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Gastrointestinal thermal homogeneity and effect of cold water ingestion

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ABSTRACT

Purpose: Gastrointestinal temperature (GIT) is a common alternative for body core temperature (CT) monitoring via an ingestible pill connected to an external monitor. However, its reliability could depend on thermal homogeneity, regardless of the gastrointestinal tract location. The purpose of this study was to evaluate GIT variation during the transit of telemetric pills and the impact of cold drink ingestion compared to the time point of pill intake.

Methods: Twenty-three healthy participants ingested six e-Celsius electronic pills, one every five hours, and they ingested 150 milliliters of cold water (5 +/− 1 °C) 1, 2, 3, 4, 8, and 12 h following the first pill ingestion.

Results: The recorded temperature remained similar between pills consecutively ingested by each subject, regardless of the internal location within the gastrointestinal tract, supporting the homogeneity of GIT. GIT monitoring was significantly affected by ingestion of a cold drink two hours (-0.8 ± 0.2 °C; $p = 0.001$) and three hours following pill ingestion (-0.9 ± 0.2 °C; $p < 0.001$) in all subjects, and abnormal drops in GIT were observed in 22% of subjects up to twelve hours following pill ingestion.

Conclusion: Temperature may be considered homogenous all along the internal intestinal tract and correlates with CT, supporting telemetric monitoring as an efficient method for monitoring temperature. The interaction between GIT measurements and substance intake has to be taken into account. To avoid the effect of substance ingestion on CT data, we recommend users to employ the pill as a rectal suppository or to mark every substance ingestion time and/or allow only tepid water and food intake.

1. Introduction

Evaluating internal human temperature is one of the oldest diagnostic methods (Atkins, 1987) and still has a major impact on diagnostic procedures and follow-up in medicine. Body core temperature (CT) measurement is fundamental in many other situations which require continuous temperature measurement, including evaluation of thermoregulatory responses during prolonged exercise (Chapon et al., 2012) or temperature monitoring during exposure to extreme weather or physical working conditions (Rav-Acha et al., 2003). Temperature is also one of the most widely accepted markers of circadian rhythmicity (Hofstra and de Weerd, 2008). Moreover, in post-surgery intensive care, and particularly perioperatively, it is extremely important to follow temperature continuously (Calonder et al., 2010). Rectal, esophageal or other invasive measurement techniques are generally unsuitable for performing continuous temperature monitoring due to practical reasons and discomfort for the subject whereas non-invasive devices are less reliable (Lim et al., 2008). For this reason, the non-invasive ingestible gastrointestinal (GI) telemetric pill has recently been developed.

The GI pill continuously collects and transmits temperature data to a dedicated monitor. Several studies have reported that gastrointestinal temperature (GIT) is a valid measure of CT (Byrne and Lim, 2007). However, thermal GI homogeneity must be demonstrated because of its strong relevance in CT measurements using telemetric systems (Edwards et al., 2002; Kolka et al., 1993). In addition, the temperature of a pill located in the stomach or upper GI tract can be influenced by food and drink (Brake and Bates, 2002; Burdon et al., 2013; Fox et al., 1962; Kolka et al., 1993), and there is a lack of empirical evidence detailing the extent and duration of the effect of ingested fluids on GI pill temperature measurement.

Wilkinson et al. (2008) investigated the effect of cold water ingestion on GI pill temperature. These authors tested the effect of a substantial amount (250 mL) of cold water (5–8 °C) up to 8 h after pill ingestion. They showed that until 8 h after ingestion, the effects of cold water ingestion could be detected in some subjects. They advise waiting 10 h after pill ingestion to use GIT when water or food needs to be

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ingested. There is still a lack of data on the impact of food or drink ingestion on gastrointestinal temperature. The sensitivity of GIT recording to the smallest amount of water needs to be investigated. While Wilkinson et al. (2008) tested firefighters in hyperthermia conditions (during strenuous activity), to date the appropriateness of the pill for measuring individuals' temperature within daily living conditions needs to be established.

The main objective of this study was to evaluate GI thermal homogeneity and the effect of cold water ingestion on GI pill temperature.

2. Methods

2.1. Population

23 healthy volunteers (13 females and 10 males) aged 18–59 years participated in this study after providing written informed consent. The study was approved by the local ethics committee as well as the National Safety Agency for Medicines and Health Products (No. 2014-A01822-45). All experimental procedures were carried out in the Clinical Research Center of the University Hospital of Caen in France. Exclusion criteria for prospective participants were: pregnancy, weight < 40 kg or BMI > 30, signs of intestinal occlusion, diabetes, diverticula, inflammatory bowel disease, previous GI surgery, gag reflex or swallowing disorders, deviated nasal septum, need for a functional magnetic resonance imaging examination, and pacemakers. These criteria follow the contraindications of devices manufacturers.

2.2. Study design

The experimental protocol is illustrated in Fig. 1.

Subjects stayed at the hospital's research center for 27 h. After their arrival at 7.00 a.m., they ingested the first e-Celsius pill during breakfast at 8.00 a.m. We assessed the impact of cold drinks at six specific times after the first pill ingestion. One hour after the ingestion of the first pill, subjects were requested to drink 150 mL of cold water (5 +/ − 1 °C). This procedure was repeated 2, 3, 4, 8, and 12 h after the first pill ingestion (see Fig. 2). In order to assess the thermal homogeneity of the digestive tract, other e-Celsius pills were ingested every 5 h (1:00 p.m., .6:00 p.m., 11:00 p.m., 4:00 a.m., 9:00 a.m.). Each pill had their own identification numbers in order to differentiate them.

Subjects had lunch at 11.00 a.m. and dinner at 6.00 p.m. The food corresponded to the hospital's menu of the day without stimulant beverages. After dinner, subjects were not allowed to eat until the end of the experiment in order to evaluate digestive tract temperature homogeneity without any alimentary interference. Participants were allowed to do some very low intensity activities, such as watching TV or reading and stayed in their room. Subjects followed their usual sleeping habits.

The e-Celsius pills used in the current study were calibrated using thermostated water bath successively heated to 35, 37 and 39 °C. A thermostat bridge (JULABO®, model SE, Germany) was placed on the bath along with a heating and stirring system. This thermostat bridge was equipped with an internal temperature sensor. A PT-100® was connected to the thermostat bridge. The reported resolution of the thermostat bridge and PT-100 is 0.01 °C and the uncertainty of the system is 0.07 °C. Each pill was immersed for at least 20 min. Temperatures were then predicted with a 3-point regression line.

2.3. Data collection

Participants were monitored with the e-Celsius system. The e-Celsius® pill is 17.6 mm long, 8.6 mm in diameter, and 1.2 g in weight, with an accuracy of 0.2 °C and a temperature range of 29–45 °C. Temperature data were sampled and transmitted every 30 s and the pill includes an internal memory to avoid missing data in case of transmission failure.

2.4. Data analysis

To assess the effect of cold drink ingestion at each time tested (see Fig. 2), we compared the mean temperature of data collected for 5 min before and 5 min after each cold drink ingestion. Missing data represent 6.9% of data and were fairly well distributed between each time tested. To evaluate thermal homogeneity of the gastrointestinal tract, we retained the 30-min mean temperature values for each pill. The temperature period considered for thermal homogeneity analysis was from 9:30 a.m. to 10:00 a.m. on the second day of the experiment, i.e. 30 min after the last pill was ingested. Missing data represent 8.7% of data and were fairly well distributed between each pill.

2.5. Statistical analysis

Statistical analyses were carried out using R 3.1.2 software (www.r-project.org). To capture the effect of cold drink ingestion and evaluate the homogeneity of the gastrointestinal tract, we selected a linear mixed model (LME). For each LME, heteroscedasticity was integrated into the residual variance function. To assess whether a variable had a significant effect, the approach of Pinheiro and Bates (2000) was followed. Models with and without the respective variable were compared by means of a likelihood ratio test (LRT). The core statistical result of this model comparison was expressed as the likelihood ratio L.r. value

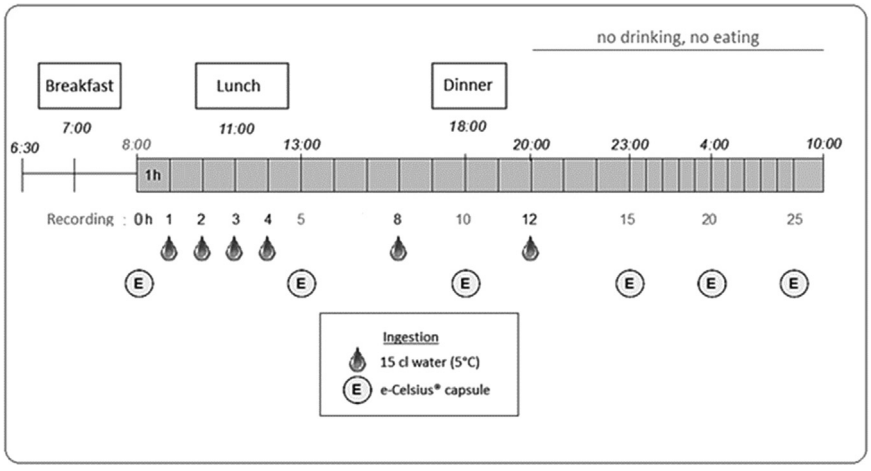

Fig. 1. Protocol summary.

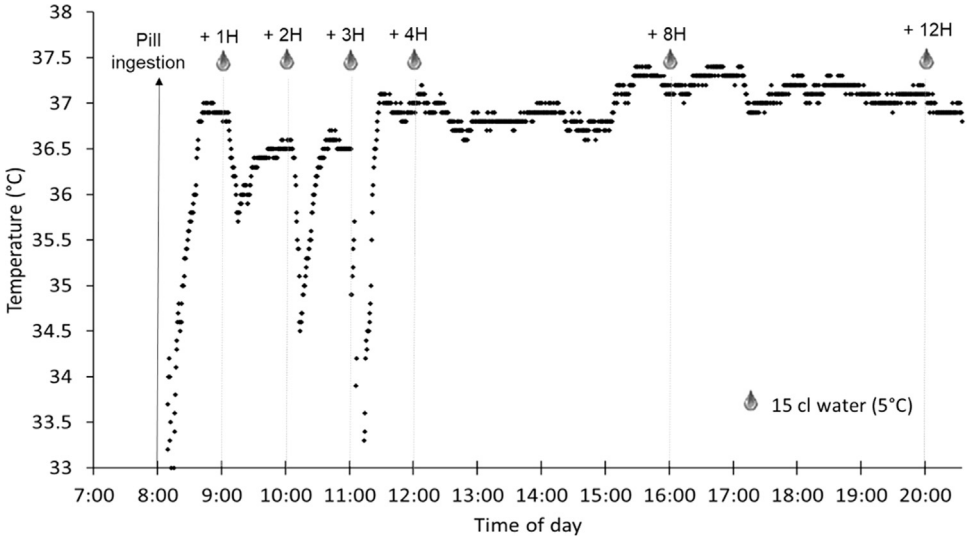

Fig. 2. Gastrointestinal temperature of participant no.14 starting from pill ingestion (8.00 a.m.) with effect of cold drink ingestion at 9.00 a.m. (+1 H), 10.00 a.m. (+2 H), 11.00 a.m. (+3 H), 12.00 p.m. (+ 4 H), 4.00 p.m. (+8 H), and 8.00 p.m. (+12 H).

and the associated *p*-value. (e.g., L.r. = XX; p = XX, in the Results section below). When the LRT indicated a significant effect of a variable ($p < 0.05$), the Tuckey HSD test was used for post hoc analysis. The level of significance was set at $p = 0.05$. Power to detect difference (1 – probability of type II error) were calculated for each non-significant result. Observational error between pills were measured using standard deviation for each individual.

3. Results

3.1. Effect of cold drinks on GIT

We observed a pre - post ingestion effect (L.r. = 6.81; $p = 0.009$) of cold drinks on GIT and a time of cold drinks ingestion effect (see Fig. 2), (L.r. = 35.82; $p < 0.001$). Fig. 3 shows ingestion time effects on GIT. Cold drinks had an impact on GIT when ingesting 2 h (−0.8 ± 0.2 °C; $p = 0.001$) and 3 h after pills swallowed (−0.9 ± 0.2 °C; $p < 0.001$) (Table 1). Cold drinks tend to decrease GIT one hour after pills swallowed, though non significantly (−0.6 ± 0.2 °C; $p = 0.073$). No effect of cold drinks ingestion were observed 4, 8 and 12 h after ingestion (Table 1, Fig. 3). However, even 12 h after pill ingestion, we noticed an abnormal temperature depression in 5 subjects. A 3-fold decrease in temperature variation exceeded the standard deviations of the mean value collected during the 5 min preceding water ingestion. The pre – post ingestion difference in these subjects were respectively −3.2 °C (S6), −0.2 °C (S14), −0.2 °C (S21), −0.5 °C (S22), and −1.7 °C (S23).

Table 1
Post hoc Tukey test comparing pre - post temperature revealed by GI telemetry pill at different cold water ingestion time after GI telemetry pill swallowed.

Post ingestion time	pre - post temperature (°C)	Standard error (°C)	z	*p*
1 h	−0.58	0.23	2.49	0.073
2 h	−0.83	0.23	3.66	**0.001**
3 h	−0.92	0.23	3.92	< **0.001**
4 h	−0.07	0.22	0.31	1.000
8 h	−0.53	0.23	2.28	0.127
12 h	−0.06	0.24	0.26	1.000

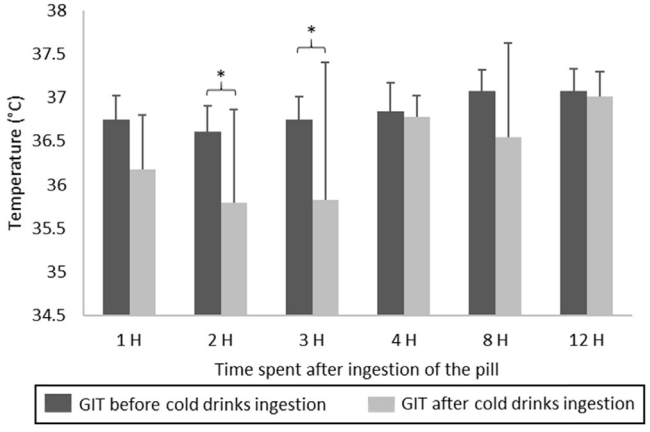

Fig. 3. Mean gastrointestinal temperature (GIT) (± SD) before and after cold drink ingestion at 9.00 a.m. (+1 H), 10.00 a.m. (+2 H), 11.00 a.m. (+3 H), 12.00 p.m. (+ 4 H), 4.00 p.m. (+8 H), and 8.00 p.m. (+12 H).

3.2. GI thermal homogeneity

The linear mixed model did not demonstrate any significant disparities between the six e-Celsius pills, although a trend was observed (L.r. = 9.32; $p = 0.097$) (Fig. 4). Statistical power was 0.67. The mean error between the six pills were 0.1 ± 0.1 °C. In two cases, individual

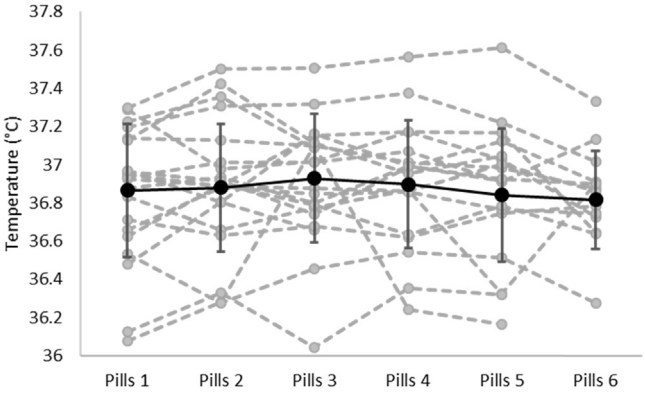

Fig. 4. Temperature recorded for 30 min by the 6 pills along the GI tract (n = 23). In black, the mean (± SD). In grey, the individual data of each subject. The temperature period considered for thermal homogeneity analysis was from 9:30 a.m. to 10:00 a.m. on the second day of the experiment, i.e. 30 min after the last pill was ingested.

error exceeded 0.2 °C. The error between the six pills in these subjects were respectively 0.3 °C (S14) and 0.4 °C (S19).

4. Discussion

In this study, we found that cold water had an impact on gastrointestinal temperature up to 3 h after pill ingestion ($p < 0.001$). Surprisingly, we observed only a statistical trend 1 h after ingestion (-0.6 ± 0.2 °C; $p = 0.073$) and supposed that the lack of significance could be linked to inter-individual variability in a small experimental group. Moreover, though not significant for the whole group, five participants in our study seemed to be affected 12 h after ingestion and three of them greater than the measurement accuracy (0.2 °C). Two previous experiments reported such an impact of cold water 8 h after pill ingestion (Wilkinson et al., 2008; Carter et al., 2007). Wilkinson et al. (2008) reported that two of their subjects experienced a drop (2–6 °C) in GIT 7–8 h after pill ingestion. To our knowledge, our study was the first to test and observe an effect up to 12 h after pill ingestion, although the volume of water was smaller than in the Wilkinson et al. (2008) report (150 mL versus 250 mL). Domitrovich et al. (2010) recommended waiting 40 min before temperature measurement after pill ingestion to ensure that the pill passes the stomach. It is unlikely that water ingestion transiently decreases gastrointestinal temperature only as a result of direct contact with the pill in the stomach and along the upper regions of the small intestine. Ingested water may cause local cooling of areas of the small and large intestines in close proximity to the stomach and duodenum. Therefore, the temperature registered by a GI pill will clearly be influenced by its position in the GI tract and its proximity to the stomach when cold fluids are ingested. The pill location is directly linked to the transit time which depends on several factors: time of day or emotional state (Schuster et al., 2002), dehydration (Van Nieuwenhoven et al., 2001), age or gender (Graff et al., 2001; Madsen and Graff, 2004; Schuster et al., 2002), physical state, and activity (Koffler et al., 1992; Oettlé, 1991). Pill transit times have been reported to range from 8 h (Lee et al., 2000) to 136 h (McKenzie and Osgood, 2004), so it is unrealistic to presume that increasing the time period between pill ingestion and temperature monitoring will necessarily decrease any influence of cold water ingestion on GIT unless the pill is close to the rectum (Livingston et al., 1983). One possible practical way to ensure that the pill is located near the rectum and free from artefacts of fluid and food ingestion is to use the pill as a rectal suppository (Keatinge and Neild, 1990). The other solution is to mark every food and water ingestion time in order to remove data afterwards and/or to use tepid water.

One mandatory condition for pill-based monitoring is the thermal homogeneity of the GI tract. Domitrovich et al. (2010) compared the temperature values from 2 different pills in the context of a 20-min exercise performed in a cold environment. Each of the 7 volunteers ingested one pill 24 h before exercising and a 2nd pill 40 min before the test. They did not report any significant differences in the recorded values. Their results suggested that pill location did not have any impact on CT data when checked at the beginning or at the end of the digestive tract. Our results, based on 6 pills in fasting subjects without any physical exercise, agree with the findings of Domitrovich et al. (2010). In addition, our study confirms thermal homogeneity all along the GI tract. Nevertheless, we observed in two subjects an individual error (between the 6 pills) above 0.2 degree. This could be due to local inflammation and/or local difference in tissue metabolism and heat exchanges (Taylor et al., 2014). Also, mean temperatures seem to decrease noticeably (see Fig. 4) as the pill approaches the rectal area, but the difference between pills remains within the range of accuracy of the device (0.2 °C) and was not significant with a quite good power to detect different (0.67). There are, however, inconsistent results regarding a possible lower rectal temperature compared to the GI tract temperature (Edwards et al., 2002; kolka et al., 1993; Lee et al., 2000; Sparling et al., 1993; Travers et al., 2016).

Telemetric devices were developed in the early 2000s, but their clinical use in medical practices for temperature measurement is not yet in common use. Chapon et al., (2016, 2016) studied clinical practices and knowledge of nursing staff regarding temperature and this innovation using a survey. The authors reported four main advantages of telemetry-based monitoring: (i) Non invasiveness, (ii) continuous measurement, (iii) time efficiency, and (iv) reliability. We suppose that a generalization of this practice could be suitable in the context of critical care, especially in anesthesia and urgent care, where CT is monitored to avoid hypothermia or hyperthermia in frail patients. Persons suffering from immunodeficiency or very contagious diseases and who have to limit contact with others could benefit from this monitoring system, avoiding the need for medical staff to enter their rooms several times a day to check their temperature. In addition, it is a way to check persons in harsh environments (e.g. soldiers, firemen, or divers). A number of studies have focused on the impact of hyperthermia on athletic performance (Domitrovich et al., 2010; Edwards et al., 2002; Kolka et al., 1993; Lee et al., 2000; Sparling et al., 1993; Travers et al., 2016). In this context, the GI pill should be an adequate device for trainers and researchers to monitor CT in athletes but our results obtained under controlled setting condition need to be confirmed in each specific environments.

5. Conclusions

This study demonstrates the thermal homogeneity of the GI tract. This main result allows reliable monitoring based on an ingestible electronic pill. However, the increased interest in the use of the GI telemetry pill for body temperature measurement implies recommendations about drink consumption. The user should note every food and water ingestion event and/or allow only tepid water intake. To avoid artefacts, the pill should be swallowed several hours before the monitoring period. Another recommendation might be to use the pill as a rectal suppository but extended investigation should be done before on this particular technic.

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Conflict of interest

Pierre Alexandre Chapon and Sébastien Moussay joined BODYCAP company. They participated to fundraising and study design but they did not participate in data recording, data analysis and paper writing. The others authors declare that there is no conflict of interest.

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