production in the CNS. Indeed, activin A induction represents a common response to acute neuronal damage of various origins in vitro (5–14) and was very similar to the response observed after hypoxic-ischemic injury. The role of such an increased secretion warrants considerations because it was proposed that the up-regulation of activin A in brain injury might serve as a neuroprotective factor: activin A enhances the survival of midbrain and hippocampal neurons (11,12); decrease ischemic brain injury in infant rats (8); and shields striatal and midbrain neurons against neurotoxic damage (12,14). However, increased activin A concentrations have been reported in amniotic fluid of a patient who subsequently died from intrauterine fetal hypoxia and in the plasma of hypoxic preterm newborns (21), suggesting a role for activin A in the events cascade leading to hypoxic ischemic brain damage. Indeed, activin A release forms part of the CNS response to challenges involved in modulating inflammatory processes in the brain (21,25), the main mechanisms involved in brain damage attributable to hypoxia/asphyxia (4), and it prevents apoptosis (26) and inhibits caspase (27), two important pathways of neuronal death (28). Its oversecretion in CSF may therefore serve to reduce cell death after brain insults.

Finally, CSF activin A concentrations were higher in the infants who developed severe HIE than in those who did not or in controls at a stage when ultrasound and other diagnostic procedures were still silent and were unable to indicate which infants would develop HIE. Conversely, already at this stage newborns with activin A above the threshold defined by the ROC curve analysis had a probability of developing HIE as high as 100%, supporting the notion that activating A assessment could provide additional information to physicians at an early stage, thereby permitting earlier adoption of therapeutic strategies.

References

22. Petraglia F, Gomez R, Luisi S, Longini M, Tanganelli D, Petraglia F, et al. Activin A in brain injury might serve as a neuroprotective factor: because it was proposed that the up-regulation of activin A might serve as a neuroprotective factor: activin A enhances the survival of midbrain and hippocampal neurons (11,12); decrease ischemic brain injury in infant rats (8); and shields striatal and midbrain neurons against neurotoxic damage (12,14). However, increased activin A concentrations have been reported in amniotic fluid of a patient who subsequently died from intrauterine fetal hypoxia and in the plasma of hypoxic preterm newborns (21), suggesting a role for activin A in the events cascade leading to hypoxic ischemic brain damage. Indeed, activin A release forms part of the CNS response to challenges involved in modulating inflammatory processes in the brain (21,25), the main mechanisms involved in brain damage attributable to hypoxia/asphyxia (4), and it prevents apoptosis (26) and inhibits caspase (27), two important pathways of neuronal death (28). Its oversecretion in CSF may therefore serve to reduce cell death after brain insults.

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Within-Person, Among-Finger Variability of Capillary Blood Glucose Measurements, Mary M. Kimberly,1 Samvel P. Caudill,1 Hubert W. Vesper,1 Steven F. Ethridge,1 Enada Archibald,1 Kimberly H. Porter,3 and Gary L. Myers1 (1 Clinical Chemistry Branch, Division of Laboratory Sciences, National Center for Environmental Health, 2 Behavioral and Clinical Surveillance Branch, Division of HIV and AIDS Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA; and 3 International Medical Press, Atlanta, GA; * address correspondence to this author at: Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention,
Many diabetic patients use home-use glucose monitors for glycemic control (1, 2). Ideally, in studies comparing and assessing the variability among monitors, testing should be done with the same type of product used by patients, i.e., capillary whole blood. Simultaneous evaluation of multiple monitors requires more sample than can effectively be collected by lancing a single finger one or more times. Samples may therefore need to be collected from multiple fingers, and if so, the among-finger variability will need to be quantified before a study of among-monitor variability can be conducted. To our knowledge, no studies have been published that report among-finger variability in blood glucose measurements within an individual patient. Because evaluation of multiple monitors using multiple samples from an individual also assumes that the within-person blood glucose will be stable for the duration of the testing period, we tested, in a pilot study using a HemoCue 201 point-of-care glucose analyzer, the assumptions that the within-person, among-finger variability (hereafter referred to as “among-finger variability”) is negligible and that the within-person blood glucose is stable over a period of 35 min.

The Institutional Review Boards at the CDC and at Research Triangle Institute (where the study was conducted) approved the protocol. Free-living, community-dwelling people recruited from the Raleigh-Durham-Chapel Hill metropolitan area of North Carolina gave informed consent. Diabetic and nondiabetic adults over 18 years of age with a fasting glucose of 700-2000 mg/L and hematocrit of 30–55% were included in the sample population. Participants were required to have the middle three fingers on both hands. We excluded people who were taking medications that alter blood viscosity (such as aspirin); people with peripheral vascular disease, kidney disease, or hemophilia; and people with obvious lipemia (based on milky appearance by visual inspection). The admission requirements for diabetic patients included diagnosis of diabetes within the last 15 years, absence of severe hypoglycemic events within the previous 3 months, and ability to recognize the symptoms of hypoglycemia. To achieve stable metabolic status, all participants were required to fast for at least 8 h before participating in the study.

Statistical power calculations were used to determine the sample size needed for the pilot study based on an assumed CV of 3.5% for HemoCue 201 analyzer measurements. Using this CV, we determined that a minimum of 11 participants would be required to detect an among-finger CV ≥2.5% (80% power, using a two-sided 0.05 level test). We actually sampled 20 individuals, and the calculated CV (by ANOVA) of the HemoCue 201 measurements was 3.7%. This CV includes the analytical imprecision of the instrument as well as any within-person, within-finger imprecision. When we recalculated the statistical power using a sample size of 20 and a CV of 3.7%, we determined that we should be able to detect an among-finger CV ≥2.1% with 80% power using a 0.05 level test.

Eight diabetic and 12 nondiabetic individuals participated in the pilot study. One trained licensed practical nurse collected and measured all samples. Fingers were lanced by use of a Tenderlett lancing device (International Technidyne Corporation). The sampling scheme was the same for all participants and involved taking capillary samples from the left and right sides of the middle three fingers of both hands. The left side of all six fingers was lanced before returning to the first finger to lance the right side. Thus, each finger was sampled twice at two different sites. The order of finger sampling was the same for all participants to minimize errors from changes in sampling protocol from person to person. Measurements were performed with a HemoCue 201 using one lot of cuvettes and control solutions. The HemoCue test system is based on the glucose dehydrogenase method. All measurements from a participant were completed within 30–35 min.

The means of the 12 blood glucose measurements ranged from 710 to 1350 mg/L for all 20 participants, from 900 to 1350 mg/L for the 8 diabetic participants, and from 710 to 1040 mg/L for the 12 nondiabetic participants. The mean (SD) difference between the 1st and 12th measurement for each person was 40 (60) mg/L (range, –60 to 180 mg/L). The mean (SD) difference between the maximum and minimum values for each person was 120 (40) mg/L (range, 60–210 mg/L). There was no apparent concentration dependence of the differences between the 1st and 12th measurements or the maximum and minimum measurements. The diabetic and nondiabetic participants did not demonstrate statistically significant differences between the 1st and 12th or between the maximum and minimum blood glucose concentrations. Statistically significant (P <0.05) increases in glucose concentrations were observed in 3 (2 nondiabetic and 1 diabetic) of the 20 participants, and a statistically significant decrease was observed in 1 diabetic individual. For the three individuals with increases, the estimated slope from a regression of glucose concentration on time of measurement predicted an increase in concentration after 35 min of 110, 188, and 130 mg/L, and for the individual with the decrease, the predicted decrease was –56 mg/L after 35 min. For all other participants, there was no significant increase or decrease in glucose concentration over the 35-min period from 1st to 12th measurement. From these data, we did not note any systematic increases or decreases in glucose over time across the population, and we concluded that the changes seen over the course of 35 min could be attributed to among-finger variation and short-term random physiologic variation.

We used ANOVA to determine the among-finger variance. Confidence intervals (CIs) were determined and are based on the χ2 distribution and the estimated degrees of freedom associated with the variance estimate (3, 4). The among-finger variance was 0.98 (95% CI, 0.81–1.21). Therefore, at a blood glucose concentration of 1000 mg/L, the estimated among-finger CV was 0.99% (95% CI, 0.90–1.1%). Correspondingly, the estimated among-finger...
CVs were 1.4% (95% CI, 1.3–1.6%) and 0.73% (95% CI, 0.67–0.81%) at blood glucose concentrations of 700 and 1350 mg/L, respectively.

These results indicate that the among-finger variability needs to be considered when assessing among-monitor variability using capillary blood from different fingers of the same individual. Although this variability is important for the assessment of variability among monitors, it is too small to be of clinical relevance and does not affect patient care. Therefore, diabetic patients or their physicians do not need to be concerned about which finger to use for consecutive capillary sampling.

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References

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Roche IFCC Methods for Lactate Dehydrogenase Tested for Duplicate Errors with Greiner and Becton-Dickinson Lithium-Heparin and Greiner Serum Samples, Goce Dimeski,1Tony Badrick,2 Robert Flatman,2 and Barry Orniston1 (1 Department of Chemical Pathology, Queensland Health Pathology Service, Princess Alexandra Hospital, Woolloongabba, Queensland Australia; 2 Department of Chemical Pathology, Sullivan and Nicolaides Pathology, Taringa, Queensland, Australia; * address correspondence to this author at: Department of Chemical Pathology, Queensland Health Pathology Service (QHPS), Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Queensland 4102, Australia; fax 61-7-3240-7070, e-mail Goce_Dimeski@health.qld.gov.au)

The new Roche IFCC-recommended method for lactate dehydrogenase (LD) has been reported (1,2) to produce duplicate errors with Becton Dickinson (BD) lithium-heparin tubes with plasma separators. Separate studies (3) of Sarstedt tubes showed no such errors. To overcome and minimize duplicate errors, Roche has modified the method to incorporate a predilution step. This modified method can be used only on dilutor systems (Modular P and Hitachi 911, 912, and 917), but not on nondilutor systems (Modular D and Hitachi 747 and 902; Roche). We tested the modified method for duplicate errors and tested lithium-heparin tubes (with plasma separator) from another major supplier for duplicate errors.

Blood samples were collected in three different tubes: Greiner Vacuette lithium-heparin tubes with plasma separator (prod. no. 455083); Greiner Vacuette serum tubes with plasma separator (prod. no. 455078); and BD Vacutainer PST II lithium-heparin tubes with plasma separator (prod. no. 367377). Three IFCC LD methods were set up on our Modular DP system: the Modular D, the Modular P IFCC method, and the Modular P IFCC modified method with predilution. The two LD methods on the Modular P system were set up to use the same reagent bottle set. The three tubes for each sample were collected, mixed without delay by inversion, centrifuged, and analyzed at the same time. After centrifugation at 3000 g for 12 min at 4 °C, the samples were immediately analyzed in duplicate first on the Modular D system, then on the Modular P by the two methods. The study was conducted over 4 days with 51 samples being analyzed in groups of 5 or 10. The LD range in the samples was 145–564 U/L.

Using the formula suggested by Bakker et al. (1), in which the 95% confidence limit = 0.028 times the mean of the duplicate, we calculated the frequency of duplicate errors for each tube/method. At the same time, we performed statistical analyses of the duplicate results, using the Bland–Altman procedure (4). The observed absolute difference range between the duplicate readings was also included. The results are shown in Table 1.

### Table 1. Frequency of duplicate errors with the mean differences of the duplicate readings with the ± 2 SD limit of the mean difference, and the absolute difference range for each tube and Modular method.

<table>
<thead>
<tr>
<th>Tube type</th>
<th>No. (%) of duplicate errors</th>
<th>Mean difference (2 SD), U/L</th>
<th>Absolute difference range, U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modular D IFCC method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greiner lithium heparin</td>
<td>15 (29)</td>
<td>−2.7 (23.0)</td>
<td>−11 to 33</td>
</tr>
<tr>
<td>Greiner serum</td>
<td>2 (4)</td>
<td>−0.7 (7.4)</td>
<td>−14 to 6</td>
</tr>
<tr>
<td>BD lithium heparin</td>
<td>16 (32)</td>
<td>−3.9 (31.4)</td>
<td>−95 to 20</td>
</tr>
<tr>
<td>Modular P IFCC method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greiner lithium heparin</td>
<td>8 (16)</td>
<td>−2.0 (21.8)</td>
<td>−24 to 60</td>
</tr>
<tr>
<td>Greiner serum</td>
<td>7 (14)</td>
<td>−0.8 (8.7)</td>
<td>−17 to 9</td>
</tr>
<tr>
<td>BD lithium heparin</td>
<td>10 (20)</td>
<td>−1 (26.1)</td>
<td>−38 to 66</td>
</tr>
<tr>
<td>Modular P modified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greiner lithium heparin</td>
<td>4 (8)</td>
<td>0.3 (19.7)</td>
<td>−13 to 64</td>
</tr>
<tr>
<td>Greiner serum</td>
<td>1 (2)</td>
<td>0 (4.8)</td>
<td>−4 to 9</td>
</tr>
<tr>
<td>BD lithium heparin</td>
<td>5 (10)</td>
<td>−1.3 (9.5)</td>
<td>−11 to 21</td>
</tr>
</tbody>
</table>