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

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28
29 **KEYWORDS:**

30 Physiology, exercise, thermoregulation, field based settings, gastrointestinal temperature,
31 temperature pill, core body temperature

32
33 **SHORT ABSTRACT:**

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

37
38 **LONG ABSTRACT:**

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

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

53

54 **INTRODUCTION:**

55 The oxidation of substrates during muscle contractions, necessary to perform exercise and physical
56 activity, importantly impacts our thermoregulatory system as only 20% is used for muscle power¹,
57 whilst the majority of the energy is released as heat (80%)^{2,3}. As a consequence, the elevated
58 metabolic heat production during physical activity and exercise typically exceeds the heat
59 dissipation capacity^{4,5}, resulting in an increase in core body temperature (Tc). Accordingly, Tc
60 rises above the hypothalamic set point, which is defined as hyperthermia⁶, and may even result in
61 an attenuated exercise performance^{5,7,8} and/or the development of heat-related disorders^{4,6}. For this
62 reason it is important to accurately measure Tc during prolonged exercise and in particular in
63 strenuous ambient conditions.

64

65 Literature describes that an ideal method to measure Tc should: 1) be easy applicable, 2) not be
66 biased by environmental conditions, 3) have a high temporal resolution to rapidly monitor changes
67 in Tc, and 4) have the capacity to detect small changes ($\Delta 0.1^{\circ}\text{C}$) in core body temperature^{9,10}. An
68 overview of the different methods to measure the Tc was given by the International Organization
69 of Standardization (ISO 9886)¹¹. It was stated that the esophageal temperature at the level of the
70 left atrium provides the closest agreement with central blood temperature, while this measure is
71 able to rapidly detect (minor) changes in temperature¹². Although esophageal temperature
72 measurements are generally accepted as the gold standard to record Tc, its invasive nature limits
73 the practical use of this method. Alternative measures to monitor Tc rely on temperature recordings
74 of external tympanic membrane, mouth, or rectum¹². These measurement sites are not optimal to
75 measure the Tc, given their invasive character, methodological difficulties and/or the potential bias
76 by environmental conditions^{9,12-14} (Table 1). This highlights the need to explore alternative
77 strategies to monitor (changes in) Tc.

78

79 Previous studies have described the use of an ingestible telemetric temperature pill as an easily
80 applicable, reliable and valid method to measure the Tgi, which is a representative estimation of
81 Tc^{9,15}. Another, important, advantage of the temperature pill is the suitability in field-based
82 situations, which is of great importance since exercise-induced elevations in Tc are generally
83 higher in field than in laboratory settings¹⁶. Currently, the temperature pill is able to measure the
84 Tgi every 10 seconds with an accuracy of $\pm 0.1^{\circ}\text{C}$, which make this technique very suitable to
85 measure the Tgi during an exercise event or an important match. Furthermore, in a study by
86 Stevens *et al.*¹⁷ is demonstrated that the telemetric temperature pill may also be used to monitor
87 intragastric temperature. The ingestible temperature pill is first described in 1961¹⁸, and further
88 developed at the Johns Hopkins University (Baltimore, USA) in collaboration with the Applied
89 Physics Laboratory of the NASA. The result is a 20 x 10 mm capsule with a telemetry system,
90 micro battery and a quartz crystal temperature sensor. The crystal sensor vibrates at a frequency
91 relative to the temperature of the surrounding substance. This temperature radio signal is
92 transmitted through the body, which can be measured by an external recorder (Figure 1). Each

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

95
96 A small magnetic strip is attached to the outside of the temperature pill, which deactivates the
97 battery. When this magnetic strip is removed, the pill is activated immediately and starts measuring
98 Tc (Figure 2). Casa and colleagues,¹⁹ used six different techniques (gastrointestinal, rectal, aural,
99 temporal, axial and forehead) to measure Tc, with the rectal temperature set as the reference value.
100 They demonstrated that the gastrointestinal measurement of Tc with the temperature pill is the
101 only technique that shows good agreement with the reference Tc. Others investigated the relation
102 between Tgi and rectal temperature and have shown a small but significant bias ranging from
103 0.07°C to 0.20°C^{9,15,20,21}. Although the direction and magnitude of the bias differed between
104 studies, the Bland and Altman 95% limits of agreement were $\pm 0.4^\circ\text{C}$, which is acceptable^{9,22}.
105 Additionally, in a review by Byrne *et al.*⁹ the Tgi is compared with the rectal and esophageal
106 temperature (gold standard) as a measure for the Tc. They demonstrate that the Tgi measured with
107 the temperature pill is a valid measure for Tc based on the good agreement between intestinal and
108 esophageal temperature. Furthermore, the 95% Bland and Altman limits of agreement were limited
109 to $\pm 0.4^\circ\text{C}$ ²², while no significant bias was found between both measurements^{9,20,21}. These results
110 suggests that the Tgi is a valid measure for Tc.

111
112 Another important aspect of a good Tc/Tgi measurement technique is a high temporal resolution
113 to rapidly monitor changes in Tc. Previous studies have demonstrated that the Tgi measured with
114 the temperature pill responds more slowly on changes in Tc compared to the esophageal
115 measurement^{15,20,23}, which can be explained due to the low heat capacity of the esophagus and the
116 proximity to the heart¹⁰. In the esophageal temperature measurement the thermistor is placed at the
117 level of the left atrium¹⁰. At this level the pulmonary artery and the esophagus are in contact and
118 isothermal²⁴, which stimulates a fast response time on changes in temperature of the esophageal
119 measurement. In contrast, the intestines and rectum are less perfused compared to the esophagus,
120 resulting in a delay in measuring temperature changes on these anatomical locations. However, the
121 ingestible telemetric temperature pill has an accuracy of $\pm 0.1^\circ\text{C}$ and is able to measure Tgi every
122 10 seconds. A previous study reported that core body temperature can raise with a maximum of
123 1°C every 5 minutes if no heat is removed during exercise²⁵. Therefore, the temporal resolution of
124 the temperature pill is suitable to measure changes in Tgi during exercise. Based on these findings,
125 it can be concluded that the temperature pill is a reliable and valid technique to measure Tgi.
126 Despite the use of the telemetric temperature pill in a large number of studies, a clear description
127 about how to use the temperature pill is missing.

128
129 Therefore, the purpose of this study is to provide a detailed description of the measurement
130 protocol using an ingestible telemetric temperature pill. Secondly, the application of the telemetric
131 temperature pill in two different study protocols are described, in which a cross-sectional design
132 (measurement every 5 km with a different recorder) and a protocol that continuously records Tgi
133 in individuals are used.

134 **PROTOCOL:**

135
136
137 The steps described in the following section are in line with and accepted by the medical ethical
138 committee of the Radboud University Medical Center in Nijmegen, The Netherlands. To our

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

143

144 **1. Exclusion criteria and Subject Instruction**

145

146 1.1 Ask subjects in written or verbal form for the exclusion criteria for using the telemetric
147 temperature pill: 1) body weight below 36.5 kg, 2) obstructive gastro-intestinal disease, 3) history
148 of gastrointestinal surgery, 4) an implanted medical device, and 5) a scheduled MRI scan during
149 the experimental period.

150

151 1.2 Write down the serial and calibration number of the temperature pill.

152

153 1.3 Instruct the subjects how to use the temperature pill (see section 2).

154

155 1.4 Give the pill to the subject together with a short instruction manual, which contains the
156 information shown in section 2. If subjects receive the temperature pill well ahead of the
157 experiment, remind the subject the day preceding the experiment to ingest the temperature pill.

158

159 **2. Temperature pill instructions**

160

161 2.1 Instruct the subject to ingest the temperature pill at least 6 hours prior to the experiment, to
162 avoid any interaction with fluid ingestion. Follow the subsequent steps to ingest the temperature
163 pill correctly.

164

165 2.2 Instruct the subject to remove the magnetic strip from the pill, to activate the battery and
166 enable measuring.

167

168 2.3 Instruct the subject to ingest the temperature pill preferably with a glass of water to enhance
169 pill ingestion.

170

171 2.4 Ask the subject to return the pill wrapping material to the research team, so they can check
172 serial and calibration numbers prior to the start of the experiment.

173

174 2.5 Instruct the subject that the temperature pill will leave the body through its natural way
175 (faeces) and it can be flushed through the toilet.

176

177 **3. Experimental protocol I: Cross sectional mode**

178

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

180

181 3.1 Adjust the recorder to the desired settings for the cross sectional measurement prior to the
182 measurement.

183

184 3.1.1 Turn on the recorder, connect the recorder with the computer with a transfer cable and push

185 the 'F2-PC Link' button to enable the recorder to connect with the computer.
186

187 3.1.2 Open the Tc software on the computer, which can be used to define the right settings. Note:
188 The software is supplied by the company with the order of the temperature pill and recorder.
189

190 3.1.3 To adjust the settings, click on 'Program' in the home screen of the software, and
191 subsequently use the 'open PC link' button to make a connection with the recorder and select the
192 correct settings.
193

194 3.1.3.1 Select the cross sectional measurement mode by selecting 'Sports mode ON'.
195

196 3.1.3.2 Select the correct temperature measurement scale (Celsius or Fahrenheit). Use the 'Write
197 Config to Recorder' button to copy the settings to the recorder.
198

199 3.1.3.3 Add the serial and calibration number of all individual subjects to the external recorder,
200 which enables the option to switch users during the experiment. Push the 'Sensor/Barcode Display'
201 button in the software and add all the serial and calibration numbers. Push the 'Write Sensors to
202 Recorder' button to copy the data to the recorder.
203

204 3.1.3.4 Check the battery of the recorder prior to the measurement, to avoid a discharged battery
205 during the measurement and therefore missing data. Note: Normally, a battery state of 75% is
206 sufficient to measure for >10 hours.
207

208 3.2 Once all preparations are completed and the predefined settings are checked, start the
209 experiment. To do so, return to the home screen of the recorder and use the 'F2-Sport' button to
210 start data acquisition.
211

212 3.3 When Player XX appears on the screen, push the 'Read' button to measure Tgi. Use the
213 'Read' button again for an extra measurement of Tgi.
214

215 3.4 To switch users, push on the correct number on the recorder and subsequently measure the
216 Tc by pushing the 'Read' button.
217

218 3.5 Stop the data collection by pushing the 'Stop' button.
219

220 3.6 When the measurement is finished, turn off the recorder in the correct way to prevent data
221 loss. To do so, use the 'Enter' button and 'Exit' becomes visible on the home screen. Push the 'F1-
222 Exit' button and the recorder shows 'turn of recorder'. Subsequently, use the power switch to turn
223 off the recorder.
224

225 3.7 Export and store the raw data from the external recorder to a computer (see section 5; data
226 handling).
227

228 **4. Experimental protocol II: Continuous mode**
229

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

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

233

234 4.1 Adjust the recorder to the right settings for the continuous measurement mode prior to the
235 measurement (see section 3, steps 3.1.1-3.1.3).

236

237 4.2 Select the continuous measurement mode by selecting 'Sports mode OFF'.

238

239 4.3 Select a measuring frequency by adjusting the 'Read Interval' to the right constant time
240 interval (hh:mm:ss), with a minimal sampling interval is 10 seconds.

241

242 4.4 Select the correct temperature measurement scale (Celsius or Fahrenheit). Use the 'Write
243 Config to Recorder' button to copy the settings to the recorder.

244

245 4.5 Check the battery of the recorder prior to the measurement, to avoid a discharged battery
246 during the measurement and therefore missing data. Note: Normally, a battery state of 75% is
247 sufficient to perform a 24 hours measurement.

248

249 4.6 Once all preparations are completed and the predefined settings are checked, start the
250 experiment. Start data acquisition by pushing the 'Run' button on the home screen of the recorder.

251

252 4.7 Subsequently, attach the recorder in a waist bag close to the abdominal area of the subject
253 (maximal 30-40 cm between the abdominal area and the recorder) to avoid measurement errors.

254

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

257

258 4.8 Stop the Tc measurement by pushing the 'Stop' button.

259

260 4.9 Use the 'F1-Exit' button to get the message 'turn off unit' and then use the power switch
261 to turn off the recorder.

262

263 4.10 Export and store the raw data from the external recorder to a computer (see section 5; data
264 extraction).

265

266 **5. Data extraction**

267

268 5.1 Connect the recorder to the computer to complete data export (section 3, step 3.1.1).

269

270 5.2 Open the software and click the 'Download' button in the home screen of the software.

271

272 5.3 Enter a file name and push the 'OK' button. Note: The data will now be stored as a .cvt
273 file, which can be opened using spreadsheet software.

274

275 5.4 Open the data file and visually check the collected data for missing data and outliers. Note:
276 A large decrease or increase of the Tgi ($\leq 1^{\circ}\text{C}$) within a short time interval (± 1 min) is very

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

279
280 5.5 Interpolate the missing values by averaging the previous and next valid value. Note:
281 Interpolation of the data is possible with a maximum of three missing values in a row.

282
283 **REPRESENTATIVE RESULTS:**
284
285 Representative results from our previous work demonstrating the methods are presented in the next
286 section, in which an example of a cross sectional (Figure 3A) and a continuous measurement
287 (Figure 3B) are given.

288
289 **Cross sectional measurement of Tgi**
290 An example of data from a cross sectional measurement is shown in Figure 3A. After obtaining
291 baseline Tgi, subjects walked 30 km at a self-selected pace. During exercise the Tgi is measured
292 every 5 km as well as directly after finishing the 30 km walking march. Figure 3A represents the
293 results of the Tgi of 4 subjects during the 30 km walking march. The figure demonstrates that the
294 cross sectional mode enables measurement of a group of subjects, using the same equipment.

295
296 **Continuous assessment of Tgi**
297 In addition to the cross sectional design, the temperature pill can be used to perform continuous
298 Tgi measurements, in which the Tgi is measured continuously at a high temporal resolution
299 (varying between 10 seconds and 1 hour). In the example presented here, Tgi of 4 healthy adults
300 is measured every minute for 24 hours, to assess the circadian rhythm of the Tgi. All measurements
301 are performed at the home of the participant. After correcting the data for outliers, the average Tgi
302 is plotted in Figure 3B. Even though the number of subjects is very low, the variation in Tc is very
303 low as can be seen from the relatively small error bars. From 09.15 AM Tgi gradually increases
304 during the day until approximately 19.15 PM. Subsequently, the Tgi decreases in the evening and
305 during night, followed by an increase in Tgi in the early morning (from 06.15 AM). The lowest
306 Tgi is found during night time (01.15 AM -06.15 AM). The results of the figure demonstrate that
307 the temperature pill is a suitable and non-invasive method to continuously measure Tgi in a home-
308 based and is able to detect small changes in Tgi.

309
310 **Figure and Table Legends:**

311
312 **Figure 1.**
313 Title: Gastrointestinal temperature measurement
314 Short description: Schematic overview of gastrointestinal temperature measurement.

315
316 **Figure 2.**
317 Title: Ingestible telemetric temperature pill
318 Short description: Ingestible telemetric temperature pill and packing material. On the left the
319 wrapping material is visible, which contains the temperature pill individual serial and calibration
320 number. On the right, the temperature pill and the magnetic stripe are shown. In this case the
321 temperature pill is not in contact with the magnetic stripe, which means that the battery is activated.

322

323 **Figure 3.**

324 Title: Representative results of gastrointestinal temperature assessment

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

329

330 **Table 1.** Overview and assessment of techniques to measure core body temperature<sup>9,10,12,15,19-
331 21,23,26-28</sup>.

332

333 **DISCUSSION:**

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

341

342 To ensure an accurate, reliable and safe assessment of Tgi with the ingestible pill, it is important
343 to follow a number of recommendations. First, the exclusion criteria should be carefully checked,
344 to be sure that the temperature pill would not be harmful for the subject. Second, it is important to
345 ingest the temperature pill at least 6 h before the experiment, to avoid any interaction with fluid
346 intake and position in the gastrointestinal tract. In literature different ingestion times prior to data
347 collection are used, ranging from 2 hours^{20,29} to more than 10-12 hours^{30,31}. Interestingly, Sparling
348 *et al.*³² found no difference in offset between the rectal and pill temperature during rest and exercise
349 in subjects who swallowed the pill 3-4 hours prior to data collection and subjects who swallowed
350 the temperature pill 8-9 hours prior to the measurement. Other studies suggest that an ingestion
351 time of 6 hours is optimal to get a stable measurement of Tgi^{9,21}, whilst an ingestion time of 2
352 hours results in variation in measured Tgi^{20,29}. Wilkinson and colleagues³¹ demonstrate that the
353 intake of 250 mL of water influenced the temperature pill assessment until approximately 5 hours
354 after pill ingestion. Therefore, a minimum ingestion time of 6 hours preceding the measurement is
355 advised, to avoid any interaction with fluid intake and sensor expulsion prior to data collection.
356 Despite the provided precautions, fluid intake might influence Tgi in some individuals. Therefore,
357 we recommend to visually inspect all raw data for unrealistic Tgi variations. As the maximum Tc
358 increase is 1°C/5 minutes²⁵ we defined unrealistic variations in Tgi as a decrease or increase of
359 Tgi $\geq 1^\circ\text{C}/\text{minute}$. These data points may be removed and the missing data can be interpolated
360 using the average of the previous and next value. To ensure valid data collection, the interpolation
361 method may only be used for a maximum of three subsequent data-points. Third, it is of great
362 importance to correctly adjust the serial and calibration number of the temperature pill in the
363 external recorder. Every temperature pill is individually calibrated and contains a unique serial and
364 calibration number. The external recorder uses temperature pill specific serial and calibration
365 numbers to converse the radio signal and measure the Tgi correctly. Thus, without correct numbers
366 the wrong conversion factor is used, resulting in a non-reliable measurement of Tgi.

367

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

369 pill (approximately \$40 per pill) is higher compared to other techniques (tympanic, mouth, or
370 rectum), in particular because the temperature pill can only be used once. Furthermore, the transit
371 time of the digestive system for a single temperature pill has to be taken into account when
372 determining the ingestion time preceding the experiment and the total duration of the experiment.
373 A study by Roach *et al.*³³ followed 11 subjects over 7 days, in which they ingested a new
374 temperature pill as the previous one had left the body. The mean transit time of the digestive system
375 for a single pill was 27.4 hours (ranging from 4.6 to 82.8 hours). Moreover, the subject with the
376 shortest transit time (4.6 hours) also reported a transit time of 26 hours, whilst the largest within
377 subject difference between transit times was 55 hours. The results of Roach and colleagues³³
378 suggest a high degree of within- and between subjects variability in transit time of the temperature
379 pill. The transit time of the gastrointestinal tract is independently influenced by several
380 physiological factors such as gender, age, diet, psycho-behavioural factors (for example short-term
381 anxiety and stress) and physical activity level³⁴⁻³⁶. Therefore, it is important to determine, based
382 on the study protocol, population and variation in transit time, if a continuous measurement over
383 a longer period is suitable to answer the research question. Still, it can be possible that the
384 temperature pill already left the body prior to the measurement. If this is the case, the measurement
385 must be rescheduled and a new pill must be ingested 6 hours preceding the experiment. In case of
386 a large amount of missing or unrealistic data it is also advisable to reschedule the experiment to
387 obtain a valid measurement for further processing.

388

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

400

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

406

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410

411 **DISCLOSURES:**

412 No conflicts of interest declared.

413

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