Peaks and troughs of the individual rhythms varied widely over the 24-h period with no evidence of synchronization among individuals or a clear relationship with the light–dark cycle [mean (SD) copeptin concentration, 4.3 (1.5) pmol/L; 11.4 (3.6) pulses/24-h period; mean pulse height, 5.1 (1.8) pmol/L] (Fig. 1). Interestingly, the expected large increase in cortisol during the second half of the night in these individuals [see (4)] is not related to copeptin. Because AVP is known to acutely stimulate cortisol via corticotropin release in stress situations, our present findings argue against both a role of AVP in the circadian release of cortisol and an important physiological role of AVP in the generation of cortisol pulses under nonstress conditions.

The highest copeptin concentration measured was 13.1 pmol/L; the mean maximum concentration for all individuals was 7.8 (2.9) pmol/L. Therefore, the variation in circadian copeptin concentration in healthy individuals remained well within the described reference interval (1). The timing of blood sampling did not appear as critical as for the interpretation of cortisol results. Our data will help to better define reference values for the use of copeptin measurements in predicting stress conditions. Reference values may be particularly important when a low copeptin concentration is used as a very early negative predictor in stress situations such as myocardial infarction (3), in which the physiological variation in copeptin has little influence on the interpretation of the results.

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Evaluation of the Quo-Test Hemoglobin A₁c Point-of-Care Instrument: Second Chance

To the Editor:

We previously reported the evaluation of 8 different hemoglobin A₁c (Hb A₁c)1 point-of-care instruments (1). Two of 8 manufacturers withdrew from that study after initial unpromising results. One of the 2 instruments withdrawn was the Quo-Test A1c (Quotient Diagnostics), which was withdrawn because of a technical problem. The manufacturer claimed to have resolved the problem and asked us to reevaluate the instrument.

The Quo-Test method is based on affinity separation and the use of fluorescence quenching and gives results in 3 min. The instrument was certified by the National Glycohemoglobin Standardization Program (NGSP) as of September 2009 (2).

We used the same approach for evaluation as in the initial study, following the CLSI EP-5 protocol for imprecision and the CLSI EP-9 protocol for method comparison. Because the American Diabetes Association has recommended Hb A₁c as the preferred test for the diagnosis of diabetes (3), we added an additional sample of approximately 6.5% Hb A₁c in the EP-5 protocol. The EP-9 protocol was performed twice with 2 different lot numbers and compared
with 3 IFCC and NGSP secondary reference measurement procedures (SRM): the Roche Tina-quant Hemoglobin A1c Gen.2 on Cobas Integra 800, immunoassay, IFCC and NGSP SRM (Roche Diagnostics); the Primus Ultra², affinity chromatography HPLC, IFCC, and NGSP SRM (Primus Diagnostics, a Trinity Biotech Company); and the Tosoh G8, cation-exchange HPLC, IFCC SRM (Tosoh Bioscience N.V./S.A.).

To check overall calibration and bias, we compared the EP-9 protocol results to the mean of the 3 SRM results. The total CV should be ≤3% (realistic goal) and for optimal clinical use ≤2% (desirable goal) (1). The total CVs in the EP-5 protocol for the Quo-Test at Hb A₁c values of 5.0%, 6.2%, and 10.2% were 5.9%, 4.5%, and 2.9%, respectively.

Comparisons between the Quo-Test with 2 reagent lot numbers and the mean of the 3 SRM are shown in Fig. 1 with the individual EP-9 results and the NGSP certification calculations. The 95% CI of the differences between the SRM and test methods should fall within ±0.75% Hb A₁c (total error) to pass the current NGSP criteria (4). The Quo-Test NGSP certification was granted in September 2009 (2) before the tightening of the NGSP criteria from ±0.85% Hb A₁c to ±0.75% Hb A₁c. To evaluate this method in the same way as the other methods in our previous study (1), we used the old criteria. The calibration of the first lot number appeared adequate, but with the EP-5 protocol we observed high variability reflected by a high total CV, and a high SE of estimates was still a matter of concern. The discrepancy with the second lot number may have been attributable to problems associated with upscaling of the production of cartridges.

Fig. 1. Hb A₁c results for 2 different lot numbers from the Quo-Test point-of-care instrument compared to the mean Hb A₁c results from 3 SRM procedures (individual EP-9 regression lines and NGSP certification criteria are shown below the graph).

The P value of the regression lines between the 2 lot numbers was <0.001, which confirmed the statistically significant difference between the 2 regression lines.

<table>
<thead>
<tr>
<th>Linear regression lines</th>
<th>Lot number 1</th>
<th>Bias SD of difference Total error</th>
<th>NGSP criteria</th>
<th>Lot number 2</th>
<th>Bias SD of difference Total error</th>
<th>NGSP criteria</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quo-Test (y) vs Ultra² (x)</td>
<td>y = 1.02x + 0.02</td>
<td>0.192</td>
<td>0.443</td>
<td>1.06</td>
<td>Fail</td>
<td>y = 0.92x - 0.04</td>
<td>-0.600</td>
</tr>
<tr>
<td>vs Tina-quant (x)</td>
<td>y = 1.06x - 0.31</td>
<td>0.330</td>
<td>0.437</td>
<td>1.19</td>
<td>Fail</td>
<td>y = 0.96x - 0.15</td>
<td>-0.506</td>
</tr>
<tr>
<td>vs Tosoh G8 (x)</td>
<td>y = 1.04x - 0.22</td>
<td>0.104</td>
<td>0.375</td>
<td>0.84</td>
<td>Pass</td>
<td>y = 0.91x - 0.02</td>
<td>-0.725</td>
</tr>
</tbody>
</table>

\[ \text{Shaded row has the same measurement principle} \]
Tests performed by using Chowstatistics for the overall differences in slope and intercept per method for lot numbers 1 and 2 showed significant differences in analytical performance between the 2 lot numbers \(P < 0.001\).

The manufacturer provided 2 controls with wide ranges: low control 4.2% to 7.5% and high control 10.5% to 15.3%. The manufacturer should narrow these ranges as was described recently (1).

Results of analysis of the analytical performance of the QuoTest showed a high total CV, large bias with 1 lot number, failed NGSP criteria, and significant differences between lot numbers. The QuoTest is officially NGSP certified and passed the NGSP criteria with only 1 lot number as tested at the manufacturer’s site (2). The results we report here demonstrate the large lot-to-lot variability in quality of the QuoTest Hb A1c point-of-care test.

Health care professionals should be aware of the clinical implications for an Hb A1c value that is determined by using a point-of-care instrument (5). Moreover, to properly interpret the result, health care professionals must know the analytical performance of the Hb A1c method used. This study and the previous study (1) prove that an NGSP certification does not guarantee the quality of results produced in the field and confirms the recommendation of the American Diabetes Association not to use Hb A1c point-of-care assays for diagnostic purposes at this time (3). Validation of a new method is always necessary and cannot be expected to be carried out by health care professionals. For this reason we think that point-of-care devices should be guided by and fall under the responsibility of a central laboratory.

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Could Susceptibility to Low Hematocrit Interference Have Compromised the Results of the NICE-SUGAR Trial?

To the Editor:

The recently published findings of the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR)\(^1\) trial have dramatically changed clinician attitudes toward the achievement of euglycemia in intensive care unit (ICU) patients (1). In defending the proof-of-concept studies that validated the efficacy of normalizing blood glucose in the ICU, Van den Berghe et al. pointed out numerous variances between their original studies and those of the NICE-SUGAR trial (2). They included differences in blood glucose targets, insulin administration, blood sampling, nutritional strategies, clinician expertise, and the relative accuracy of the glucose measurement devices. Recently, Clinical Chemistry presented a very interesting Q&A on the use of blood glucose meters to achieve tight glucose control in patients in the ICU (3). Because one of our ICUs participated in the NICE-SUGAR trial, we report here some interesting and relevant data that shed more light on the NICE-SUGAR trial, data that yield more questions than answers.

In our 30-bed general systems ICU at the University of Alberta Hospital, point-of-care glucose concentrations can be measured in 2 different ways: respiratory therapists measure arterial blood gases, hemoglobin, electrolytes, and glucose values with the Radiometer 800 blood gas system (BGA) and nurses measure arterial blood and capillary

\(^1\) Nonstandard abbreviations: NICE-SUGAR, Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation; ICU, intensive care unit; BGA, blood gas system; BGM, blood glucose meter.