content may increase to 150\% of control or more.\(^1\) Furthermore, the finding of more substantial decreases in calcium levels of ischemic stroke patients than of transient ischemic attack and controls may also support this hypothesis.\(^7\) However, whether the amount would be sufficient to change the serum levels to the degree noted in our study is unknown. A comparison of MR images quantifying the extent of brain injury or measurement of Ca\(^{2+}\) concentration in the cerebrospinal fluid\(^8\) versus serum Ca\(^{2+}\) levels would provide insight as to whether greater cerebral damage is associated with lower Ca\(^{2+}\) levels.

Interestingly, the potential role of serum calcium as a clinical prognosticator is not limited to ischemic stroke. Studies of general medical conditions, particularly among the critically ill, have shown that those with hypocalcemia tend to be more severely ill, and have higher mortality rates than those with normocalcemia.\(^{24-27}\) We did not have information on medical complications after the strokes in the mRECT trial, and so it is conceivable that the 72- to 96-hour Ca\(^{2+}\) levels we observed may have been influenced by the subsequent development of intercurrent illnesses, especially given the marked difference in 72- to 96-hour NIHSS scores among the 72- to 96-hour serum Ca\(^{2+}\) quartiles, a difference that was not seen in the baseline NIHSS scores among early Ca\(^{2+}\) quartiles.

Both early and delayed albumin-corrected calcium levels did not have any prognostic significance in this study. In a

### Table 2. Bivariate Analysis of Early (<4.5 hours) and Delayed (72 to 96 hours) Calcium Quartiles Versus Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early (&lt;4.5 hours) Serum Calcium Quartile, ×mg/dL</th>
<th>Delayed (72 to 96 hours) Serum Calcium Quartile, ×mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1, ≤8.82 (n=167)</td>
<td>Q2, 8.83 to 9.18 (n=163)</td>
</tr>
<tr>
<td>Median baseline NIHSS score</td>
<td>14.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Median 72- to 96-hour NIHSS score</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Median ΔNIHSS</td>
<td>−3.0</td>
<td>−5.0</td>
</tr>
<tr>
<td>Median 72- to 96-hour BI score</td>
<td>20.0</td>
<td>25.0</td>
</tr>
<tr>
<td>% 72- to 96-hour mRS score ≥2</td>
<td>90.3</td>
<td>86.6</td>
</tr>
<tr>
<td>Overall mean 72- to 96-hour mRS score (SD)</td>
<td>3.8 (1.4)</td>
<td>3.8 (1.4)</td>
</tr>
<tr>
<td>Median 3-month BI score</td>
<td>80.0</td>
<td>85.0</td>
</tr>
<tr>
<td>% 3-month mRS score ≥2</td>
<td>74.4</td>
<td>66.9</td>
</tr>
<tr>
<td>Overall mean 3-month mRS score (SD)</td>
<td>2.7 (1.5)</td>
<td>2.5 (1.6)</td>
</tr>
</tbody>
</table>

### Table 3. Multivariable Analysis for Baseline and 72- to 96-Hour Outcomes for Early (<4.5 hours) and Delayed (72 to 96 hours) Serum Calcium Quartile Levels

<table>
<thead>
<tr>
<th>Outcome</th>
<th>&lt;4.5-Hour Serum Calcium Quartiles</th>
<th>72- to 96-Hour Serum Calcium Quartiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P Value*</td>
<td>P Value†</td>
</tr>
<tr>
<td>Baseline median NIHSS score</td>
<td>0.74</td>
<td>0.08</td>
</tr>
<tr>
<td>72- to 96-hour NIHSS score</td>
<td>0.50</td>
<td>0.07</td>
</tr>
<tr>
<td>ΔNIHSS</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>72- to 96-hour BI score</td>
<td>0.24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>72- to 96-hour mRS score ≥2</td>
<td>0.41</td>
<td>0.08</td>
</tr>
</tbody>
</table>

BI indicates Barthel Index; mRS, modified Rankin Scale.

\(^*\)P value for trend across quartiles, adjusted for age, glucose, history of atrial fibrillation, history of stroke, initial systolic blood pressure, initial temperature.

\(^†\)P value for trend across quartiles with adjustment of aforementioned variables, and initial stroke severity.
prior acute stroke study, that compared total Ca\(^{2+}\), ionized Ca\(^{2+}\) and albumin-corrected Ca\(^{2+}\), only the total serum Ca\(^{2+}\) level was shown to be of prognostic value.\(^7\) Furthermore, some have questioned the accuracy of widely used albumin-corrected Ca\(^{2+}\) formulas, and have suggested that total calcium may be more accurate than albumin-corrected Ca\(^{2+}\) if ionized Ca\(^{2+}\) itself cannot be directly measured.\(^28\)

This study has limitations. It was a secondary analysis of a completed randomized trial, not a prospective study designed to address this issue. Thus, although we controlled for clinical and biological factors known to influence ischemic stroke outcomes, we cannot exclude the possibility that unmeasured confounding may explain some of our findings. We did not collect data on ionized Ca\(^{2+}\), which is the physiologically active component of serum Ca\(^{2+}\) levels. Additionally, we were constrained by lack of stroke subtyping information because small-vessel disease stroke subtype may carry a better prognosis than other subtypes. However, given the mRECT NIHSS score inclusion criteria,\(^10\) it is likely that mostly moderate-to-severe strokes were enrolled in this trial and small-vessel type strokes were in the minority. We also do not know whether there were any systematic differences in secondary preventative treatments between Ca\(^{2+}\) groups which may have impacted 3 month outcomes, although the relation between Ca\(^{2+}\) levels and 72- to 96-hour clinical outcomes is similar to that of the 3-month outcomes, and so we doubt that postdischarge prevention therapies were substantially different among Ca\(^{2+}\) groups. Finally, we lacked brain-imaging data to investigate the relationship between infarct volume and serum Ca\(^{2+}\) level.

In conclusion, we found Ca\(^{2+}\) levels obtained within 72 to 96 hours to be of prognostic significance after ischemic stroke. Specifically designed prospective studies are needed to confirm these findings, profile the time course of serum Ca\(^{2+}\) alterations in acute stroke, and investigate the pathophysiologic underpinnings for this potential association.

**Acknowledgments**

The authors are grateful to Rita Engelhardt, PhD, for her help with statistics, Myzoon Ali for data processing, and to the mRECT trial investigators for contributing their data to the Virtual International Stroke Trials Archive (VISTA).

**Disclosures**

None.

**References**


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**Table 4. Multivariable Analysis for 3-Month BI Score and mRS Score Outcomes for Early (<4.5 hours) and Delayed (72 to 96 hours) Serum Calcium Quartile Levels**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartiles, mg/dL</th>
<th>3-Month Multivariate Median BI Score*</th>
<th>95% CI</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early calcium (&lt;4.5 hours)</td>
<td>Q1, ≤8.82</td>
<td>69</td>
<td>61.8 to 76.2</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>Q2, 8.83 to 9.18</td>
<td>82.4</td>
<td>75.5 to 89.3</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Q3, 9.19 to 9.5</td>
<td>67</td>
<td>60.3 to 73.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4, ≥9.5</td>
<td>78.3</td>
<td>71.3 to 86.3</td>
<td></td>
</tr>
<tr>
<td>Delayed calcium (72 to 96 hours)</td>
<td>Q1, ≤8.6</td>
<td>55.4</td>
<td>50.6 to 60.3</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>Q2, 8.7 to 8.9</td>
<td>71.7</td>
<td>66.6 to 76.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Q3, 9.0 to 9.3</td>
<td>75.1</td>
<td>70.4 to 79.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4, ≥9.4</td>
<td>76.9</td>
<td>72.2 to 81.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quartiles, mg/dL</th>
<th>3-Month Multivariate Odds Ratio for mRS = 2</th>
<th>95% CI</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early calcium (&lt;4.5 hours)</td>
<td>Q1, ≤8.82</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q2, 8.83 to 9.18</td>
<td>0.54</td>
<td>0.29 to 0.99</td>
</tr>
<tr>
<td></td>
<td>Q3, 9.19 to 9.5</td>
<td>0.72</td>
<td>0.39 to 1.33</td>
</tr>
<tr>
<td></td>
<td>Q4, ≥9.5</td>
<td>0.53</td>
<td>0.28 to 0.98</td>
</tr>
<tr>
<td>Delayed calcium (72–96 hours)</td>
<td>Q1, ≤8.6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q2, 8.7 to 8.9</td>
<td>0.87</td>
<td>0.41 to 1.83</td>
</tr>
<tr>
<td></td>
<td>Q3, 9.0 to 9.3</td>
<td>0.54</td>
<td>0.27 to 1.10</td>
</tr>
<tr>
<td></td>
<td>Q4, ≥9.4</td>
<td>0.52</td>
<td>0.26 to 1.04</td>
</tr>
</tbody>
</table>

BI indicates Barthel Index; mRS, modified Rankin Scale; OR = 1, reference level; Ref, reference level.

*Adjusted for age, glucose, history of atrial fibrillation, history of stroke, systolic blood pressure, temperature and admission stroke severity.

†P value for trend.


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Stroke. 2008;39:2231-2236; originally published online June 26, 2008;
doi: 10.1161/STROKEAHA.107.513499
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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