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Prediction of gastroesophageal reflux episodes by smooth muscle electromyography: A translational study in rats and adolescents

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Aims: Our aim was to measure the myoelectric modifications during gastric acid secretion along with the gastric pH in a rat model and to detect the gastrointestinal (GI) myoelectric changes in adolescents suffering from gastroesophageal reflux disease (GERD) along with the esophageal pH measurement.
Main methods: In anesthetized rats, gastric acid secretion was initiated with intragastric histamine (50 mg/kg), and gastric pH, GI myoelectric activity and mechanical GI contractions were measured with intragastric pH electrode, subcutaneously implanted smooth muscle electromyography (SMEMG) electrodes and organ implanted strain gauges, respectively. In the clinical study, esophageal pH and GI myoelectric activity were measured in adolescents suffering from GERD with intraesophageal pH electrode and SMEMG electrodes placed on the abdominal surface, respectively. The SMEMG records were analyzed by fast Fourier transformation (FFT) and power spectrum density maximum (PsD_{max}) values were calculated for the GI segments.
Key findings: In rats, histamine initiated an immediate increase in gastric PsD_{max}, which preceded the significant reduction in gastric pH by 75 min. The myoelectric change was independent of mechanical GI contractions. In adolescents, the GERD episodes were preceded by a significant increase in gastric PsD_{max} 45 min earlier. These changes were independent of motion or meals.
Significance: Increased gastric myoelectric activity during histamine stimulation or GERD might be linked to the enhanced activity of the gastric proton pump, indicating a link between gastric acid secretion and GERD episodes. It is supposed that SMEMG might be a tool for predicting forthcoming reflux episodes in GERD.

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1. Introduction

Gastric hyperacidity is a condition that can lead to several gastrointestinal (GI) disorders, including functional dyspepsia (FD) and gastroesophageal reflux disease (GERD) [1]. In childhood and adolescence, the symptoms of FD include gastric pain, early satiety, and post-prandial fullness [2]. In GERD, the reflux of gastric contents irritates or damages the mucous membrane of the esophagus, causing inflammation and upturning, which may manifest itself in symptoms, complaints, or complications in the digestive system or other organs [3]. GERD is known from early childhood, and it shows an age-dependent increase in prevalence. In adolescents, its prevalence reaches 20%, which is the same as in adults [4]. Additionally, the cutoff scores determining the presence of GERD in adolescents by questionnaire show varieties, leading to different results and questioning the reliability of these methods [5].

Gastric hyperacidity is caused by the overproduction of gastric acid. Gastric acid is secreted by H^+-K^+-ATPase (proton pump) in the parietal cells of the stomach. This pump maintains a proton gradient of more than a million-fold across the membrane, which makes it one of the highest capacity pumps operating in mammals and humans [6]. Although the intermittent dysfunction of the lower esophageal sphincter is considered as a major factor for GERD [7], the hypersecretion episodes of gastric acid production controlled mainly by gastrin, histamine, and acetylcholine [8] are still considered as one of the main causes of the disease [9]. GERD was defined as a reflux event with esophageal pH below 4.0 [10] There is clear evidence that reducing the gastric acid level is one of the most efficacious therapies for GERD [11,12], which also proves that the secretion and the amount of gastric acid have an impact on GERD. On the other hand, GERD is a multifactorial disease, therefore other factors, such as defects in the lower esophageal sphincter or altered transdiaphragmatic pressure, also play a role in the pathogenesis of the disease [13].

Smooth muscle electromyography (SMEMG) is a method to detect the myoelectric waves of abdominal organs, including the GI tract and the pregnant uterus, by using organ-specific spectrum analysis of the raw traces [14,15]. The method is applicable in wakeful rats, pigs or even humans in a non-invasive (humans, pigs) or lightly invasive (rats) way [16,17]. Since SMEMG records the changes in the electric activities of different segments of the GI tract, we hypothesized that the H^+-K^+-ATPase-induced strong high proton gradient may also have some signal that can be detected and characterized.

2. Aims of the study

Our aim was to measure the myoelectric modifications during histamine-induced gastric acid secretion along with the gastric pH in a rat model. Our further aim was to measure the GI myoelectric changes in adolescents suffering from GERD as well as to detect the esophageal pH, using the findings from the animal experiments for the analysis of human data.

3. Materials and methods

3.1. Animal experiments

3.1.1. Housing and handling of the animals

The minimum number of experimental animals required to obtain evaluable results was calculated using Power and Sample Size program (version 3.1.6) [18] with the following parameters: $\alpha = 0.0125$ (type I error); $1\text{-}\beta = 0.8$ test power; $m = 1$ (control and treated animals per group considered equal; effect size $= 1.66$, which is the difference between the means of the treatment groups divided by the standard deviation of the data. As a result of this estimation, experiments were designed with $n = 14$ animals/group. Since 2 groups were experimented (control and histamine treated), a total of 28 male Sprague-Dawley rats (ANIMALAB Ltd, Vác, Hungary) were involved in the study. The animals were treated in accordance with the European Communities Council Directive (2016/63/EU) and the Hungarian Act for the Protection of Animals in Research (Article 32 of Act XXVIII). All the animal experiments were accomplished with the approval of the Hungarian Ethical Committee for Animal Research (registration number: XIII./3234/2022). The rats were placed at 22–24 °C, in a relative humidity of 30–70%, under a 12 h light/12 h dark cycle. Tap water and standard rodent pellet food (Altromin 1324) were given *ad libitum* and Tapvei aspen bedding was used in the cages (ANIMALAB Ltd, Vác, Hungary).

3.1.2. Combined measurement of GI myoelectric activity and mechanical contractions, and gastric pH

Rats (240–280 g) were fasted for 24 h before SMEMG and mechanical contraction measurements with tap water availability. The animals were anesthetized with the inhalation of isoflurane-carbogen mixture (4% and 2% isoflurane for induction and maintenance, respectively). The rats were placed onto a heated operating table (MSB-MET Ltd, Balatonfüred, Hungary) to maintain the body temperature (37 °C). To detect myoelectric activity, electrocardiogram (ECG) and heart rate (HR), a bipolar disk electrode pair (MSB-MET Ltd) was placed subcutaneously on the abdominal surface, as described earlier [17]. The silver-silver chloride disk electrode pair was fixed subcutaneously 1 cm right from the midline above the GI tract. The signals of the electrode were detected with a Holter system and recorded with Easy Chart software (both MSB-MET Ltd).

The abdominal cavity was then opened, and implantable strain gauges (SEN-04-FSG2; MSB-MET Ltd) were sutured on the surfaces of the stomach, small intestine, and large intestine, along with the long axis of the muscle fibers to detect mechanical contractions as described previously [15,19]. The contractions were recorded and analyzed by using S·P.E.L. Advanced ISOSYS Data Acquisition System (MSB-MET Ltd).

After the implantation of the strain gauges, the stomach was slightly lifted, a small incision was made on its glandular surface, and a pH electrode (FC 23 B, Hanna Instruments Ltd, Szeged, Hungary) was inserted and fixed. The pH values were measured with an HI 8314-1 device (Hanna Instruments Ltd, Szeged, Hungary). Close to the esophagus, another incision was made on the stomach to insert a polyethylene cannula for histamine administration. After the completion of all these interventions, the abdomen was closed with surgical staples.

Basal GI myoelectric activity was registered along with ECG, HR, mechanical contractions, and gastric pH for 30 min. After the control phase, gastric acid secretion was induced by the intragastric administration of a water solution of histamine hydrochloride (Merck Ltd, Budapest, Hungary) through the gastric cannula in a dose of 50 mg/kg in 0.5 ml volume. For each animal, the pH of the histamine solution was adjusted to the pH of the gastric juice to avoid the change in gastric pH by the solution itself. Then the registration of each parameter was continued for 90 min. In the control group, physiological saline solution (0.5 ml) adjusted to the pH of the gastric juice was administered into the stomach. The changes were evaluated every 15 min. The pH sensor operated independently of the recording software, so pH values were read from the digital screen and manually recorded as a single value at the end of each 15-min period.

The recorded myoelectric signals were analyzed by fast Fourier transformation. The frequencies of the myoelectric waves were characterized in cycle per minute (cpm), and the magnitude of the activity was described as the maximum of power spectrum density (PsD_{max}) The characteristic cpms for the stomach, small intestine and large intestine were 3–5, 20–25 and 0–3, respectively [14]. Area under the curve (AUC) analysis was used to evaluate the mechanical contractions. The gastric pH values were followed continuously, and the values at the end of each 15-min interval were used for comparison. Statistical significance was evaluated by the one-way ANOVA Bonferroni post hoc test by using the computer program Prism 5.0. (GraphPad Software, San Diego, USA). The values of each 15-min period were compared to the basal period followed by the insertion of the pH electrode and preceding histamine administration.

3.2. Human studies

3.2.1. Subjects

The study was carried out in accordance with the guidelines of the Hungarian Medical Research Council (235/2009 (×.20) § 32 (3)) and with the authorization of the National Institute of Pharmacy and Nutrition (permission number OGYÉI/48477–4/2017).

Subjects younger than 18 years with GERD were selected for the study, after appropriate informed written consent including parents. The study involved 128 subjects, the mean age was 13.0 ± 3.17, from both sexes (50.5% male, 49.5% female), with GERD suspected in primary care, 74 of the 128 patients were found to have GERD by a specialist investigation in the Department of Gastroenterology, Heim Pal National Pediatric Institute using 24-h esophageal pH measurement and DeMeester score calculation [20]. Exclusion criteria were consent withdrawal, esophageal surgery, hiatus hernia, acute illness before or during the measurement, skin rash, contact allergy to electrodes, or any medical condition that endangered the patients or contraindicated the performance of the test. Three-parameter detection (non-invasive SMEMG, ECG and invasive pH measurements) was performed simultaneously in 74 patients, none of whom were excluded from the study. During the measurements, the patients were not treated with any medication and a standard meal was provided three times a day, considering the disease (age-appropriate light-mixed diet, with the consideration of individual diets). Special functional activities (vomiting, urination, nausea, sleep disturbance, etc.) were recorded in an individual patient's diary.

3.2.2. Measurement of the esophageal pH

The 24-h study was performed with single sensor monitoring. A single crystal antimony multi-use pH catheter (Synectics Medical Ltd, Portugal) was positioned into the esophagus through the nostrils and pharynx in awake and fasting conditions with the continuous support of X-ray monitoring. The sensor was placed 5 cm above the lower border of esophageal sphincter. The catheter was connected

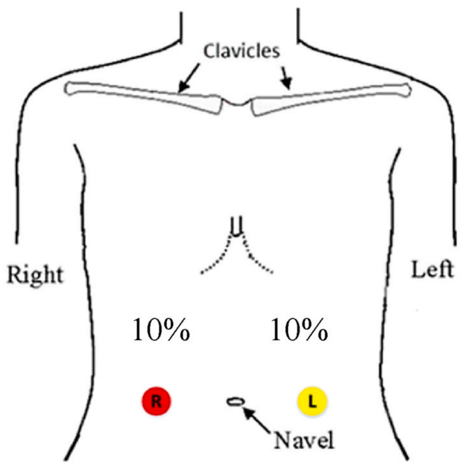


Fig. 1. A schematic figure for the placement of the electrode pairs, taking the navel as the baseline point. The electrodes were positioned in 10% of the abdominal circumference both to the left (L) and to the right (R) of the navel.

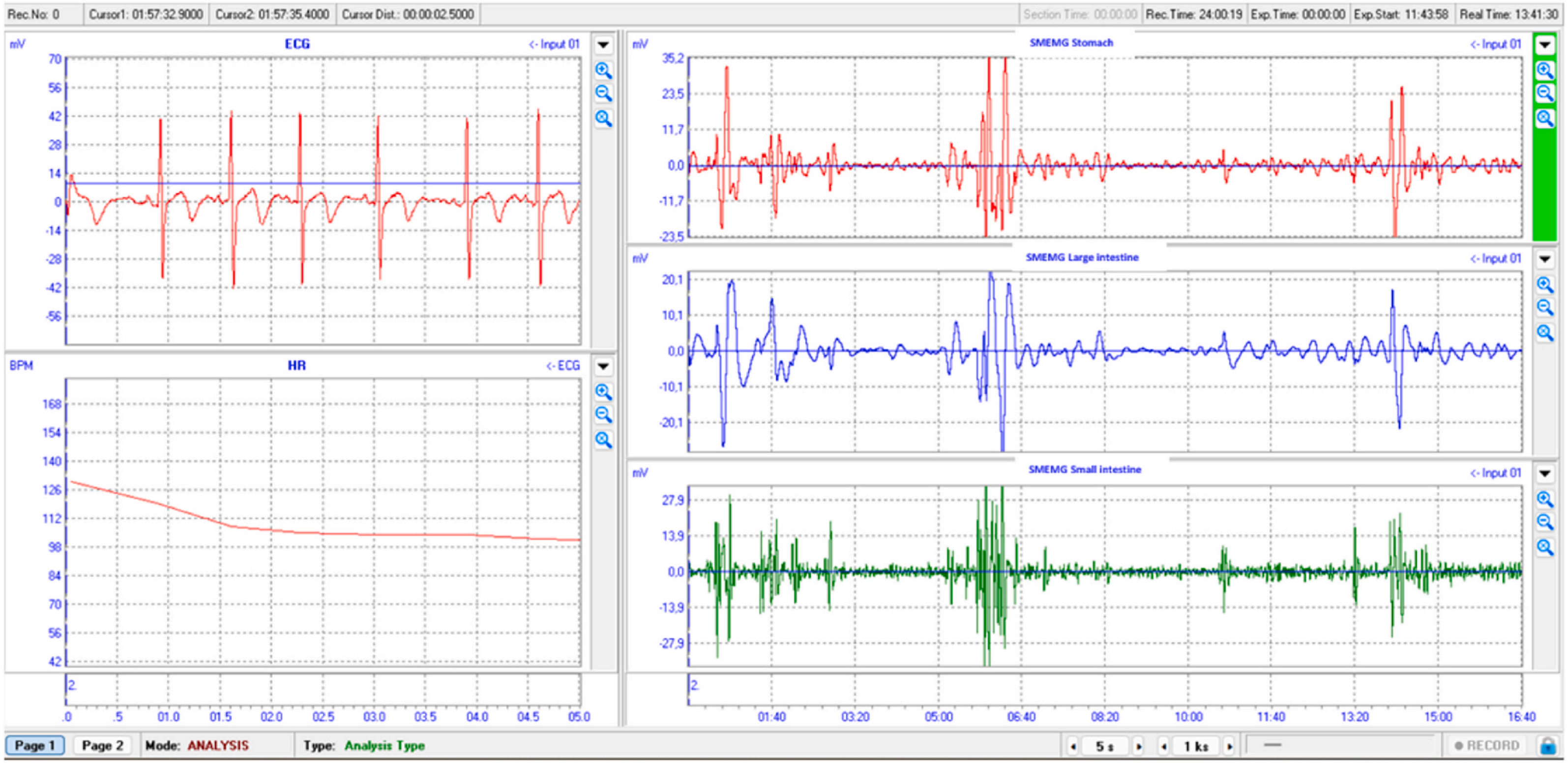
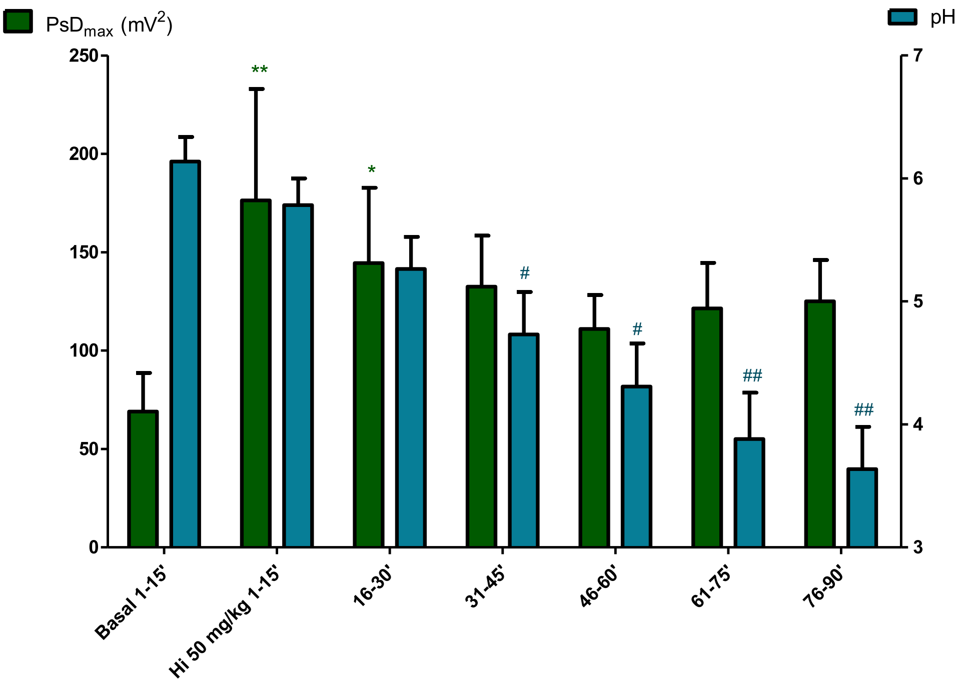


Fig. 2. Representative raw traces for ECG and SMEMGs in a multiple display mode in adolescents. The electrocardiogram (ECG, top left corner) and the calculated heart rate (HR, bottom left corner) reveal the cardiac signals, while the smooth muscle electromyograms of the stomach (red line, top right panel), large intestine (blue line, middle right panel) and small intestine (green line, bottom right panel) show the GI tract signals. The synchronized wave nodes on all the three SMEMG traces are artefacts resulting from motions or other activities and were removed with a digital limiter.

A



B

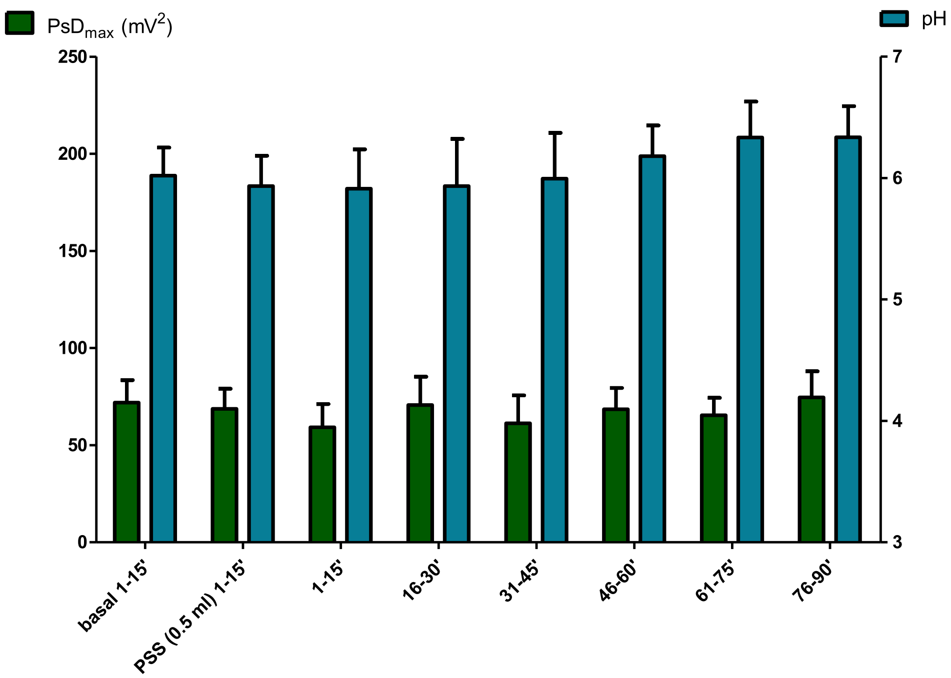


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Fig. 3. Changes in gastric PsD_{max} (green columns) and pH (blue columns) after direct histamine injection (50 mg/kg) (A) or PSS (control, 0.5 ml/animal) (B) into the stomach of the rat (n = 14/group). The PsD_{max} values were calculated in 15-min intervals by fast Fourier transformation (filtering in the frequency range of 3–5 cpm), while a single pH value was read at the end of each 15 min period. Hi: histamine; PSS: physiological salt solution *:$p < 0.05$, **$p < 0.01$ compared to the basal PsD_{max} value; $^{\#}$:$p < 0.05$, $^{\#\#}$:$p < 0.01$ compared to the basal pH value, deviation is standard error of the mean.

to the Holter unit of the pH measuring device (pHday2, Medica S. p.A. Italy), which was placed in a side bag and fixed on the device holder belt. After successful connection to the software of the device and checking, the 24-h measurement was started. The pH measuring device detected the actual pH value every 4 s. The measured pH values were stored in the memory of the Holter unit. The stored data were transferred to a computer containing the analysis software after the measurement was completed. pH less than 4.0 for minimum 16 (4 × 4) seconds was considered as a reflux episode, as described earlier in pediatric cases [21]. Based on the measured pH and the patient's diary, we distinguished reflux events (pH value lower than 4), artefact reflux events (linked to meal or motion) and non-reflux periods.

3.2.3. GI smooth muscle electromyography

The GI myoelectric changes of the subjects were recorded non-invasively on the abdominal surface in parallel with the esophageal pH detection. The measurement procedure with the Holter device was painless. The waves detected by the electrodes were amplified and digitized with an appropriate analogue amplifier and A/D conversion, respectively.

Abdominal circumference was measured before positioning the electrodes. As a standard, 10% of the abdominal circumference was considered as the measurement distance from the baseline (navel) (Fig. 1).

The skin surface was cleaned with an alcohol gauze, and a conductive gel (AC Cream, Spes Medica S. r.l. Italy) was applied on the skin, which provided both high conductance and the pre-fixation of the large electrodes (EM80, Beuer GmbH, Germany). Final fixation was done with Omnifix tape (Hartman Hungary Ltd, Hungary) and Ramofix flexible tubular mesh bandage (Ramofix Trade Ltd, Hungary). After the electrodes were placed and connected, the Holter unit (DR4CH/01 MSB-MET Ltd, Hungary) was initialized to the central unit (CR8CH/02 MSB-MET Ltd, Hungary) and a 10-min fasting recording was made (Bluetooth - Bluetooth connection) in rest. This initial recording was performed between 9.00 and 10.00 a.m. After the setting, the unit was disconnected from the central unit and 24-h data collection was started – simultaneously with the pH Holter. The electrodes also measured the electrocardiogram (ECG) which was used to confirm the noise-free detection of the myoelectric waves. The raw traces were recorded by Easy Chart software (Fig. 2). Motion artefacts were cut by using a digital limiter built into the software. Most of the motion-induced artefacts in SMEMG did not cause artefacts in pH detection.

During the FFT analysis of the GI tract segments, the filter was set to 0–3 cpm, 3–5 cpm and 10–14 cpm for the stomach, small

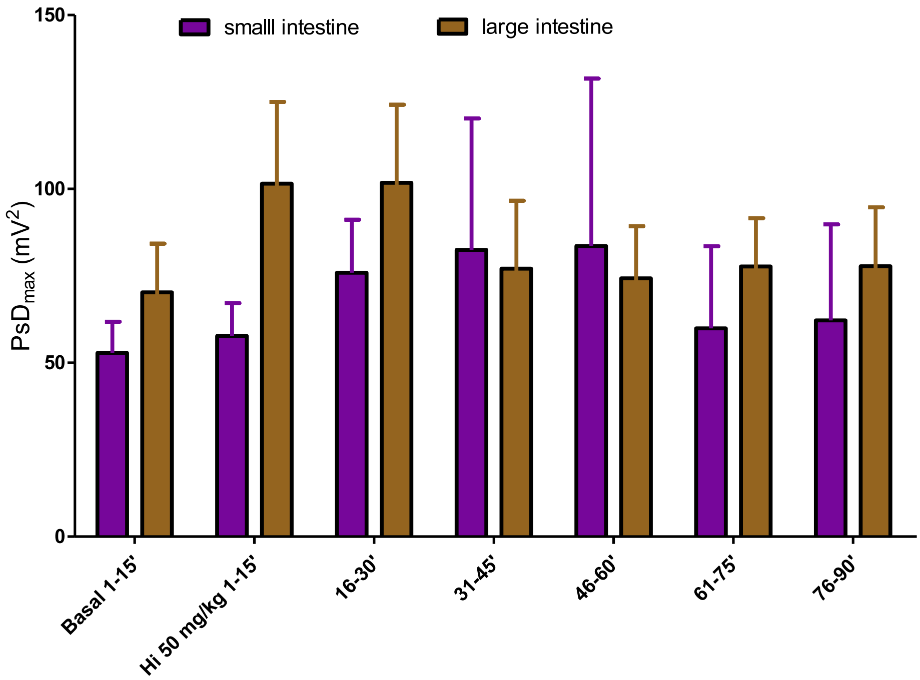

Fig. 4. Changes in PsD_{max} in the small intestine (purple columns) and the large intestine (brown columns) in rats after direct histamine injection (50 mg/kg) into the stomach of the rat (n = 14). The PsD_{max} values were calculated in 15-min intervals by fast Fourier transformation (filtering in the frequency range of 20–25 cpm for the small intestine and 0–3 cpm for the large intestine). Comparisons were made to the basal value of each digestive tract, but no significant change was found. Hi: histamine, deviation is standard error of the mean.

intestine, and large intestine, respectively [17]. The PsD_{max} values of each 15-min period were compared to the value of the 0-15-min period preceding the reflux event. As in the animal experiment, statistical significance was assessed using the one-way ANOVA Bonferroni post hoc test.

4. Results

4.1. Rat studies

The placement of the pH electrode into the stomach (control) alone did not affect the gastric pH or the intensity of the myoelectric signals 30 min after implantation. Histamine at a dose of 50 mg/kg delivered directly into the stomach significantly increased the PsD_{max} of the stomach myoelectric activity in the first 30 min after administration but showed no difference from 31 to 45 min until the end of the 90-min period as compared with the control. Gastric pH decreased significantly from the 45th minute after histamine administration, but the pH fell below 4.0 only after 75 min of histamine administration (Fig. 3A). The PsD_{max} and pH values remained unchanged in the control group (Fig. 3B).

We also investigated whether the histamine-induced change in PsD_{max} is only detectable in the stomach, or whether it can also be measured in other parts of the GI tract. Therefore, we performed the FFT analysis of the myoelectric waves for the small intestine and the large intestine as well. We found that, compared to the control values, no significant change was measured in the other GI segments (Fig. 4). The PsD_{max} values also remained unchanged in the control group (data not shown).

Since histamine has a smooth muscle contracting effect, we also investigated whether the increase in the PsD_{max} values of the stomach after histamine treatment is related to the contraction of the gastric smooth muscle or possibly to a process independent of contraction. No significant change was observed in gastric contractions after histamine administration, measured with a strain gauge detecting direct mechanical contractions. The contractions in the small and large intestine also remained unchanged after histamine treatment (Fig. 5). Contractions were also unchanged in the control group (data not shown).

When comparing the changes in the gastric pH, PsD_{max} and contractions, it was found that the histamine-induced increase in PsD_{max} was followed by a decrease in gastric pH value which decreased significantly after a 45 min delay, while it was independent of real mechanical gastric contractions.

4.2. Human studies

Esophageal pH and GI myoelectric changes were detected in parallel for 24 h. We searched for all non-reflux episodes lasting at least 2 h, as well as reflux episodes with their corresponding preceding 2-h non-reflux episodes. Before FFT analysis, the motion artefacts were removed with a digital limiter. The FFT analyses for the stomach, small and large intestine were done for the preceding 2-h

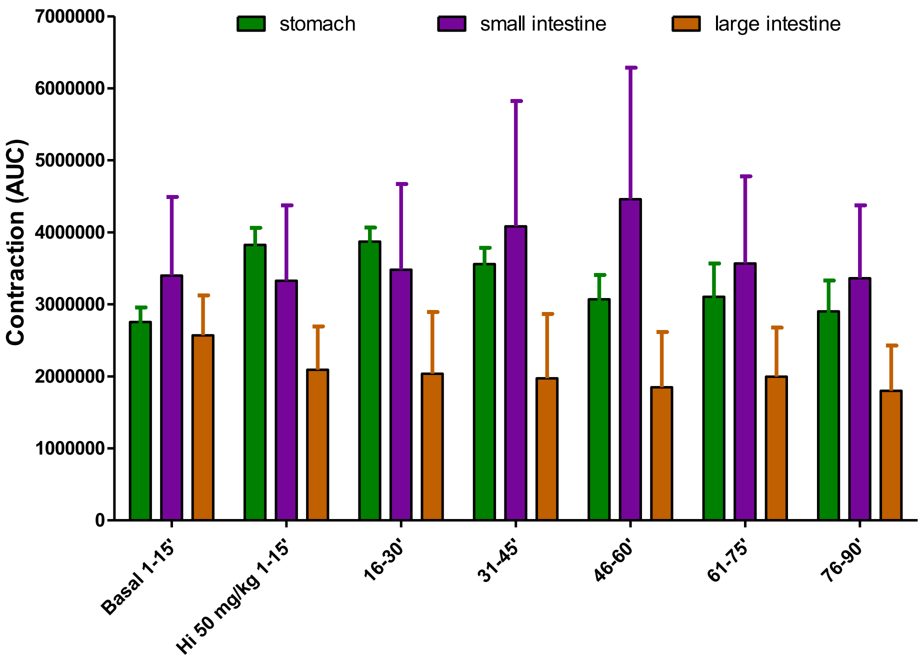

Fig. 5. Changes in the contractions of the stomach (green columns), small intestine (purple columns) and large intestine (brown columns) in rats after direct histamine injection (50 mg/kg) in the rat (n = 14). The contractions were measured by the application of strain gauges and recorded with an online computer. The contractions were expressed in the area under the curve (AUC) in the given period. Comparisons were made to the basal value of each digestive tract, but no significant change was found. Hi: histamine, deviation is standard error of the mean.

periods of the reflux event in every 15 min (Figs. 6 and 7).

The FFT analysis revealed that in the case of a reflux event, the preceding 31-45-min period in gastric myoelectric activity had significantly higher PsD_{max} as compared to the other 15-min periods within the preceding 2-h interval. Such a change was not

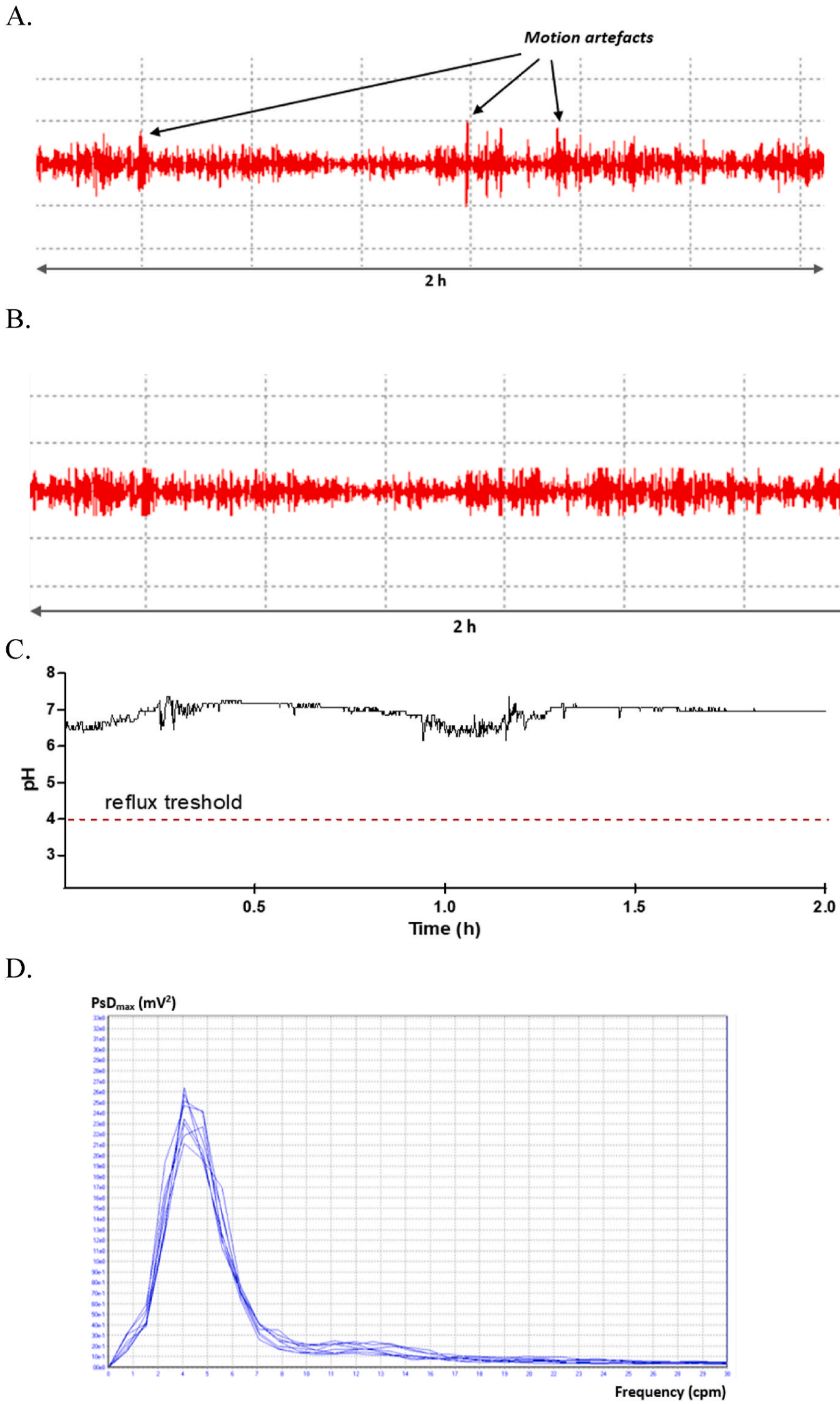

Fig. 6. Representative raw trace (A) and limiter modified trace (B) of SMEMG along with the pH values (C) and the FFT spectra for the stomach (filtering 3–5 cpm) of every 15 min (D) in a subject in a 2-h interval of a non-reflux period. The esophageal reflux threshold was at pH 4. The pH and the PsD_{max} values did not show any differences.

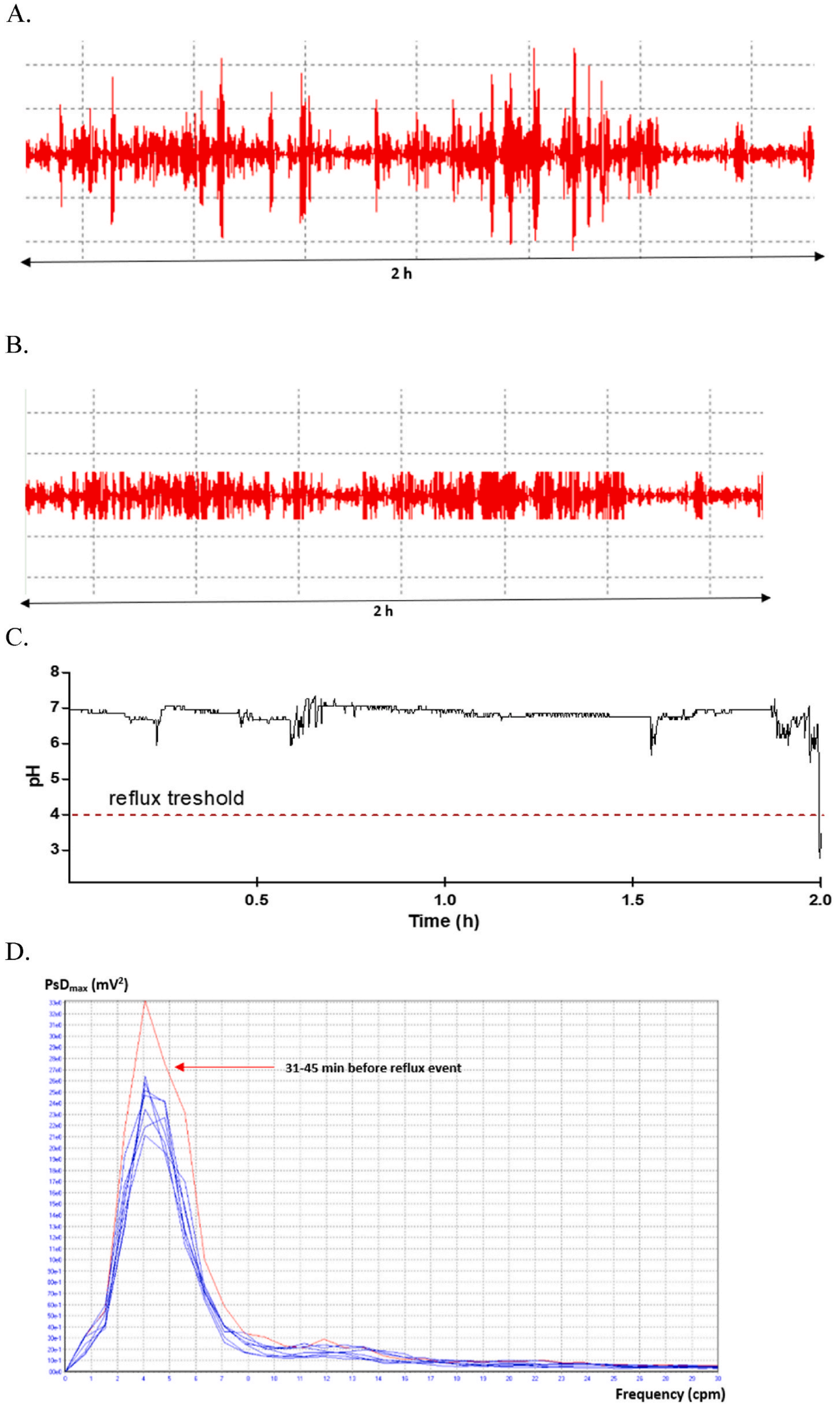

Fig. 7. Representative raw trace (A) and limiter modified trace (B) of SMEMG along with the pH values (C) and the FFT spectra for the stomach (filtering 3–5 cpm) of every 15 min (D) in a subject in the preceding 2-h interval of a reflux event. The esophageal reflux threshold was at pH 4. The PsD_{max} value of the 31–45 min before the reflux episode showed a higher level as compared with the other preceding 15-min periods.

detectable in artefact reflux events or non-reflux periods (Fig. 8).

The FFT analysis did not show any significant modifications in PsD_{max} values for the small or the large intestine, regardless of the reflux, non-reflux, or artefact reflux events (Figs. 9 and 10).

5. Discussion

GERD is one of the greatest challenges in gastroenterology, the prevalence of the disease is continuously increasing [22]. Even the young generation is heavily affected by the illness, and their diagnosis and treatment pose a special difficulty for clinical practice [23]. The correlation between gastric acid secretion and GERD episodes is a matter of debate [24], although it is indisputable that gastric acid reduction alleviates the symptoms and frequency of GERD episodes [25,26].

For the clinical diagnosis, the 24-h esophageal pH measurement and the calculated DeMeester score, or other scores are widely accepted methods [20]. The DeMeester score is a composite score based on six parameters obtained from the pH measurement [10]. According to the authoritative scientific opinion, pH detection and the calculation of the DeMeester score provide the best tools for the diagnosis of GERD [27]. This combined method, however, is not able to predict GERD episodes, and no method is available for the prediction of GERD episodes in gastroenterological practice.

Our aim was to measure putative GI myoelectric modifications linked to reflux episodes using SMEMG. First, we developed a rat model in which we measured the myoelectric waves along with gastric pH and GI contractions. Earlier, we clarified the characteristic SMEMG signals of the segments of the GI tract [14]. We hypothesized that the increase in gastric acid secretion should have a myoelectric trace in the GI, since H^+-K^+-ATPase makes a huge proton gradient in the parietal cell membranes [28]. Histamine is a well-known stimulator of gastric acid secretion [29], therefore we were able to time the process of gastric acid secretion and monitor the myoelectric, pH and contraction changes with the closest tracking and in a combined way. Although the average basal gastric pH of the fasting rats was higher than usual (6.1 instead of 4.8–5.0), the relatively higher initial pH may be linked to the distension caused by

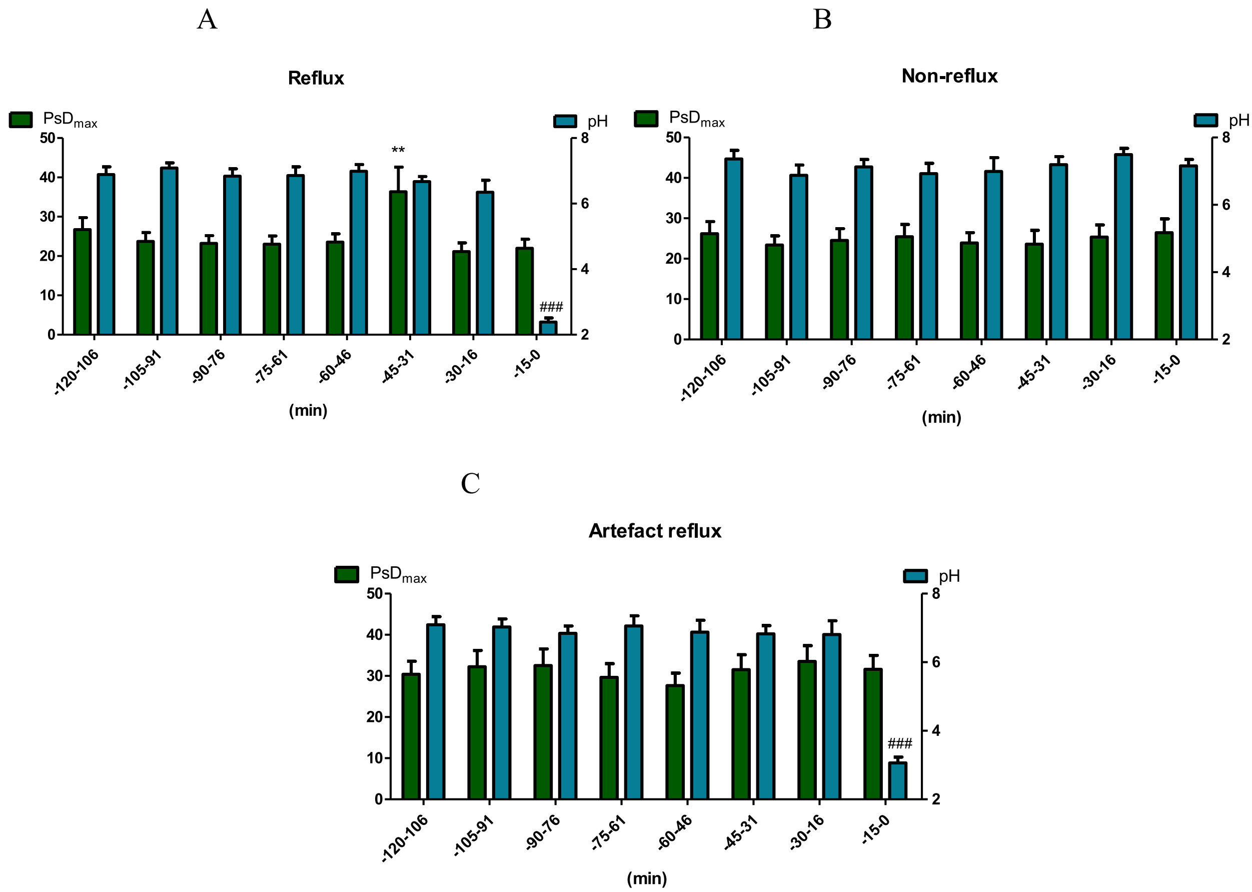

Fig. 8. Changes in gastric PsD_{max} values (green columns) and pH (blue columns) in reflux (A), non-reflux (B) and artefact reflux 120 min before the events (esophageal pH less than 4) after FFT analysis (filtering 3–5 cpm) in adolescents. The artefact reflux includes both motion- and meal-induced decrease in pH. Significant increases were only detected in the 31–45 min before the reflux event, and no change was observed in any other cases in PsD_{max} values. **:$p < 0.01$ compared to the -15-0-min period, $^{###}p < 0.001$ compared to the pH value of -120-106-min period; deviation is standard error of the mean.

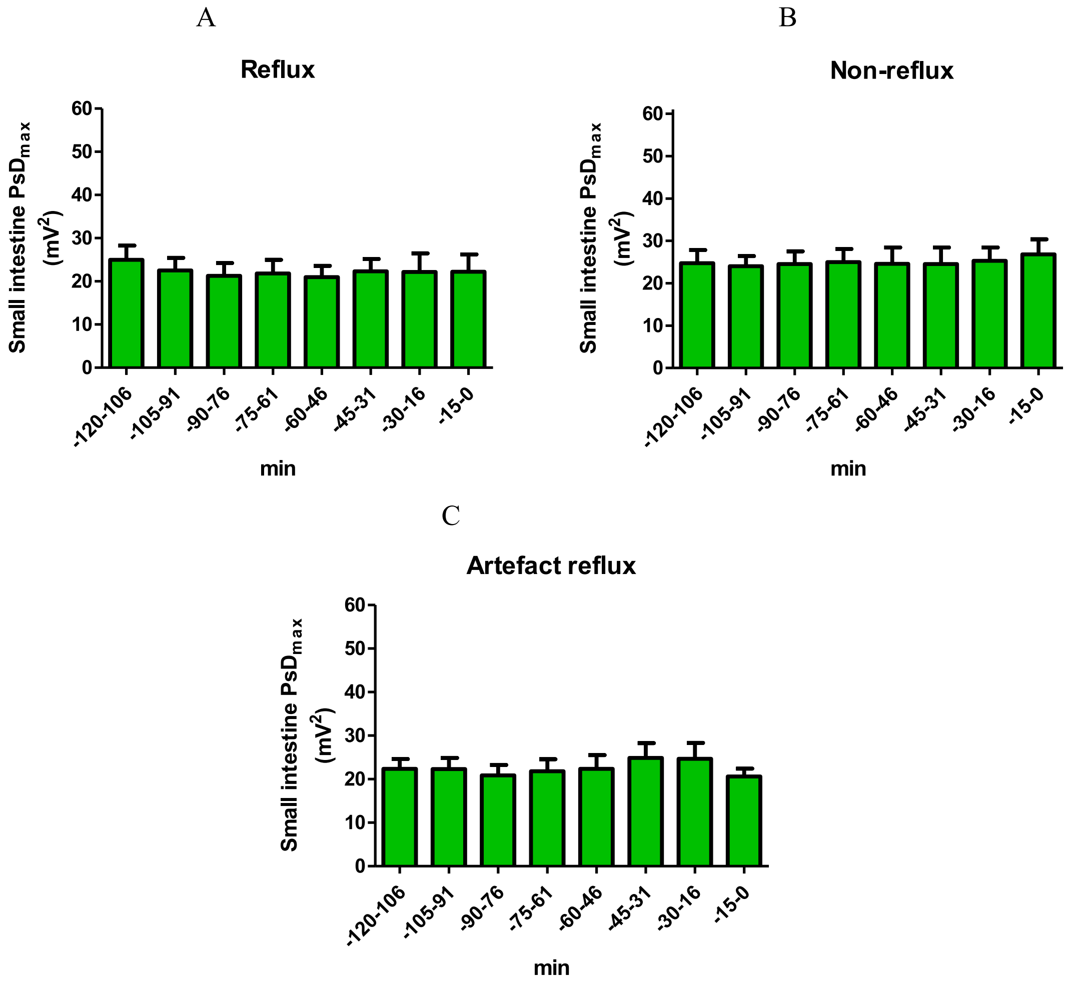

Fig. 9. Changes in small intestine PsD_{max} values in reflux (A), non-reflux (B) and artefact reflux 120 min before the events after FFT analysis (filtering 10–14 cpm) in adolescents. No significant change was detected in any of the cases within the analyzed 2-h interval. Deviation is standard error of the mean.

the intragastric pH sensor, since gastric distension reduces the gastric acid secretion [30]. As a result of the pilot experiments, we found that 50 mg/kg dose of histamine, equivalent to the dose applied earlier [31], was able to increase the gastric acid secretion without inducing GI smooth muscle contraction. Thus, it is probable that the detected myoelectric changes are linked to gastric acid secretion.

We found a surprising significant delay between the histamine initiated PsD_{max} increase (in frequency interval 3–5 cpm) and the decrease in gastric pH in our rat model. While the effect of histamine on PsD_{max} was immediate and lasted for 30 min, gastric pH was reduced permanently below the value 4.0 only after 75 min. So far, such a delay has been unknown, however, the intragastric application of histamine is also very exceptional, most of the studies apply intravenous or subcutaneous administration [32,33]. Anyhow, our rat experiments suggest that the histamine-induced activation of the proton pump results in significant gastric pH reduction more than 1 h later. This finding raised the question whether such a similar phenomenon might be detected in human GERD as well as a prediction of a forthcoming GERD episode.

During the clinical study, we made combined esophageal pH and GI SMEMG measurements to search for the link between the PsD_{max} change of any GI segment and the GERD episode in adolescents. The 24-h measurement with the strict patient's diary allowed us to distinguish between artefact and real GERD episodes. The parallel detection of ECG ensured that the record was free from any disturbing electric noise, as we did in our previous study [16]. Based on the delay found in the rat experiments, we hypothesized that the possible characteristic SMEMG signal should precede the GERD episode. Therefore, we selected clear GERD (esophageal pH below 4.0 for at least 16 s), artefact GERD (esophageal pH lower than 4.0 during motion or other activities) and non-GERD (esophageal pH above 4.0 for at least 2 h) events, and we analyzed their preceding 2 h in 15-min intervals by using the FFT method, as we did in rat experiments. In the case of GERD episodes, we found a clear increase in the gastric PsDmax value between the preceding 31–45 min, but such a change or even any other kind of modifications were not detected either in artefact or non-GERD episodes. Thus, we proved that a GERD episode can be predicted half an hour earlier by measuring gastric myoelectric activity with SMEMG. Such a link between gastric dysrhythmia and GERD had been supposed [34], however, we assume that our finding is independent of gastric motility and the

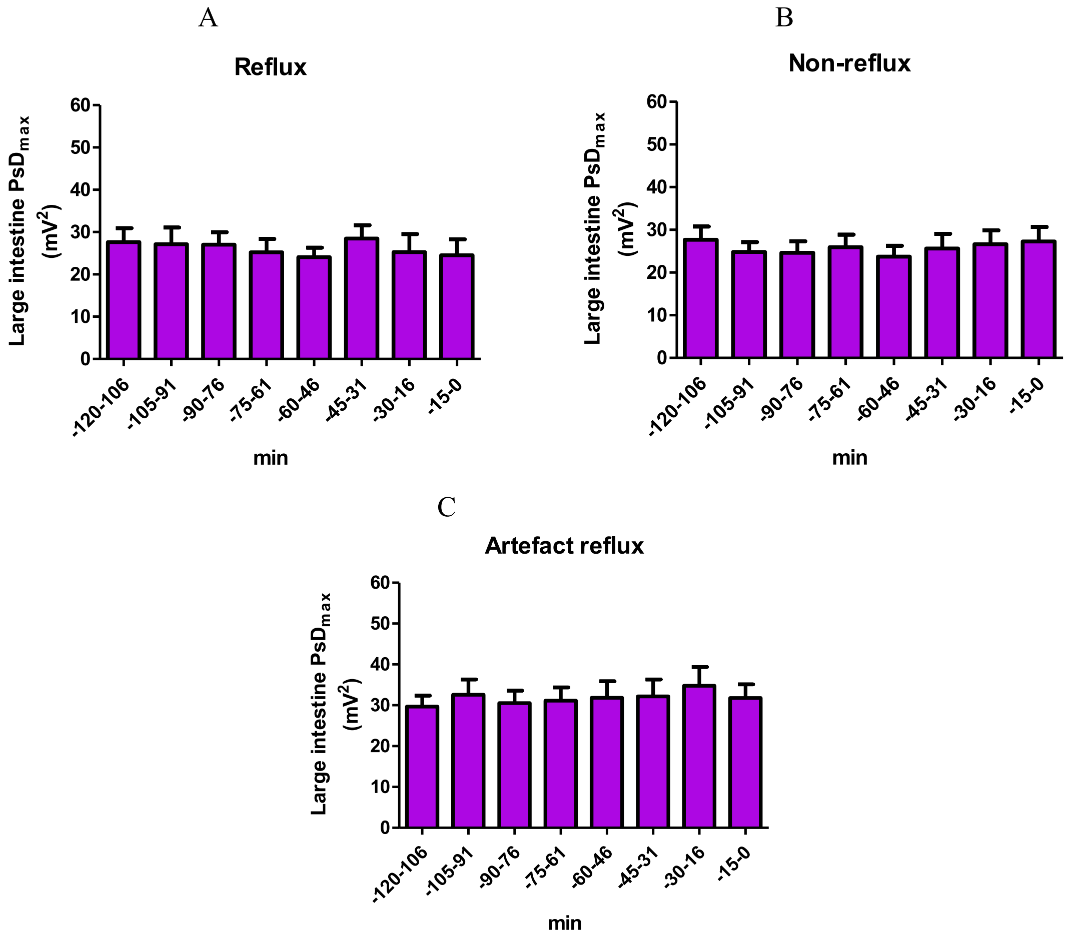

Fig. 10. Changes in large intestine PsD_{max} values in reflux (A), non-reflux (B) and artefact reflux 120 min before the events after FFT analysis (filtering 0–3 cpm) in adolescents. No significant change was detected in any of the cases within the analyzed 2-h interval. Deviation is standard error of the mean.

myoelectric signal rather belongs to the process of acid secretion.

The limitations of our study must be emphasized. Firstly, our rat experiments were a hyperacidity model, and the pH changes that we detected were measured in the stomach and not in the esophagus. Therefore, our finding might be just a coincidence with the human GERD processes. Secondly, we excluded the GERD episodes induced by meals from the clinical study and considered them as an artefact GERD. However, it is known that even meals can induce GERD episodes in patients but can also contribute to their reduction [35]. In our studies, we did not consider the effect of food as true GERD episodes, as we had to avoid any confounding factors to basically define the associated SMEMG signals. Although patients were given a recommended diet for GERD, this alone was not an assurance that the diet would not cause artefacts.

Despite its limitations, the SMEMG-based device can predict reflux episodes in a way that is convenient for the patient supporting the pharmacotherapy and the disease management. Fully automatic online evaluation of the data should be provided to avoid misleading artefacts caused by movement or meals. Since artefact waves are relatively easy to identify due to their different characters, the development of a digital filter suitable for everyday clinical use is feasible.

6. Conclusion

Both in rats and humans, we found an increase in the gastric myoelectric signals preceding the pH decrease in the stomach and the esophagus, respectively. This increase was independent of the mechanical GI contractions in rats and was not modified by motion or meals in adolescents. We hypothesize that the increased gastric myoelectric activity preceding GERD episodes is linked to the enhanced activity of the gastric proton pump. Our findings raise again the possibility of a relationship between gastric acid secretion and GERD. Based on the animal and human studies, we suppose that SMEMG might be a tool to predict forthcoming reflux episodes in GERD. Predicting reflux episodes with SMEMG can have a dual significance. It may have diagnostic significance without the inconvenience of intraesophageal pH measurement, especially in pediatrics. On the other hand, the dosing regimen of drugs for the treatment of GERD can be varied and modified according to the actual reflux episodes.

Author contribution statement

Anikó Nagy, Róbert Gáspár: Conceived and designed the experiments; Wrote the paper.
Kálmán F. Szűcs: Performed the experiments; Analyzed and interpreted the data.
György Grosz, Miklós Süle: Conceived and designed the experiments; contributed reagents, materials, analysis tools or data.
Ferenc Fekete, Anna Karoliny: Performed the experiments.
Mariann Borsos, Zsuzsanna Papp: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Dóra Vigh: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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