Postprandial Plasma Concentrations of ProANP in Patients with Type 2 Diabetes and Healthy Controls

To the Editor:

Atrial natriuretic peptide (ANP)[1] plays an important role in blood pressure and intravascular water homeostasis. Together with its biosynthetic precursor proANP, ANP is released from cardiomyocytes in response to dietary sodium and volume overload with concomitant cardiac strain. Recently, ANP secretion was also shown to be stimulated by the incretin hormone glucagon-like peptide-1 (GLP-1) in mice *(1)*. In line with this observation, obesity and diabetes (both types) are associated with lower ANP and proANP concentrations in circulation compared to concentrations in individuals with normal weight. This may suggest that the cardiac natriuretic peptides are involved in metabolic regulation *(2)*. In a recent letter published in this journal, we reported that proANP concentrations in healthy individuals decrease 2 h after meal intake *(3)*. To further elucidate this observation, we examined the plasma proANP response to oral glucose and 3 isocaloric and isovolemic liquid meals in patients with type 2 diabetes (T2D) and matched controls.

Detailed descriptions of the experimental procedures and the study participants have been reported previously *(4)*. In brief, proANP concentrations were measured in plasma from 15 patients with T2D [mean duration of diabetes 7.5 years (range 6–20 years); mean age 59.4 years (SD 9.6 years); body mass index (BMI) 28.0 kg/m^2 (SD 2.2 kg/m^2); hemoglobin A_{1c} 7.5% (SD 1.4%)] and 15 healthy age-, sex-, and BMI-matched controls [mean age 59.7 years (SD 10.0 years); BMI 27.9 kg/m^2 (SD 2.0 kg/m^2); hemoglobin A_{1c} 5.2% (SD 0.2%)] undergoing 4 separate 4-h meal tests: a 75-g oral glucose tolerance test (OGTT) and 3 isocaloric (500 kcal) and isovolemic (350 mL) liquid meals. Plasma proANP concentrations were measured by an automated midregion-directed proANP immunoassay (Thermo-Fisher). Intraassay and interassay CVs were <2.5% and ≤6.5%, respectively. The functional assay sensitivity (at an interassay precision of 20% CV) has been assessed as being 10 pmol/L.

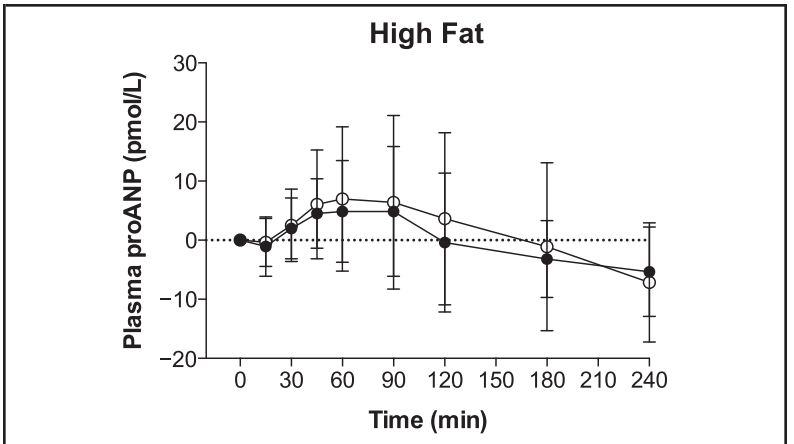

Fig. 1. Baseline-subtracted plasma proANP concentrations following high-fat liquid meal (40 g fat, 32 g carbohydrate and 3 g protein) in healthy controls (n = 15, closed symbols) and patients with T2D (n = 15, open symbols).
Mean (SD) values are shown.

Baseline-subtracted proANP concentrations (high-fat meal) are shown in Fig. 1. Mean fasting proANP concentrations were comparable between controls and T2D patients [63 pmol/L (95% CI 54–7 pmol/L) vs 68 pmol/L (95% CI 45–91 pmol/L), P = 0.7]. However, 2 T2D patients had concentrations near 100 and 200 pmol/L, respectively. In both groups, all meal stimuli resulted in small increases in mean proANP concentrations with the largest changes (peak vs baseline) observed following the OGTT [controls: 6.9 pmol/L (95% CI 0.6–13.2 pmol/L; P = 0.03; T2D 7.8 pmol/L (95% CI −0.03 to 10.1 pmol/L), P = 0.05] and the high-fat meal [4.9 pmol/L (95% CI −0.1 to 9.8 pmol/L), P = 0.05 and 6.9 pmol/L (95% CI 0.2–13.5 pmol/L), P = 0.04]. ANCOVA analyses of these differences revealed no difference between controls and T2D patients [OGTT: 0.9 pmol/L (95% CI −10.6 to 12.4); high fat meal: 2.2 pmol/L (95% CI −7.1 to 11.6)]. After 150–180 min, mean plasma proANP concentrations decreased below baseline concentrations in nearly all participants.

The present results extend our previous observations in healthy individuals, where proANP concentrations decrease late after meal intake. Altered secretory patterns in patients with T2D could not be demonstrated, suggesting that proANP concentrations are largely unaffected by glucose homeostasis. Interestingly, proANP concentrations increased from approximately 30 min following all meal stimuli, suggesting that factors from the gut rapidly modify proANP secretion (gut–ANP axis). A possible hormonal candidate is GLP-1, which has been shown to

[1] Nonstandard abbreviations: ANP, atrial natriuretic peptide; proANP, ANP biosynthetic precursor; GLP-1, glucagon-like peptide 1; T2D, type 2 diabetes; BMI, body mass index; OGTT, oral glucose tolerance test.

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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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.