increase proANP secretion in mice *(1)*. Both our groups exhibited a 2- to 3-fold increase in postprandial GLP-1 concentrations, but no differences in GLP-1 secretion were demonstrated *(4)*. Importantly, other important gut hormones as well as glucose, glucagon, and insulin varied considerably depending on meal type and thus are not likely to explain either the rise or the fall in postprandial proANP concentrations *(4)*. However, a recent study showed that glucose decreases expression of the gene that encodes ANP [*NPPA* (natriuretic peptide type A; also known as *ANP*)] via a miRNA *(5)*.

In conclusion, we report that plasma proANP concentrations are initially increased and subsequently suppressed following a wide variety of standardized liquid meals in patients with T2D and healthy controls. Given the different meal types, it seems unlikely that a single dietary component mediates this secretory pattern. Our findings thus provide further evidence in support of the presence of a gut–ANP axis in humans, which may be a combined effect of gut endocrinology as well as the resulting glucose concentrations. For now, we recapitulate that fasting conditions before proANP measurement seem necessary, in particular when plasma proANP is used as a biomarker in patients with metabolic dysfunction.

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References

1. Kim M, Platt MJ, Shibasaki T, Quaggin SE, Backx PH, Seino S, et al. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. Nat Med 2013;19:567–75.
2. Zois NE, Bartels ED, Hunter I, Kousholt BS, Olsen LH, Goetze JP. Natriuretic peptides in cardiometabolic regulation and disease. Nat Rev Cardiol 2014;11:403–12.
3. Goetze JP. Plasma proANP decreases after meal intake. Clin Chem 2013;59:1270–1.
4. Sonne DP, Rehfeld JF, Holst JJ, Vilsbøll T, Knop FK. Postprandial gallbladder emptying in patients with type 2 diabetes: potential implications for bile-induced secretion of glucagon-like peptide 1. Eur J Endocrinol 2014;171:407–19.
5. Arora P, Wu C, Hamid T, Arora G, Agha O, Allen K, et al. Acute metabolic influences on the natriuretic peptide system in humans. J Am Coll Cardiol 2016;67:804–12.

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Moving Average for Continuous Quality Control: Time to Move to Implementation in Daily Practice?

To the Editor:

Recently, Ng et al. described a new method for optimization of moving average (MA)[1] QC procedures *(1)*. The accompanying editorial mentioned that, during the last 50 years, slow but continuous improvements have been made in the understanding and methodology of MA in the move toward continuous analytical quality assurance *(2)*. Although these improvements are being made, general implementation of MA for continuous QC on clinical laboratories has failed and many laboratories are struggling with the implementation and application of MA QC. In this letter, we address several steps that we consider to be important to support a more general implementation of MA as a continuous QC instrument in medical laboratories.

Most improvements that really affected the use of MA in clinical laboratories originate from the 1970s and 1980s. For example, the algorithms described by Bull et al. in 1974 are still the basis of the application of MA today in most, if not all, hematology analyzers *(3)*. Interestingly, Bull et al. stated that, because their findings were based on visual inspection of MA patterns, future MA research should focus on developing objective measures of MA performance *(3)*. Recently, 2 methods have been described that allow more objective and realistic insight into MA performance. Ng et al. *(1)* described an MA optimization method that used the average number of patient samples affected until error detection (ANP_{ed}), and we reported

[1] Nonstandard abbreviations: MA, moving average; LIS, laboratory information system.

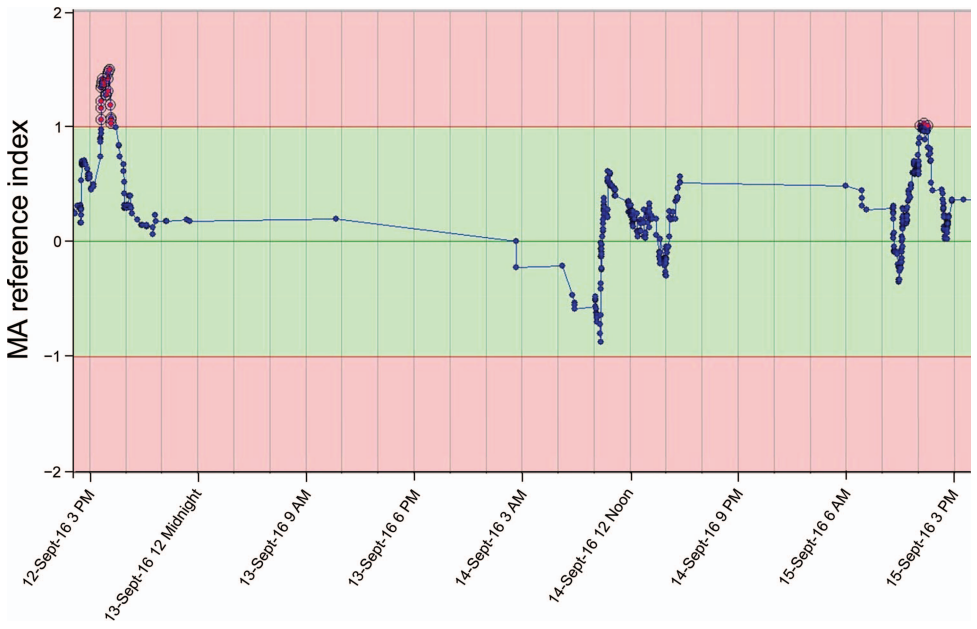

Fig. 1. Detection of temporary sodium ion-selective electrode (ISE) failure by MA.

MA is plotted in an accuracy plot. The green area represents the reference range of the MA and is bounded by the upper 1 and lower −1 MA control limits [van Rossum and Kemperman *(5)*]. One *y*-axis unit represents half of the MA reference range and is referred to as the dimensionless quantity MA reference index. Blue dots represent generated MA values and red dots with blue circles represent MA values outside the control limits. GLIMS (MIPS) LIS software is used for MA management and graphical presentation. MA sodium alarm case: the first MA sodium alarm (September 12, 2016) was followed up according to our standard procedure. The alarm was due to a sodium ISE failure that seemed to be resolved without intervention; internal QC results were within limits and reproducibility (n = 20) of 1 sample revealed no outliers, and the CV was appropriate. Reanalyzing the patient samples (as part of the MA alarm workup) resulted in 30 sodium results that were considered to have a clinically significant error. Subsequently, these results were corrected and the physicians were informed. Despite extensive troubleshooting, the cause of the ISE failure was not identified and the MA alarm was thought to have resulted from temporary contamination of a mixing cup, or sample probe. Two days after the first alarm, a second sodium MA alarm occurred. The manufacturer was contacted again and (after about 4 h of troubleshooting) it was established that a valve in the ISE unit did not always close properly. Assay failure was not detected by routine internal QC because of the temporary nature of the assay failure.

the use of bias detection curves and MA validation charts for the selection of optimal MA settings *(4)*. Both methods meet the requirement of a low "manageable" number of false MA alarms. In our opinion, this is an essential MA requirement for the introduction of MA as a continuous QC instrument in daily practice.

Optimized MA procedures allow continuous analytical QC with fast detection of systematic errors and detection of temporary assay failures *(5)*. Fig. 1 presents an MA alarm case that illustrates a clinically relevant temporary assay failure detected by MA, which was not detected by regular scheduled internal QC measurements due to the temporary nature of the assay failure. This case illustrates the added value of continuous analytical QC by MA. However, implementation of MA as a continuous analytical QC instrument in clinical laboratories is hampered by the complexity of obtaining optimal MA procedures for each specific laboratory. A major obstacle is that no commercial tools are available to generate optimal MA settings. By applying new MA optimization methods, both Ng et al. and our group were able to implement MA for continuous analytical QC in daily practice *(1, 5)*. Therefore, it is time to make these new MA optimization methods available to clinical laboratories, in an understandable and easy-to-use format.

After obtaining optimal MA procedures, the next step is to implement these in the clinical laboratory. Most laboratories have an option to use either analyzer software, middleware, laboratory information system (LIS), or other dedicated software to perform MA. We recently performed an MA trial using our LIS for MA management, and experienced some MA management issues that are not unique to the LIS software used *(5)*. One reason we chose our LIS for MA management was that our LIS allowed MA calculation after each new assay result and MA calculation frequency did not need to depend on the MA calculation algorithm. Using our optimized MA

settings for sodium we always were able to detect a ≥6% bias within 10 patient results. Waiting for more than 10 patient results would result in an unnecessary MA alarm delay *(4, 5)*. Furthermore, before starting the MA trial some additional features were incorporated in the LIS to allow practical management of MA and MA alarms. These included the option to exclude specific patients or samples from the MA calculation (e.g., nonpatient materials and specific patients with confirmed extreme results) and graphical presentation of MA values in an accuracy graph as presented in Fig. 1*(5)*. Also, if MA protocols are properly designed, they should yield a low number of false MA alarms and as such all MA alarms must be investigated promptly. We identified some practical consequences during our MA trial: MA alarms should be generated real time and immediately detected by laboratory staff; a protocol should be available that clearly describes how to determine the relevance of the MA alarm (also during evening, night, and weekend shifts); after an MA alarm workup, an MA reset is helpful to prevent subsequent false MA alarms *(5)*.

The MA management issues encountered during our trial and the additional software features we needed to incorporate in the LIS for MA management purposes emphasize the need for improvements in the available MA management software. Addressing these issues is the necessary final step to allow a more general implementation of continuous QC by MA in clinical laboratories.

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References

1. Ng D, Polito FA, Cervinski MA. Optimization of a moving averages program using a simulated annealing algorithm: the goal is to monitor the process not the patients. Clin Chem 2016;62:1361–71.
2. Bennett ST. Continuous improvement in continuous quality control. Clin Chem 2016;62:1299–301.
3. Bull BS, Elashoff RM, Heilbron DC, Couperus J. A study on various estimators of the derivation of quality control procedures from patient erythrocyte indices. Am J Clin Pathol 1974;61:473–81.
4. van Rossum HH, Kemperman H. Optimization and validation of moving average quality control procedures using bias detection curves and moving average validation charts. Clin Chem Lab Med 2017;55:218–24.
5. van Rossum HH, Kemperman H. Implementation and application of moving average as continuous analytical quality control instrument demonstrated for 24 routine chemistry assays. Clin Chem Lab Med [Epub ahead of print 2017 Jan 11].

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Total Analytic Error for Low Cardiac Troponin Concentrations (≤10 ng/L) by Use of a High-Sensitivity Cardiac Troponin Assay

To the Editor:

There are considerable data suggesting that low cardiac troponin (cTn)[1] concentrations measurable only by high-sensitivity cTn (hs-cTn) assays can be used for medical decision-making *(1)*. However, there are limited data on the long-term analytical performance of hs-cTn related to the bias and imprecision associated with cTn concentrations ≤10 ng/L, which are not measurable with contemporary assays *(2)*. For quality assurance purposes having a total analytic error (TAE) criterion at low concentrations would help identify problematic hs-cTn reagent/calibrator lots and suboptimal analyzer performance. This is a practical concern, as previous negative biases with the Roche hs-cTnT assay were identified and ultimately corrected by the manufacturer, but only after multiple different reagent lots were used clinically *(3)*. Lot-to-lot or batch-to-batch evaluations for reagents and calibrators to identify minor shifts in hs-cTn results can be difficult, time-consuming, and expensive. The goal of this analysis was to establish a realistic TAE for cTnI concentrations ≤10 ng/L measured by the Abbott assay by assessing concentration biases between different lots of reagents/calibrators and imprecision at low cTn concentrations.

Our approach to evaluating new hs-cTn lots involved comparing approximately 10 samples (fresh, not frozen) with cTn concentrations that spanned the measuring range

[1] Nonstandard abbreviations: cTn, cardiac troponin; hs-cTn, high-sensitivity cTn; TAE, total analytic error.