CNG-NGM-004

Clinical Trial Report

Clinical Assessment of Potential Drug and Substance Interference on the Performance of the CNOGA TensorTip COMBO GLUCOMETER (CoG)

PROTOCOL NO.: CNG-NGM-004

prepared by

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This final study report was prepared and approved by the principal study investigator Prof. Andreas Pfützner, MD, PhD. With the signatures below, it is confirmed that the report correctly displays the results of the study performed in accordance with protocol CNG-NGM-004.

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1. Introduction

1.1. General

Frequent blood glucose readings are the most cumbersome aspect of diabetes treatment for many patients [1, 2]. Therefore, devices are under development, which assess glucose by means of non-invasive (NI) technologies. TensorTip CoG (CoG, CNOGA Medical Ltd, Caesarea, Israel) employs optical measurements from reflection and transmission of visible and near-infrared light at the tip of any finger. The light is absorbed by a color image sensor in which a change in the tissue pattern tint is identified by a dedicated mathematical algorithm as a change in a tissue glucose or other physiological body tissue signals. The mathematical algorithm is derived from chaos theory in order to deal with the disorder of the raw data collected by the color image sensor. In preparation of regular operations, the device needs a comprehensive calibration procedure with frequent comparator measurements between the NI readings and an incorporated regular invasive glucose-oxidase-based blood glucose meter module. In a previous clinical trial, the CoG device was shown to accurately track glucose changes in standardized meal experiment in healthy subjects and in people with type 1 and type 2 diabetes after a calibration period of one week [3].

The purpose of this clinical study was to investigate the impact of several drugs (acetylsalicylic acid, acetaminophen etc.), nutritional supplements (vitamin C, xylose, mannose etc.) and nutritional components (caffeine & alcohol) on the non-invasive and the invasive device results, when operated according to the instructions for use and in comparison to a capillary blood reference method (YSI 2300 STAT Plus) and a venous reference method (COBAS).

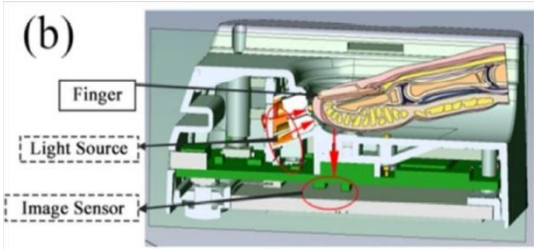
1.2. Device Technology -Principle of Operation

The TensorTip CoG consists of medical and control subsystems. The medical subsystem contains a color image sensor, LEDs and a Digital Signal Processor (DSP) which is responsible for the image acquisition, the image processing, the lighting control system and the extraction of the clinical parameters values. The control subsystem contains four touch-buttons, a display, an audio-speaker and a Microcontroller Unit which is in charge of the user interface, the process management, the internal storage and the device's power management. As shown in Figure 1 (b) the TensorTip CoG consists of a finger compartment, four monochromatic light sources in the visual to IR spectrum (~600 nm to ~1000 nm), a color image sensor and an invasive module glucometer. The invasive module is identical to the approved Okmeter match device K090609 (OK Biotech Co., Ltd., Hsinchu City, Taiwan).

Figure 1.: TensorTip representative picture

(a)

(b)



The invasive module is used for calibration of the non-invasive component. As described in a review manuscript, [4], the technology of the TensorTip CoG is based on a real time color image sensor which provides the ability to analyze tissue pigmentation over spatial-temporal-color domain. Color image sensor provides richer information compared to other known devices, such as a standard pulse oximetry. The TensorTip device uses four monochromatic light source and color image sensor absorbing continuous wavelength light usually in the range from blue to IR. The color image raw data is acquired by the color image sensor and stored in a memory buffer to be used for the computation of a dedicated algorithm executed in the device DSP component.

1.3. Device Intended Use

- TensorTip CoG is a personally calibrated device intended for the single user for whom the device has been calibrated.

- The system is intended for the purpose of enhancing frequent assessment of blood glucose as described in the indications for use.
- TensorTip CoG's invasive module is a blood glucose monitoring system intended for use outside the body (in vitro diagnostic only). It should be used for quantitative measurement of glucose in capillary whole blood from the finger only by people with diabetes as an aid in monitoring the effectiveness of a diabetes control program and for the calibration of the non-invasive module.
- The device is to be used only by adults aged 18 years and older.
- In the US, TensorTip CoG device has to be prescribed by a physician.
- Medication intake/ treatment decisions should not be based on the non-invasive measurements obtained with the CoG.
- The CoG is not intended to be used for diagnosis.

2. Study Objectives

The purpose of this clinical study was to investigate the potential impact of ingestion of several drugs and nutrition components on TensorTip CoG device performance.

2.1. Primary Endpoint

- The purpose of this clinical study was to investigate the impact of several drugs (acetylsalicylic acid, acetaminophen etc.), nutritional supplements (vitamin C, xylose, mannose etc.) and nutritional components (caffeine & alcohol) on the non-invasive CoG module performance, when operated according to its instructions for use.

2.2. Secondary Endpoints

- Investigate impact of different drugs and/or nutritional supplements on the invasive CoG module in comparison to the YSI reference method
- Investigate impact of different drugs and/or nutritional supplements on the performance of the YSI device in comparison to a standard laboratory method.

3. Study Measures

3.1. Performance measures

- To evaluate potential interference on the non-invasive CoG performance, the experiment is optimally carried out at stable blood glucose levels and with oral uptake of the investigated substance. Under otherwise stable metabolic conditions, it can be assumed that changes in non-invasive glucose results are only induced by the ingested substance and are most pronounced at the time of maximal plasma concentration
- The impact of potentially interfering substances on the non-invasive and invasive CoG modules was evaluated by calculating the mean bias of the results from the capillary standard reference method (YSI) before oral substance uptake and when reaching the maximal plasma concentration of the applied oral substance (C_{max}), degradation down to 50% of C_{max} ($C_{-halfmax}$), and additional three time points in order to capture the pharmacokinetic curve of the respective interferent.
- The impact of potentially interfering substances on the YSI reference method was evaluated by comparing the mean bias from the venous standard laboratory method (COBAS) before oral substance uptake and at the time-points when reaching maximal plasma concentration of the applied oral substance (C_{max}), after degradation down to 50 % of C_{max} ($C_{-halfmax}$), and additional three time points in order to capture the pharmacokinetic curve of the relevant interferent.

4. Study Design

4.1. Overview of Study Design

This study was performed as an open label, prospective, monocentric study

4.2. Regulatory Approvals and Study Conduct

The study was approved by the local Institutional Review Board/Ethics Committee for Human Research of the State of Rheinland-Pfalz on June 12th, 2018 and by the National German Medical Agency (BfARM, Bundesinstitut für Arzneimittel und Medizinprodukte) on June 6th, 2018. It was conducted in accordance with all applicable local regulations and standards. The study was conducted from October 2018 to February 2019. First patient visit was on November 2nd, 2018. The last patient visit was on February 25th, 2019.

During the clinical study, the CNOGA devices readings did not influence the participants in any way. The reference measurements were done with either capillary or venous blood using standard invasive measurement devices and by health care professionals. The potential interfering substances were ingested at doses or quantities, which are approved as medium to high doses (drugs) or are recommended for daily supplement (nutrition supplements). Alimentary substances (alcohol, 3-Omega fatty acids etc.) were applied in quantities far below established acute toxicity levels. Therefore, the study presented no major risk to the participants.

4.3. Subjects Selection

All 10 participants were healthy men and women. In summary, subjects had to be able to complete and understand informed consent and had to be 18 years old or above. They were not allowed to be treated with chronic medication and their safety biochemistry and blood count had to be with exclusively values in normal range. For detailed selection criteria please refer to the protocol. Each subject participated in ten experiments with the 10 interfering substances tested.

4.4. Interferent Selection

The interferent substances were chosen, based on the company risk analysis process using the following considerations: The TensorTip CoG device is measuring glucose in the fingertip tissue. Finger tissue glucose is combined from the glucose concentrations in arterioles, venules, capillaries, interstitial fluid, and intracellular glucose information. It is expected that general conditions with potential impact on the local anatomical and physiological conditions of the finger tissue will be considered by the software in the calibration process. However, uptake of substances, which may influence the local tissue compartment composition in an acute and quantitative manner, e.g. exerting a vasoconstrictive or vasodilatative action on the microcirculation in the finger, might potentially interfere with the non-invasive device readings.

Another criterion for substance selection was a reasonably high probability that patients would ingest such a substance during normal life.

Therefore, a mix of popular nutrients and nutrition supplies (caffeine, vitamin C, 3-Omega fatty acids, alcohol) and frequently used over the counter drugs (acetyl salicylic acid, acetaminophen, ibuprofen, diclofenac) with known potential impact on microcirculation were chosen. In addition, we selected mannose and xylose, as carbohydrates with similar chemical and spectral properties with glucose to check for potential interference of such molecules.

This study tested possible exogenous interfering factors. Additional factors, defined in the device risk assessment, were tested and discussed in the CNG-NGM-003 study.

4.4.1. Acetaminophen

Acetaminophen (paracetamol), also commonly known as *Tylenol*, is the most common analgesic worldwide and is recommended as first-line therapy in pain conditions by the World Health Organization (WHO) [5]. It is also used for its antipyretic effects, helping to reduce fever. This drug was initially approved by the U.S. FDA in 1951 and is available in a variety of forms including syrup form, regular tablets, effervescent tablets, injection, suppository, and other forms. It is therefore to be expected that patients using the TensorTip CoG will do so while taking acetaminophen. In addition, it has been found to have a potential impact on skin blood flow and blood pressure in particular in febrile patients [6]. The selected dose of 1000 mg reflects the upper dose range used by patients for self-medication.

4.4.2. Ascorbic Acid

Ascorbic acid (vitamin C) is an essential micronutrient that is acquired primarily through the consumption of fruit, vegetables, supplements, fortified beverages, and fortified breakfast or "ready-to-eat" cereals [7]). Vitamin C is a powerful aqueous-phase antioxidant that reduces oxidative stress [8] and enhances endothelial function and lowers blood pressure through effects on nitric oxide production [9-11]. Nowadays, this substance is also applied topically. Intake recommendations for vitamin C and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine (IOM) of the National Academies (formerly National Academy of Sciences). The upper daily recommended dose for adults is 2000 mg for males and females [12]. Since some subjects are known to take a spoonful of ascorbic acid every morning with their tea, we have chosen a single dose of 5000 mg for the interference experiment.

4.4.3. Diclofenac

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) with antipyretic and analgesic actions. It is used to treat mild to moderate pain, or signs and symptoms of osteoarthritis or rheumatoid arthritis. It is also indicated for the treatment of ankylosing spondylitis. The Cataflam brand of this drug is also used to treat menstrual cramps. It has been shown that diclofenac can impact local skin composition by increasing histamine response to inflammation [13] resulting in an increased microcirculation, but also an increase in the lymphatic cell count after drug intake [14]. Oral uptake of diclofenac may therefore have a potential impact on the tissue composition and may potentially influence the signal measured by the CoG device.

4.4.4. Ibuprofen

Ibuprofen is a very popular non-steroidal anti-inflammatory drug, which has moderate but definite anti-inflammatory, analgesic and antipyretic properties, with considerably less gastrointestinal adverse effect than other drugs in the same family. It inhibits cyclooxygenase activity and subsequently the production of prostaglandins. Ibuprofen is a very frequently prescribed drug for joint pain and also available as over-the-counter drug without medical prescription. It has been reported that nitric oxide is involved in the analgesic effects of the

drug, and that it influences microvascular dynamics. One of the most commonly known side effects is skin rash [15, 16]. It was therefore selected as a potentially interfering substance to be tested in this study.

4.4.5. Ethyl alcohol

The regular consumption of alcohol plays an important social role in many cultures. Most countries have laws regulating the production, sale, and consumption of alcoholic beverages. Regular use and abuse of alcohol are common practice in all Western societies, by all ages, genders and ethnicities. During in vitro animal studies, low doses of alcohol have been demonstrated to increase release of nitric oxide and augment endothelium-mediated vasodilatation, whereas higher doses impair endothelium-dependent relaxation responses. [17]. Low concentrations of alcohol induce increased release of NO from the endothelium due to activation and expression of NO synthase (NOS). In contrast, administration of high concentrations of alcohol or its chronic ingestion impairs endothelial functions in association with reduced NO bioavailability [18]. Because of the acute impact of alcohol on nutritional blood flow, it was assumed that there may be a potential impact on the CoG signal and a regular oral shot of gin (0.2 g/kg body weight) was selected for this experiment.

4.4.6. Caffeine

The most well-known source of caffeine is the coffee bean, the seed of *Coffea* plants. Beverages containing caffeine are ingested to relieve or prevent drowsiness and to improve performance. Caffeine-containing drinks, such as coffee, tea, and cola, are very popular. As of 2014, 85% of American adults consumed some form of caffeine daily at an average dose of 164 mg [19]. Most studies found that regular coffee intake increases blood pressure slightly and raises plasma cholesterol and homocysteine levels [20], whereas coffee consumption is associated with a reduced incidence of type 2 diabetes mellitus [21], a decrease in inflammatory markers [22] and improved endothelial function [23]. After drinking a single cup of coffee, endothelium-dependent vasodilatation in the skin is acutely enhanced and blood flow in the fingertip is substantially reduced [24]. Intake of caffeine through drinking caffeinated coffee acutely augments microvascular reactivity [25]. It was therefore decided to include caffeine at a dose of 150 mg (2 cups of strong coffee) into this study protocol.

4.4.7. Acetyl Salicylic Acid

Acetylsalicylic acid (ASA) is an over-the-counter drug used for pain relief and fever suppression. Low dose ASA is also used long-term to help prevent further heart attacks, strokes, and blood clots in people at high risk [26]. As a nonselective cyclooxygenase-inhibitor, ASA has systemic effects that may influence hypothalamic-mediated temperature regulation and may reduce axon-reflex current-induced vasodilation in humans [27, 28]. Like the other non-steroid-anti-inflammatory drugs, ASA was selected for this study because of the widespread use and because of the acute drug-induced changes in the tissue of the fingertip, which may have an influence on the non-invasive TensorTip CoG signal.

4.4.8. Xylose

The pentose carbohydrate xylose is the main component for the hemicellulose xylan, which comprises about 9 % - 30% of plants. Xylose is found in the seeds and embryos of most edible plants (e.g. Guava, Pears, Blackberries, Raspberries, Echinacea, Boswellia, Broccoli, Spinach, Eggplant, Peas, Green Beans, and Corn). The most interesting property of xylose for the current food industry is its caloric value: xylose metabolically contains 0 calories per gram, which as investigated almost 80 years ago [29]. The sweetness of xylose is about 70% of cane sugars. D-Xylose is accepted by FDA as a safe food ingredient (GRAS). In the EU, xylose's status is also food ingredient. In functional foods, xylose provides a multi-functional solution. It is a food application, feed application, sweetener, flavor agent, browning agent and is 100% natural, while containing 0 calories. D-Xylose is used in food industries, in the production of savory flavors, as it is highly effective at inducing Maillard reactions, which helps to produce golden brown color in food applications such as batters and breadcrumbs [30, 31]. Because of its negligible caloric content, xylose is frequently used in functional food designed for people with diabetes. It has been shown that xylose is an interfering substance for blood glucose meters employing a glucose-dehydrogenase based test-strip technology [32]. In summary, xylose is increasingly used for diabetic dietary products and uptake is very likely to happen by the intended users of the CoG device.

4.4.9. Mannose

As a natural bioactive monosaccharide, d-mannose is - like xylose - a popular nutritional and health-beneficial food supplement all over the world [33]. Because of its diversified

properties, d-mannose has attracted increasing attention from the food industry and academia. It is especially used as a dietary supplement influencing glyconutrient contribution on human health [34]. Mannose was also included in the list of potentially interfering substances as an example for other hexoses, carbohydrates with very close chemical composition to glucose. Packed as the nutritional supplement "d-mannose", it is a sugar monomer of the aldohexose series of carbohydrates. Mannose is important in human metabolism, especially in the glycosylation of certain proteins. It is also commonly used for treatment of recurrent urinary tract infections, where doses of 3-5 g per day are recommended [35]. Blood has a metabolically active pool of 50–150 μm mannose in steady state; however, mannose homeostasis is not well understood [36]. Dietary contribution is insignificant [37], arguing that most of it is probably derived from an endogenous source. More than 95% of incoming mannose is catabolized, and most of the mannose released by intracellular processing is expelled from the cells as free mannose [38]. Therefore, a high dose of 15 g of oral mannose uptake was chosen in this experiment to increase the likelihood to detect any potentially interfering effect with the CoG signal.

4.4.10. 3Ω-fatty acids

Omega−3 fatty acids are polyunsaturated fatty acids (PUFAs) characterized by the presence of a double bond three atoms away from the terminal methyl group in their chemical structure. They are widely distributed in nature, being important constituents of animal lipid metabolism, and they play an important role in the human diet and in human physiology [39]. The three types of omega−3 fatty acids involved in human physiology are α-linolenic acid (ALA), found in plant oils, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both commonly found in marine oils [40]. Because of a variety of well-established health benefits, regular uptake or substitution of PUFAs has become very popular in the US and EU. Major natural sources of PUFAs are cold water fish (e.g. salmon, herring, mackerel) and the World Health Organization recommends regular fish consumption (1-2 servings per week, equivalent to 200 to 500 mg/day EPA + DHA) as protective against coronary heart disease and ischemic stroke. The benefit appears to be on the order of a 9% decrease in relative risk [41]. In the absence of upper limits of daily consumption, the FDA has advised that adults can safely consume up to a total of 3 grams per day of combined DHA and EPA, with no more than 2 g from dietary supplements [42]. It has been reported that relative to

placebo, DHA, but not EPA, enhances vasodilator mechanisms and attenuates constrictor responses in the forearm microcirculation [43]. The authors of this study conclude that improvements in endothelium-independent mechanisms appear to be predominant and may contribute to the selective blood pressure-lowering effect observed with DHA compared with EPA in humans. It was therefore decided to include omga-3 fatty acids into the list of potentially interfering substances.

4.5. Study Procedures

After signing informed consent, a TensorTip CoG device was individually assigned and calibrated by the participant at home during a first calibration week according to the instruction for use. The same device was used in all follow-up visits to track the glucose values occurring before and after uptake of a potentially interfering substance. At each of six time points (T_0, T_{max}, and $T_{halfmax}$ and additional three time points in order to capture the pharmacokinetic curve of the relevant interferent) capillary blood was taken for a series of measurements; YSI Stat 2300 measurement before; CoG invasive; CoG non-invasive, YSI measurement after. Additionally, venous blood samples were drawn for assessment of blood glucose by means of the second reference method (COBAS 6800, Roche Diagnostics, Mannheim, Germany). The actual substance concentration at each of the six measuring time points per visit/substance was evaluated in an external lab. The methods used for these determinations are provided in Table 1.

Table 1.: Methods employed for the determination of the plasma levels of the potentially interfering substances

Substance	Method
Acetaminophen	Enzyme Immunoassay
Ascorbic acid	High Pressure Liquid Chromatography
Diclofenac	Liquid Chromatography followed by Mass Spectrometry & Mass Spectrometry
Ibuprofen	High Pressure Liquid Chromatography
Ethyl alcohol	Photometry
Caffeine	Liquid Chromatography followed by Mass Spectrometry & Mass Spectrometry
Acetylsalicylic acid	Photometry
Xylose	Photometry
Mannose	Photometry
Omega3-fatty acids	Gas Chromatography

4.6. Statistical Analysis

The impact of potentially interfering substances on the non-invasive CoG performance was evaluated by calculating the mean absolute relative difference of the non-invasive result from the capillary standard reference method (YSI) before oral substance uptake and at five time-points thereafter the substance intake. The attempt was to draw blood at the time of maximal plasma concentration of the applied oral substance (C_{max}) and degradation down to 50 % of C_{max} ($C_{\text{-halfmax}}$) and additional three time points. The individual time points for each substance are provided in the result section.

The following formulas and definitions were used to perform the statistical analysis of the data.

1. *Positive difference = CoG measurement ≥ Reference measurement*
2. *Negative difference = CoG measurement < Reference measurement*

**** All negative values carry the minus sign (-)***

3. $Positive\ Group\ Size = N_p$
4. $Negative\ Group\ Size = N_n$
5. $Total\ Readings = N = N_p + N_n$
6. $\alpha_p = \frac{N_p}{N}$
7. $\alpha_n = \frac{N_n}{N}$
8. $Absolute\ Difference\ (AD) = \varepsilon_i = |Cnoga_i - Ref_i|$
9. $Positive\ Difference\ (PD) = \varepsilon_p^i = Cnoga_i - Ref_i\ ;\ For\ Cnoga_i \geq Ref_i$
10. $Negative\ Difference\ (ND) = \varepsilon_n^i = Cnoga_i - Ref_i\ ;\ For\ Cnoga_i < Ref_i$
11. $Mean\ Absolute\ Difference\ (MAD) = \frac{1}{N}\sum_{i=1}^{N} \varepsilon_i$
12. $Mean\ Positive\ Difference\ portion\ of\ MAD\ (MPDM) = \alpha_p \cdot \frac{1}{N_p}\sum_{i=1}^{N_p} \varepsilon_p^i = \frac{1}{N}\sum_{i=1}^{N_p} \varepsilon_p^i$
13. $Mean\ Negative\ Difference\ portion\ of MAD\ (MNDM) = \alpha_n \cdot \frac{1}{N_n}\sum_{i=1}^{N_n} \varepsilon_n^i = \frac{1}{N}\sum_{i=1}^{N_n} \varepsilon_n^i$
14. $Absolute\ Relative\ Difference\ (ARD) = R_i = \frac{|Cnoga_i - Ref_i|}{Ref_i}$
15. $Positive\ Relative\ Difference (PRD) = R_p^i = \frac{Cnoga_i - Ref_i}{Ref_i}\ ; For\ Cnoga_i \geq Ref_i$
16. $Negative\ Relative\ Difference\ (NRD) = R_n^i = \frac{Cnoga_i - Ref_i}{Ref_i}\ ; For\ Cnoga_i < Ref_i$
17. $Mean\ Absolute\ Relative\ Difference\ (MARD) = \frac{1}{N}\sum_{i=1}^{N} R_i$
18. $Mean\ Positive\ Relative\ Difference\ portion\ of\ MARD\ (MPRDM) = \alpha_p \cdot \frac{1}{N_p}\sum_{i=1}^{N_p} R_p^i = \frac{1}{N}\sum_{i=1}^{N_p} R_p^i$
19. $Mean\ Negative\ Relative\ Difference\ portion\ of MARD\ (MNRDM) = \alpha_n \cdot \frac{1}{N_n}\sum_{i=1}^{N_n} R_n^i = \frac{1}{N}\sum_{i=1}^{N_n} R_n^i$

The above relationships satisfy:

20. $MAD = MPDM + |MNDM|$
21. $MARD = MPRDM + |MNRDM|$

The absolute relative differences (ARD) of the different time-points were calculated and plotted against the respective substance concentration. Interference was assumed, when:

1. The slope of the curve regression line was higher than 10%, raising the possibility for interference, and when in this case
2. An individual MARD of more than 10% or below -10% from the absolute glucose value as determined by the reference method and after correction for the MARD at baseline was detected at highest substance concentrations. This criterion confirmed interference. If a MARD of more than 10% or below –10 % was detected with lower substance concentrations or with random distribution, interference was not considered to be confirmed.
3. In case that the YSI results indicated substance interference vs. COBAS, the analyses under 1. and 2. with the two CoG modules were repeated using COBAS as the reference method.

4.7. Drop outs and handling of missing data

There were no drop-outs in this study. All 10 healthy subjects enrolled performed the study per protocol. Any missing data from the experimental visits was handled by means of calculating the mean value of the previous and the consecutive observation, or by the “Last Observation Carried Forward” approach in case of a missing final value, or the “Next Observation carried backwards” approach in case of a first missing value, to mitigate the risk of wrong result interpretation.

5. Results

A total of 12 subjects were initially screened with two subjects turning out to be screening failures because of pathologic values in some of the safety parameters.

The remaining 10 healthy subjects were enrolled and completed the study per protocol. This study was an exploratory study to explore the potential impact of several frequently used drugs and nutritional supplements on the performance of the non-invasive module of the CoG device. The number of 10 subjects deemed sufficient for this purpose.

The subject characteristics are provided in Table 2.

Table 2.: Patient characteristics

Subject No.	Gender	Age [yrs.]	Weight [kg]	BMI [kg/m²]
1	M	35	78	23.3
2	F	55	105	30.0
3	M	53	100	26.0
4	M	40	94	29.3
5	F	31	97	33.6
6	M	56	90	30.1
7	F	24	64	22.4
8	F	26	51	18.9
9	M	60	110	32.1
10	M	29	62.5	18.9
All	5f/5m	41±14	85±20	26.5±5.4

The raw data collected during the interference experiments, including the patient's characteristics, is provided in Appendix A.

5.1. Safety Results

All experimental procedures were well tolerated and there were no adverse events observed during any of the interference experiments.

One serious adverse event was reported for patient 9, which was classified to be unique and of moderate severity, with complete recovery and not to be related to the study device and/or the study procedures.

The patient was admitted to hospital on Dec. 16th 2018 for correction of an induratio penis plastica. This was a long planned elective surgery event, which originally had been scheduled for a time after the study (March 2019). However, the hospital regained capacity for such surgery earlier and asked the patient to come in December already. The event meets SAE criteria, because the patient stayed three days in the hospital.

5.2. Results of the Interference Experiments

The results for the different tested potentially interfering substances, as well as the technical details of the exact experimental procedures, are listed hereafter per substance.

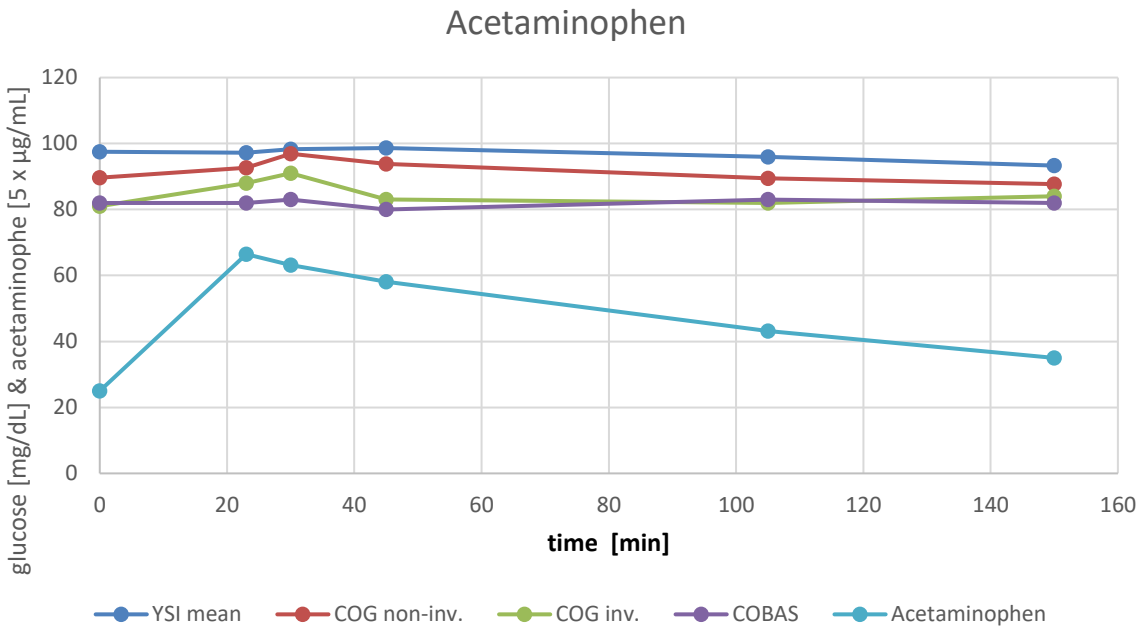
The mean results from all ten participants were calculated for each of the devices and analyzed per substance with respect to bias (in comparison to the reference method) and in relation to the substance plasma concentrations.

5.2.1. Acetaminophen

Substance	Acetaminophen
Dose	1000 mg, p.o.
Time-points for blood draw	0, 23, 30, 45, 105, 150 min

The mean acetaminophen levels, as well as the mean glucose values measured with the different methods, are provided in Figure 1.

Figure 1.: Mean glucose and acetaminophen values observed during the acetaminophen experiments. Error bars were left out for better readability, the acetaminophen results were multiplied by factor 5 to better visualize the pharmacokinetic drug profile in the same graph.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean acetaminophen concentration. The results are provided in Figures 2 and 3.

Figure 2.: Mean absolute relative difference of the non-invasive CoG readings vs. YSI as a function of mean acetaminophen concentrations (regression line: y = -0.003*x+0.131, r^2=0.481).

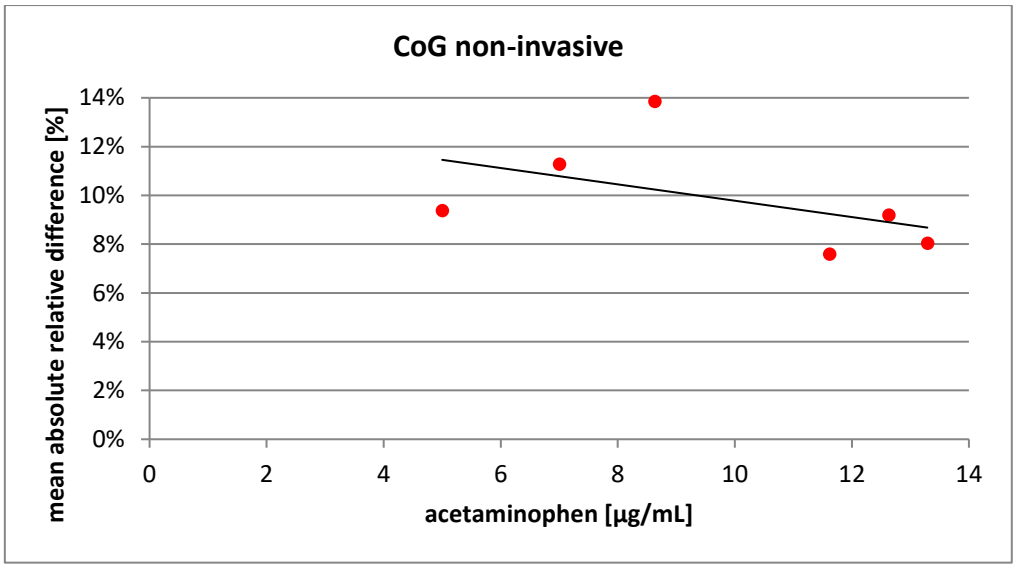
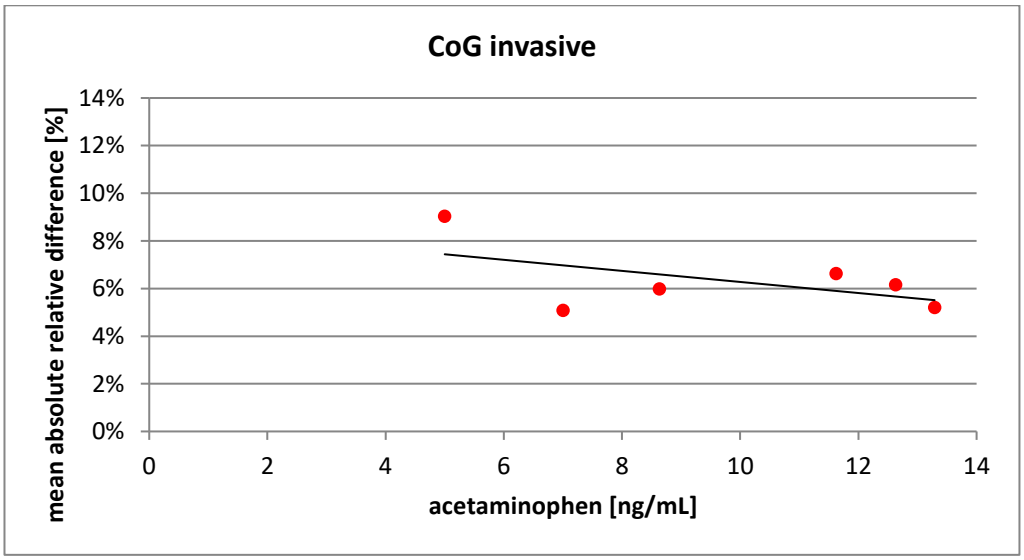
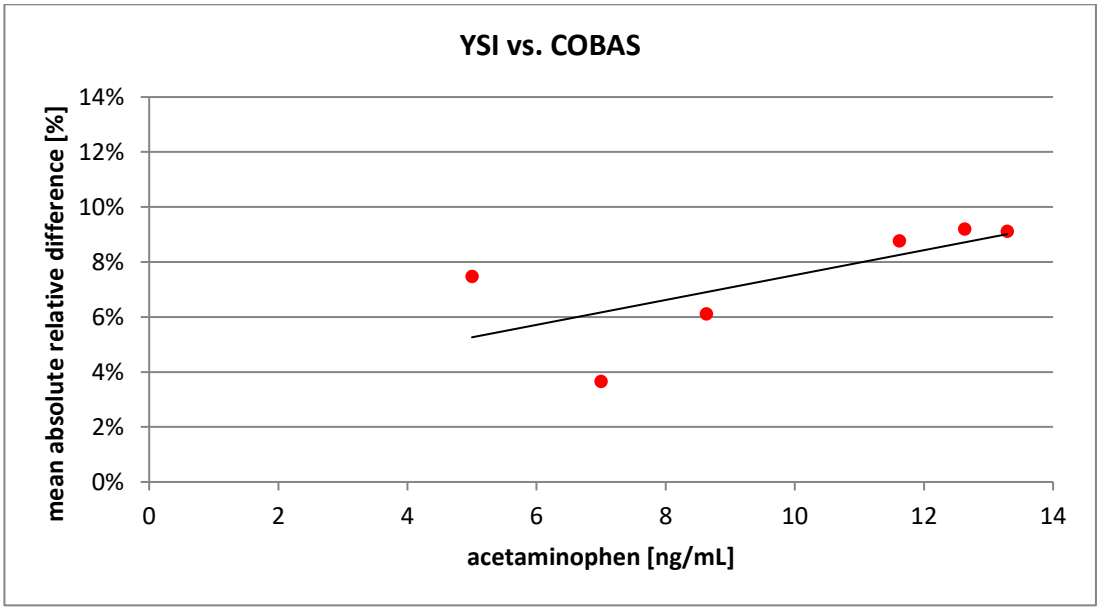


Figure 3.: Mean absolute relative difference of the invasive CoG readings vs. YSI as a function of mean acetaminophen concentration (regression line: y=-0.002*x+0.086 r^2=0.538).



YSI dependence on acetaminophen concentrations was investigated by comparing the bias vs. COBAS as a function of acetaminophen concentration. The results are depicted in Figure 4.

Figure 4.: Mean absolute relative bias of the YSI readings vs. COBAS as a function of the mean acetaminophen concentration (regression line: y=0.005*x+0.03, r^2=0.693).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 3.

Table 3.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of acetaminophen

acetaminophen		Non-invasive CoG vs. YSI		Invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [µg/mL]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	5.0	9.4%	0.0%	9.0%	0.0%	7.5%	0.0%
23	13.3	8.0%	-1.3%	5.2%	-3.8%	9.1%	1.6%
30	12.6	9.2%	-0.2%	6.2%	-2.9%	9.2%	1.7%
45	11.6	7.6%	-1.8%	6.6%	-2.4%	8.8%	1.3%
105	8.6	13.8%	4.5%	6.0%	-3.1%	6.1%	-1.4%
150	7.0	11.3%	1.9%	5.1%	-4.0%	3.7%	-3.8%

Conclusion for acetaminophen

Based on the above analyses it can be concluded that there was no interference observed for acetaminophen. Changes in device performance stayed within the level of the acceptance criteria of 10% for the observed acetaminophen plasma concentrations. The slopes of the regression lines were -0.34 % for the non-invasive CoG module and -0.23 % for the invasive module. The observed baseline-corrected MARD differences were in the range of -1.3 % to 4.5 % and -4.0 % to 0.0 % for the non-invasive and the invasive module, respectively. The YSI reference method was also not influenced by acetaminophen (slope vs. COBAS: 0.45 %, MARD differences: -3.8 % to 1.7 %).

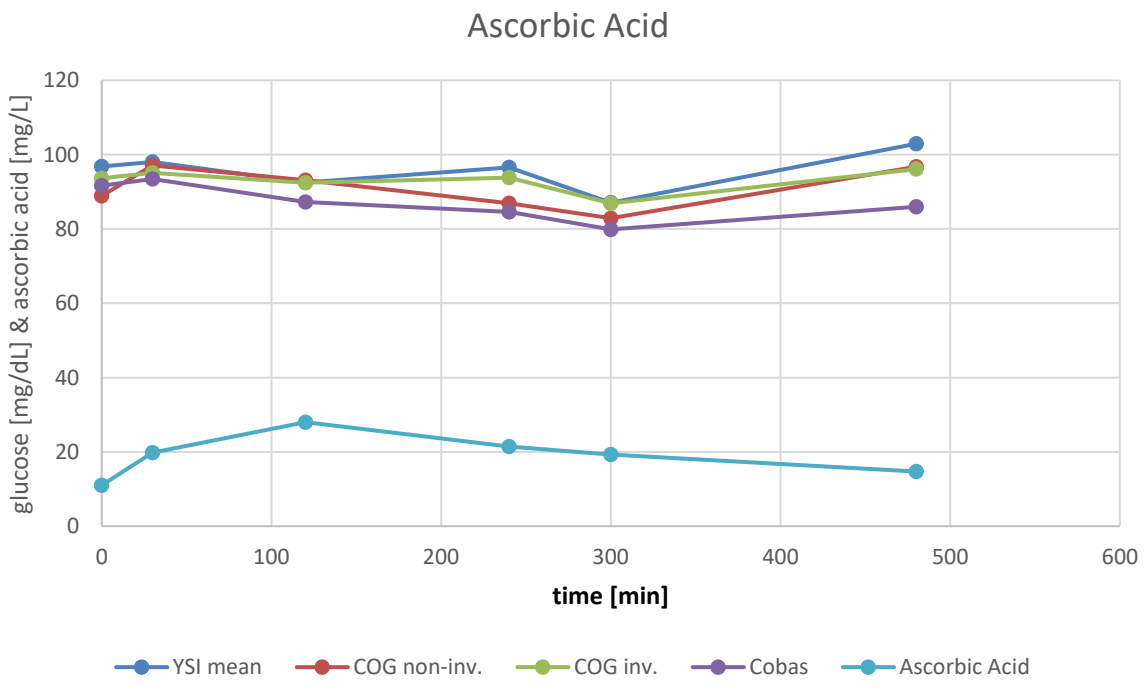
In summary, no interfering influence of acetaminophen on the non-invasive and the invasive CoG was detected at normal to high acetaminophen doses.

5.2.2. Ascorbic Acid- Vitamin C

Substance	Ascorbic Acid
Dose	5000 mg, p.o.
Time-points for blood draw	0, 30, 120, 240, 300, 480 min

The mean ascorbic acid levels, as well as the glucose values measured with the different methods, are provided in Figure 5.

Figure 5.: Mean glucose and ascorbic acid values observed during the ascorbic acid experiments. Error bars were left out for better readability.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean ascorbic acid concentration. The results are provided in Figures 6 and 7.

Figure 6.: MARD of the non-invasive CoG readings vs. YSI as a function of mean ascorbic acid concentrations (regression line: y=0.000*x+0.087, r^2=-0.108)

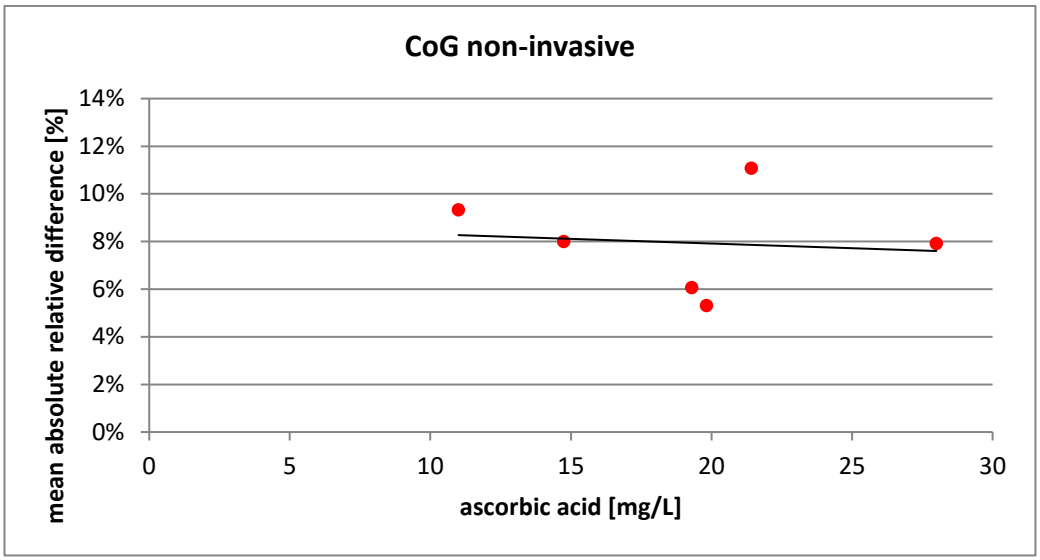
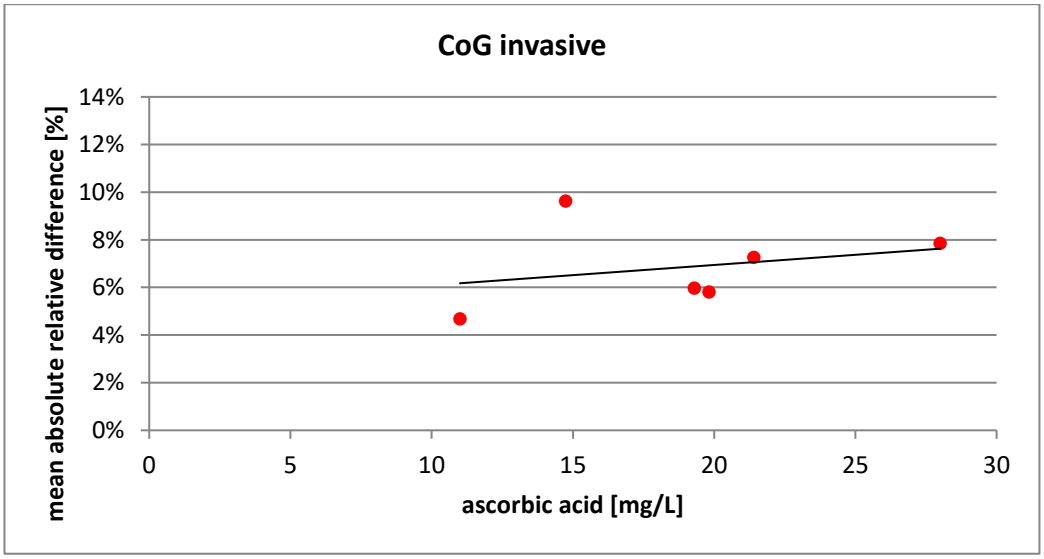
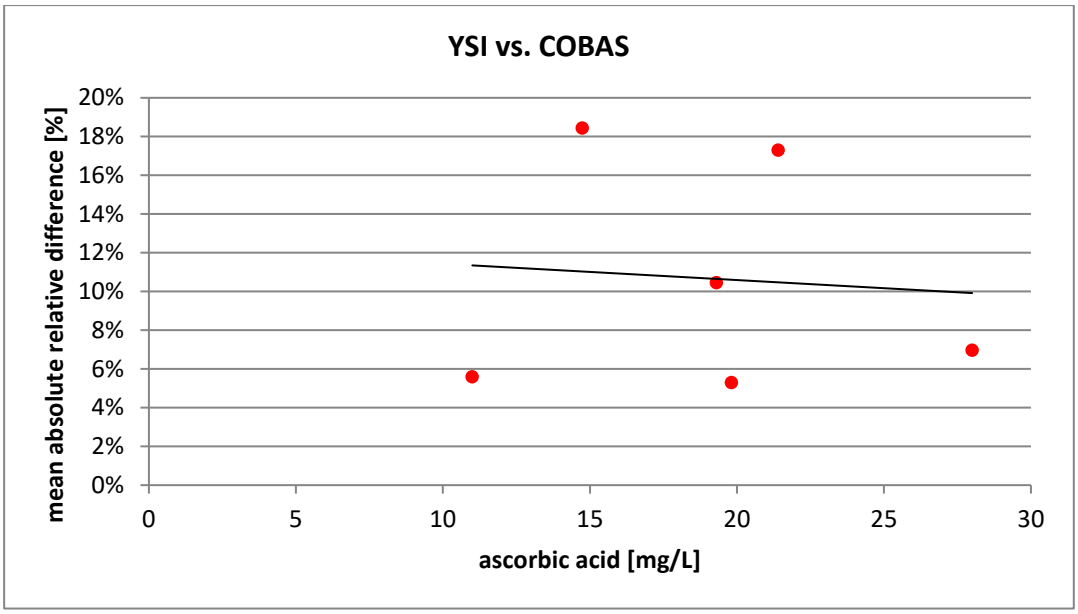


Figure 7.: MARD of the invasive CoG readings vs. YSI as a function of mean ascorbic acid concentrations (regression line: y=0.001*x-0.052, r^2=0.283).



YSI dependence on ascorbic acid concentrations was investigated by comparing the bias vs. COBAS as a function of ascorbic acid concentration. The results are depicted in Figure 8.

Figure 8.: MARD bias of the YSI readings vs. COBAS as a function of the mean ascorbic acid concentrations (regression line: y=-0.001*x+0.123, r^2= -0.083).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 4.

Table 4: Mean absolute relative differences for CoG vs. YSI and YSI vs. COBAS after uptake of ascorbic acid

ascorbic acid		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [mg/L]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	11.0	9.3%	0.0%	4.7%	0.0%	5.6%	0.0%
30	19.8	5.3%	-4.0%	5.8%	1.1%	5.3%	-0.3%
120	28.0	7.9%	-1.4%	7.9%	3.2%	7.0%	1.4%
240	21.4	11.1%	1.8%	7.3%	2.6%	17.3%	11.7%
300	19.3	6.1%	-3.3%	6.0%	1.3%	10.5%	4.9%
480	14.7	8.0%	-1.3%	9.6%	4.9%	18.4%	12.8%

Conclusion for ascorbic acid

Based on the above analyses it can be concluded that there was no indication for an interference by ascorbic acid, which reaches the level of clinical relevance for the observed ascorbic acid plasma concentrations. After uptake of a very high substitution dose of 5 g (=2.5x the recommended substitution dose [12]), the slope for the non-invasive module bias and the invasive module bias was -0.04 % and 0.09 %, respectively, and therefore within the acceptance criteria for non-interference (±10%). No baseline corrected MARD larger than 10 % was seen with the non-invasive or the invasive module.

Slope for YSI vs. COBAS was -0.08 %. At two timepoints (45 min and 150 min) a larger than 10 % bias was observed, but this was not seen with Cmax and was therefore considered to be an artefact. In conclusion YSI results were also not affected by ascorbic acid.

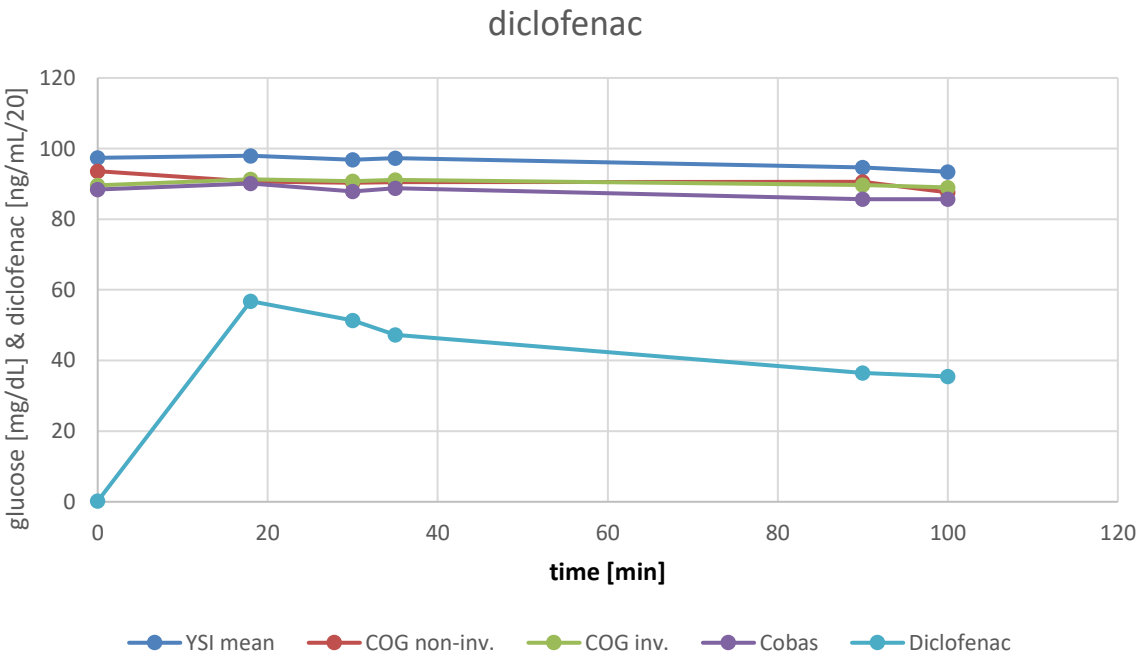
In summary, a potential interfering influence of ascorbic acid on the non-invasive and the invasive CoG modules readings can be ruled out.

5.2.3. Diclofenac

Substance	Diclofenac
Dose	50 mg, p.o.
Time-points for blood draw	0, 18, 30, 35, 90, 100 min

The mean diclofenac levels, as well as the glucose values measured with the different methods, are provided in Figure 9.

Figure 9.: Mean glucose values observed during the diclofenac experiments. Error bars were left out for better readability, the diclofenac results were divided by factor 20 to better visualize the pharmacokinetic drug profile in the same graph.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean diclofenac concentration. The results are provided in Figures 10 and 11.

Figure 10.: MARD of the non-invasive CoG readings vs. YSI as a function of mean diclofenac concentrations (regression line: y=0.000*x+0.092, r^2=-0.118).

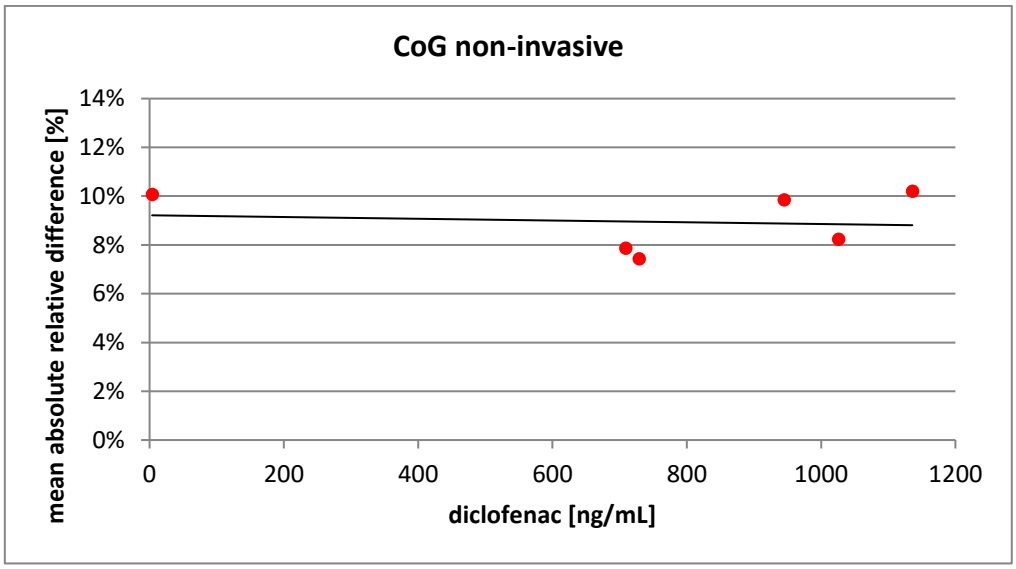
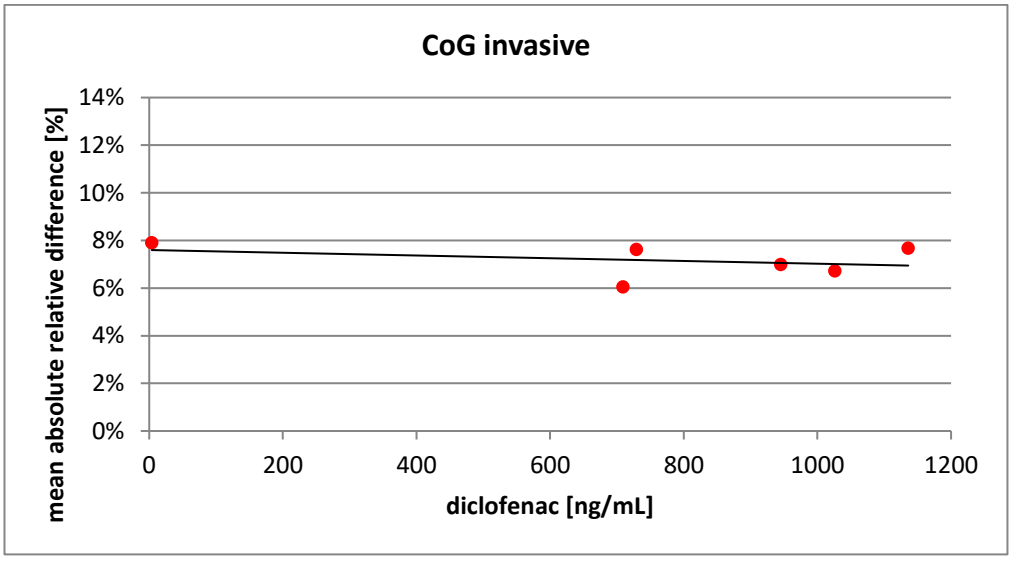
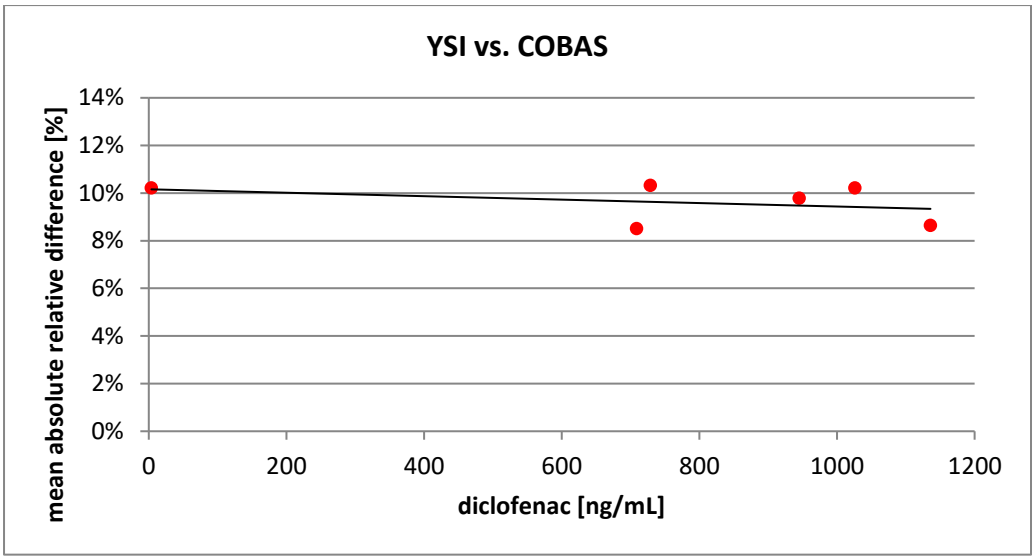


Figure 11.: MARD of the invasive CoG readings vs. YSI as a function of mean diclofenac concentrations (regression line: y=0.000*x+0.076, r^2=0.330).



YSI dependence on diclofenac concentrations was investigated by comparing the MARD vs. COBAS as a function of diclofenac concentration. The results are depicted in Figure 12.

Figure 12.: MARD of the YSI readings vs. COBAS as a function of mean diclofenac concentrations (regression line: y=-0.000*x+0.102, r^2=-0.354).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 5.

Table 5.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of diclofenac

diclofenac		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [µg/mL]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	3.8	10.1%	0.0%	7.9%	0.0%	10.2%	0.0%
18	1135.9	10.2%	0.1%	7.7%	-0.2%	8.6%	-1.6%
30	1026.0	8.2%	-1.8%	6.7%	-1.2%	10.2%	0.0%
35	945.0	9.9%	-0.2%	7.0%	-0.9%	9.8%	-0.4%
90	729.0	7.4%	-2.6%	7.6%	-0.3%	10.3%	0.1%
100	709.0	7.9%	-2.2%	6.0%	-1.9%	8.5%	-1.7%

Conclusion for diclofenac:

Based on the above analyses it can be concluded that there was no interference by diclofenac. After a high oral substitution dose of 50 mg, the bias for the slope for the non-invasive module bias and the invasive module bias was 0.00 % for both modules, and therefore within the acceptance criteria for non-interference (±10%). Baseline corrected MARD was also below 10 % with both devices and at all time-points.

YSI results were not influenced by diclofenac (slope vs. COBAS: 0.00 %, baseline-corrected MARD: -1.7 % to 0.1 %).

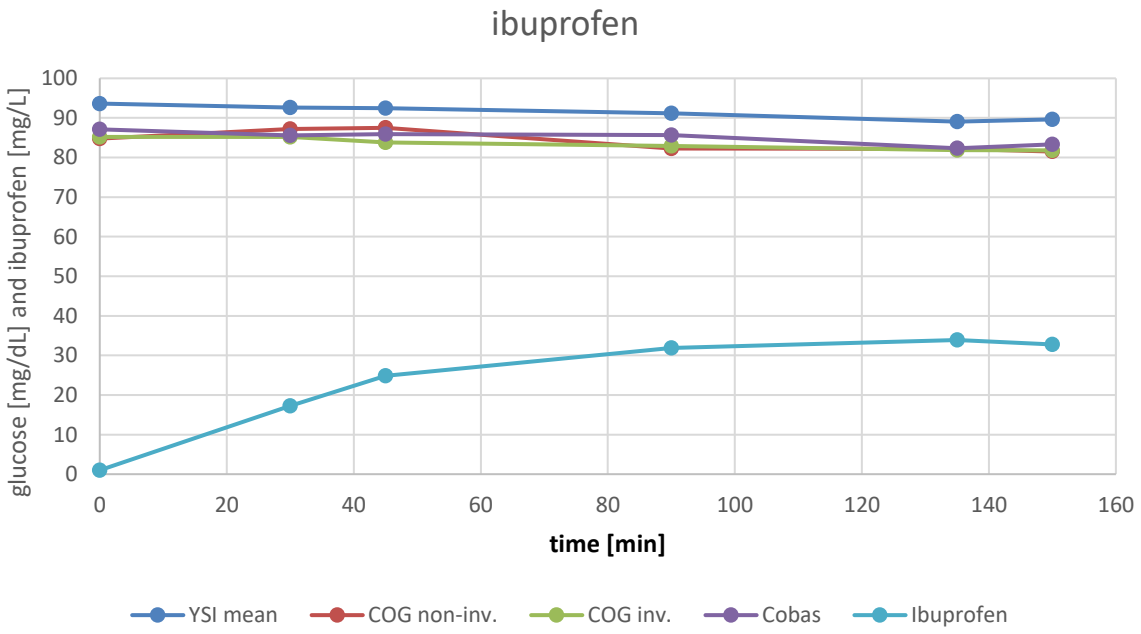
In summary, a potential interfering influence of diclofenac on the non-invasive and the invasive CoG device readings can be ruled out.

5.2.4. Ibuprofen

Substance	Ibuprofen
Dose	600 mg, p.o.
Time-points for blood draw	0, 30, 45, 90, 135, 150 min

The mean ibuprofen levels, as well as the glucose values measured with the different methods, are provided in Figure 13.

Figure 13.: Mean glucose and ibuprofen values observed during the ibuprofen experiments. Error bars were left out for better readability.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean Ibuprofen concentration. The results are provided in Figures 14 and 15.

Figure 14.: MARD of the non-invasive CoG readings vs. YSI as a function of mean Ibuprofen concentrations (regression line: y=0.000*x+0.090, r^2=0.026).

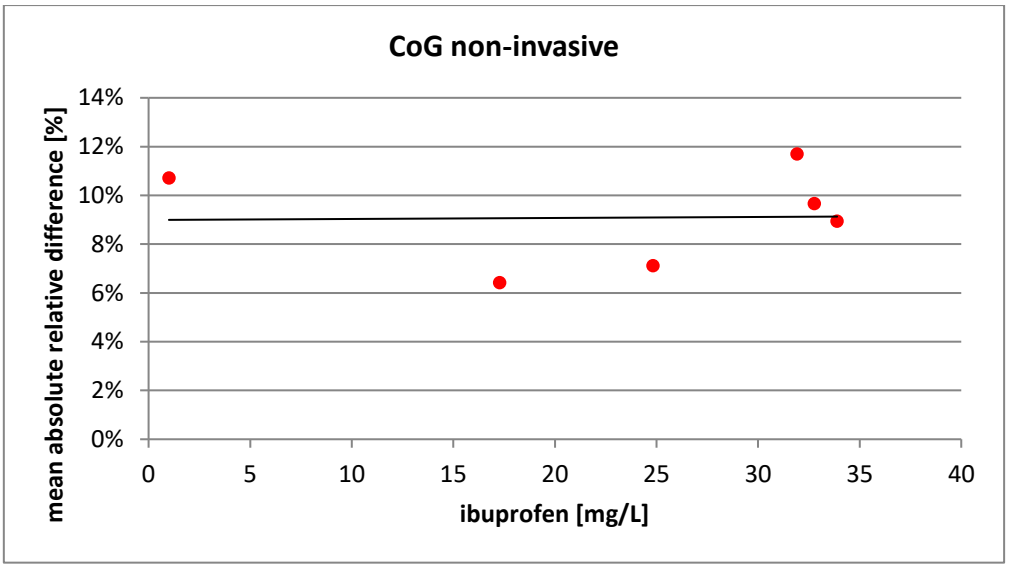
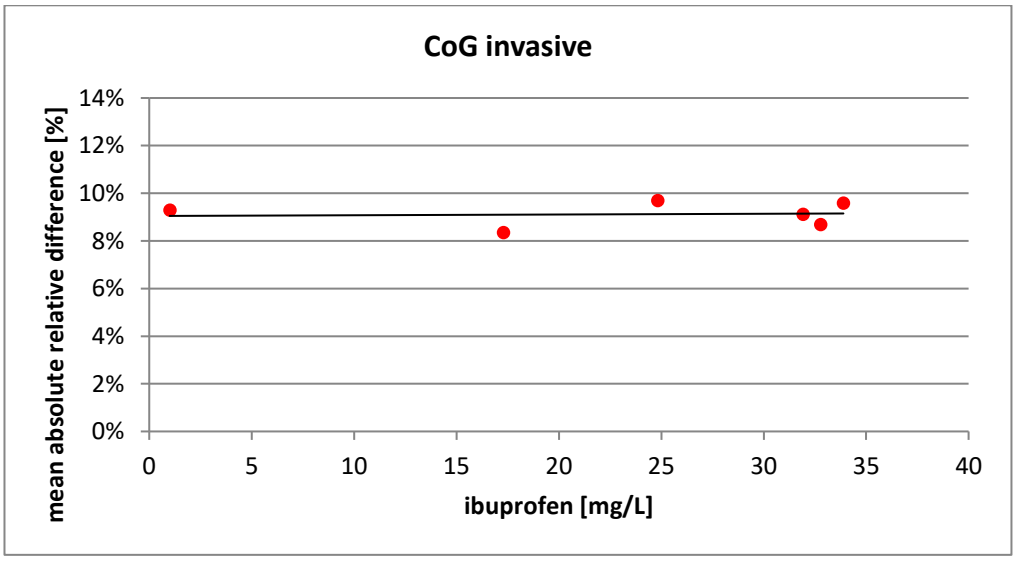
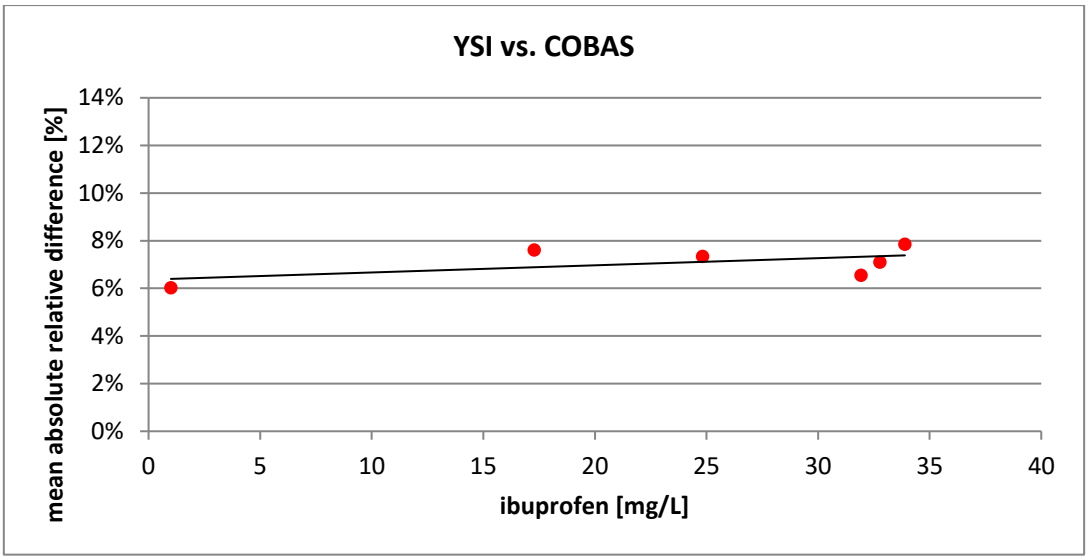


Figure 15.: MARD of the invasive CoG readings vs. YSI as a function of Ibuprofen concentrations (regression line: y=0.000*x+0.091, r^2=0.075).



YSI dependence on Ibuprofen concentrations was investigated by comparing the bias vs. COBAS as a function of ibuprofen concentration. The results are depicted in Figure 16.

Figure 16.: MARD of the YSI readings vs. COBAS as a function of mean Ibuprofen concentrations (regression line: y=0.032*x+4.7, r^2=0.735).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 6.

Table 6.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of Ibuprofen.

Ibuprofen		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [mg/L]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	1.0	10.7%	0.0%	9.3%	0.0%	6.0%	0.0%
23	17.3	6.4%	-4.3%	8.3%	-0.9%	7.6%	1.6%
30	24.8	7.1%	-3.6%	9.7%	0.4%	7.3%	1.3%
45	31.9	11.7%	1.0%	9.1%	-0.2%	6.5%	0.5%
105	33.9	8.9%	-1.8%	9.6%	0.3%	7.8%	1.8%
150	32.8	9.7%	-1.0%	8.7%	-0.6%	7.1%	1.1%

Conclusion for ibuprofen:

Based on the above observations it can be concluded that there was no interference by Ibuprofen. After uptake of 600 mg of the drug, the bias for the slope for the non-invasive module bias and the invasive module bias was 0.00% for both modules, and therefore within the acceptance criteria for non-interference (±10%). None of the baseline-corrected MARD values at any time-point was larger than 10% with both modules.

YSI results were not influenced by Ibuprofen (slope vs. COBAS: 0.0 %, baseline-corrected MARD: 0,0% to 1.8%).

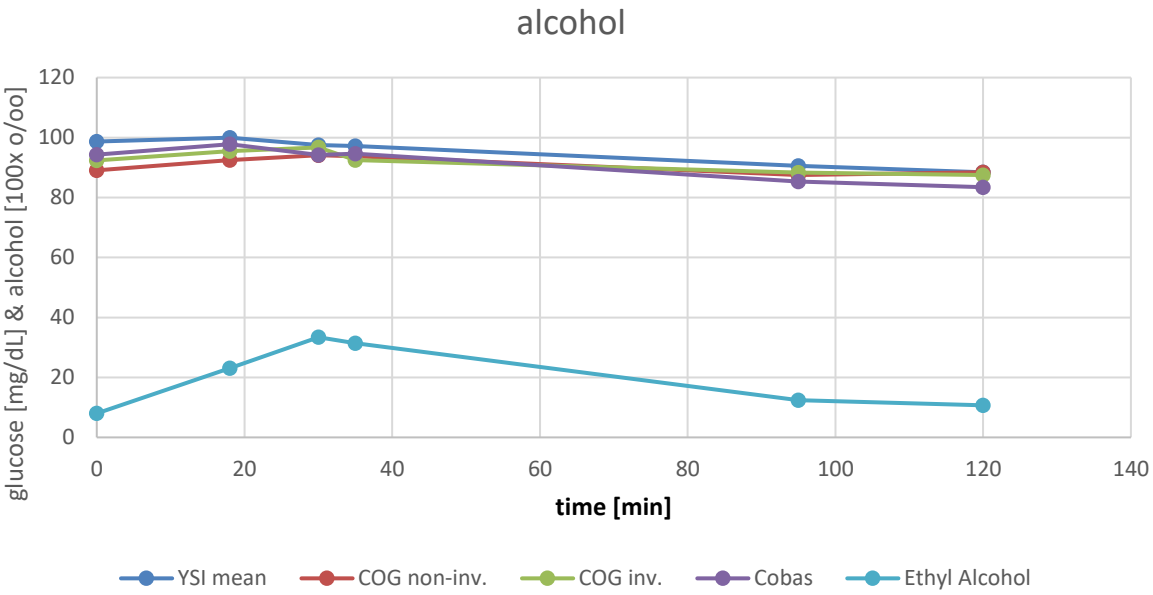
In summary, a potential interfering influence of Ibuprofen on the non-invasive and the invasive CoG device readings can be ruled out.

5.2.5. Ethyl alcohol (Vodka)

Substance	Ethyl alcohol
Dose	0.2 g/kg body weight
Time-points for blood draw	0, 18, 30, 35, 95, 120 min

The mean alcohol levels, as well as the glucose values measured with the different methods, are provided in Figure 17.

Figure 17.: Mean glucose and alcohol values observed during the alcohol experiments. Error bars were left out for better readability, the alcohol results were multiplied by factor 100 to better visualize the pharmacokinetic profile of alcohol in the same graph.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean alcohol concentration. The results are provided in Figures 18 and 19.

Figure 18.: MARD of the non-invasive CoG readings vs. YSI as a function of mean alcohol concentrations (regression line: y=-0.055*x+0.090.3; r^2=-0.444).

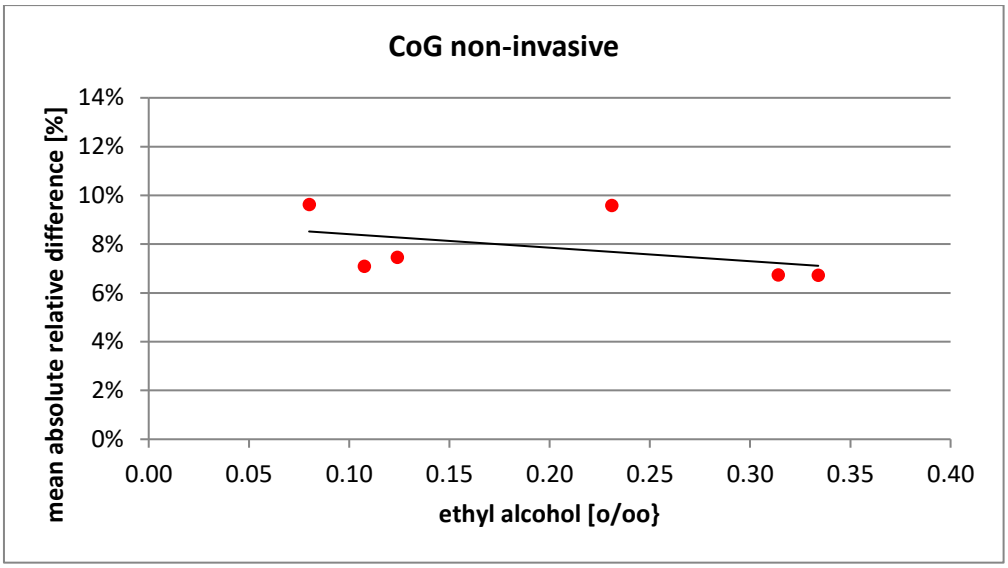
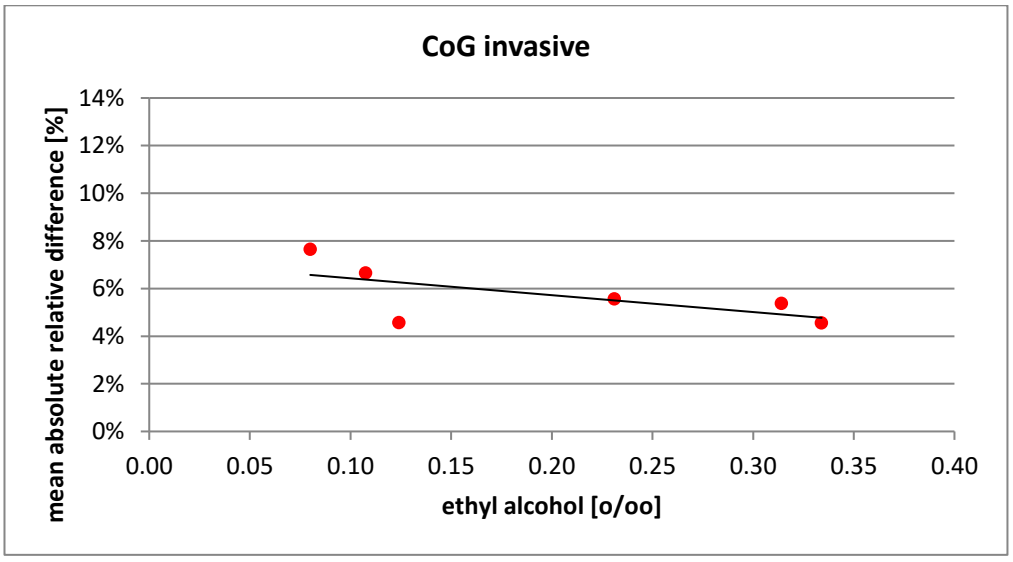
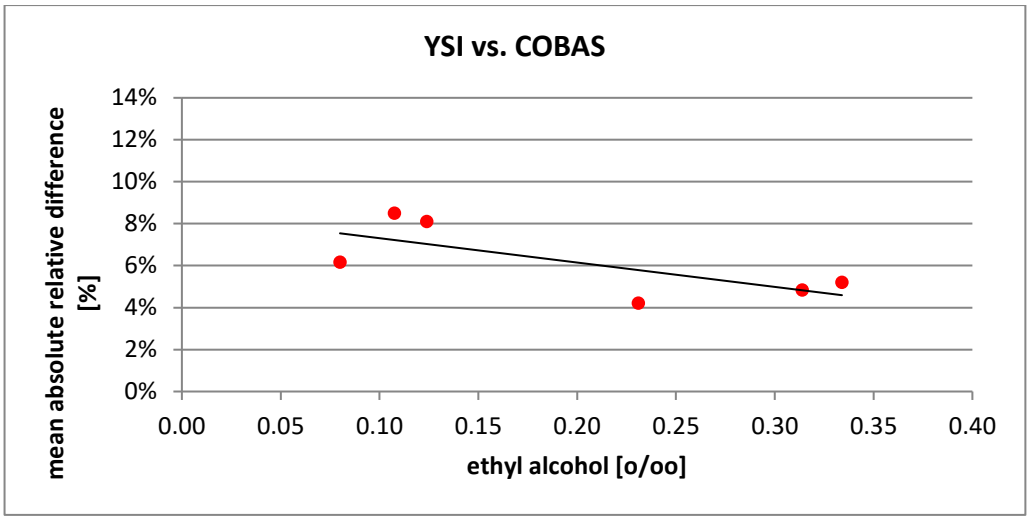


Figure 19.: MARD of the invasive CoG readings vs. YSI as a function of mean alcohol concentrations (regression line: y=-0.071*x+0.071, r^2=-0.643).



YSI dependence on alcohol concentrations was investigated by comparing the MARD vs. COBAS as a function of alcohol concentration. The results are depicted in Figure 20.

Figure 20.: MARD of the YSI readings vs. COBAS as a function of mean alcohol concentrations (regression line: y=-0.116*x+0.085, r^2=-0.721).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 7.

Table 7.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of ethyl alcohol

Ethyl alcohol		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [o/oo]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	0.1	9.6%	0.0%	7.6%	0.0%	6.2%	0.0%
18	0.2	9.6%	0.0%	5.6%	-2.1%	4.2%	-2.0%
30	0.3	6.7%	-2.9%	4.6%	-3.1%	5.2%	-1.0%
35	0.3	6.7%	-2.9%	5.4%	-2.3%	4.8%	-1.3%
95	0.1	7.4%	-2.2%	4.6%	-3.1%	8.1%	1.9%
120	0.1	7.1%	-2.5%	6.7%	-1.0%	8.5%	2.3%

The regression line for YSI vs. COBAS results showed a slope of -11.6 % indicating a potential interference. Therefore, the analyses for the two CoG modules was repeated with the COBAS results as reference values. The results are provided in Figures 21 and 22.

Figure 21.: Mean absolute bias of the non-invasive CoG readings vs. COBAS as a function of mean alcohol levels (regression line: y=-0.006*x+0.080.3; r^2=-0.031).

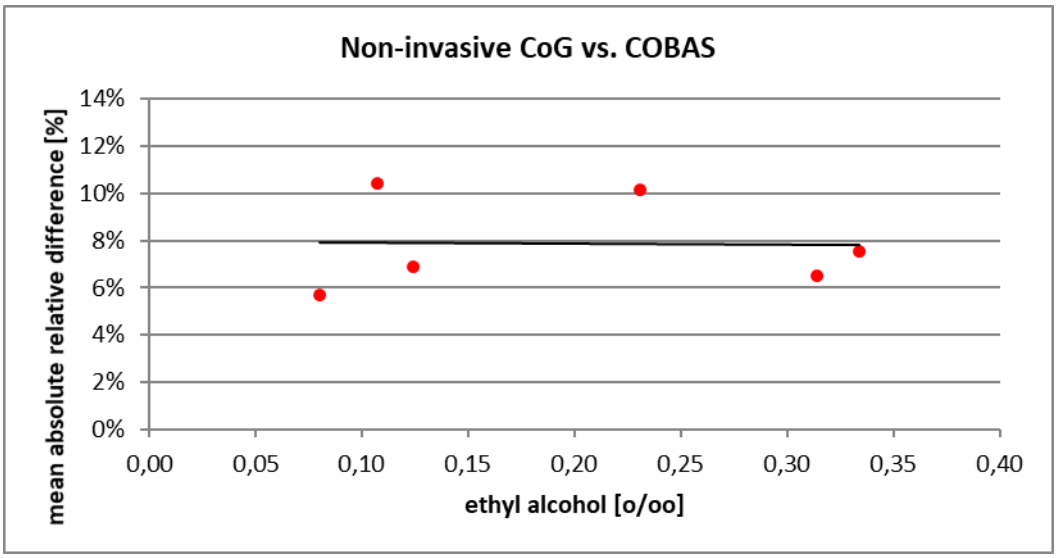
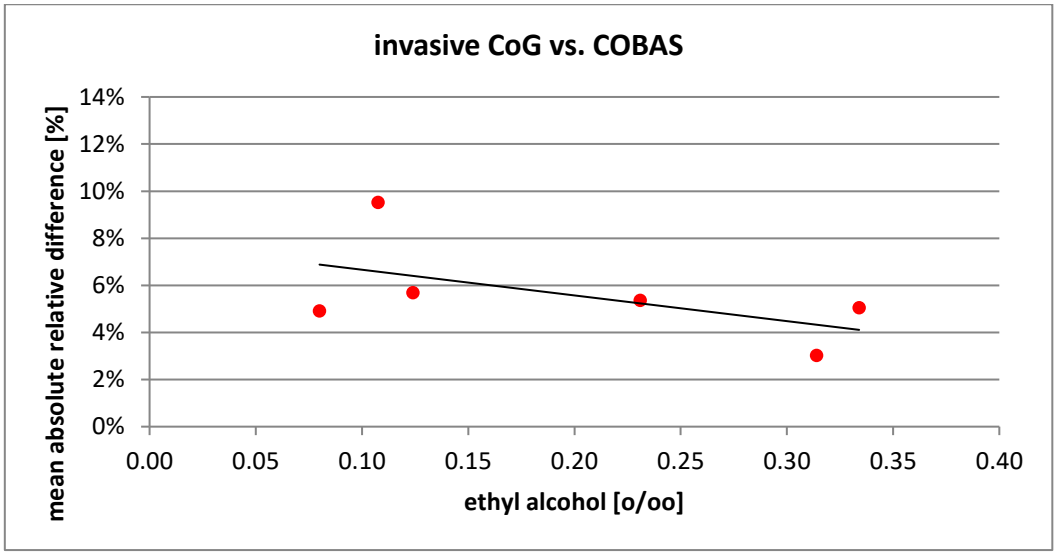


Figure 22.: Mean absolute bias of the invasive CoG readings vs. COBAS as a function of mean alcohol concentrations (regression line: y=-0.109*x+0.078, r^2=-0.562).



A slope of -10.9 % was observed for the regression line of the invasive results. The mean absolute relative differences for both device components vs. COBAS are provided in Table 8.

Table 8.: Mean absolute relative differences for the two CoG modules vs. COBAS after uptake of ethyl alcohol

Ethyl alcohol		Non-invasive CoG vs. COBAS		Invasive CoG vs. COBAS	
Time [min]	Conc. [o/oo]	MARD	Baseline corrected	MARD	Baseline corrected
0	0.1	5.7%	0.0%	4.9%	0.0%
18	0.2	10.2%	4.4%	5.4%	0.4%
30	0.3	7.5%	1.8%	5.0%	0.1%
35	0.3	6.5%	0.8%	3.0%	-1.9%
95	0.1	6.9%	1.2%	5.7%	0.8%
120	0.1	10.4%	4.7%	9.5%	4.6%

Conclusion for alcohol

After uptake of a high dose of 0.2 g/kg body weight (e.g. 40 g alcohol for an 80 kg person), the slope of the regression line for the non-invasive module bias and the invasive module bias was -5.54 % and -7.09 %, respectively, which is within the acceptance criteria for non-interference (±10%). None of the baseline-corrected MARD values at any time-point was larger than 10 % with both modules.

YSI results appeared to be influenced by alcohol (slope vs. COBAS: -11.61 %). But none of the baseline-corrected MARD values (YSI vs. COBAS) at the different timepoints was > 10 % (range: -2.0 % to 2.3 %).

Due to possible interference on the YSI results, based on the regression line slope < -10%, an additional analysis with COBAS as the reference method for the two CoG modules was performed. The slope of the regression line for the non-invasive module MARD and the invasive module MARD was 0.56 % and -10.92 %, respectively vs. COBAS. Again, none of the MARD values for the invasive CoG module vs. COBAS at the different timepoints was above 10 % or below -10% (range: -1.9 % to 4.6 %). Therefore, interfering impact of alcohol on the performance of the CoG device modules was ruled out.

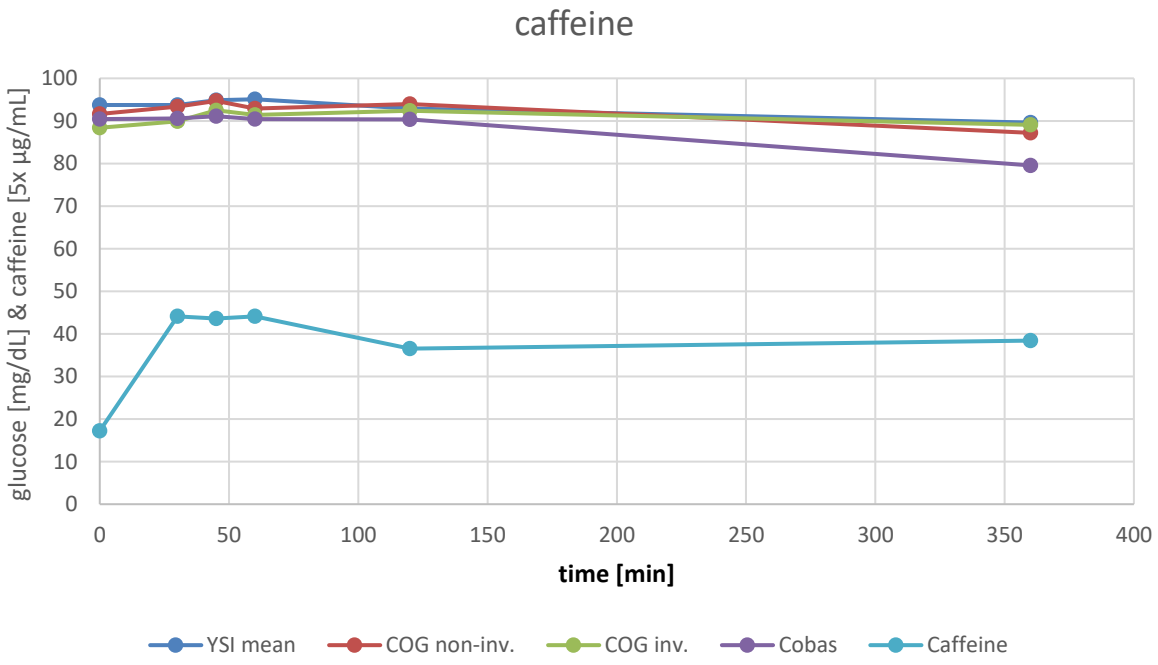
While based on the above analyses, a clinically relevant interfering influence of alcohol on the non-invasive and the invasive CoG module readings could be ruled out, it should be considered to add a warning regarding a potential influence combined with impaired decision making on the device performance when drinking alcohol.

5.2.6. Caffeine

Substance	Caffeine
Dose	150 mg, p.o.
Time-points for blood draw	0, 30, 45, 60, 120, 360 min

The mean caffeine levels, as well as the glucose values measured with the different methods, are provided in Figure 23.

Figure 23.: Mean glucose and caffeine values observed during the caffeine experiments. Error bars were left out for better readability, the caffeine results were multiplied by factor 10 to better visualize the pharmacokinetic drug profile in the same graph.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean caffeine concentration. The results are provided in Figures 24 and 25.

Figure 24.: MARD of the non-invasive CoG readings vs. YSI as a function of mean caffeine concentrations (regression line: y=0.004*x+0.075, r^2=0.280).

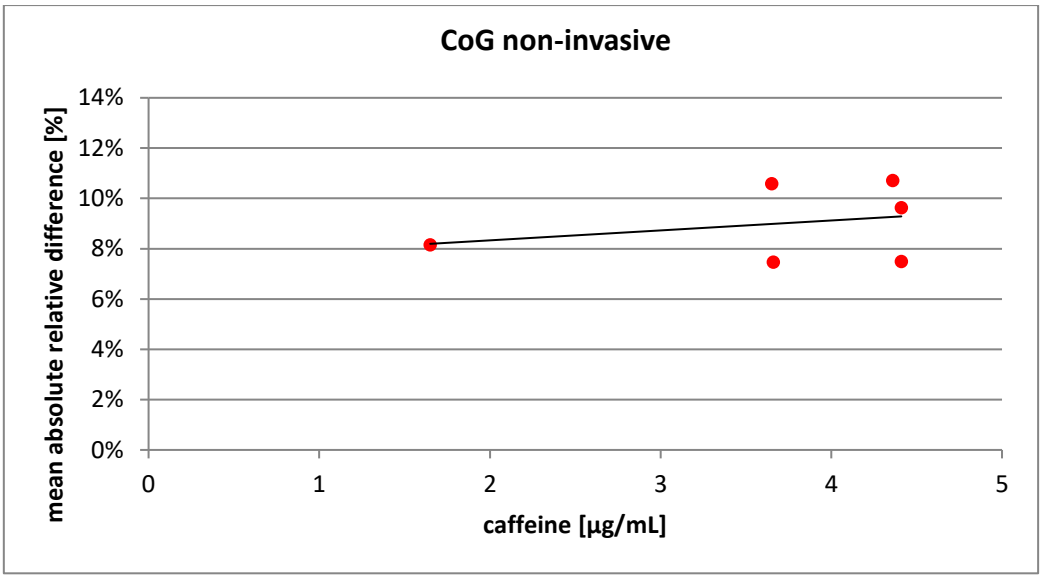
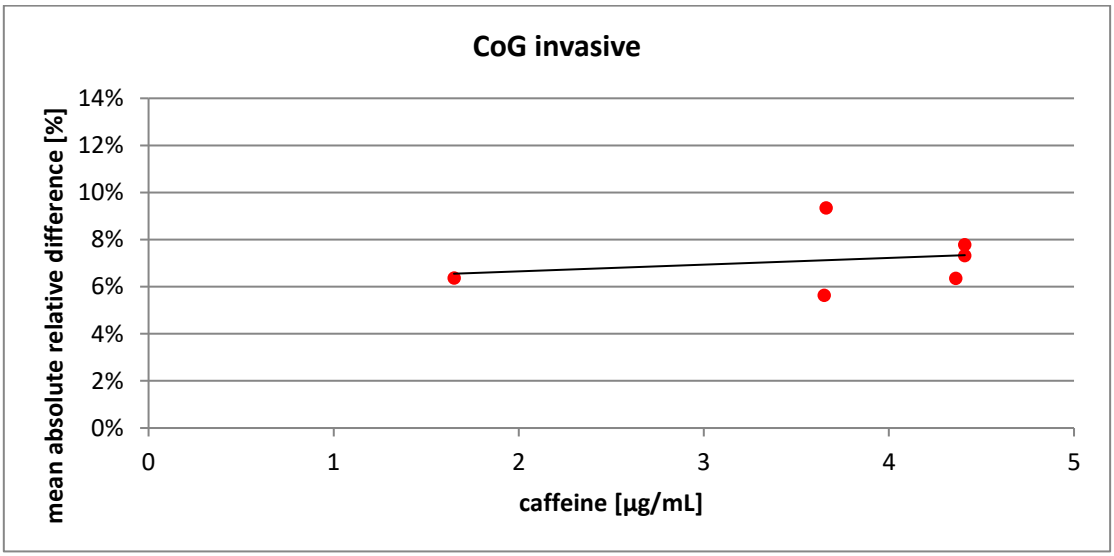
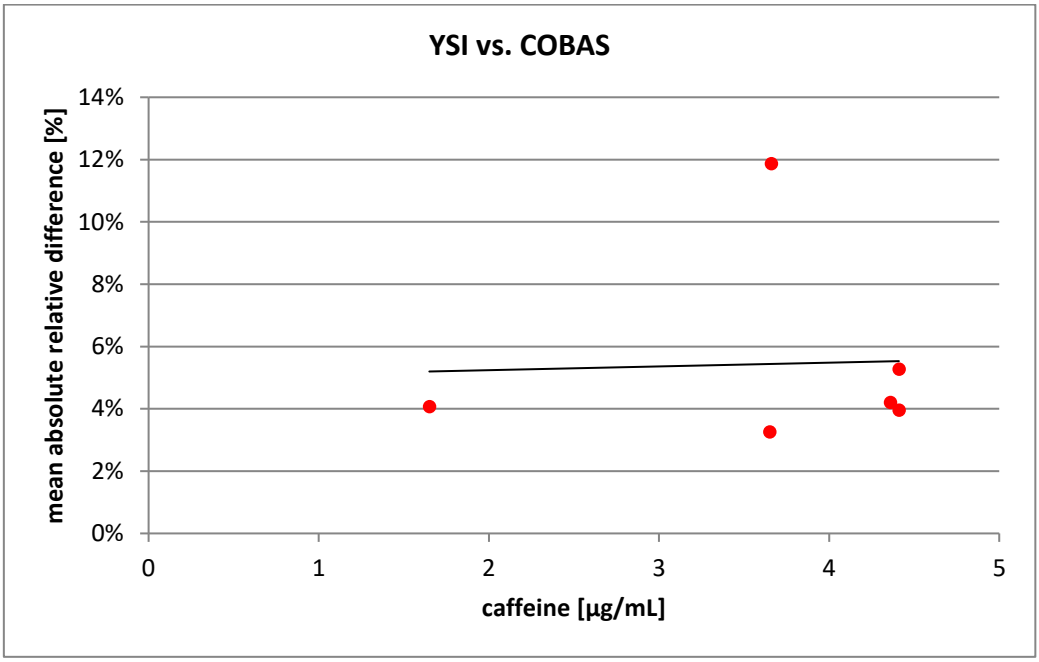


Figure 25.: MARD of the invasive CoG readings vs. YSI as a function of mean caffeine concentrations (regression line: y=0.003*x+0.061, r^2=0.229).



YSI dependence on caffeine concentrations was investigated by comparing the MARD vs. COBAS as a function of caffeine concentration. The results are depicted in Figure 26.

Figure 26.: Mean absolute bias of the YSI readings vs. COBAS as a function of the mean caffeine concentrations (regression lin: y=0.001*x+0.050, r^2=0.040).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 9.

Table 9.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of caffeine

caffeine		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [µg/mL]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	1.65	8.1%	0.0%	6.4%	0.0%	4.1%	0.0%
30	4.41	9.6%	1.5%	7.8%	1.4%	4.0%	-0.1%
45	4.36	10.7%	2.6%	6.4%	0.0%	4.2%	0.1%
60	4.41	7.5%	-0.7%	7.3%	0.9%	5.3%	1.2%
120	3.65	10.6%	2.4%	5.6%	-0.7%	3.3%	-0.8%
360	3.66	7.5%	-0.7%	9.3%	3.0%	11.9%	7.8%

Conclusion for caffeine:

Based on the above analyses it can be concluded that there was no interference by caffeine. Despite a high substitution dose of 150 mg, the slope of the regression line for the non-invasive module MARD and the invasive module MARD was 0.40 % and 0.29 %, respectively, which is within the acceptance criteria for non-interference (±10%). None of the baseline-corrected MARD values at any time-point were larger than 10% with both modules.

YSI results were not influenced by caffeine (slope vs. COBAS: 0.12 %, baseline-corrected MARD: -0.8 % to 7.8 %).

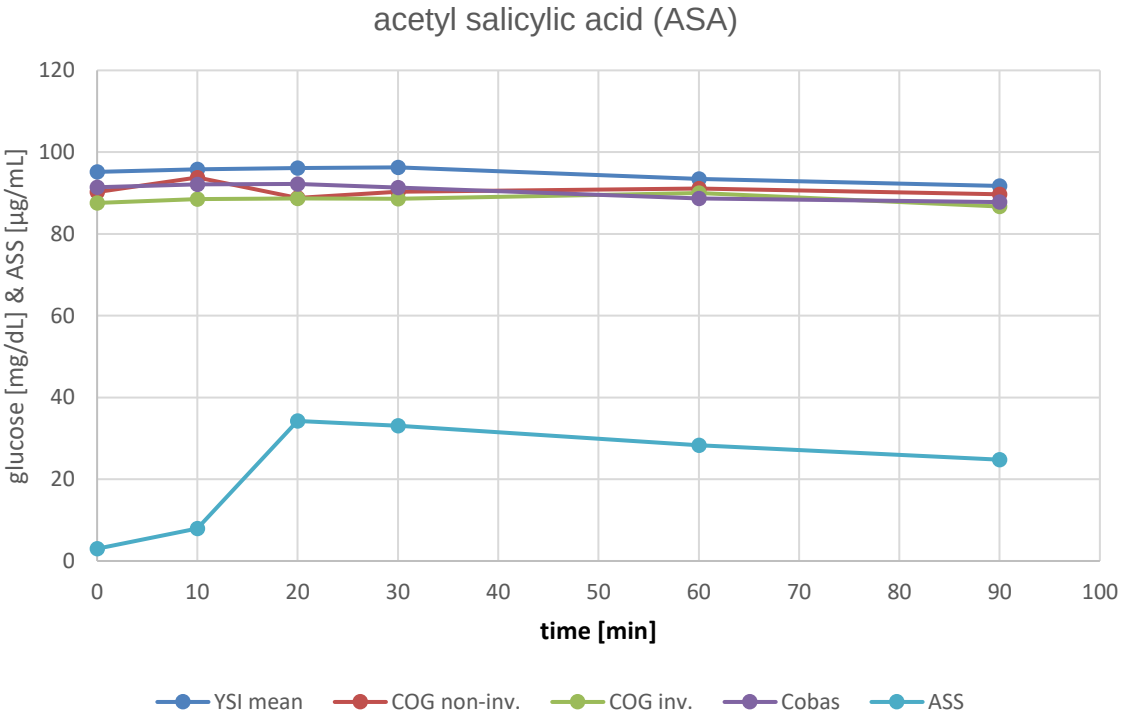
In summary, a potential interfering influence of caffeine on the non-invasive and the invasive CoG device readings can be ruled out.

5.2.7. Acetyl salicylic acid

Substance	Acetyl salicylic acid, ASA
Dose	500 mg, p.o.
Time-points for blood draw	0, 10, 20, 30, 60, 90 min

The mean acetyl salicylic acid levels, as well as the glucose values measured with the different methods, are provided in Figure 27.

Figure 27.: Mean glucose and acetyl salicylic acid values observed during the acetyl salicylic acid experiments. Error bars were left out for better readability.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean acetyl salicylic acid concentration. The results are provided in Figures 28 and 29.

Figure 28.: MARD of the non-invasive CoG readings vs. YSI as a function of mean ASA concentrations (regression line: y=-0.001*x+0.105, r^2=-0.624).

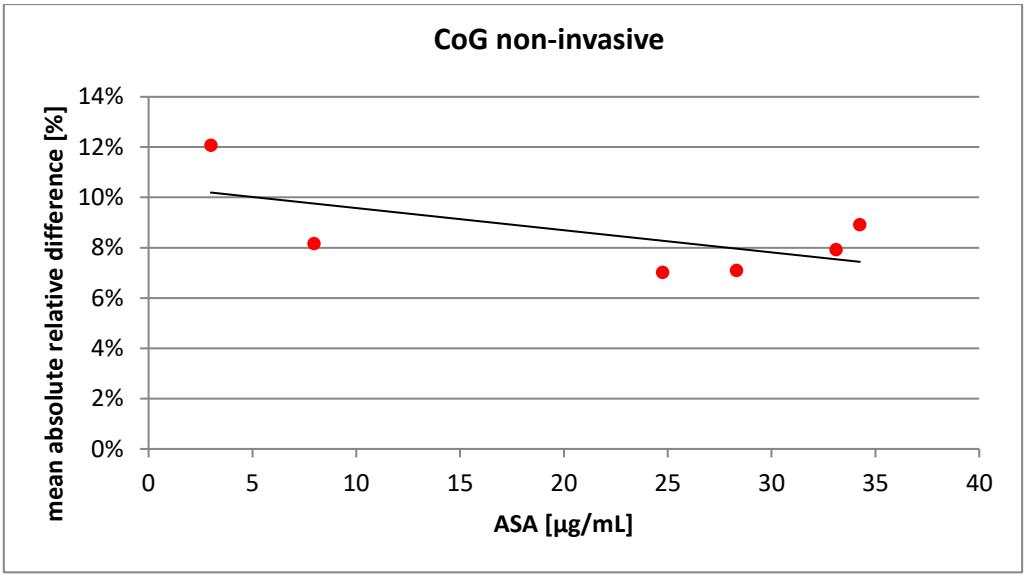
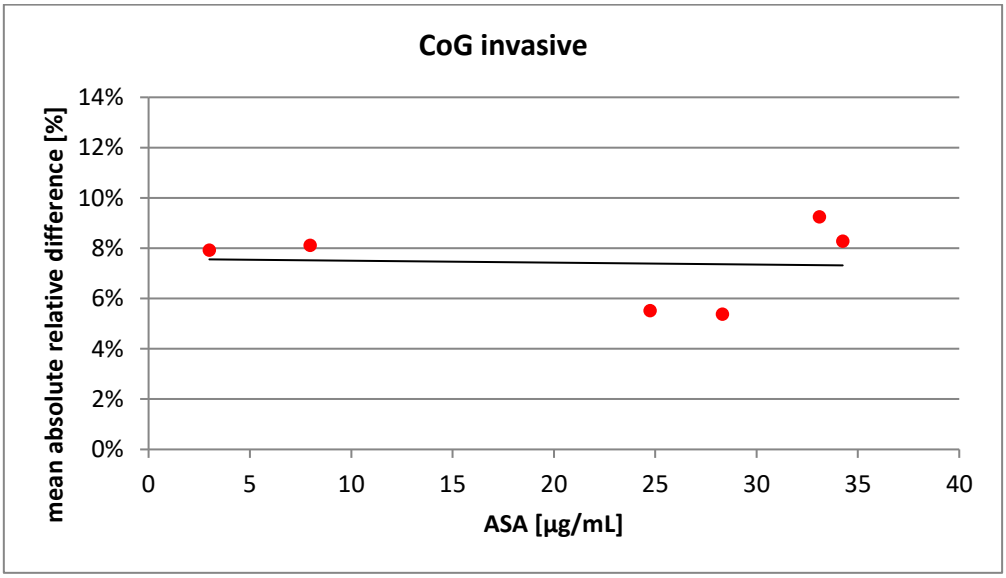
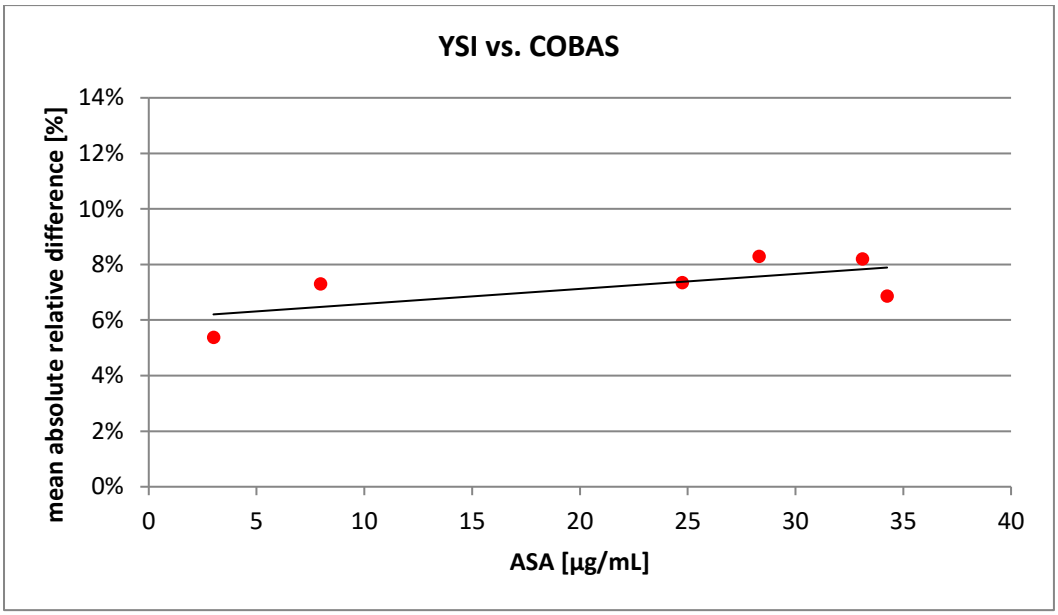


Figure 29.: MARD of the invasive CoG readings vs. YSI as a function of mean ASA concentrations (regression line: y=0.000*x+0.076, r^2=-0.056).



YSI dependence on acetyl salicylic acid concentrations was investigated by comparing the MARD vs. COBAS as a function of ASA concentration. The results are depicted in Figure 30.

Figure 30.: MARD of the YSI readings vs. COBAS as a function of mean ASA concentrations (regression line: y=0.001*x+0.060, r^2=0.674).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 10.

Table 10.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of acetyl salicylic acid

Acetyl salicylic acid		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [µg/mL]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	3.0	12.1%	0.0%	7.9%	0.0%	5.4%	0.0%
10	8.0	8.2%	-3.9%	8.1%	0.2%	7.3%	1.9%
20	34.3	8.9%	-3.2%	8.3%	0.4%	6.9%	1.5%
30	33.1	7.9%	-4.2%	9.2%	1.3%	8.2%	2.8%
60	28.3	7.1%	-5.0%	5.4%	-2.5%	8.3%	2.9%
90	24.8	7.0%	-5.1%	5.5%	-2.4%	7.3%	2.0%

Conclusion for acetyl salicylic acid

There was no interference observed for acetyl salicylic acid. After uptake of a dose of 150 mg, the slope of the regression line for the non-invasive module MARD and the invasive module MARD was 0.09 % and 0.01 %, respectively, which is within the acceptance criteria for non-interference (±10%). None of the baseline-corrected MARD values at any time-point was larger than 10% with both modules.

YSI results were not influenced by acetyl salicylic acid (slope vs. COBAS: 0.05 %, baseline-corrected MARD: 0.0 % to 2.9 %).

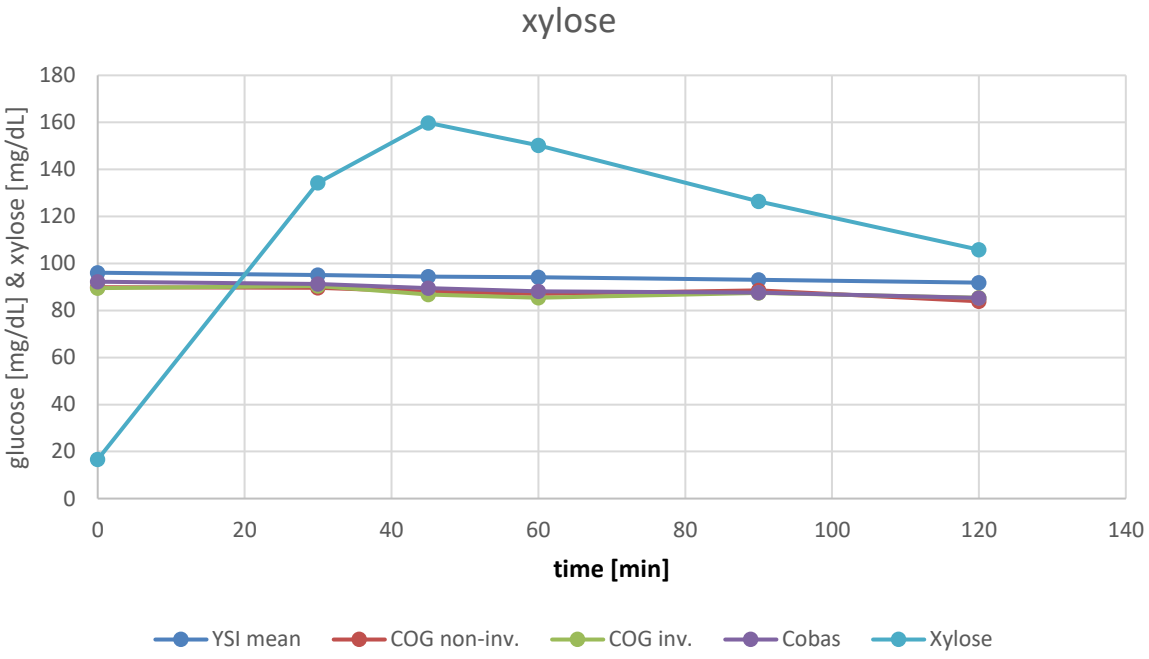
In summary, a potential interfering influence of acetyl salicylic acid on the non-invasive and the invasive CoG device readings can be ruled out.

5.2.8. Xylose

Substance	Xylose
Dose	5000 mg, p.o.
Time-points for blood draw	0, 30, 45, 60, 90, 120 min

The mean xylose levels, as well as the glucose values measured with the different methods, are provided in Figure 31.

Figure 31.: Mean glucose and xylose values observed during the xylose experiments. Error bars were left out for better readability.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean xylose concentration. The results are provided in Figures 32 and 33.

Figure 32.: MARD of the non-invasive CoG readings vs. YSI as a function of mean xylose concentrations (regression line: y=0.000*x+0.092, r^2=-0.375).

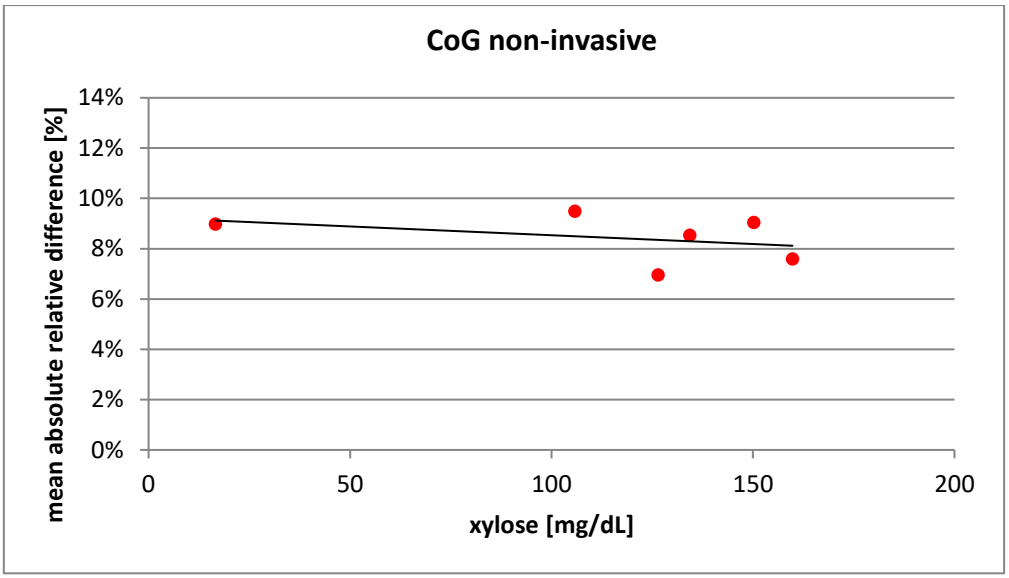
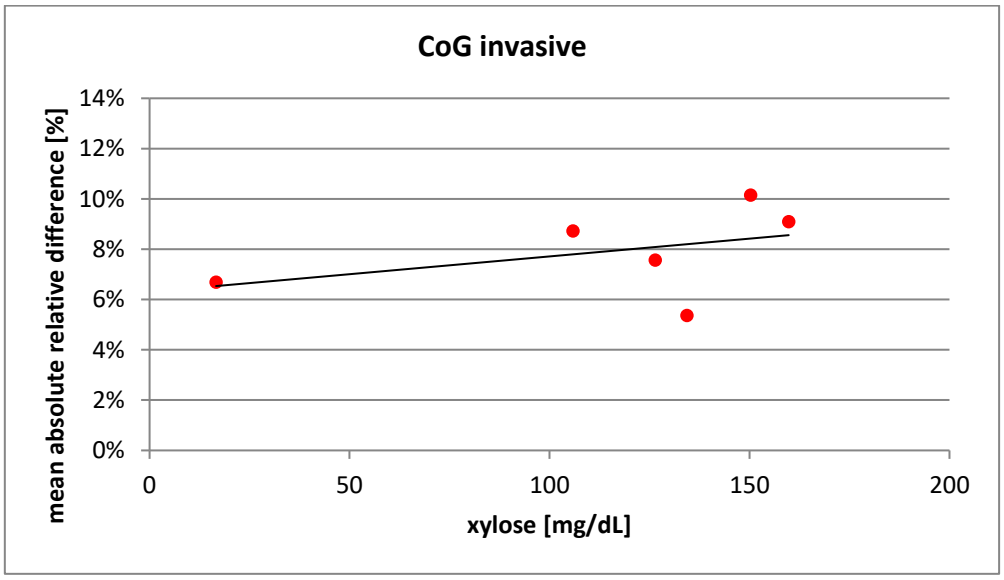
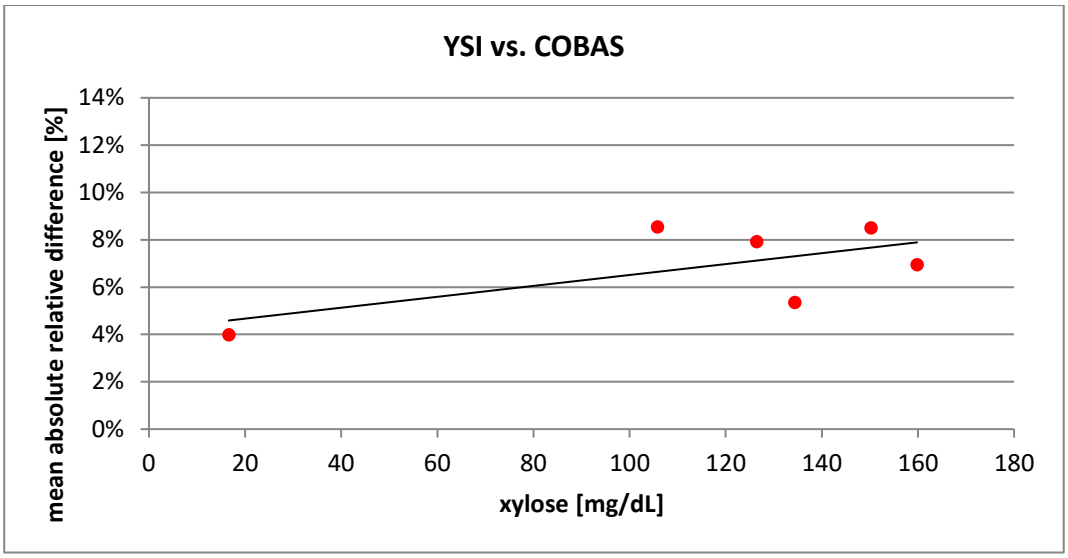


Figure 33.: MARD of the invasive CoG readings vs. YSI as a function of mean xylose concentrations (regression line: y=-0.000*x+0.063, r^2=0.422).



YSI dependence on xylose concentrations was investigated by comparing the MARD vs. COBAS as a function of xylose concentration. The results are depicted in Figure 34.

Figure 34.: Mean absolute bias of the YSI readings vs. COBAS as a function of mean xylose concentration (regression line: 0.0002*x+0.042, r^2=0.646).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 11.

Table 11.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of xylose

Xylose		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [mg/dL]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	16.62	9.0%	0.0%	6.7%	0.0%	4.0%	0.0%
30	134.34	8.5%	-0.4%	5.4%	-1.3%	5.3%	1.4%
45	159.80	7.6%	-1.4%	9.1%	2.4%	6.9%	3.0%
60	150.22	9.0%	0.1%	10.1%	3.5%	8.5%	4.5%
90	126.42	6.9%	-2.0%	7.6%	0.9%	7.9%	3.9%
120	105.81	9.5%	0.5%	8.7%	2.0%	8.5%	4.6%

Conclusion for xylose

It can be concluded that there was no interference by xylose. After uptake of a dose of 5000 mg, the slope of the regression line for the non-invasive module bias and the invasive module bias was -0.01% and 0.01%, respectively, which is within the acceptance criteria for non-interference (±10%). None of the baseline-corrected MARD values at any time-point was larger than 10% with both modules.

YSI results were not influenced by xylose (slope vs. COBAS: 0.02%, baseline-corrected MARD: 0.0% to 4.6%).

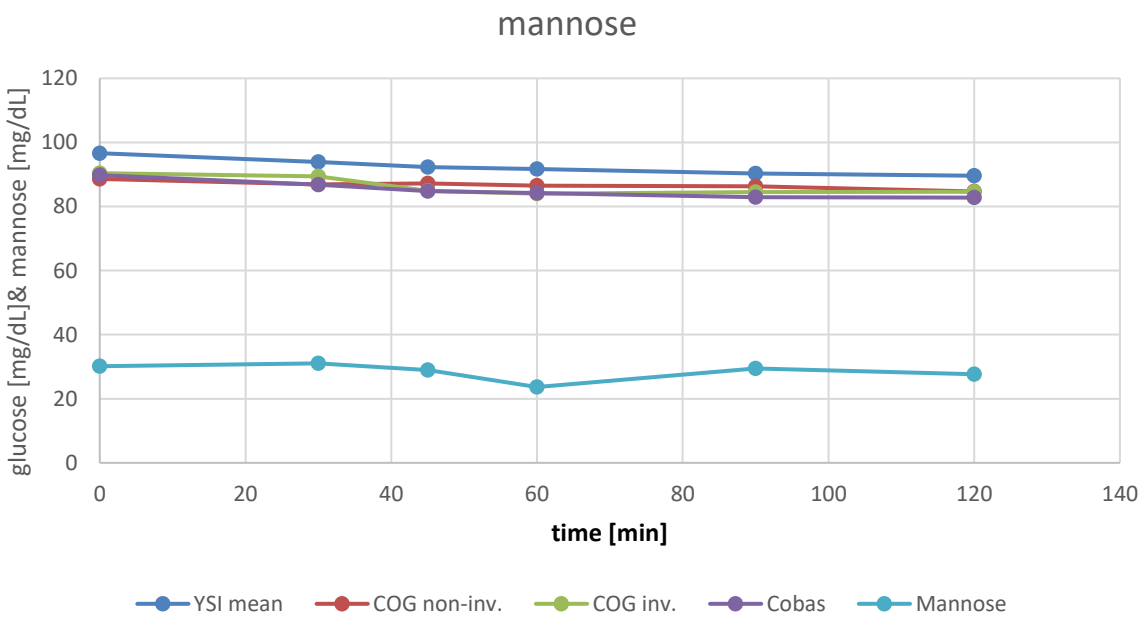
In summary, a potential interfering influence of xylose on the non-invasive and the invasive CoG device performance can be ruled out.

5.2.9. Mannose

Substance	Mannose
Dose	15000 mg, p.o.
Time-points for blood draw	0, 30, 45, 60, 90, 120 min

The mean mannose levels after uptake of 15 g, as well as the glucose values measured with the different methods, are provided in Figure 35.

Figure 35.: Mean glucose and mannose values observed during the mannose experiments. Error bars were left out for better readability.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean mannose concentration. The results are provided in Figures 36 and 37.

Figure 36.: MARD of the non-invasive CoG readings vs. YSI as a function of mean mannose concentrations (regression line: y=0.002*x+0.029, r^2=0.377).

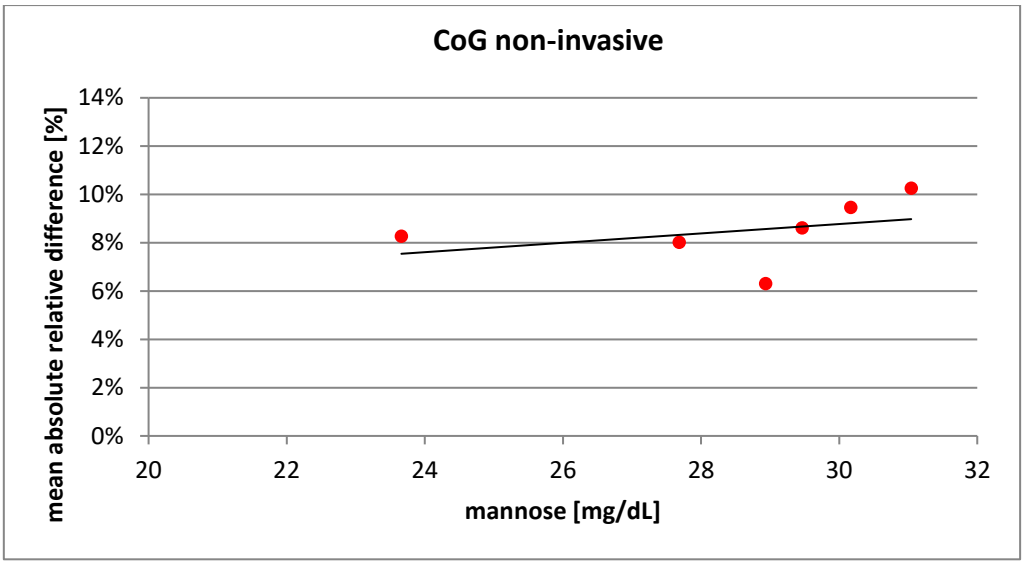
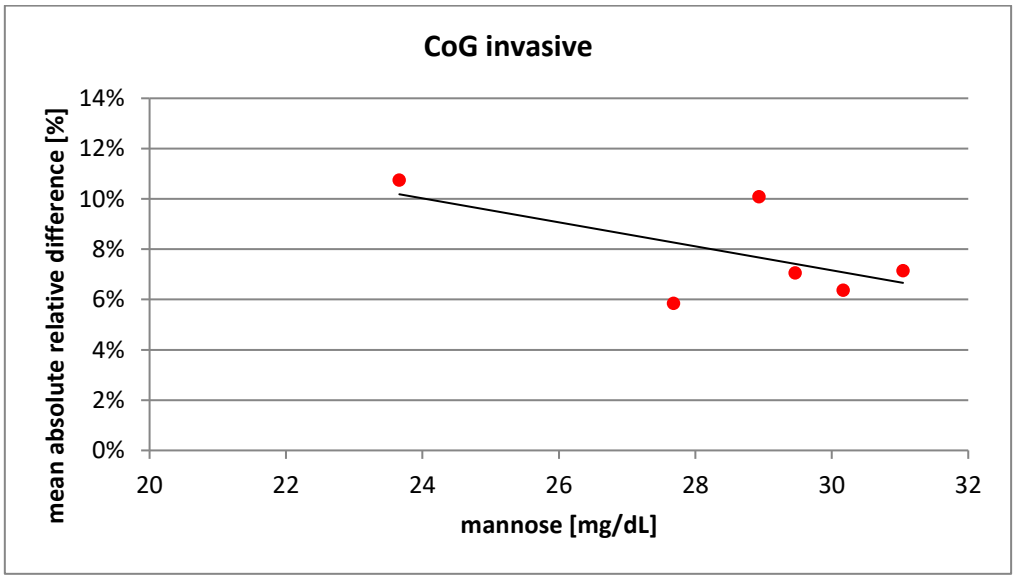
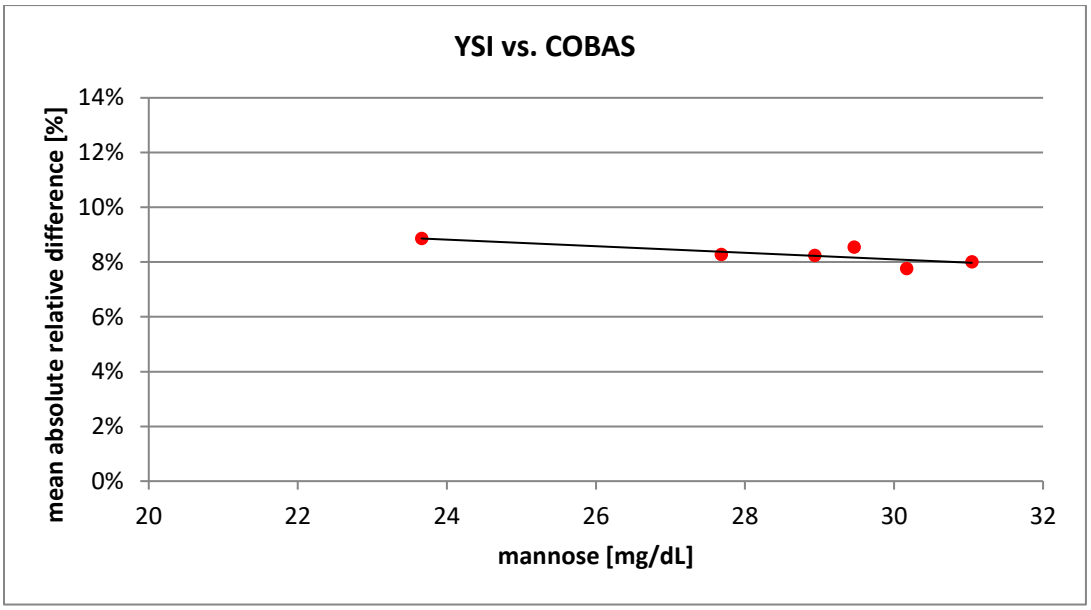


Figure 37.: MARD of the invasive CoG readings vs. YSI as a function of mean mannose concentrations (regression line: y=-0.005*x+0.215, r^2=-0.615).



YSI dependence on mannose concentrations was investigated by comparing the MARD vs. COBAS as a function of mannose concentration. The results are depicted in Figure 38.

Figure 38.: MARD of the YSI readings vs. COBAS as a function of mean mannose concentrations (regression line: -0.001*x+0.117, r^2=-0.808).



The mean absolute relative differences for both device components vs. YSI as well as for YSI vs. COBAS are provided in Table 12.

Table 12.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of mannose

Mannose		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [mg/dL]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	30.2	9.5%	0.0%	6.4%	0.0%	7.8%	0.0%
30	31.0	10.3%	0.8%	7.1%	0.8%	8.0%	0.3%
45	28.9	6.3%	-3.2%	10.1%	3.7%	8.2%	0.5%
60	23.7	8.3%	-1.2%	10.8%	4.4%	8.9%	1.1%
90	29.5	8.6%	-0.8%	7.1%	0.7%	8.5%	0.8%
120	27.7	8.0%	-1.4%	5.9%	-0.5%	8.3%	0.5%

Conclusion for mannose

It can be concluded that there was no interference by mannose. After uptake of a dose of 15 g, the slope of the regression line for the non-invasive module bias and the invasive module bias was 0.19% and -0.48%, respectively, which is within the acceptance criteria for non-interference (±10%). None of the baseline-corrected MARD values at any time-point was larger than 10% with both modules.

YSI results were not influenced by mannose (slope vs. COBAS: -0.12 %, baseline-corrected MARD: 0.0% to 1.1%).

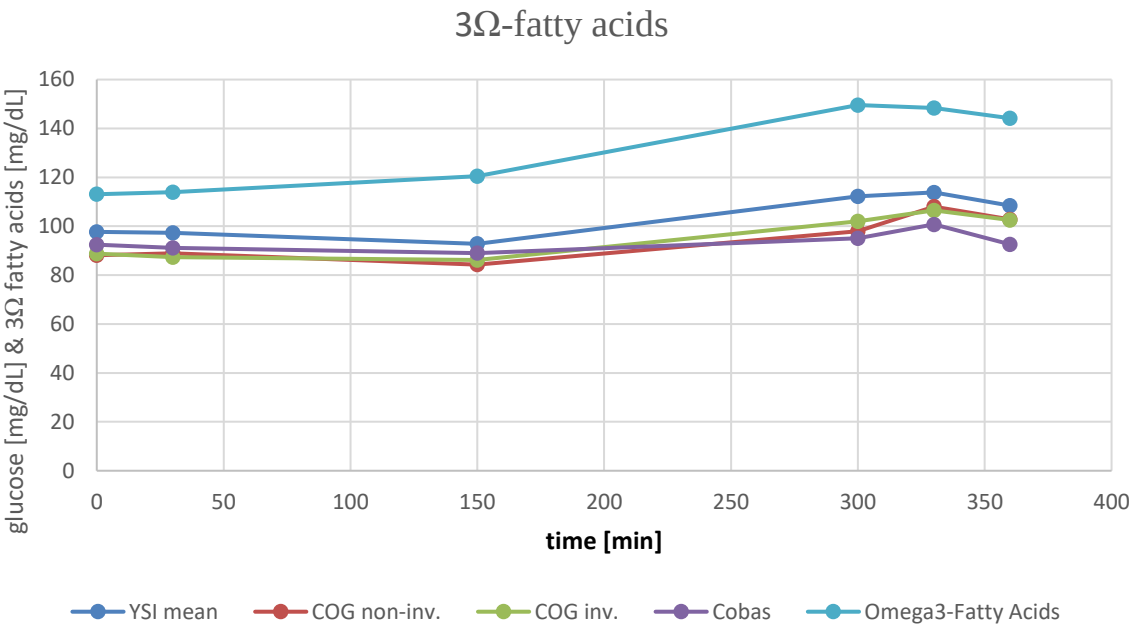
In summary, a potential interfering influence of mannose on the non-invasive and the invasive CoG device readings can be ruled out.

5.2.10. 3Ω-fatty acids

Substance	3Ω-fatty acids (ALA, EPA, DHA)
Dose	2000 mg, p.o. in fish oil
Time-points for blood draw	0, 30, 150, 300, 330, 360 min

The mean 3Ω-fatty acids levels, as well as the glucose values measured with the different methods, are provided in Figure 39. The individual acids (ALA, EPA, and DHA) did not show any differences when analyzed separately. The most pronounce effect was seen for all acids analyzed together.

Figure 39.: Mean glucose and 3Ω-fatty acids values observed during the 3Ω-fatty acids experiments. Error bars were left out for better readability.



To demonstrate a potential interference, the mean absolute relative difference (MARD) between the CoG readings and the YSI reference was calculated and graphically displayed as a function of the mean 3Ω-fatty acids concentration. The results are provided in Figures 40 and 41.

Figure 40.: MARD of the non-invasive CoG readings vs. YSI as a function of mean 3Ω-fatty acid concentrations (regression line: y=-0.001+0.163, r^2=-0.367).

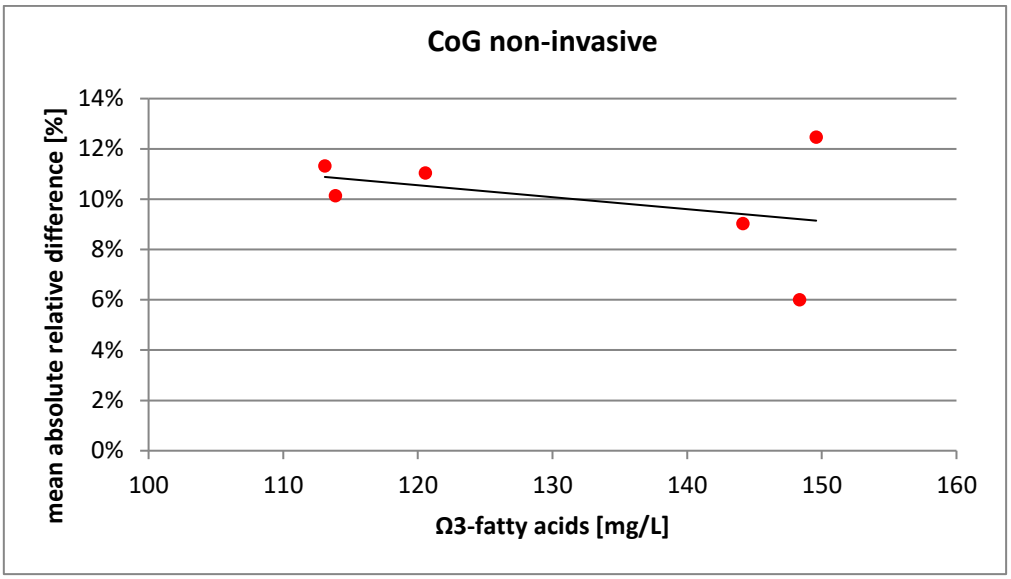
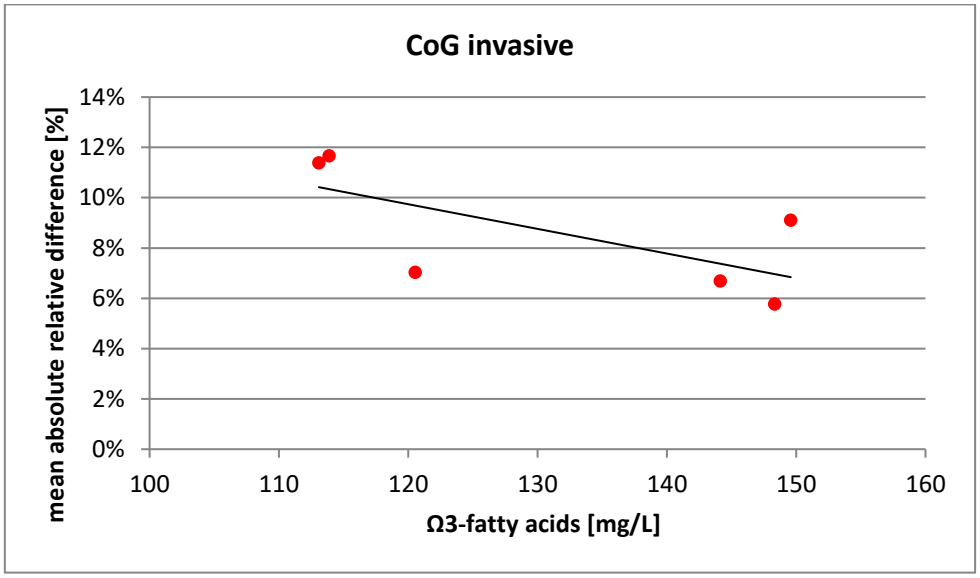
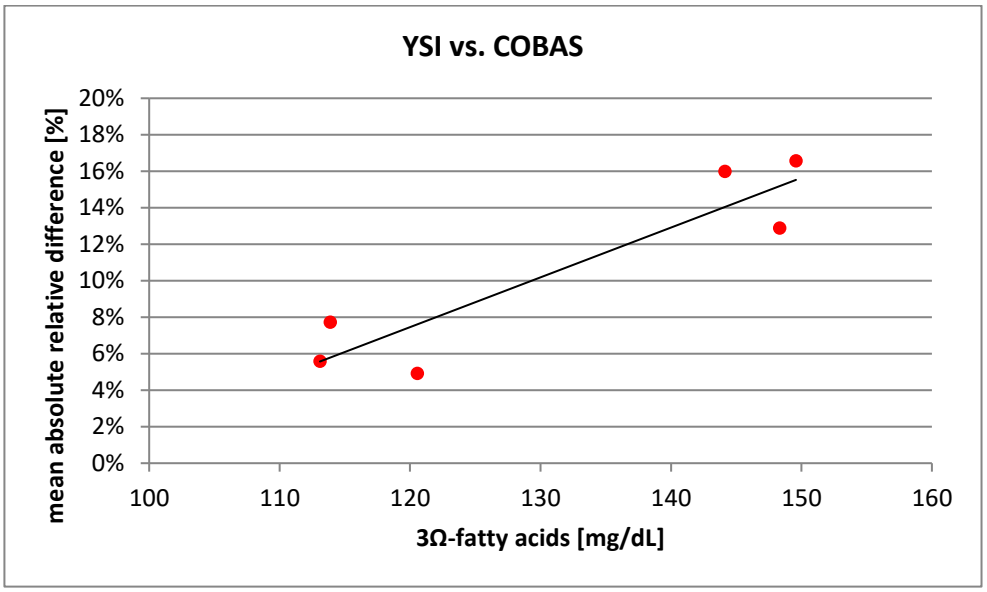


Figure 41.: MARD of the invasive CoG readings vs. YSI as a function of mean 3Ω-fatty acid concentrations (regression line: y=-0.001*x+0.215, r^2=-0.685).



YSI dependence on 3Ω-fatty acids concentrations was investigated by comparing the MARD vs. COBAS as a function of 3Ω-fatty acids concentration. The results are depicted in Figure 42.

Figure 42.: MARD of the YSI readings vs. COBAS as a function of mean 3Ω-fatty acid concentrations (regression line: y=0.003*x-0.253, r^2=0.919).



The mean absolute and mean percent differences for both device components are provided in Table 13.

Table 13.: Mean absolute relative differences CoG vs. YSI and YSI vs. COBAS after uptake of 3Ω-fatty acids

3Ω-fatty acid		Non-invasive CoG vs. YSI		invasive CoG vs. YSI		YSI vs. COBAS	
Time [min]	Conc. [mg/dL]	MARD	Baseline corrected	MARD	Baseline corrected	MARD	Baseline corrected
0	30.2	11.3%	0.0%	11.4%	0.0%	5.6%	0.0%
30	31.0	10.1%	-1.2%	11.7%	0.3%	7.7%	2.1%
150	28.9	11.0%	-0.3%	7.0%	-4.3%	4.9%	-0.7%
300	23.7	12.5%	1.1%	9.1%	-2.3%	16.6%	11.0%
330	29.5	6.0%	-5.3%	5.8%	-5.6%	12.9%	7.3%
360	27.7	9.0%	-2.3%	6.7%	-4.7%	16.0%	10.4%

While the slope of the regression line was well within the acceptance criteria (0.3%), an indication for a potential impact on the YSI results by 3Ω-fatty acids still became apparent with MARD values above 10% (10.4 and 11.0 %) for higher 3Ω-fatty acids concentrations. Since there was no interference seen between CoG module results and YSI results, another

analysis was conducted for the two CoG components vs. COBAS, which are shown in Figures 43 and 44.

Figure 43.: MARD of the non-invasive CoG readings vs. COBAS as a function of mean 3Ω-fatty acid concentrations (regression line: y=0.001*x-0.01, r^2=0.697).

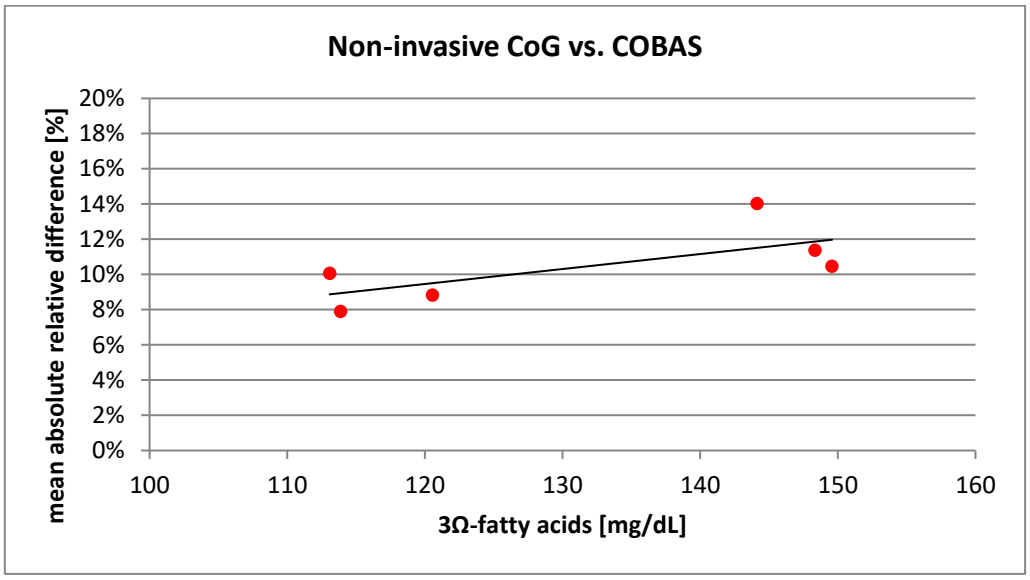


Figure 44.: MARD of the invasive CoG readings vs. COBAS as a function of mean 3Ω-fatty acid concentrations (regression line: y=-0.000*x+0.049, r^2=0.182).

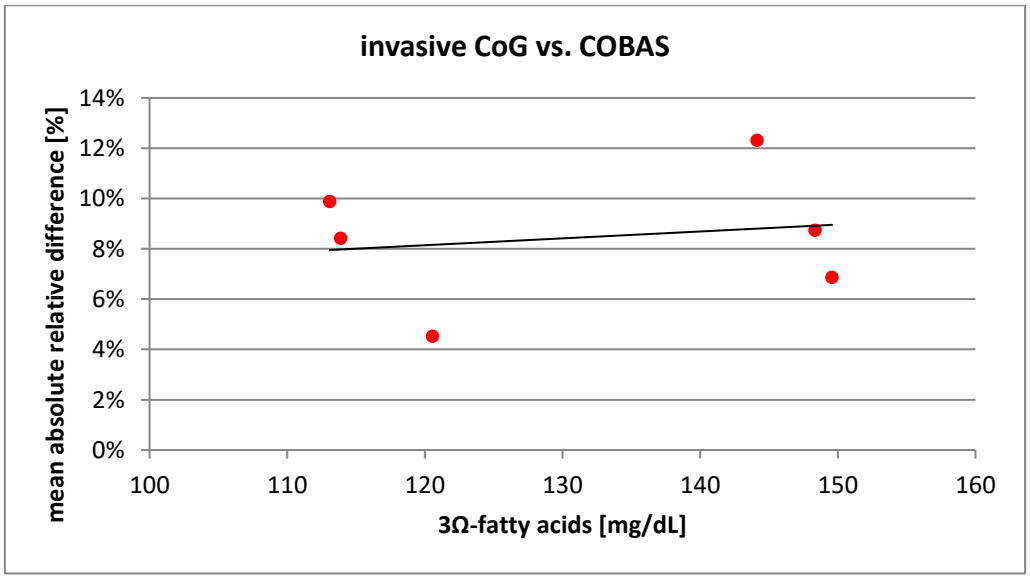


Table 14: Mean absolute relative differences for the two CoG modules vs. COBAS after uptake of 3Ω-fatty acids

3Ω-fatty acids		Non-invasive CoG vs. COBAS		Invasive CoG vs. COBAS	
Time [min]	Conc. [o/oo]	MARD	Baseline corrected	MARD	Baseline corrected
0	30.2	10.1%	0.0%	9.9%	0.0%
30	31.0	7.9%	-2.2%	8.4%	-1.5%
150	28.9	8.8%	-1.2%	4.5%	-5.4%
300	23.7	10.5%	0.4%	6.9%	-3.0%
330	29.5	11.4%	1.3%	8.7%	-1.1%
360	27.7	14.0%	4.0%	12.3%	2.4%

Conclusion for 3Ω-fatty acids

After uptake of a dose of 2000 mg of polyunsaturated fatty acids from fish oil, the slope of the regression line for the non-invasive module MARD and the invasive module MARD was -0.10 % and -0.10%, respectively, which is within the acceptance criteria for non-interference (±10%). None of the baseline-corrected MARD values at any time-point was larger than 10% with both modules.

YSI results were not influenced by 3Ω-fatty based on the regression line criteria (slope vs. COBAS: -0.3%). However, there was a suspect influence of YSI results by 3Ω-fatty acids because of individual MARD results > 10% for two of the higher 3Ω-fatty acid concentrations (10.4 % and 11.0 %).

In order to rule out that an interference of 3Ω-fatty acids with the YSI results may mask an interference also with the CoG modules, an additional analysis was performed to investigate the MARD of the two CoG modules in comparison to the COBAS results. The slope of the regression line vs. COBAS for the non-invasive module MARD and the invasive module MARD was 0.10% and 0.00%, respectively, which is within the acceptance criteria for non-interference (±10%). None of the baseline-corrected MARD values at any time-point was larger than 10% with both modules.

In summary, there was no clinically relevant interference and impact of 3Ω-fatty acid on the CoG device performance can be neglected in routine care.

Sub analysis for the different 3Ω-fatty acid components (alpha-linoleic acid, eicosapentanoic acid and docosahexanoic acid) did not reveal any differences as compared to the combined results (data not shown, raw data can be found in Appendix A).

5.3. Total Accuracy Analysis

The total MARD vs. the YSI reference method was determined for the combined results of all subjects and from all experiments (total number of measurements = 600). The observed blood glucose ranged from 71 mg/dL to 158 mg/dL. The results are provided in Table 15.

Table 15: Accuracy analysis for the entire data set for the non-invasive and the invasive device modules (vs. YSI and vs. COBAS)

Parameter	Total	Negative		Positive	
	MARD	nMARD	Weight	pMARD	Weight
vs. YSI					
Non-invasive	8.8 %	-7.1 %	0.722	1.7 %	0.278
Invasive	7.4 %	-6.5 %	0.805	0.9 %	0.195
vs. COBAS					
Non-invasive	8.2 %	-3.5 %	0.523	5.7 %	0.477
Invasive	7.6 %	-2.8 %	0.508	4.8 %	0.492

6. Discussion and Conclusion

In this trial, the potential influence of several over the counter drugs (acetaminophen, acetyl salicylic acid, diclofenac, ibuprofen), nutritional supplements (ascorbic acid, 3Ω-fatty acids), and nutrition components (caffeine, alcohol, xylose, mannose) on the performance of the invasive and the non-invasive modules of the TensorTip CoG device was investigated. Almost all substances were selected for this trial because a potential acute impact on nutritional skin blood flow or thermoregulation directly after oral uptake was indicated by the literature (see section 4.4).

This protocol was not intended and designed to identify chronic metabolic or physiological conditions with potential impact on the non-invasive CoG device performance. This chronic interference analysis is subject of a different protocol and was performed no data collected from the intended user population during CNG-NGM-003 study.

The study was intentionally performed in healthy subjects with stable glucose values and with high doses of the respective substance to highlight any potential acute interfering action by the investigated substances without deterioration of glucose values. The uptake of the interfering substances was well tolerated, and no adverse event was reported. One serious adverse event (brief hospitalization for elective surgery) was not related to the device use.

Both the invasive and the non-invasive modules of the CoG device showed high accuracy in the normal blood glucose range (71 mg/dL to 158 mg/dL) and accuracy was not influenced in a clinically significant and relevant way by any of the substances tested in this study. MARD for the non-invasive module was found to be 8.8 % (invasive module: 7.4 %). None of the substance tested reached the pre-defined interference level of ±10% that would have required risk mitigation action. The most pronounced influence from any of the tested substances was seen for ethyl alcohol and for 3Ω-fatty acids, which however interfered with the YSI reference readings (vs. COBAS) to a larger extend than with the CoG readings.

While the YSI readings vs. COBAS with 3Ω-fatty acids indicated a possible interference, the bias observed with the non-invasive module and the invasive CoG module was within the acceptance criteria, when compared with both reference methods. A summary of the interference test results is provided in Table 16.

Table 16: Summary of the acute exogenous interference test results

Substance (and dose)	Slope of the MARD regression curve		Maximally Observed baseline corrected MARD	
	Non-invasive	Invasive	Non-invasive	Invasive
Acetaminophen (1000 mg)	-0.3%	-0.2%	4.5 %	-4.0 %
Acetyl salicylic acid (500 mg)	-0.1%	0.0%	-5.1 %	-2.5 %
Ascorbic acid (5000 mg)	0.0%	0.1%	-4.0 %	4.9 %
Caffeine (150 mg/dL)	0.4%	0.3%	2.6 %	3.0 %
Diclofenac (50 mg)	0.0%	0.0%	-2.6 %	-1.9 %
Ethyl alcohol (0.2 g/kg)	-5.5%/0.6%*	-7.1%/-10.9%*	-2.9 %/4.7 %*	-3.1 %/4.6 %*
Ibuprofen (600 mg)	0.0%	0.0%	-4.3 %	-0.9 %
Mannose (15000 mg)	0.2%	0.5%	-3.2 %	4.4 %
Xylose (15000 mg)	0.0%	0.0%	-2.0 %	3.5 %
3Ω-fatty acids (2000 mg)	0.1%	-0.1%	-5.3 %	-5.6 %

*There was no interference for the CoG modules vs. YSI. However, there was an interference observed (-11%) for the YSI device when compared to COBAS. Therefore, the MARD regression analysis was also performed for the CoG modules vs. COBAS. The results are indicated by the Asterix.

There was no interference of alcohol observed for the non-invasive module vs. COBAS, but the invasive module showed a slope of – 11% of the MARD regression curve. This finding, however, translates clinically into a too low reading by 11% in case that the user has an alcohol level of 1.0 o/oo, or ~20% too low readings at an alcohol level of 2 o/oo. These plasma alcohol values indicate that the user is drunken or already intoxicated, respectively.

In conclusion, uptake of substances with established acute and pronounced immediate or short-term impact on nutritional blood flow and microcirculation, and which may therefore modify the tissue composition as taken up by the employed non-invasive technology in the fingertip had no relevant impact on the non-invasive CoG module performance. The invasive module was also not modulated in its performance by any substance, except for a minor impact of ethyl alcohol at higher concentrations, which should be mentioned in the instructions for use as a caution to the users. Additional evaluation of the invasive module by means of laboratory samples was performed under a separate protocol of the CNG-NGM-006 study.

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Appendix A

Numbers in red color indicate missing values, which were replaced by either calculation of the mean of neighboring values, last observation carried forward of next observation carried backwards procedures**.**

Raw Data Acetaminophen

Pat No	Conc. [µg/mL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	< 5.0	0	98.9	83.0	83.0	89.0	97.2
	12.6	23	96.7	88.0	96.0	89.0	97.4
	12.8	30	100.9	102.0	92.0	90.0	98.8
	11.5	45	98.5	91.0	93.0	88.0	97.7
	6.7	105	97.5	88.0	89.0	91.0	95.3
	5.3	150	94.2	78.0	82.0	86.0	94.9
2	< 5.0	0	93	95	87	76	93.1
	16.7	23	89.1	92	94	76	90.2
	13.8	30	90.4	95	88	74	92.8
	12.6	45	97.2	94	93	82	96.5
	9	105	91.2	71	91	78	91.2
	7.1	150	89.2	81	91	85	90.5
3	< 5.0	0	92.3	87	83	82	89.9
	10.4	23	92.1	90	96	82	90.7
	9.2	30	93	88	93	87	92.5
	6.8	45	94.1	91	83	85	92.3
	< 5.0	105	86.6	84	81	83	88.5
	< 5.0	150	86.6	71	91	86	85.9
4	< 5.0	0	116	97	111	112	116.0
	10	23	108	97	103	100	106
	9	30	105	100	101	99	103
	7.7	45	103	90	98	97	102
	5.9	105	103	82	94	97	104
	< 5.0	150	97	98	90	94	96
5	< 5.0	0	97.1	87.0	88.0	89.0	97.5
	15	23	100.5	94.0	91.0	92.0	104.5
	13.7	30	103.5	92.0	113.0	97.0	106.5
	11.9	45	106.0	94.0	98.0	101.0	107.0
	9.7	105	100.5	115.0	89.0	100.0	100.5
	7.4	150	97.5	84.0	92.0	95.0	98.0
6	< 5.0	0	106	111	109	102	107
	10.4	23	110	107	123	108	110
	10.1	30	109	128	115	104	111
	12.2	45	107	101	114	105	107

Pat No	Conc. [µg/mL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
	10.6	105	105	126	104	104	106
	7.8	150	106	124	109	107	105
7	< 5.0	0	88.9	76	73	82	90.7
	18.9	23	90.9	74	82	80	90.4
	16.1	30	91.8	76	87	83	92.3
	15.4	45	88.7	94	87	82	89.6
	11.7	105	91.2	78	86	84	91.9
	9.3	150	87.3	80	86	82	90.3
8	< 5.0	0	84.9	74	83	80	86.2
	15.7	23	86.1	94	86	81	89.3
	16.9	30	87.6	96	89	82	89.3
	16.7	45	91.5	91	86	83	91
	15.5	105	90.5	77	84	84	90.8
	12.9	150	85.3	76	81	85	86.7
9	< 5.0	0	107	101	95	105	108
	8.2	23	107	93	106	105	106.5
	11.6	30	111	95	81	104	109
	9.1	45	113	93	99	107	112
	< 5.0	105	105	94	102	103	106
	< 5.0	150	101.5	94	99	100	102
10	< 5.0	0	90	85	81	82	90
	15	23	90	98	88	82	90
	13.1	30	90	97	91	83	88
	12.3	45	90	99	83	80	88
	7.2	105	88	80	82	83	87
	5.2	150	85	91	84	82	87

Raw Data Ascorbic Acid

Pat No	Conc. [mg/L]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	5.3	0	96.3	87	90	92	96
	13	30	98.3	89	99	90	97.5
	23.4	120	90	105	88	83	89.9
	20.5	240	92.4	77	87	70	91.8
	17.5	300	93.9	84	92	81	94.8
	15.5	480	86.5	86	79	78	85.5
2	12.2	0	88.5	90	85	78	87.5
	19.4	30	90.4	91	95	86	91.5
	30.6	120	85.7	94	96	72	86.3
	33.2	240	95.2	101	111	82	97.6
	29.4	300	80.4	81	94	73	81.8
	22.7	480	109	92	117	93	109.5
3	6.4	0	93.8	77	92	86	94.9
	13.9	30	95.3	98	95	84	93.6
	21.2	120	88.2	95	94	86	87
	17.7	240	83.3	80	78	70	84.5
	15	300	86.8	78	86	73	85.4
	12.5	480	115	115	122	102	113
4	4.2	0	106.5	90	99	102	104
	9.2	30	102.5	96	94	100	101.5
	27.4	120	91.5	84	92	85	90.5
	17.4	240	117	108	119	112	114
	17.4	300	95.8	92	92	93	97.6
	9	480	103.5	87	91	86	100.5
5	7.4	0	109.5	105	108	106	109
	20.1	30	113.5	105	99	109	115.5
	25.8	120	108	94	82	100	107
	17.5	240	93.4	77	85	84	95.7
	16.1	300	85.4	78	80	77	87.4
	13.2	480	71.3	61	65	60	71.4
6	5.9	0	103.5	95	102	106	107
	13.9	30	107	121	102	106	107
	22.8	120	99.4	106	114	99	98.7
	15.7	240	114	105	113	101	113.5

Pat No	Conc. [mg/L]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
	14.9	300	87.8	86	92	81	88.4
	11.9	480	104.5	109	80	90	104
7	8.1	0	86.6	78	86	81	88.9
	14.2	30	86.3	90	91	83	84.8
	21.7	120	86.7	78	89	81	84.5
	19.5	240	92.3	78	90	81	94.2
	16.2	300	86.4	82	83	83	85.7
	14.7	480	94.9	92	93	79	95.4
8	10.9	0	85.3	90	85	76	87.4
	20.9	30	89.7	88	88	82	89.8
	29.2	120	89.3	92	87	81	89.7
	20.2	240	76.2	71	63	67	78.2
	18.5	300	80.6	81	82	76	80.9
	13.3	480	114	111	108	90	116.5
9	39.2	0	102	95	108	98	101
	57.4	30	101	96	105	101	102
	53.7	120	99.6	93	90	98	97.5
	34.8	240	107.5	97	108	94	107
	31.2	300	90	95	96	82	88.8
	21.8	480	118.5	96	106	96	118
10	10.4	0	94.4	82	81	90	94.6
	16.2	30	96.3	97	83	92	96.9
	24.2	120	90.7	90	92	83	89.6
	17.6	240	92.5	75	84	70	91.1
	16.8	300	81.5	72	72	71	82
	12.8	480	114.5	118	100	95	113

Raw Data Diclofenac

Pat No	Conc. [ng/mL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	< 3.0	0	99.85	90	85	95	102
	425	18	104.5	82	95	98	105
	390	30	104.5	80	93	96.5	105.5
	540	35	104.5	82	87	95	104
	1240	90	102.5	80	90	94	102.5
	905	100	102	83	99	95	103
2	< 3.0	0	89	93	88	80	89.5
	1410	18	89.1	93	91	81	91.1
	1750	30	87.3	93	91	78	88
	1750	35	90	88	89	77	87.9
	415	90	89.3	91	96	74	88.4
	385	100	87.3	92	82	74	87
3	11	0	95.5	79	86	92	97.6
	915	18	94.4	80	93	91	97.5
	1020	30	96.5	78	90	92	98.9
	1050	35	96.7	78	91	93	96.6
	1310	90	91	92	90	86	91.1
	970	100	90.2	78	81	89	89.8
4	< 3.0	0	102	100	89	97	102
	29	18	98.4	92	88	93	97.6
	100	30	94.7	94	93	90	95.7
	105	35	94.4	95	83	91	95.8
	55	90	93.3	91	82	89	92.3
	115	100	88.4	86	87	88	88
5	<3.0	0	97.2	86	92	93	99.5
	190	18	105	82	93	100	107
	755	30	102	84	91	95	103.5
	730	35	103	86	89	97	106
	430	90	93.2	83	85	89	96
	320	100	92.6	93	77	86	93.1
6	<3.0	0	105.5	94	103	103	104
	220	18	104	111	108	104	103.5
	550	30	105	108	105	103	105
	425	35	104	100	108	104	105

Pat No	Conc. [ng/mL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
	160	90	100.7	109	93	100	101
	125	100	103.5	97	109	101	103
7	<3.0	0	83.4	102	81	78	84.5
	1900	18	83	88	81	76	83.2
	1400	30	79.8	80	80	80	80
	1050	35	80.4	96	78	80	83
	490	90	84.2	90	78	81	86.7
	380	100	79.1	84	74	78	81.7
8	< 3.0	0	92	93	82	79	93.3
	2450	18	93.5	89	82	84	92.5
	1660	30	92.7	93	87	78	91.9
	1400	35	93.2	92	85	81	94.2
	1270	90	88.8	84	94	79	90.8
	1690	100	87.1	81	85	80	87.6
9	< 3.0	0	110	95	99	79	108.5
	2450	18	105.5	95	93	84	106
	1660	30	104.5	96	97	78	106
	1400	35	104.5	93	104	81	104
	1270	90	102	91	90	79	100.2
	1690	100	100.2	92	95	80	103
10	<3.0	0	96.6	104	91	92	96.4
	1370	18	99.9	95	89	94	98.8
	975	30	97.2	97	81	92	97.3
	1000	35	99.9	95	97	91	99.2
	650	90	98.8	95	99	91	100.9
	510	100	100	90	101	93	102

Raw Data Ibuprofen

Pat No	Conc. [mg/L]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	<1	0	88.3	72	79	79	87
	7.9	30	99.1	86	86	88	99.4
	11.3	45	96	88	87	87	97.6
	25.1	90	92.9	78	76	87	93.4
	40	135	94.5	87	81	87	95.1
	48.3	150	94	85	78	86	92.9
2	<1	0	93.7	95	87	80	91.6
	19.9	30	89.8	92	89	81	90.4
	32.9	45	89.2	92	91	78	91.6
	40.9	90	89.9	75	90	77	90.1
	38.7	135	87.2	77	88	74	86.3
	39.6	150	87.6	77	87	74	88.8
3	<1	0	87.9	78	80	82	91.4
	18.6	30	87.3	79	80	77	84.7
	26.5	45	84.2	82	71	76	86
	30	90	85.9	94	81	82	85.4
	28.8	135	89.1	95	81	81	90
	25.2	150	87.3	74	78	81	87.1
4	<1	0	79.9	66	64	73	81.4
	<1	30	79.1	76	69	77	78.4
	<1	45	80.7	71	70	76	81
	10.7	90	75.2	75	66	73	77.7
	23.2	135	76.7	76	67	73	76.1
	22.5	150	75.9	76	71	75	77.2
5	<1	0	104	85	92	107	103
	27.8	30	97.3	89	88	88	99.2
	34	45	100.2	89	87	95	99.7
	33.1	90	98.3	80	81	93	97.8
	27.5	135	92.9	76	75	82	93.8
	24.4	150	94.2	88	85	89	92.9
6	<1	0	109	107	105	105	107.5
	3.4	30	106.5	103	107	106	106
	4.1	45	105	111	99	104	104
	13.3	90	106	94	100	104	105.5

Pat No	Conc. [mg/L]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
	15.9	135	99.1	93	105	97	99
	17.9	150	99.9	94	97	96	101
7	<1	0	86.4	83	81	82	87.3
	16.5	30	82.5	81	76	81	83.9
	23.8	45	84.5	80	74	82	84.5
	49.9	90	84.1	77	80	85	85.3
	43.7	135	82.7	76	81	86	86.7
	40.1	150	88	75	77	88	91.5
8	<1	0	84.5	88	75	80	84.6
	43.9	30	85.2	87	71	77	85.2
	55	45	86	86	72	77	84.2
	58.7	90	82.9	85	74	74	82.7
	56.1	135	78.6	80	72	71	79.2
	51.1	150	76.6	80	77	71	76.4
9	<1	0	103.5	83	97	96	102.5
	9.3	30	104	89	96	95	103
	16.4	45	103.5	86	96	98	104.5
	15.8	90	103	85	93	96	101
	31.1	135	96.1	85	85	90	97.5
	30.9	150	96.6	86	90	89	96.9
10	<1	0	99.8	91	92	95	99.2
	24.5	30	94.7	90	90	92	96.5
	43.2	45	93.2	90	91	91	93.4
	41.7	90	92.3	80	88	87	94.6
	33.9	135	91.6	77	84	87	89.2
	27.7	150	93.1	80	78	88	94.2

Raw Data Ethyl Alcohol

Pat Nr	Alcohol [mL]	Conc. [o/oo]	Time [min]	Glucose results				
				YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	48.8	< 0.08	0	99	92	87	94	101.5
		0.21	18	101	90	99	94	102.5
		0.38	30	97.5	90	96	94	97.2
		0.36	35	98.8	88	96	93	96.3
		0.12	95	91.1	84	88	84	93
		< 0.08	120	91	84	86	83	90.4
2	65.6	< 0.08	0	93.4	92	99	90	92.1
		0.5	18	94.9	89	99	96	96.7
		0.58	30	93.7	96	106	92	93.8
		0.54	35	93.4	91	91	92	93.9
		0.25	95	85.9	88	87	79	84.5
		0.22	120	86.3	88	93	78	86.2
3	62.5	< 0.08	0	97.4	78	91	92	96.5
		0.21	18	96.1	94	92	91	95.2
		0.35	30	92.8	96	88	91	92.6
		0.3	35	92.2	93	88	90	92.2
		0.09	95	84.6	95	86	78	84.4
		< 0.08	120	80.5	95	83	76	80.7
4	58.8	< 0.08	0	99.3	89	93	95	102
		< 0.08	18	103.5	87	94	101	104
		0.27	30	99.9	100	98	99	102
		0.28	35	99.9	100	100	97	101
		0.09	95	90.9	89	88	89	89.7
		< 0.08	120	86.1	96	96	84	88.1
5	60.6	< 0.08	0	107.5	90	107	102	107
		0.24	18	112.5	96	107	114	113
		0.37	30	111	96	107	107	108
		0.33	35	109	103	107	110	109
		0.11	95	95.7	96	98	93	97
		0.1	120	93.8	96	92	91	92.8
6	56.3	< 0.08	0	105.5	94	98	105	106
		0.24	18	115	95	109	115	114
		0.36	30	114	96	112	111	114
		0.39	35	112	99	105	112	112

Pat Nr	Alcohol [mL]	Conc. [o/oo]	Time [min]	Glucose results				
				YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
		0.2	95	106	94	109	103	104
		0.13	120	97.7	95	105	99	98.1
7	40.0	< 0.08	0	87.9	76	81	77	87
		0.13	18	84.6	74	83	80	84.9
		0.24	30	82.3	76	80	76	83.3
		0.22	35	83.4	72	72	74	84.7
		0.09	95	82.1	73	72	72	82.1
		< 0.08	120	81.6	78	81	71	82.6
8	31.8	< 0.08	0	96.3	89	91	92	96.2
		0.21	18	91.6	100	94	84	91
		0.24	30	91.4	96	87	79	89
		0.28	35	88.8	94	90	85	87.5
		0.13	95	85.5	91	83	79	87
		0.09	120	84.7	89	78	81	87.3
9	68.8	<0.08	0	105.5	103	96	102	104.5
		0.19	18	107	110	97	105	107
		0.31	30	103	109	109	99	104
		0.2	35	101	111	96	99	103
		<0.08	95	95.3	88	89	91	95.2
		<0.08	120	92.2	83	81	88	92.6
10	39.1	<0.08	0	94	88	81	85	93.9
		0.3	18	92.4	90	81	83	92.1
		0.24	30	89.1	86	84	82	91.3
		0.24	35	92.2	87	80	80	93.8
		0.08	95	87.2	77	83	74	90.9
		<0.08	120	87.2	80	80	69	88.2

Raw Data Caffeine

Pat Nr	Conc. [µg/mL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	<1.0	0	94.9	92	86	92	95.6
	4.5	30	97.4	95	89	93	98.5
	3.8	45	99.8	94	88	94	100.4
	3.3	60	98.7	97	86	93	99
	2.8	120	96.4	89	86	93	96.8
	1.4	360	90	65	75	84	90.3
2	2.3	0	90	102	90	87	92.2
	7.4	30	89.7	104	88	88	90.7
	6.2	45	92	100	94	87	90.7
	6.1	60	89.6	99	83	84	89.9
	5.4	120	88.7	98	98	81	89.7
	7.9	360	101.5	108	105	82	101.5
3	1.1	0	93.9	79	92	89	95.7
	3.8	30	91.8	81	104	88	94.1
	3.3	45	92.5	100	97	88	93
	3.1	60	92.1	82	94	85	94.7
	2.8	120	90	97	90	85	88.2
	3.7	360	85.3	83	83	69	87.3
4		0	75.5	80	72	73	72.9
	2.4	30	80	83	76	77	79.7
	3.4	45	86.9	81	82	83	88.3
	2.9	60	86.7	89	83	84	88.7
	2	120	78.9	77	79	78	82.2
	2	360	94	91	98	75	91.2
5	<1.0	0	104	92	100	101	104.5
	3.8	30	93.4	85	81	92	93.9
	3.4	45	95	97	90	93	97.8
	3.5	60	98.2	97	95	93	99.5
	2.9	120	96.3	71	81	95	95.6
	1.9	360	74.8	80	73	72	75.4
6	<1.0	0	102	101	98	96	102
	4.3	30	102	122	105	99	101
	5.1	45	99.1	123	105	96	101
	4.7	60	99.2	99	106	98	101.5

Pat Nr	Conc. [µg/mL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
	4	120	99.6	120	105	99	99.1
	7	360	87.8	98	111	73	88.5
7	<1.0	0	87.1	97	81	85	86.4
	4.8	30	86.2	92	89	87	85.8
	4.6	45	82.2	94	81	86	84.9
	5.1	60	84.7	95	88	86	78.8
	3.7	120	83.3	94	87	90	86
	2.1	360	86.9	88	84	92	89.8
8	<1.0	0	91.1	89	79	87	93.4
	5.6	30	99	88	75	89	97.3
	6.3	45	96.7	73	84	91	96.7
	5.8	60	98.9	80	81	92	99.5
	5.3	120	94.9	97	95	91	94.3
	4.2	360	87	84	77	79	88.3
9	4	0	107	103	109	104	105
	6.5	30	105.5	105	103	102	105
	5.9	45	106.5	103	113	102	105.5
	5.8	60	107	103	110	99	105
	4.8	120	103	110	110	101	105
	2.9	360	95.5	94	104	90	97.4
10	3.1	0	90.2	81	77	86	91.2
	< 1.0	30	92.4	79	89	87	91.7
	1.6	45	94	82	91	90	94
	3.8	60	93.5	88	88	89	96.5
	2.8	120	95.5	87	93	88	95
	3.5	360	90.4	81	81	90	89.4

Raw Data Acetyl Salicylic Acid

Pat Nr	Conc. [µg/mL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	<3.0	0	99.8	93	100	94	99.4
	4.5	10	101	93	91	97	100
	48.1	20	101	94	103	98	101.5
	36.7	30	100	91	90	96	100
	31.4	60	97	95	93	94	97.8
	28.2	90	96.7	86	91	92	96.4
2	<3.0	0	81.9	101	82	68	85.3
	<3.0	10	85.4	89	81	72	88.1
	15.1	20	86.3	84	82	74	89.3
	26.9	30	87	87	82	69	90.8
	22.7	60	88	92	89	67	88.5
	19.3	90	86.5	94	81	75	85.5
3	<3.0	0	84.2	75	80	80	86
	13.2	10	85.5	85	85	82	85.7
	19	20	84.7	86	82	81	87.2
	16.6	30	86.5	86	86	81	87.2
	13	60	82.1	87	88	78	85.4
	8.5	90	82.8	87	84	78	84.4
4	<3.0	0	116	90	103	112	116.5
	<3.0	10	112	96	93	110	114
	30.7	20	112	97	92	110	114
	27.7	30	112	93	94	107	111
	22.4	60	106.5	96	98	104	107.5
	20.1	90	102	96	99	98	99.3
5	<3.0	0	101.5	84	87	103	104
	<3.0	10	103	107	99	104	100
	27.7	20	104	83	86	103	104.5
	26.5	30	104	101	110	104	103.5
	23	60	98.9	96	91	97	101.5
	19.5	90	94.2	83	91	92	96.6
6	<3.0	0	108.5	121	99	108	110
	<3.0	10	109	99	93	108	111
	40.9	20	111	104	108	110	112
	40.1	30	113.5	123	106	110	114

Pat Nr	Conc. [µg/mL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
	35.3	60	108	122	104	108	109
	30.8	90	106.5	115	97	105	106.5
7	<3.0	0	82.1	82	71	76	83.2
	4.8	10	79	78	75	78	82.8
	41.2	20	82.9	79	75	78	86.1
	39.6	30	82.1	81	78	79	85.3
	34.9	60	85.9	70	77	79	85.3
	30.7	90	88.2	85	79	79	87.2
8	<3.0	0	86.9	71	74	83	88.4
	17.6	10	88.7	78	74	80	89.2
	52.1	20	85.7	70	75	78	85.9
	52.7	30	86.4	70	74	79	86.9
	45.7	60	83.7	84	78	77	82.2
	42.9	90	80.9	84	74	75	81.1
9	<3.0	0	104.5	109	102	99	104
	5.2	10	104.5	114	105	98	106
	31.8	20	103	111	105	98	104
	27.8	30	103.5	93	95	97	105
	21.6	60	101	96	103	94	98.9
	18.5	90	99.6	90	94	96	101.5
10	<3.0	0	79.2	76	78	72	81.6
	22.4	10	84.4	99	89	71	86
	35.9	20	83.7	80	79	75	83.2
	36.4	30	82.9	78	71	75	83.9
	33.1	60	80	73	79	73	82.2
	29	90	79.2	77	77	69	79.5

Raw Data Xylose

Pat Nr	Conc. [mg/dL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	15.5	0	97.4	93	87	94	98.1
	197	30	99.2	95	95	94	98.5
	197	45	97.5	94	89	93	100
	172	60	95.6	93	93	89	97.2
	142	90	96.4	93	90	92	97.8
	125	120	96.8	86	85	89	96.9
2	9.2	0	92.3	89	91	80	92.8
	121	30	89	92	91	81	88
	141	45	90.2	90	91	78	91.3
	124	60	86.3	91	89	70	85.6
	106	90	86	89	93	74	87.7
	89.7	120	82.4	88	90	75	85.4
3	9.6	0	92.6	80	85	84	90.7
	142	30	87.6	79	84	78	89
	137	45	90.8	79	88	82	89.9
	113	60	90.4	80	93	80	92.3
	94.8	90	90.3	98	91	80	90.4
	81.5	120	88.3	76	90	80	88.3
4	27.9	0	108	94	97	109	111.5
	99.4	30	109	94	103	109	109.5
	173	45	107	94	86	104	105.5
	163	60	103.5	95	88	102	105
	129	90	98.4	94	90	96	97.9
	114	120	96.7	93	85	93	97.1
5	15.1	0	95.7	84	93	101	98.2
	141	30	103.5	81	91	104	104
	178	45	98.3	82	84	97	99.9
	172	60	98.7	83	84	98	100
	136	90	94.1	84	83	93	93.8
	136	120	92.8	93	85	72	93.4
6	18.4	0	107.5	98	97	102	108
	140	30	105.5	110	101	102	105
	148	45	107	97	97	101	107
	137	60	108.5	92	92	104	108

	113	90	108	105	97	107	109
	96.1	120	108.5	95	98	107	110.5
7	14	0	81.1	83	78	81	82.4
	118	30	78.3	73	74	79	79.8
	133	45	78.1	81	74	75	79.8
	164	60	79.6	79	74	79	81.5
	134	90	82.9	81	76	78	84.2
	106	120	78.6	72	68	79	80
8	14.5	0	83.6	92	81	81	85.6
	159	30	86	90	83	81	85.1
	215	45	83.2	85	76	79	83.1
	187	60	81.7	73	66	77	82.8
	163	90	84	76	74	75	84.4
	137	120	83.1	73	79	80	83.8
9	27	0	105	109	103	98	104.5
	107	30	102	103	99	94	101.5
	103	45	101	102	107	96	101.5
	91.2	60	100	104	96	94	102.5
	91.4	90	101	87	96	93	99.6
	83	120	99.4	86	99	93	98.6
10	15	0	92.6	77	83	86	93.5
	119	30	89.7	79	83	83	90.7
	173	45	87.5	76	76	80	89.2
	179	60	90.4	80	79	79	92.2
	155	90	87.1	79	84	79	88.9
	120	120	87.7	77	75	82	88.4

Raw Data Mannose (MAX = 100 mg/dL)

Pat Nr	Conc. [mg/dL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	20.3	0	99.4	94	89	91	99.4
	20.9	30	95.2	92	86	83	94.9
	16.6	45	91.9	94	75	83	93.2
	15.8	60	92.3	94	82	83	95.1
	16.8	90	91.2	86	84	80	92.9
	19.0	120	91.1	85	80	79	93.2
2	12.8	0	88	89	88	83	89.7
	14.6	30	86.3	74	80	80	87.4
	16.7	45	84.8	77	83	78	87.1
	19.2	60	85.1	74	79	76	87.7
	14.5	90	84.1	91	84	75	83.1
	14.9	120	82	76	75	74	82.3
3	18.5	0	93.2	81	91	87	93
	23.1	30	88.9	78	87	84	89.7
	22.4	45	87.7	80	79	78	87.2
	19.6	60	85.9	79	77	78	85.7
	16.2	90	84.5	78	76	74	85.4
	22.2	120	84.2	80	84	80	86.4
4	12.2	0	82.9	72	76	80	83.5
	13.7	30	83.7	76	74	79	85
	13.7	45	80.9	72	73	78	82.7
	12.9	60	81.2	70	70	78	81.7
	11.8	90	76.6	67	68	76	78
	14.6	120	79.9	73	73	77	80.7
5	99.2	0	99.4	82	97	92	102
	>Max	30	102	84	98	96	101
	85.7	45	98.1	84	85	92	99
	34.3	60	98.4	83	81	91	97
	99.2	90	93.9	97	84	88	92.4
	66.8	120	88.1	78	80	85	88.8
6	6.7	0	107	99	94	101	106.5
	8.7	30	102	102	104	98	105
	7.8	45	104	98	91	97	105
	7.8	60	102	104	97	95	102

Pat Nr	Conc. [mg/dL]	Time [min]	Glucose results				
			YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
	8.8	90	102	90	92	99	104
	7.0	120	100.5	99	102	94	104
7	9.7	0	92	76	88	87	92
	8.8	30	86.6	96	96	80	87.5
	8.9	45	86.1	86	90	75	87.6
	9.1	60	86.8	93	83	79	89
	10.9	90	86.3	78	85	79	88.4
	11.9	120	88.5	79	89	79	88.3
8	18.5	0	88.8	91	83	89	91.9
	17.0	30	86	74	74	83	89.7
	14.4	45	85.3	81	75	82	85.8
	15.2	60	85.8	78	74	82	86.3
	13.4	90	86.1	74	75	80	84.8
	17.4	120	85.1	75	80	84	86.6
9	3.8	0	108.5	112	107	98	106
	3.6	30	107	111	108	98	109
	3.1	45	109	110	115	100	107.5
	2.8	60	104.5	108	115	96	104.5
	3.0	90	102	110	105	95	103.5
	3.0	120	102	107	98	93	101.5
10	> Max	0	104.5	90	91	89	105
	> Max	30	95.1	82	87	89	96.6
	> Max	45	92.7	90	83	91	90.2
	> Max	60	91.4	82	82	85	91.9
	> Max	90	92.9	92	92	87	93.3
	> Max	120	90.7	95	85	83	88.3

Raw Data 3Ω-Fatty Acids

Pat Nr	Conc. [mg/dL]				Time [min]	Glucose results				
	αLA	EPA	DHA	3ΩFA		YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
1	25.2	32.1	98.1	155.4	0	107	93	93	100	107
	25.4	31.5	90.5	147.4	30	104	101	98	96	106.5
	23.7	31.6	96.8	152.1	150	99.8	89	92	87	97.6
	30.1	44.1	112.1	186.3	300	101	102	92	81	100.2
	27.1	37.9	103	168	330	98.8	102	98	81	99.1
	27.1	37.9	103	168	360	92.2	98	88	82	91.4
2	13.2	15.5	70	98.7	0	99.5	102	111	86	99.3
	13.9	15	68.3	97.2	30	96.4	102	103	88	97.8
	14.3	20.9	78.4	113.6	150	92.7	91	89	89	95.2
	13.8	26.5	84.4	124.7	300	89.4	80	85	85	87.3
	16.7	29.6	86.8	133.1	330	86.4	84	88	87	89
	14.5	24.5	81.9	120.9	360	92.1	74	82	89	92.6
3	17.3	22.6	36.5	76.4	0	95.9	79	83	89	96.8
	19	25.1	46.7	90.8	30	96.2	82	78	90	96.3
	14.7	20.7	42.2	77.6	150	91.7	74	85	83	91.7
	53.4	45.5	69.7	168.6	300	128.5	118	121	113	128.5
	40.5	35.6	54.4	130.5	330	131.5	134	131	117	130
	64.9	48.1	72.9	185.9	360	128.5	145	135	103	130.5
4	21.6	16.4	80.3	118.3	0	89.1	95	80	88	90.2
	18.4	15.8	77.7	111.9	30	87.9	76	73	84	90.1
	15.1	16.5	79.7	111.3	150	75.4	86	76	77	79.3
	19.3	21.7	87.4	128.4	300	153.5	116	136	125	153
	18.1	20.9	85.7	124.7	330	157	136	126	133	159.5
	18.6	22	83.5	124.1	360	130	110	112	103	128.5
5	27.7	27.5	69.6	124.8	0	112.5	83	91	106	117
	34.5	28.9	71	134.4	30	103	83	88	94	105
	19.5	33.7	70.5	123.7	150	94.1	83	88	92	94.6
	18.4	38.6	73.4	130.4	300	91.7	76	80	84	92.2
	19.6	39.1	76.8	135.5	330	80.9	74	80	77	81.3
	15.6	33.6	68	117.2	360	74	74	72	71	74.7
6	18.9	20.1	90.5	129.5	0	94.1	95	92	91	95.4
	19.4	21.1	94.2	134.7	30	99.3	101	97	92	99.1
	20.6	22.5	101.3	144.4	150	97.4	96	97	95	99.1
	18.8	26.5	106.5	151.8	300	102	95	92	84	102.5

Pat Nr	Conc. [mg/dL]				Time [min]	Glucose results				
	αLA	EPA	DHA	3ΩFA		YSI 1	COG non.inv	COG inv.	Cobas	YSI 2
	21.2	28.9	114.5	164.6	330	99	97	100	88	99.8
	19.2	26.1	107.4	152.7	360	108	102	104	95	109.5
7	22.1	10.7	63.9	96.7	0	86.3	77	74	82	87.9
	20.9	10.3	61.9	93.1	30	90	83	83	87	90.6
	20.1	12.8	67.8	100.7	150	84.9	74	80	89	88.9
	30.7	24.4	73.2	128.3	300	110.5	102	102	93	113.5
	47.7	24.6	75.9	148.2	330	120	118	105	94	119
	36	20.9	71.2	128.1	360	115	117	120	105	121.5
8	15	16.4	25.9	57.3	0	85.5	65	70	81	86.4
	16.1	15.4	31.6	63.1	30	91.8	76	73	83	91.1
	15.6	17	34.6	67.2	150	91.2	74	80	87	93.5
	51.2	35.7	50.3	137.2	300	105	83	89	89	104.5
	40.9	41.2	50.1	132.2	330	129	126	124	121	130
	48	36.1	44.9	129	360	116	97	107	94	116
9	47.8	38	81.8	167.6	0	111.5	106	105	109	111
	46.4	35.9	79.6	161.9	30	110.5	102	99	106	110
	67.5	43.5	93.1	204.1	150	105	88	93	102	104
	71.4	43.8	92.9	208.1	300	117	91	102	102	117.5
	69.7	42.2	92.6	204.5	330	112.5	96	102	109	112.5
	53.8	38.7	86.7	179.2	360	97.3	88	86	91	96.4
10	15.9	13.7	76.6	106.2	0	89.5	86	89	85	91.4
	13.9	13.4	77	104.3	30	89.4	83	81	84	92
	13	16	81.8	110.8	150	88.9	88	82	84	91.1
	14.1	27	90.9	132	300	122	117	121	105	124
	17.4	27.8	96.9	142.1	330	121.5	113	111	101	120
	16.6	25.9	93.7	136.2	360	125.5	123	120	97	129.5