TITLE: Using an Ingestible Telemetric Temperature Pill to Assess Gastrointestinal Temperature During Exercise.

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KEYWORDS:
Physiology, exercise, thermoregulation, field based settings, gastrointestinal temperature, temperature pill, core body temperature

SHORT ABSTRACT:
This study describes an accurate, reliable and non-invasive technique to continuously measure gastrointestinal temperature during exercise. The ingestible telemetric temperature pill is suitable to measure gastrointestinal temperature in laboratory settings as well as in field based settings.

LONG ABSTRACT:
Exercise results in an increase in core body temperature (Tc), which may reduce exercise performance and eventually can lead to the development of heat-related disorders. Therefore, accurate measurement of Tc during exercise is of great importance, especially in athletes who have to perform in challenging ambient conditions. In the current literature a number of methods have been described to measure the Tc (esophageal, external tympanic membrane, mouth or rectum). However, these methods are suboptimal to measure Tc during exercise since they are invasive, have a slow response or are influenced by environmental conditions. Studies described the use of an ingestible telemetric temperature pill as a reliable and valid method to assess gastrointestinal

temperature (Tgi), which is a representative measurement of Tc. Therefore, the goal of this study was to provide a detailed description of the measurement of Tgi using an ingestible telemetric temperature pill. This study addresses important methodological factors that must be taken into account for an accurate measurement. It is recommended to read the instructions carefully in order to ensure that the ingestible telemetric temperature pill is a reliable method to assess Tgi at rest and during exercise.

INTRODUCTION:

The oxidation of substrates during muscle contractions, necessary to perform exercise and physical activity, importantly impacts our thermoregulatory system as only 20% is used for muscle power[1], whilst the majority of the energy is released as heat (80%)[2,3]. As a consequence, the elevated metabolic heat production during physical activity and exercise typically exceeds the heat dissipation capacity[4,5], resulting in an increase in core body temperature (Tc). Accordingly, Tc rises above the hypothalamic set point, which is defined as hyperthermia[6], and may even result in an attenuated exercise performance[5,7,8] and/or the development of heat-related disorders[4,6]. For this reason it is important to accurately measure Tc during prolonged exercise and in particular in strenuous ambient conditions.

Literature describes that an ideal method to measure Tc should: 1) be easy applicable, 2) not be biased by environmental conditions, 3) have a high temporal resolution to rapidly monitor changes in Tc, and 4) have the capacity to detect small changes (Δ0.1°C) in core body temperature[9,10]. An overview of the different methods to measure the Tc was given by the International Organization of Standardization (ISO 9886)[11]. It was stated that the esophageal temperature at the level of the left atrium provides the closest agreement with central blood temperature, while this measure is able to rapidly detect (minor) changes in temperature[12]. Although esophageal temperature measurements are generally accepted as the gold standard to record Tc, its invasive nature limits the practical use of this method. Alternative measures to monitor Tc rely on temperature recordings of external tympanic membrane, mouth, or rectum[12]. These measurement sites are not optimal to measure the Tc, given their invasive character, methodological difficulties and/or the potential bias by environmental conditions[9,12-14] (Table 1). This highlights the need to explore alternative strategies to monitor (changes in) Tc.

Previous studies have described the use of an ingestible telemetric temperature pill as an easily applicable, reliable and valid method to measure the Tgi, which is a representative estimation of Tc[9,15]. Another, important, advantage of the temperature pill is the suitability in field-based situations, which is of great importance since exercise-induced elevations in Tc are generally higher in field than in laboratory settings[16]. Currently, the temperature pill is able to measure the Tgi every 10 seconds with an accuracy of ±0.1°C, which make this technique very suitable to measure the Tgi during an exercise event or an important match. Furthermore, in a study by Stevens *et al*.[17] is demonstrated that the telemetric temperature pill may also be used to monitor intragastric temperature. The ingestible temperature pill is first described in 1961[18], and further developed at the Johns Hopkins University (Baltimore, USA) in collaboration with the Applied Physics Laboratory of the NASA. The result is a 20 x 10 mm capsule with a telemetry system, micro battery and a quartz crystal temperature sensor. The crystal sensor vibrates at a frequency relative to the temperature of the surrounding substance. This temperature radio signal is transmitted through the body, which can be measured by an external recorder (Figure 1). Each

temperature pill has a unique serial and calibration number, which can be used by the recorder to covert the radio signal and measure the corresponding Tgi.

A small magnetic strip is attached to the outside of the temperature pill, which deactivates the battery. When this magnetic strip is removed, the pill is activated immediately and starts measuring Tc (Figure 2). Casa and colleagues,[19] used six different techniques (gastrointestinal, rectal, aural, temporal, axial and forehead) to measure Tc, with the rectal temperature set as the reference value. They demonstrated that the gastrointestinal measurement of Tc with the temperature pill is the only technique that shows good agreement with the reference Tc. Others investigated the relation between Tgi and rectal temperature and have shown a small but significant bias ranging from 0.07°C to 0.20°C [9,15,20,21]. Although the direction and magnitude of the bias differed between studies, the Bland and Altman 95% limits of agreement were ±0.4°C, which is acceptable[9,22]. Additionally, in a review by Byrne *et al*.[9] the Tgi is compared with the rectal and esophageal temperature (gold standard) as a measure for the Tc. They demonstrate that the Tgi measured with the temperature pill is a valid measure for Tc based on the good agreement between intestinal and esophageal temperature. Furthermore, the 95% Bland and Altman limits of agreement were limited to ±0.4°C [22], while no significant bias was found between both measurements[9,20,21]. These results suggests that the Tgi is a valid measure for Tc.

Another important aspect of a good Tc/Tgi measurement technique is a high temporal resolution to rapidly monitor changes in Tc. Previous studies have demonstrated that the Tgi measured with the temperature pill responds more slowly on changes in Tc compared to the esophageal measurement[15,20,23], which can be explained due to the low heat capacity of the esophagus and the proximity to the heart[10]. In the esophageal temperature measurement the thermistor is placed at the level of the left atrium[10]. At this level the pulmonary artery and the esophagus are in contact and isothermal[24], which stimulates a fast response time on changes in temperature of the esophageal measurement. In contrast, the intestines and rectum are less perfused compared to the esophagus, resulting in a delay in measuring temperature changes on these anatomical locations. However, the ingestible telemetric temperature pill has an accuracy of ±0.1°C and is able to measure Tgi every 10 seconds. A previous study reported that core body temperature can raise with a maximum of 1°C every 5 minutes if no heat is removed during exercise[25]. Therefore, the temporal resolution of the temperature pill is suitable to measure changes in Tgi during exercise. Based on these findings, it can be concluded that the temperature pill is a reliable and valid technique to measure Tgi. Despite the use of the telemetric temperature pill in a large number of studies, a clear description about how to use the temperature pill is missing.

Therefore, the purpose of this study is to provide a detailed description of the measurement protocol using an ingestible telemetric temperature pill. Secondly, the application of the telemetric temperature pill in two different study protocols are described, in which a cross-sectional design (measurement every 5 km with a different recorder) and a protocol that continuously records Tgi in individuals are used.

PROTOCOL:

The steps described in the following section are in line with and accepted by the medical ethical committee of the Radboud University Medical Center in Nijmegen, The Netherlands. To our

knowledge, 3 different commercial systems of ingestible temperature pills are currently available for researchers. The user manual of the ingestible temperature pills is brand-specific (Table of specific materials), but all systems are suitable for measurements during exercise and under resting conditions.

1. Exclusion criteria and Subject Instruction

1.1 Ask subjects in written or verbal form for the exclusion criteria for using the telemetric temperature pill: 1) body weight below 36.5 kg, 2) obstructive gastro-intestinal disease, 3) history of gastrointestinal surgery, 4) an implanted medical device, and 5) a scheduled MRI scan during the experimental period.

1.2 Write down the serial and calibration number of the temperature pill.

1.3 Instruct the subjects how to use the temperature pill (see section 2).

1.4 Give the pill to the subject together with a short instruction manual, which contains the information shown in section 2. If subjects receive the temperature pill well ahead of the experiment, remind the subject the day preceding the experiment to ingest the temperature pill.

2. Temperature pill instructions

2.1 Instruct the subject to ingest the temperature pill at least 6 hours prior to the experiment, to avoid any interaction with fluid ingestion. Follow the subsequent steps to ingest the temperature pill correctly.

2.2 Instruct the subject to remove the magnetic strip from the pill, to activate the battery and enable measuring.

2.3 Instruct the subject to ingest the temperature pill preferably with a glass of water to enhance pill ingestion.

2.4 Ask the subject to return the pill wrapping material to the research team, so they can check serial and calibration numbers prior to the start of the experiment.

2.5 Instruct the subject that the temperature pill will leave the body through its natural way (faeces) and it can be flushed through the toilet.

3. Experimental protocol I: Cross sectional mode

Note: In the cross sectional mode it is possible to measure up to 99 subjects simultaneously.

3.1 Adjust the recorder to the desired settings for the cross sectional measurement prior to the measurement.

3.1.1 Turn on the recorder, connect the recorder with the computer with a transfer cable and push

the ‘F2-PC Link’ button to enable the recorder to connect with the computer.

3.1.2 Open the Tc software on the computer, which can be used to define the right settings. Note: The software is supplied by the company with the order of the temperature pill and recorder.

3.1.3 To adjust the settings, click on ‘Program’ in the home screen of the software, and subsequently use the ‘open PC link’ button to make a connection with the recorder and select the correct settings.

3.1.3.1 Select the cross sectional measurement mode by selecting ‘Sports mode ON’.

3.1.3.2 Select the correct temperature measurement scale (Celsius or Fahrenheit). Use the ‘Write Config to Recorder’ button to copy the settings to the recorder.

3.1.3.3 Add the serial and calibration number of all individual subjects to the external recorder, which enables the option to switch users during the experiment. Push the ‘Sensor/Barcode Display’ button in the software and add all the serial and calibration numbers. Push the ‘Write Sensors to Recorder’ button to copy the data to the recorder.

3.1.3.4 Check the battery of the recorder prior to the measurement, to avoid a discharged battery during the measurement and therefore missing data. Note: Normally, a battery state of 75% is sufficient to measure for >10 hours.

3.2 Once all preparations are completed and the predefined settings are checked, start the experiment. To do so, return to the home screen of the recorder and use the ‘F2-Sport’ button to start data acquisition.

3.3 When Player XX appears on the screen, push the ‘Read’ button to measure Tgi. Use the ‘Read’ button again for an extra measurement of Tgi.

3.4 To switch users, push on the correct number on the recorder and subsequently measure the Tc by pushing the ‘Read’ button.

3.5 Stop the data collection by pushing the ‘Stop’ button.

3.6 When the measurement is finished, turn off the recorder in the correct way to prevent data loss. To do so, use the ‘Enter’ button and ‘Exit’ becomes visible on the home screen. Push the ‘F1-Exit’ button and the recorder shows ‘turn of recorder’. Subsequently, use the power switch to turn off the recorder.

3.7 Export and store the raw data from the external recorder to a computer (see section 5; data handling).

4. Experimental protocol II: Continuous mode

Note: The continuous mode enables to continuously measure and save the Tgi of an individual

subject on a predefined constant time interval, for example every 20 seconds. In the next section, the step sequence used to perform this type of measurement is described.

4.1 Adjust the recorder to the right settings for the continuous measurement mode prior to the measurement (see section 3, steps 3.1.1-3.1.3).

4.2 Select the continuous measurement mode by selecting 'Sports mode OFF'.

4.3 Select a measuring frequency by adjusting the 'Read Interval' to the right constant time interval (hh:mm:ss), with a minimal sampling interval is 10 seconds.

4.4 Select the correct temperature measurement scale (Celsius or Fahrenheit). Use the 'Write Config to Recorder' button to copy the settings to the recorder.

4.5 Check the battery of the recorder prior to the measurement, to avoid a discharged battery during the measurement and therefore missing data. Note: Normally, a battery state of 75% is sufficient to perform a 24 hours measurement.

4.6 Once all preparations are completed and the predefined settings are checked, start the experiment. Start data acquisition by pushing the 'Run' button on the home screen of the recorder.

4.7 Subsequently, attach the recorder in a waist bag close to the abdominal area of the subject (maximal 30-40 cm between the abdominal area and the recorder) to avoid measurement errors.

Note: After the start of the experiment, every predefined time interval a measurement of Tc will be taken. With the 'Read' button extra sampling points can be added.

4.8 Stop the Tc measurement by pushing the 'Stop' button.

4.9 Use the 'F1-Exit' button to get the message 'turn off unit' and then use the power switch to turn off the recorder.

4.10 Export and store the raw data from the external recorder to a computer (see section 5; data extraction).

5. Data extraction

5.1 Connect the recorder to the computer to complete data export (section 3, step 3.1.1).

5.2 Open the software and click the 'Download' button in the home screen of the software.

5.3 Enter a file name and push the 'OK' button. Note: The data will now be stored as a .cvt file, which can be opened using spreadsheet software.

5.4 Open the data file and visually check the collected data for missing data and outliers. Note: A large decrease or increase of the Tgi ($\leq$1°C) within a short time interval ($\pm$1 min) is very

unrealistic and may be caused by a disturbance of the radio signal. As a result, the unrealistic data point can be removed for further analysis.

5.5 Interpolate the missing values by averaging the previous and next valid value. Note: Interpolation of the data is possible with a maximum of three missing values in a row.

REPRESENTATIVE RESULTS:

Representative results from our previous work demonstrating the methods are presented in the next section, in which an example of a cross sectional (Figure 3A) and a continuous measurement (Figure 3B) are given.

Cross sectional measurement of Tgi

An example of data from a cross sectional measurement is shown in Figure 3A. After obtaining baseline Tgi, subjects walked 30 km at a self-selected pace. During exercise the Tgi is measured every 5 km as well as directly after finishing the 30 km walking march. Figure 3A represents the results of the Tgi of 4 subjects during the 30 km walking march. The figure demonstrates that the cross sectional mode enables measurement of a group of subjects, using the same equipment.

Continuous assessment of Tgi

In addition to the cross sectional design, the temperature pill can be used to perform continuous Tgi measurements, in which the Tgi is measured continuously at a high temporal resolution (varying between 10 seconds and 1 hour). In the example presented here, Tgi of 4 healthy adults is measured every minute for 24 hours, to assess the circadian rhythm of the Tgi. All measurements are performed at the home of the participant. After correcting the data for outliers, the average Tgi is plotted in Figure 3B. Even though the number of subjects is very low, the variation in Tc is very low as can be seen from the relatively small error bars. From 09.15 AM Tgi gradually increases during the day until approximately 19.15 PM. Subsequently, the Tgi decreases in the evening and during night, followed by an increase in Tgi in the early morning (from 06.15 AM). The lowest Tgi is found during night time (01.15 AM -06.15 AM). The results of the figure demonstrate that the temperature pill is a suitable and non-invasive method to continuously measure Tgi in a home-based and is able to detect small changes in Tgi.

Figure and Table Legends:

Figure 1.
Title: Gastrointestinal temperature measurement
Short description: Schematic overview of gastrointestinal temperature measurement.

Figure 2.
Title: Ingestible telemetric temperature pill
Short description: Ingestible telemetric temperature pill and packing material. On the left the wrapping material is visible, which contains the temperature pill individual serial and calibration number. On the right, the temperature pill and the magnetic stripe are shown. In this case the temperature pill is not in contact with the magnetic stripe, which means that the battery is activated.

Figure 3.
Title: Representative results of gastrointestinal temperature assessment
Short description: (A) Representative results of a cross sectional measurement of Tgi during exercise in a field settings. Data represents Tgi (n=4) measured every 5 km during a 30-km walking march. (B) Representative results of a longitudinal measurement of Tgi (n=4), measured every minute for 24 hours. Data are presented as mean±SE.

Table 1. Overview and assessment of techniques to measure core body temperature[9,10,12,15,19-21,23,26-28].

DISCUSSION:

The ingestible telemetric temperature pill has the ability to provide a continuous, valid and non-invasive measurement of the Tgi. Furthermore, an advantage of the temperature pill is the fact that, once ingested, the subjects are unaware of the presence of the pill in the body or that the measurements are performed. Therefore, this method is easily applicable under resting conditions as well as during exercise, a minimal burden for study participants, and can therefore be used in field and laboratory settings. Another advantage is the possibility to measure a large group of subjects with only a single recorder.

To ensure an accurate, reliable and safe assessment of Tgi with the ingestible pill, it is important to follow a number of recommendations. First, the exclusion criteria should be carefully checked, to be sure that the temperature pill would not be harmful for the subject. Second, it is important to ingest the temperature pill at least 6 h before the experiment, to avoid any interaction with fluid intake and position in the gastrointestinal tract. In literature different ingestion times prior to data collection are used, ranging from 2 hours[20,29] to more than 10-12 hours[30,31]. Interestingly, Sparling *et al.*[32] found no difference in offset between the rectal and pill temperature during rest and exercise in subjects who swallowed the pill 3-4 hours prior to data collection and subjects who swallowed the temperature pill 8-9 hours prior to the measurement. Other studies suggest that an ingestion time of 6 hours is optimal to get a stable measurement of Tgi[9,21], whilst an ingestion time of 2 hours results in variation in measured Tgi[20,29]. Wilkinson and colleagues[31] demonstrate that the intake of 250 mL of water influenced the temperature pill assessment until approximately 5 hours after pill ingestion. Therefore, a minimum ingestion time of 6 hours preceding the measurement is advised, to avoid any interaction with fluid intake and sensor expulsion prior to data collection. Despite the provided precautions, fluid intake might influence Tgi in some individuals. Therefore, we recommend to visually inspect all raw data for unrealistic Tgi variations. As the maximum Tc increase is 1°C/5 minutes[25] we defined unrealistic variations in Tgi as a decrease or increase of Tgi ≥1°C/minute. These data points may be removed and the missing data can be interpolated using the average of the previous and next value. To ensure valid data collection, the interpolation method may only be used for a maximum of three subsequent data-points. Third, it is of great importance to correctly adjust the serial and calibration number of the temperature pill in the external recorder. Every temperature pill is individually calibrated and contains a unique serial and calibration number. The external recorder uses temperature pill specific serial and calibration numbers to converse the radio signal and measure the Tgi correctly. Thus, without correct numbers the wrong conversion factor is used, resulting in a non-reliable measurement of Tgi.

It is important to notice that this technique has some limitations. First, the cost of the temperature

pill (approximately $40 per pill) is higher compared to other techniques (tympanic, mouth, or rectum), in particular because the temperature pill can only be used once. Furthermore, the transit time of the digestive system for a single temperature pill has to be taken into account when determining the ingestion time preceding the experiment and the total duration of the experiment. A study by Roach *et al*.[33] followed 11 subjects over 7 days, in which they ingested a new temperature pill as the previous one had left the body. The mean transit time of the digestive system for a single pill was 27.4 hours (ranging from 4.6 to 82.8 hours). Moreover, the subject with the shortest transit time (4.6 hours) also reported a transit time of 26 hours, whilst the largest within subject difference between transit times was 55 hours. The results of Roach and colleagues[33] suggest a high degree of within- and between subjects variability in transit time of the temperature pill. The transit time of the gastrointestinal tract is independently influenced by several physiological factors such as gender, age, diet, psycho-behavioural factors (for example short-term anxiety and stress) and physical activity level[34-36]. Therefore, it is important to determine, based on the study protocol, population and variation in transit time, if a continuous measurement over a longer period is suitable to answer the research question. Still, it can be possible that the temperature pill already left the body prior to the measurement. If this is the case, the measurement must be rescheduled and a new pill must be ingested 6 hours preceding the experiment. In case of a large amount of missing or unrealistic data it is also advisable to reschedule the experiment to obtain a valid measurement for further processing.

It is important to ensure that the external recorder is close to the temperature pill to receive the radio signal and convert it to a correct Tgi. The maximal distance between the external recorder and temperature pill is approximately 0.65 meter, which is sufficient to measure Tgi in humans. In case of obese participants, it can be recommended to measure Tgi at the posterior instead of the anterior side of the body. Furthermore, it is important to avoid that ≥2 participants are within close distance (<1.5 meter) of each other, as interference of radio signals may occur. Finally, the storage of the temperature pills needs special attention to ensure that the sensors stay off and the batteries do not drain. Therefore, it is important to follow the storage guidelines that are provided by the manufacturer and include: I) at least one inch spacing between each sensor; II) never store the temperature pills near metallic objects; III) preferably keep the temperature pills in the custom-made foam inserts of the shipping package.

Taken together, the telemetry pill represents a reliable and valid method to measure the Tgi in both laboratory and field settings. Due to the good measuring accuracy and frequency, the ability to measure in field based situations and the non-invasive character of the temperature measurement (Table 1), the ingestible telemetric temperature pill is a suitable method to assess Tgi during exercise.

ACKNOWLEDGMENTS:

This work was supported by STW (12864, C.C.W.G.B) and the Netherlands Organization for Scientific Research (Rubicon Grant 825.12.016, T.M.H.E).

DISCLOSURES:

No conflicts of interest declared.

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