Wireless Monitoring of Gastrointestinal Transit Time, Intra-luminal pH, Pressure and Temperature in Experimental Pigs: A Pilot Study

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ABSTRACT

Background: There is no single gold standard for investigation of gastrointestinal motility function. Wireless motility monitoring involves a novel concept which provides a complex information on gastrointestinal function (gastrointestinal transit time, intra-luminal pH, pressure and temperature). Gastrointestinal motility functions of experimental pigs are very similar to those of humans. That is why porcine studies have already provided suitable experimental models for several preclinical projects.

Aims: The aim of our study was to adopt methods of non-invasive wireless monitoring of gastrointestinal functions in experimental pigs.

Methods: Five experimental adult female pigs were enrolled into the study. Wireless motility capsules were delivered into the porcine stomach endoscopically. Gastrointestinal transit and intra-luminal conditions were recorded for five days.

Results: Records of animals provided good (3 pigs) or very good quality files (2 pigs). 31150 variables were evaluated. Mean time of the presence of capsules in the stomach was 926 ± 295 min, transfer of a capsule from the stomach into the duodenum lasted 5–34 min. Mean small intestinal transit time was 251 ± 43 min. Food intake was associated with an increase of gastric luminal temperature and a decrease of intra-gastric pressure. The highest intra-luminal pH was present in the ileum. The highest temperature and the lowest intra-luminal pressure were found in the colon. All data displayed a substantial inter-individual variability.

Conclusions: This pilot study has proven that a long-term function monitoring of the gastrointestinal tract by means of wireless motility capsules in experimental pigs is feasible. However, both ketamine-based induction of general anaesthesia as well as long-lasting general anaesthesia (> 6 hours) should be avoided to prevent retention of a capsule in the porcine stomach.

KEYWORDS

acetylcholinesterase inhibitors; experimental pigs; gastrointestinal transit time; intra-luminal pH; pressure and temperature; oncology; toxicology; wireless capsule monitoring

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INTRODUCTION

Motility function of the entire gastrointestinal tract belongs to the most complex and most fragile systems in human body (1). There is no single gold standard for its investigation. Usually, it is necessary to combine several methods. Motor function of the oesophagus is mostly investigated by means of oesophageal impedance/pH-metry, reflux scintigraphy and/or high-resolution manometry (2–7). Examination of the gastric motility function uses gastric emptying scintigraphy, ^{13}C-acetate or ^{13}C-octanoic acid breath tests, electrogastrography, magnetic resonance imaging, antroduodenal manometry, ancillary testing (including barostat and satiety testing) or EndoFLIP (Endoscopic Functional Lumen Imaging Probe: high-resolution impedance planimetry system). EndoFLIP may be also used for the assessment of oesophageal motility function, in fact, it can replace oesophageal manometry in some patients (8–18). Investigation of the intestinal motor function is the most demanding and the least accurate. There are only a few methods available for routine clinical practice so far. Examinations usually rely on the oro-caecal, small intestinal and/or colonic transit time measurements (lactose-(13C)ureide breath test, indirectly hydrogen & methane breath tests, scintigraphic transit time testing, radio-opaque markers and pellets propulsion) (19–21). Synucleinopathy is an indirect marker of motor dysfunction (e.g. in Parkinson disease) (22). Important part of a complex investigation is small intestinal bacterial overgrowth testing (23–25).

Wireless motility monitoring involves a novel concept which provides a complex information on gastrointestinal function. The wireless motility/pH capsule is an orally ingested, non-digestible, data recording device that enables a simultaneous assessment of a segmental and whole gut transit. This capsule was approved by the US Food and Drug Administration for the evaluation of patients with suspected delayed gastric emptying and the evaluation of colonic transit time in patients with chronic idiopathic constipation. The device continuously measures temperature, pH, and pressure of its surrounding structures while passing through the gastrointestinal tract (via gut peristalsis) until exiting the body through the anus. Validated patterns in pH and temperature recordings allow accurate measurements of gastric emptying, small bowel transit, colonic transit, and whole gut transit times (26–28).

Gastrointestinal motility functions of experimental pigs are very similar to those of humans. That is why porcine studies have already provided suitable experimental models for several preclinical projects (29–31). Group of Professor Griffin published an important study of wireless recording of the gastrointestinal motility and luminal conditions in experimental pigs (32). The aim of our current study was to adopt Professor Griffin's methods to our own porcine experimental setting. Studies on gastrointestinal motility are of utmost importance, especially in the context of side effects induced by drugs, e.g. medication used for treatment of dementia and malignancies.

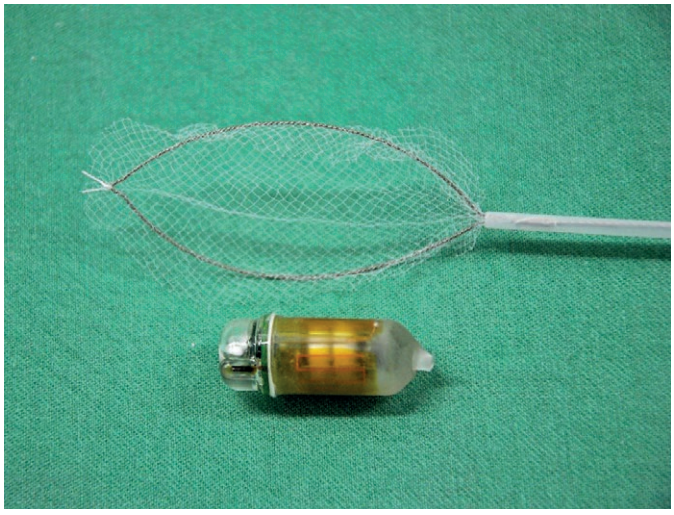

Fig. 1 Wireless motility capsule measures 27 × 12 mm (weight 4.5 g). A special roth net was used for capsule delivery into the porcine stomach.

METHODS

PRELIMINARY TESTING

Preliminary data were obtained from three experimental adult female pigs (*Sus scrofa* f. *domestica*, hybrids of Czech White and Landrace breeds; 4-month-old; mean weight 40.2 ± 1.5 kg; median 39.5 kg). The aim of this preliminary part was planned to check the feasibility of wireless data acquisition. However, both ketamine-based induction of anaesthesia (20 mg/kg i.m.) in one animal and long-term general anaesthesia (> 6 hours) in another two pigs were associated with a retention of motility capsules in the porcine stomach during the entire 5-day period.

ANIMALS

Another five experimental adult female pigs (*Sus scrofa* f. *domestica*, hybrids of Czech White and Landrace breeds; 4-month-old; mean weight 41.2 ± 5.5 kg; median 39.5 kg) were enrolled into the main part of the study. The animals were purchased from a certified breeder (Štěpánek, Dolní Ředice, Czech Republic; SHR MUHO 2050/2008/41). The pigs were housed in an accredited animal laboratory (Faculty of Military Health Sciences, Hradec Králové). During a two-week acclimatization, all animals were fed with a standard assorted A1 food (Ryhos, Nový Rychnov, Czech Republic) in equal amounts twice a day, and had free access to a drinking water.

DESIGN OF THE STUDY

All experiments were commenced in the morning on overnight fasting animals. Drugs used as an induction of anaesthesia were medetomidine 0.1 mg/kg i.m., butorphanol 0.3 mg/kg i.m. and midazolam 0.3 mg/kg i.m. Subsequent short-term general anaesthesia was maintained by i.v. propofol (repeated one-mL boluses per 20 mg, in total less than 5 mL; time < 10 min.) only for the endoscopic delivery of motility capsules into the middle part of the gastric body.

Wireless motility capsules (SmartPill, Medtronic, Dublin, Ireland) were purchased from Imedex (Hradec Králové, Czech Republic). Capsules were delivered into the porcine stomach endoscopically using a video-gastroscope GIF-Q180 (Olympus Optical Co, Tokyo, Japan) dedicated for animal use only. A special roth net (Steris, US Endoscopy, Mentor, OH, USA) was used to facilitate this installation (Figure 1). After full recovery from a short-term general anaesthesia, animals were free to move in unlimited manner with an unrestricted access to water. Food intake was allowed from four hours onwards. Data from wireless motility capsules was recorded for five days continuously, and these were available for subsequent detailed analysis.

STATISTICS

All data was tested statistically by means of the SigmaStat software (Version 3.1, Jandel Corp, Erkrath, Germany). Distribution of data was assessed by Kolmogorov-Smirnov test; Shapiro-Wilko test was used for evaluation of normality of sampled data. Descriptive statistics, unpaired t-test (for normal distribution) and Mann-Whitney rank sum test (for non-normal distribution) were used to treat variables.

ETHICS

The Project was approved by the Institutional Review Board of the Animal Care Committee of the University of Defence (Protocol Number MO 171673/2019-684800), Faculty of Military Health Sciences, Hradec Králové. The study was conducted in accordance with the policy for experimental and clinical studies (33). Animals were held and treated in conformity with the European Convention for the Protection of Vertebrate Animals (34).

RESULTS

Records of animals of the main study part provided good (3 pigs) or very good quality files (2 pigs), see Figure 2. Mean time of overall recording was 6537 ± 712 min. (median 6538 min.). In total, 31150 variables were evaluated. Mean time of the presence of capsules in the stomach was 926 ± 295 min. (median 1091 min.), transfer of a capsule from the stomach into the duodenum lasted 5–34 min. (median 8 min.). Capsules migrated back from the duodenum into the stomach spontaneously three times (for 13, 14 and 63 min.). Mean small intestinal transit time was 251 ± 43 min. (median 233 min.). Other major results are shown in Table 1 and Figures 3–6.

DISCUSSION

We have implemented investigation of gastrointestinal motility function by means of wireless capsules to our experimental practice successfully. Yet, our initial experience is still limited, therefore it is required to evaluate our first findings with caution.

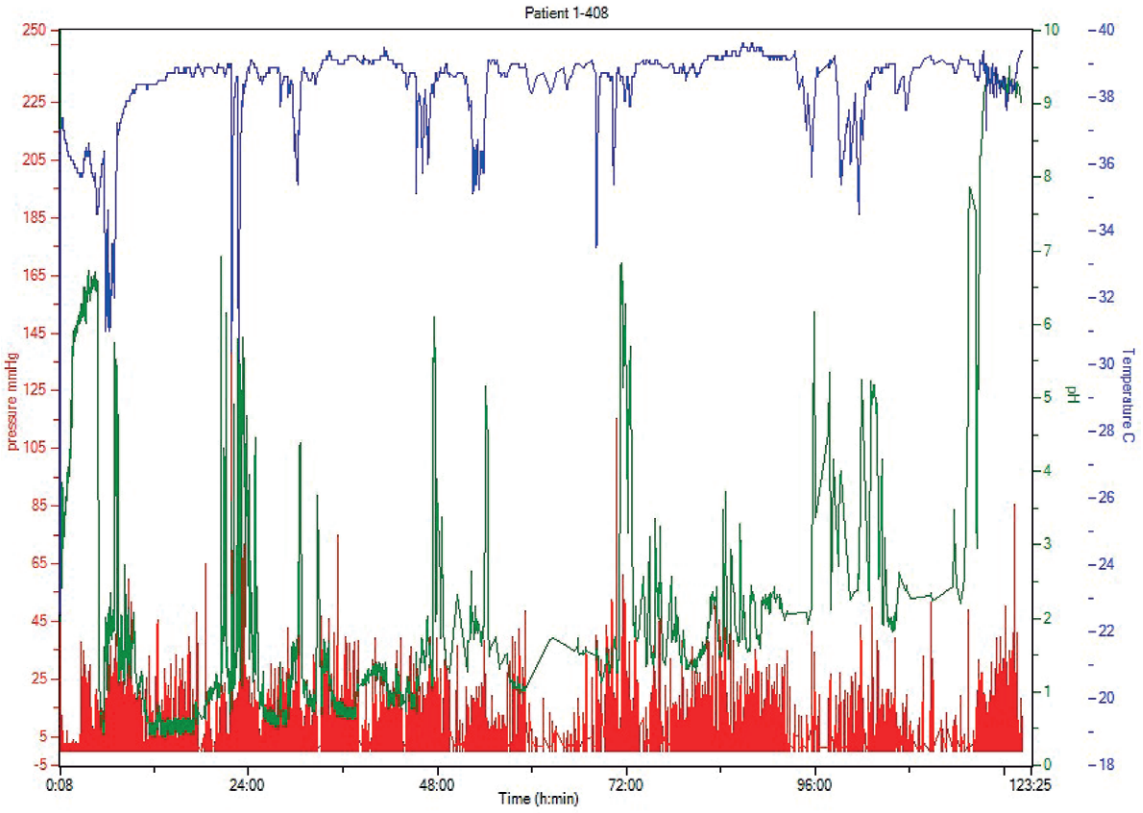

Fig. 2 Intra-luminal pressure is recorded 120-times per minute (mm Hg), pH is registered 12-times per minute and temperature is measured 3-times per minute (°C). Pressure in red, pH in green, temperature in blue.

Tab. 1 Wireless monitoring of intra-luminal pH, temperature and pressure.

Parameter	A Mean ± Std. Dev. Median IQR	B Mean ± Std. Dev. Median IQR	C Mean ± Std. Dev. Median IQR	D Mean ± Std. Dev. Median IQR	E Mean ± Std. Dev. Median IQR	F Mean ± Std. Dev. Median IQR	Relevant significance
pH	1.1 ± 0.6 1.1 0.6–1.4	4.5 ± 0.7 4.6 4.3–4.9	4.4 ± 1.5 4.7 3.1–5.2	8.1 ± 1.3 8.4 7.8–8.8	9.0 ± 0.2 8.9 8.9–9.1	7.5 ± 0.5 7.3 7.1–7.8	B > A (p < 0.001) E > D (p < 0.001) E > F (p<0.001)
Temperature	38.8 ± 1.4 39.3 38.9–39.5	39.2 ± 0.4 39.3 39.1–39.4	39.1 ± 0.2 39.1 39.1–39.3	39.1 ± 0.6 39.1 38.8–39.6	39.2 ± 0.7 39.4 38.5–39.8	40.0 ± 0.4 40.0 39.6–40.3	B > A (p = 0.004) F > D (p < 0.001) F > E (p < 0.001)
Pressure	2.4 ± 1.3 2.1 1.5–2.8	2.1 ± 1.6 1.5 1.1–2.5	3.5 ± 3.7 2.3 1.5–3.8	3.6 ± 2.2 3.2 2.5–4.2	4.1 ± 2.4 3.6 2.7–4.8	2.1 ± 1.6 1.6 1.0–2.6	A > B (p < 0.001) C > B (p < 0.001) E > D (p < 0.001) E > F (p < 0.001)
Maximal pressure	10.4 ± 11.1 7.0 3.8–13.7	11.3 ± 13.6 6.8 3.1–16.1	27.9 ± 64.7 9.9 3.2–17.3	18.4 ± 30.4 14.1 9.7–18.9	19.3 ± 13.5 17.3 11.3–23.3	10.1 ± 9.8 7.7 3.1–14.3	A > B (p = 0.018) C > B (p = 0.014) E > D (p < 0.001) E > F (p < 0.001)

Group A: stomach under fasting condition; B: stomach after food intake; C: passage of a capsule from the stomach to the duodenum; D: jejunum; E: ileum; F: colon. The pH inversely indicates the concentration of hydrogen ions in the solution; values of temperature are given in degrees Celsius (°C); values of pressure are measured in Torr (mm Hg).
pH = −log(H+) = −log([H+]/M); Std. Dev.: standard deviation; IQR: inter-quartile range

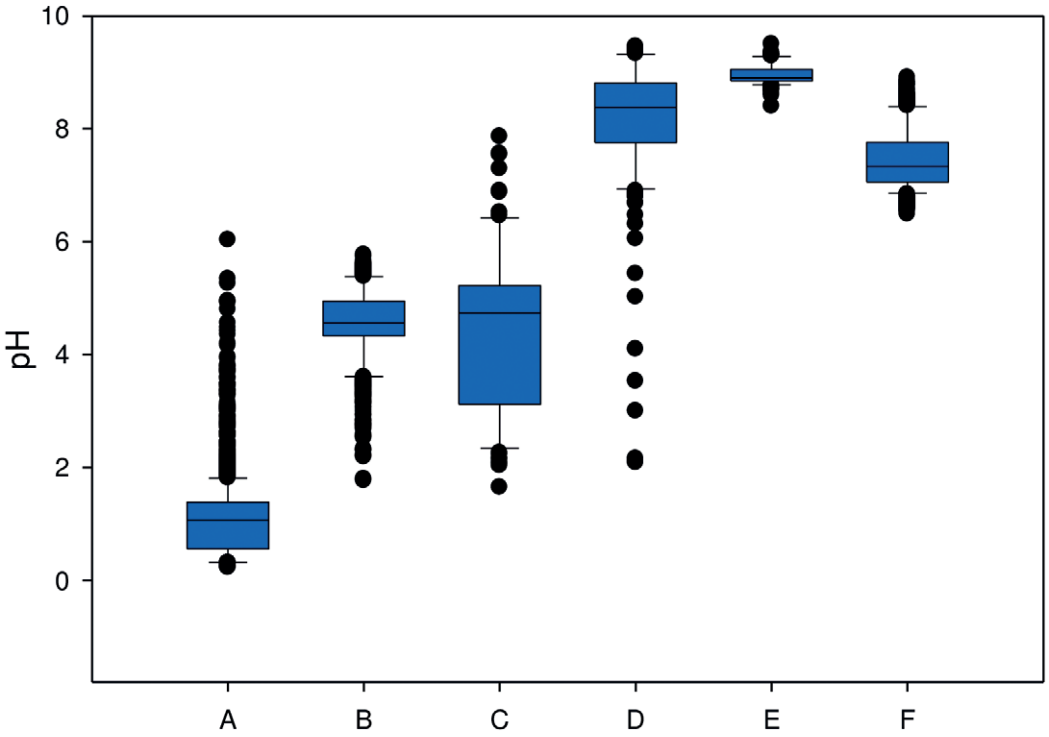

Fig. 3 Monitoring of intra-luminal pH. Group A: stomach under fasting condition; B: stomach after food intake; C: passage of a capsule from the stomach to the duodenum; D: jejunum; E: ileum; F: colon. Median, inter-quartile range and outliers. Selected statistically significant differences: B > A (p < 0.001); E > D (p < 0.001); E > F (p < 0.001).

To highlight our results, the presence of capsules in the stomach was surprisingly long. We assume that this time does reflect rather delayed expulsion of a capsule from the porcine stomach than real gastric emptying time. Nevertheless, according to our previous endoscopic experience, the porcine stomach has almost always contained remnants of food, even after a long fasting period. Torus pyloricus (muscular gatekeeper of the pylorus) contributes to this fact. Food intake was associated with an increase of gastric luminal temperature and a decrease of intra-gastric pressure. Total small intestinal transit time was relatively short (entire length of the porcine small bowel is around 12 metres). The highest intra-luminal pH was present in the ileum. The highest temperature and the lowest intra-luminal pressure were found in the colon. All data displayed a substantial inter-individual variability.

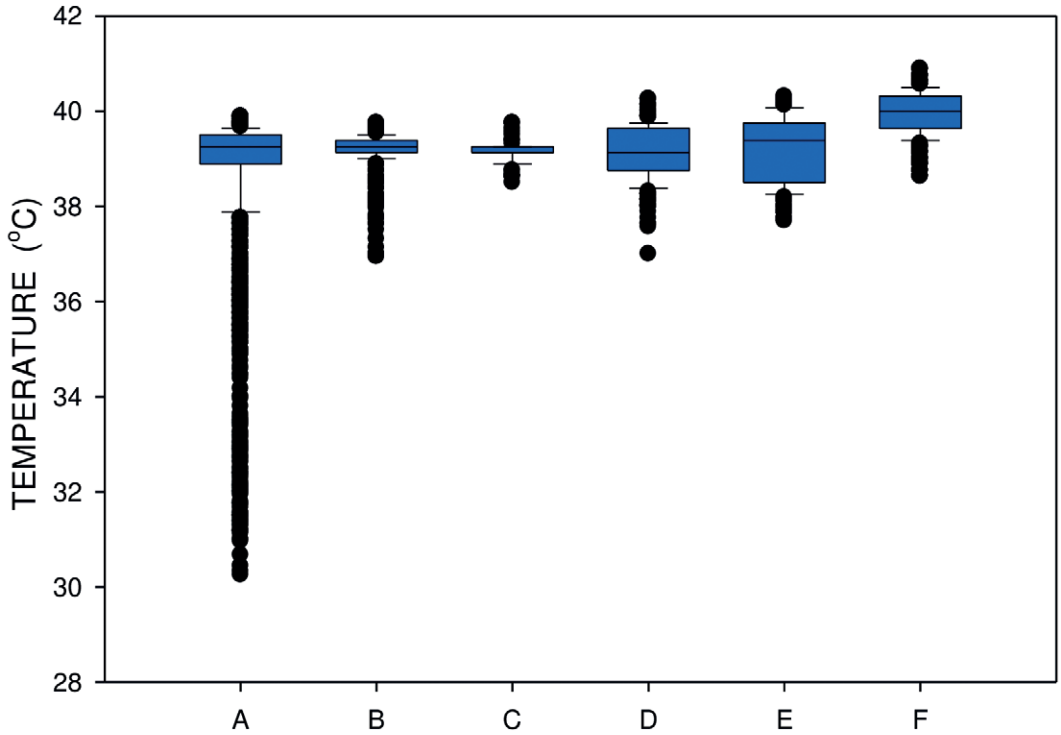

Fig. 4 Intra-luminal temperature. Group A: stomach under fasting condition; B: stomach after food intake; C: passage of a capsule from the stomach to the duodenum; D: jejunum; E: ileum; F: colon. Median, inter-quartile range and outliers. Selected statistically significant differences: B > A ($p = 0.004$); F > D ($p < 0.001$); F > E ($p < 0.001$).

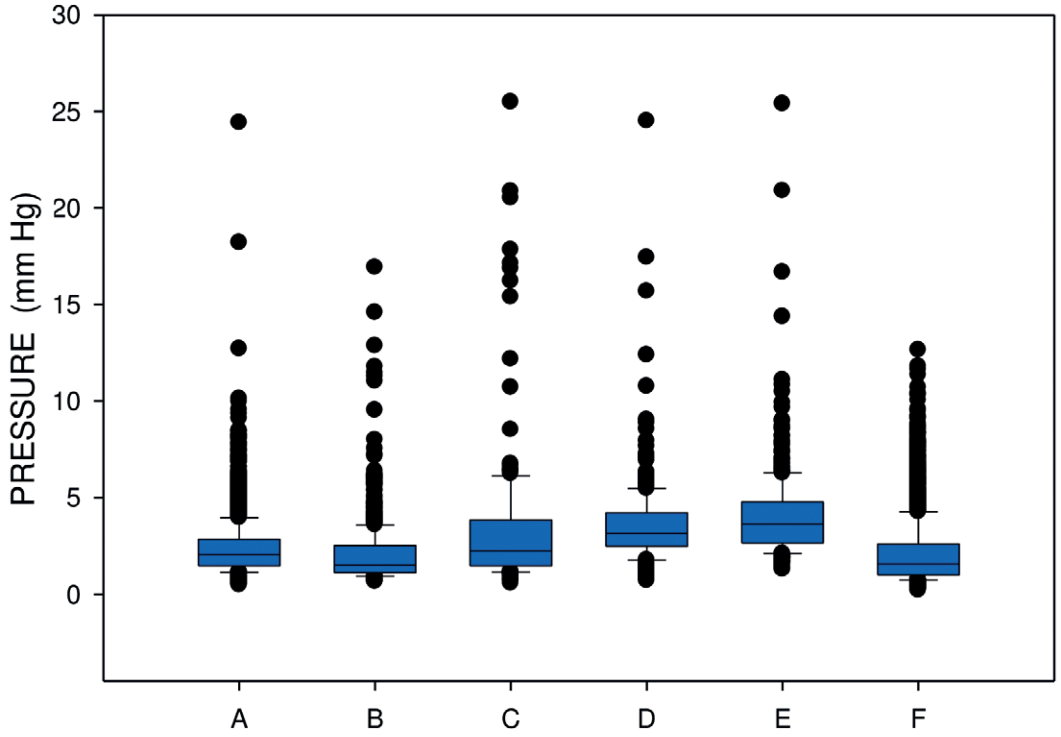

Fig. 5 Intra-luminal pressure. Group A: stomach under fasting condition; B: stomach after food intake; C: passage of a capsule from the stomach to the duodenum; D: jejunum; E: ileum; F: colon. Median, inter-quartile range and outliers. Selected statistically significant differences: A > B ($p < 0.001$); C > B ($p < 0.001$); E > D ($p < 0.001$); E > F ($p < 0.001$).

Similar variability features were found in experimental porcine electrogastrography, too (35–38). In this study, we decided to deliver the wireless capsule endoscopically, so that gastric content could be removed from the stomach before the capsule was placed (drunk water, gastric juice, regurgitated bile). Endoscopy also enabled a quick insertion of a capsule and thus shortened the duration of general anaesthesia.

There are only sparse experimental studies available so far (32, 39–41). The most detailed data on the use of

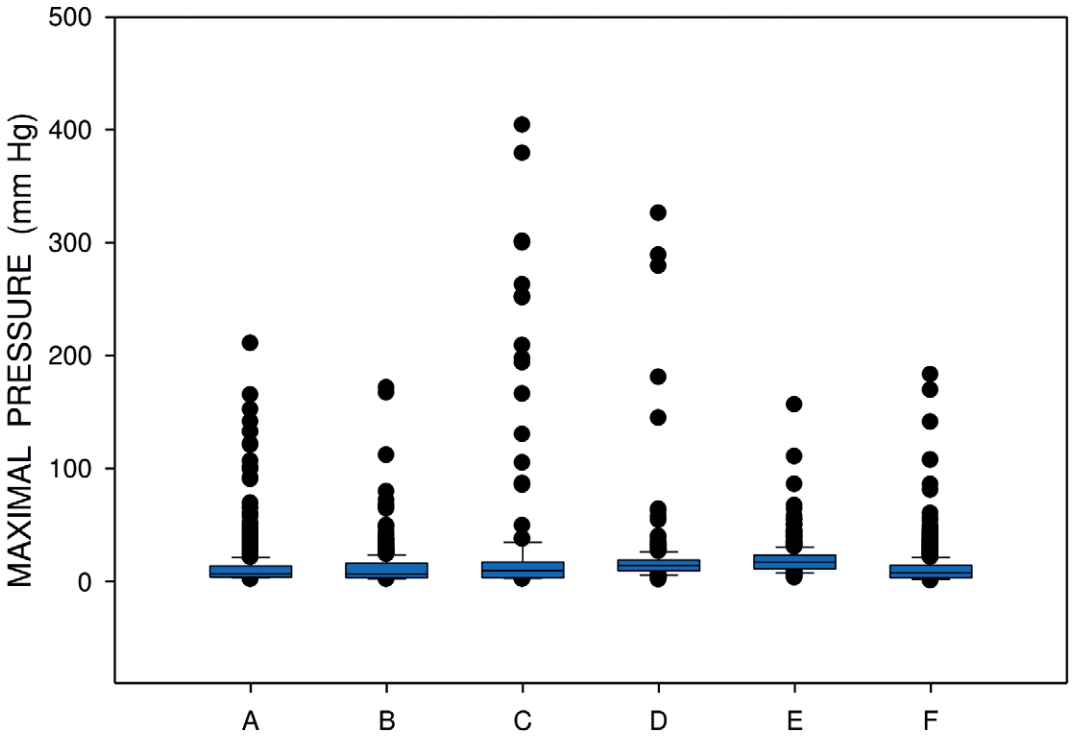

Fig. 6 Maximal intra-luminal pressure. Group A: stomach under fasting condition; B: stomach after food intake; C: passage of a capsule from the stomach to the duodenum; D: jejunum; E: ileum; F: colon. Median, inter-quartile range and outliers. Selected statistically significant differences: A > B ($p = 0.018$); C > B ($p = 0.014$); E > D ($p < 0.001$); E > F ($p < 0.001$).

wireless motility capsules in experimental pigs was published by Henze et al. (32). They investigated four male piglets (15–17 kg). Gastric emptying time under fasting conditions ranged from 68 to 233 hours. Transit times through the porcine small intestine were much more consistent than for the gastric compartment and ranged between 2–4 hours. The mean colonic transit time in this study was highly variable (21–169 hours) (32).

Warrit et al. (41) studied wireless motility capsules in adult healthy dogs. Median gastric emptying time was 20 hours (wide range 6–119 hours). Gastric pressure pattern and pH was dependent on the phase of food consumption. Mean small intestinal transit time was 3 hours (range 2–5 hours). Mean large bowel transit time was 21 hours (range 1–69 hours). There was a considerable inter-individual variation in motility patterns and transit times in dogs (41).

Last but not least, it is necessary to point out that both ketamine-based induction of general anaesthesia as well as long-lasting general anaesthesia (> 6 hours) were associated with a retention of motility capsules in the porcine stomach during the entire 5-day period. In our previous study on electrogastrography in experimental pigs we found out that ketamine, administered even in a single intramuscular dose, affected myoelectric function of the porcine stomach (42). Henze et al. (32) also found a capsule retention in the stomach in 3 of 8 piglets in their study. The authors did not mention what type of anaesthesia they used and did not state if ketamine was omitted for the induction of general anaesthesia (32).

Clinical use of wireless motility capsules has been reported since early 2010s (43–46). Motility pattern was studied in gastroparesis (43), irritable bowel syndrome (44) and for assessment of the effect of different drugs (e.g. erythromycin or morphine) (45). Wireless motility data correlated with scintigraphy in delayed gastric emptying (46).

Wireless, non-invasive complex investigation of gastrointestinal function will enable future experimental studies of gastrointestinal side effects of oncology chemotherapy. It also will facilitate further research of acetylcholinesterase inhibitors, modulators and re-activators and last but not least will extend possibilities of preclinical pharmacokinetic projects.

We are aware of possible limits of this pilot study. In spite of the assisting dedicated software that suggests time frames, we were not able to set time intervals fully precisely. Different parameters were combined to estimate particular periods. Fasting condition is associated with low gastric pH while intake of food is characterized by an increase of pH and temperature. The passage of a capsule from the stomach to the duodenum is associated with an increase of intra-luminal pressure and pH. Intra-luminal pressure in the colon is lower compared to the small intestine. The most questionable point is the time border between the jejunum and ileum. It is impossible to set it exactly even at porcine gross anatomy and histology (with an assumption of two equal lengths) (47–51).

CONCLUSIONS

Our methodical study has proven that a long-term function monitoring of the gastrointestinal tract by means of

wireless motility capsules in experimental pigs is feasible. However, both ketamine-based induction of general anaesthesia as well as long-lasting general anaesthesia (> 6 hours) should be avoided to prevent retention of a capsule in the porcine stomach.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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