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Original Research Article

Gastroesophageal reflux is not associated with short-term variability of parasympathetic activity in children

Jan Krzysztof Nowak [a,*], Agata Łaźniak [b], Aleksandra Lisowska [a], Zdzisława Kycler [c], Waldemar Bobkowski [b], Jarosław Walkowiak [a]

[a] Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Poznan, Poland
[b] Department of Pediatric Cardiology, Nephrology and Hypertension of the Developmental Age, Poznan University of Medical Sciences, Poznan, Poland
[c] Department of Pediatric Pneumonology, Allergology and Clinical Immunology, Poznan University of Medical Sciences, Poznan, Poland

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ABSTRACT

Purpose: A lower parasympathetic activity was described in patients with the gastroesophageal reflux disease. We aimed to determine whether gastroesophageal reflux (GER) episodes are associated with a short-term parasympathetic tone variability in children.
Methods: In order to address this question we performed simultaneous 24-h esophageal multichannel intraluminal impedance-pH and electrocardiographic monitoring in 16 children (age range 6–18 years), including 8 with asthma and 2 with gastroesophageal reflux disease. After describing duration, height, and acidity of 483 GER episodes we also measured parasympathetic-related heart rate variability parameters in 4 time periods: preceding, containing, following GER, and in-between GERs (control). High frequency (HF) power and root-mean square differences of successive R–R intervals (r-MSSD) were assessed in 2.5-min and 1-min periods, respectively.
Results: We did not identify the searched short-term parasympathetic tone changes.
Conclusions: In conclusion, GER episodes and their characteristics were not associated with short-term variability of parasympathetic activity in children.

1. Introduction

Gastroesophageal reflux (GER) episodes occur physiologically. The underlying mechanisms of GER involve an interplay of neural, enterohormonal, motor, anatomic, and physical stimuli; their disturbance may lead to gastroesophageal reflux disease (GERD). Several studies, including a 24-h analysis of heart rate variability (HRV), showed that in patients with GERD the function of the autonomic nervous system (ANS) is altered [1,2]. The most consistent finding was the negative association of high frequency power (HF; 0.15–0.4 Hz) with GERD. Since HF reflects parasympathetic cardiac activity [3,4], these results implicate a vagal tone reduction in pathologic GER and point toward its possible role in physiologic GER. HF, a parameter that is best described among all the frequency domain HRV parameters, closely correlates with r-MSSD, which is another HRV measure of the parasympathetic tone [5].

Recently, short-term GER-related changes of vagal activity were reported in neonates [6]; the parasympathetic tone was lower in the minutes preceding GER. However, it remains unknown: (1) whether analogous changes exist in children and (2) if they are associated with characteristics of individual GER episodes.

The main aim of our study was to determine whether GER episodes are associated with a short-term variability of parasympathetic activity in children. The secondary objective was to check if this is true in subgroups defined by GER episode characteristics: duration, height, and acidity.

2. Material and methods

The patients were recruited in Karol Jonscher University Hospital of Poznan University of Medical Sciences, Poznan, Poland in November and December 2015. Inclusion criteria comprised: referral for 24-h esophageal pH-monitoring, age ≥6 years, height ≥100 cm. Exclusion criteria comprised anatomic anomalies, neurological disability, and a history of surgery of the esophagus. No antacids or other drugs were allowed during the study. Before inclusion in the study, two children were receiving omeprazole and

* Corresponding author at: Szpitalna 27/33, 60-572 Poznan, Poland.
E-mail address: jan.nowak@ump.edu.pl (J.K. Nowak).

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one child was receiving a magnesium-alginate-based preparation to relieve symptoms; none of them was diagnosed with GERD at the time. Prior to participating in this research, all patients with asthma were already receiving treatment for asthma.

The recording procedure was as follows. A standard electrocardiogram (ECG) was performed and assessed. The 3-channel Holter monitor Schiller AR12 Plus (Schiller Reomed AG, Dietikon, Switzerland) was installed and 24-h recording was started. Then a single-use internal-reference multichannel intraluminal impedance-pH (MII-pH) probe (Comfortec Z/pH ZAN-BG-44, Sandhill Scientific Inc., Highlands Ranch, USA) was calibrated in standard buffers and placed transnasally in the esophagus at a depth calculated using the formula that we previously described [7]. A properly placed ZAN-BG-44 probe had electrodes measuring impedance at the following approximate height above the lower esophageal sphincter: 2–4, 4–6, 6–8, 8–10, 14–16, 16–18 cm (Fig. 1). A chest X-ray was taken and, if necessary, the position of the probe was corrected to meet the EuroPIG standards [8]. Afterwards, 24-h MII-pH recording was started (ZepHr, Sandhill Scientific Inc., Highlands Ranch, USA); the patients used ZepHr to note body position, meals, and symptoms. The exact times at which Holter and pH-impedance recording commenced were read from the same external clock (hour, minute, second). In all patients, the recordings were performed in the course of a diagnostic hospitalization.

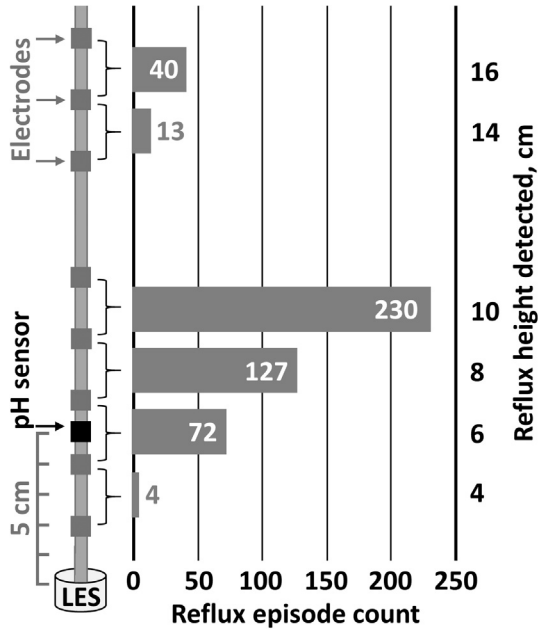

Fig. 1. The count of refluxes attaining various heights as measured using esophageal multichannel intraluminal impedance in 16 pediatric patients. Probe (on the left) is equipped with 8 electrodes for a total of 6 channels; the pH sensor is approx. 5 cm above the lower esophageal sphincter (LES) (third vertebrae above the diaphragm).

The MII-pH data were analyzed using BioVIEW 5.4.3 (Sandhill Scientific Inc., Highlands Ranch, USA): first Reflux AI 4.9.2 algorithmic analysis was launched, the entire recording was then inspected in detail by a physician, and the analysis was manually corrected where required. A reflux episode was identified when retrograde reductions of impedance greater than 50% compared with the baseline occurred in at least two distal channels. Four exceptions to this rule were made in the entire study, in which a reduction in impedance in the lowest channel followed the typical GER pattern, of length between 11 and 24 s, and was accompanied by a time-related reduction in pH. Thus, all the reflux episodes were identified and a set of characteristics was described: time (hour, minute, second), duration as measured using MII (seconds), time of clearance (until esophageal pH = 4; seconds), acid ($pH < 4$ at any time point; yes/no), the highest MII channel attained (1–6), recumbent position (yes/no), and meal (yes/no).

The Holter ECG trace was analyzed using DARWIN2 Enterprise (Schiller Reomed AG, Dietikon, Switzerland) by experienced clinicians. Frequency domain parameters for 2.5-min periods and time domain parameters for 1-min periods were automatically obtained, including root-mean square differences of successive R–R intervals (r-MSSD). A spreadsheet software package was used to adjust for the time difference using starting times recorded by the internal clocks of both devices and by the external clock.

Each reflux episode started within a 2.5-min ECG recording period. This was then designated as "reflux-containing" and its HRV parameters were noted. The same was done for the preceding and the following 2.5-min periods (Fig. 2). If the reflux episode spanned across two periods, then the one containing the larger part was chosen. Accordingly, the preceding and the following periods were the ones closest to the reflux-containing interval, but never contained the reflux. In cases of high frequency of refluxes, there occurred some instances where the 2.5-min period following a

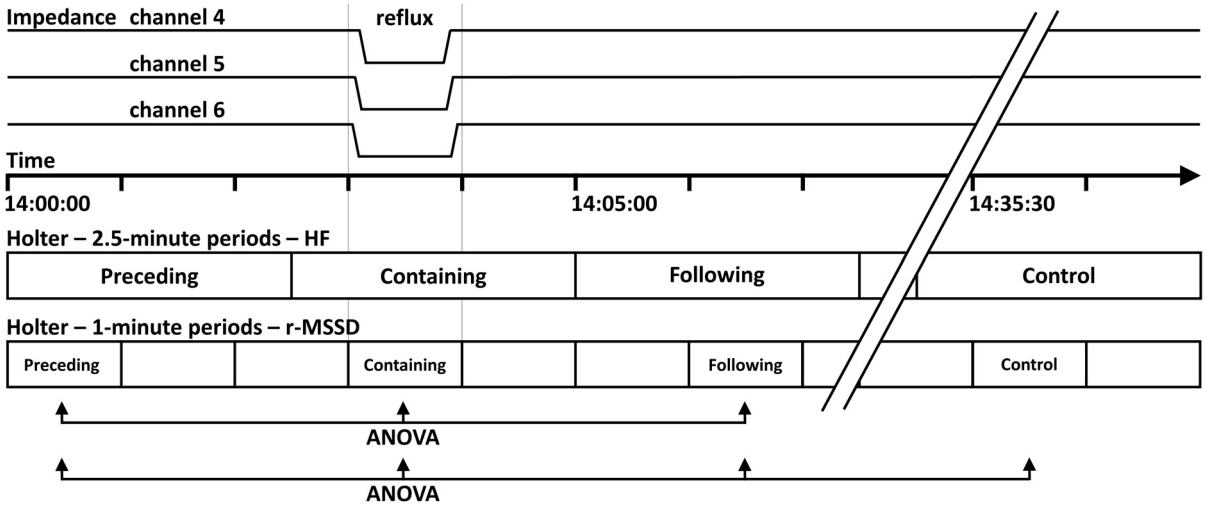

Fig. 2. The method of HF and r-MSSD measurement in time periods containing, preceding, and following a gastroesophageal reflux. ANOVA concerned either parameters described in those three periods or additionally included read-outs from in-between reflux-free control periods. HF – high frequency, r-MSSD – root-mean square differences of successive R–R intervals.