ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2020 July 28; 26(28): 3998-4181

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents Weekly Volume 26 Number 28 July 28, 2020

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dr. Osamu Toyoshima is a Director of Toyoshima Endoscopy Clinic in Tokyo, Japan. Dr. Toyoshima graduated from the University of Tokyo with his master´s degree in Medicine. After graduating, he joined the Department of Gastroenterology and Surgical Oncology at the University of Tokyo Hospital and engaged in clinical practice and medical research. After that, he established the Toyoshima Endoscopy Clinic with his father, Dr. Hiroshi Toyoshima. Toyoshima Endoscopy Clinic is an endoscopy-specialized clinic, which performs 10000 endoscopies annually. Dr. Osamu Toyoshima mainly conducts research using clinical data from Toyoshima Endoscopy Clinic. He is an expert in the field of gastroenterology, especially of gastric cancer risk evaluation based on the endoscopic gastritis and of quality indicators of colonoscopy such as colorectal polyp detection.

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for *WJG* as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
July 28, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2020 July 28; 26(28): 4159-4169

DOI: 10.3748/wjg.v26.i28.4159

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Detection of reflux-symptom association in children with esophageal atresia by video-pH-impedance study

Settachote Maholarnkij, Anapat Sanpavat, Katawaetee Decharun, Termpong Dumrisilp, Chomchanat Tubjareon, Benjawan Kanghom, Tanisa Patcharatrakul, Nataruks Chaijitraruch, Voranush Chongsrisawat, Palittiya Sintusek

ORCID number: Settachote Maholarnkij 0000-0002-7091-4962; Anapat Sanpavat 0000-0002-6425-3379; Katawaetee Decharun 0000-0003-4449-0323; Termpong Dumrisilp 0000-0001-7110-0664; Chomchanat Tubjareon 0000-0002-2995-3070; Benjawan Kanghom 0000-0002-7091-4963; Tanisa Patcharatrakul 0000-0003-1324-2394; Nataruks Chaijitraruch 0000-0002-6665-8046; Voranush Chongsrisawat 0000-0002-6106-0504; Palittiya Sintusek 0000-0003-4441-0151.

Author contributions: Maholarnkij S participated in design of the study, drafted the manuscript, collected the data, assisted with data analysis; Sunpavat A interpreted the histopathological data; Decharun K was involved with data collection and approved the final manuscript; Dumrisilp T, Tubjareon C and Kanghom B was involved with data collection; Chaijitraruch N, Patcharatrakul T and Chongsrisawat V approved the final manuscript; Sintusek P designed and oversight of the study, involved with data collection, interpretation and analysis, draft and approved the final manuscript.

Institutional review board statement: The study was

Settachote Maholarnkij, Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Anapat Sanpavat, Division of Pathology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Katawaetee Decharun, Division of Pediatric Surgery, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Katawaetee Decharun, Benjawan Kanghom, Nataruks Chaijitraruch, Palittiya Sintusek, Division of Gastroenterology, and Pediatric Gastroenterology and Hepatology STAR (Special Task Force for Activating Research), Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Termpong Dumrisilp, Chomchanat Tubjareon, Benjawan Kanghom, Nataruks Chaijitraruch, Voranush Chongsrisawat, Palittiya Sintusek, Division of Gastroenterology, Department of Pediatrics, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Tanisa Patcharatrakul, Center of Excellence in Neurogastroenterology and Motility, Department of Gastroenterology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Tanisa Patcharatrakul, Division of Gastroenterology, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand

Corresponding author: Palittiya Sintusek, MD, Assistant Professor, Department of Gastroenterology and Pediatric Liver Diseases and Immunology STAR (Special Task Force for Activating Research), Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University, No. 1873, Rama 4 Road, Pathumwan, Bangkok 10330, Thailand. palittiya.s@chula.ac.th

Abstract

BACKGROUND

Children with esophageal atresia (EA) have risk of gastroesophageal reflux

reviewed and approved by the Institional Review Board of Chulalongkorn University, Thailand (IRB number 243/61).

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrolment.

Conflict-of-interest statement: The authors of this manuscript having no conflict of interest to disclose.

Data sharing statement: There is no additional data available.

STROBE statement: The authors have read the STROBE statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

Manuscript source: Invited manuscript

Received: March 12, 2020
Peer-review started: March 12, 2020
First decision: April 25, 2020
Revised: April 30, 2020
Accepted: July 14, 2020
Article in press: July 14, 2020
Published online: July 28, 2020

P-Reviewer: Gallo G, Polat F, Yellanthoor RB
S-Editor: Wang JL
L-Editor: A
E-Editor: Ma YJ

disease (GERD), suggesting reflux monitoring for prompt management.

AIM
To evaluate GERD in children with EA and specific symptom association from combined Video with Multichannel Intraluminal Impedance and pH (MII-pH) study.

METHODS
Children diagnosed with EA with suspected GERD and followed up at King Chulalongkorn Memorial Hospital between January 2000 and December 2018 were prospectively studied. All underwent esophagogastroduodenoscopy with esophageal biopsy and Video MII-pH study on the same day. Symptoms of GERD which included both esophageal and extra-esophageal symptom were recorded from video monitoring and abnormal reflux from MII-pH study based on the statement from the European Paediatric Impedance Group. Prevalence of GERD was also reported by using histopathology as a gold standard. Endoscopic appearance was recorded using Los Angeles Classification and esophagitis severity was graded using Esohisto criteria.

RESULTS
Fifteen children were recruited with age of 3.1 (2.2, 9.8) years (40%, male) and the common type was C (93.3%). The symptoms recorded were cough (75.2%), vomiting (15.2%), irritability or unexplained crying (7.6%) and dysphagia (1.9%) with the symptom-reflux association of 45.7%, 89%, 71% and 0%, respectively. There were abnormal endoscopic appearance in 52.9%, esophagitis in 64.7% and high reflux score in 47.1%. Video MII-pH study has high diagnostic value with the sensitivity, specificity and accuracy of 72.7%, 100% and 82.4%, respectively.

CONCLUSION
Prevalence of GERD in children with EA was high. Video MII-pH study to detect GERD in children with EA had high diagnostic value with the trend of specific symptom association.

Key words: Gastroesophageal reflux disease; Esophageal atresia; Children; Impedance pH study; Video; Symptom association

Core tip: This was a cross sectional study with 15 patients diagnosed with esophageal atresia (EA) and suspected gastroesophageal reflux disease (GERD). Combined Video Multichannel Intraluminal Impedance and pH study has a good diagnostic accuracy to diagnose GERD in these children and there was a trend of specific symptom-reflux association in children diagnosed with EA.

Citation: Maholarnkij S, Sanpavat A, Decharun K, Dumrisilp T, Tubjareon C, Kanghom B, Patcharatrakul T, Chaijitraruch N, Chongsrisawat V, Sintusek P. Detection of reflux-symptom association in children with esophageal atresia by video-pH-impedance study. *World J Gastroenterol* 2020; 26(28): 4159-4169
URL: https://www.wjgnet.com/1007-9327/full/v26/i28/4159.htm
DOI: https://dx.doi.org/10.3748/wjg.v26.i28.4159

INTRODUCTION

Esophageal atresia (EA) is a common digestive malformation occurring in 1:2400-4500 births. Improvements in operative and medical care enable them to have longer life expectancy but suffering from comorbidities including pathological gastroesophageal reflux (GER). Although GER disease (GERD) is defined as the reflux of gastric contents lead to troublesome symptoms[1], unlike other children, EA children with GERD could be asymptomatic or present with extraesophageal symptoms[2]. Therefore, the recent European Society of Paediatric Gastroenterology, Hepatology and Nutrition and

North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN) guideline for EA children recommended to routinely prescribe proton pump inhibitors (PPIs) up to the first year of life and monitor reflux episodes using combined esophageal Multichannel Intraluminal Impedance and pH (MII-pH) monitoring and/or endoscopy at time of discontinuation and during long-term follow up[2].

The prevalence of GERD in EA patients varied from 22%-45%, depending on the diagnostic criteria[3-7]. Esophageal histopathology is the gold standard test to diagnose pathological reflux but it has low sensitivity compared to others[8]. MII-pH monitoring is one of the best diagnostic tools for GERD as its ability to detect the frequency, height and type of reflux event. However, the normal value of reflux event in children is scarce hence the data should be interpreted with caution. The international guideline[9] recommended using MII-pH study to correlate persistent troublesome symptoms with reflux episodes instead. Using video monitoring, symptoms should be recorded more precisely with time of reflux than by caregivers in EA children. We aim to study the prevalence of GERD and the symptom correlation in EA children using Video MII-pH.

MATERIALS AND METHODS

Patients

Children diagnosed with EA who received esophageal anastomosis and regularly followed up at King Chulalongkorn Memorial Hospital between 1 January 2000 and 31 December 2018 were recruited. This cross sectional study has been approved by the Institutional Review Board of Chulalongkorn University (IRB number 243/61). Written informed consent was obtained from all parents and informed assent from patients over 7 years old before any procedure was performed.

Data collection and outcome measurements

All patients were admitted. Detailed demographic data, comorbidities, signs and symptoms followed the international guidelines[9] (Table 1), and previous investigations were collected by investigator's interview and medical records.

Esophagogastroduodenoscopy

On the following day, all patients were nil by mouth for at least 6 h before esophagogastroduodenoscopy (EGD) under general anesthesia. Esophageal biopsy was performed at 3-5 cm above z-line for at least 2 pieces.

Combined Video MII-pH monitoring

The age appropriate catheter (Pediatric ZandorpH catheter with 1 Antimony and 6 impedance rings with 2 cm interval, Laborie, The Netherlands) was inserted after EGD and under general anesthesia. When the patient woke up, the catheter position was adjusted to place pH sensor at 2 vertebraes above the diaphragm from a plain chest x-ray in upright and full inspired position, followed the statement from British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) motility working group[10]. All chest X-ray was reviewed by a pediatric gastroenterologist (Sintusek P) to confirm the proper position. Then combined MII-pH machine (Ohmega, Laborie, The Netherlands) was started and monitored for at least 24 h. Video monitoring was done and the MII-pH study was synchronized with the video. All signs and symptoms of GERD according to ESPGHAN and NASPGHAN guidelines[9] were recorded by instructed caregivers while the main investigator (Maholarnkij S) independently recorded them from the video record. Carbonated drink, juices and acidic foods were prohibited from the patient during the monitoring.

Combined Video MII-pH analysis

Tracing from MII-pH study results were initially analyzed using Laborie automated analysis software (MMS database software, The Netherlands) and revised visually and manually analyzed by the pediatric gastroenterologist (Sintusek P). The criteria for all parameters followed the position statement by BSPGHAN Motility Working Group[10] and the normal values of reflux followed the European Paediatric Impedance Group (EURO-PIG)[11]: (1) Reflux is classified as acid (pH < 4), weakly acid (pH 4-7), and weakly alkaline (pH > 7); (2) Reflux index (RI) is defined as percentage of time with esophageal pH through the pH sensor above lower esophageal sphincter < 4. We considered pathological acid reflux if RI > 3% in children aged > 1 year; (3) Number of

Table 1 Symptoms and signs that may be associated with gastroesophageal reflux in infants and children[9]

Symptoms	Signs
General	**General**
Discomfort/irritability[1]	Dental erosion
Failure to thrive	Anemia
Feeding refusal	
Dystonic neck posturing (Sandifer syndrome)	
Gastrointestinal	**Gastrointestinal**
Recurrent regurgitation with/without	Esophagitis
vomiting in the older children	Esophageal stricture
Heartburn/chest pain[2]	Barrett esophagus
Epigastric pain[2]	
Hematemesis	
Dysphagia/odynophagia	
Airway	**Airway**
Wheezing	Apnea spells
Stridor	Asthma
Cough	Recurrent pneumonia associated with aspiration
Hoarseness	Recurrent otitis media

[1]If excessive irritability and pain is the single manifestation, it is unlikely to be related to gastroesophageal reflux disease.
[2]Typical symptoms of gastroesophageal reflux disease in older children.

refluxes is defined as the number of retrograde bolus movements that ≥ 100 episodes in infant and ≥ 70 episodes in children aged > 1 year considered to be pathologic; (4) Symptom index is defined as the following formula: [Reflux-related symptom events/the total symptoms events] × 100. It was considered positive if the value ≥ 50%; (5) Symptom sensitivity index is defined as the following formula: [Number of symptom-associated reflux/total number of reflux episodes] × 100. It is positive if the value ≥ 10% for each symptom; (6) Symptom association probability (SAP) is from complex statistical calculation by the machine in for the symptom correlation in each 2-min window of the study. SAP values are considered positive if the value ≥ 95%; (7) Esophageal acid clearance is defined as the time from drop in esophageal pH at pH channel < 4 to restoration of pH above ≥ 4; (8) Mean bolus clearing time is defined as the mean time in seconds required for the impedance, distal channel, to go back to the initial value after an episode of reflux; and (9) Longest reflux period (min) is defined as the total time that esophageal pH above pH channel < 4.

Esophageal gross finding

Endoscopic appearance was recorded by the pediatric gastroenterologist using Los Angeles Classification[12]. Grade A indicated ≥ 1 mucosal breaks confined to the mucosal folds ≤ 5 mm length. Grade B indicated ≥ 1 mucosal breaks > 5 mm, but not continuous between the 2 mucosal folds. Grade C indicated continuous mucosal breaks < 75% of the esophageal circumference. Grade D indicated mucosal breaks which involves ≥ 75% of the esophageal circumference.

Esophageal histopathology finding

Histopathological severity were reported by a pathologist using modified Esohisto criteria[13]. The criteria included the first 4 in these 6 parameters: (1) Basal cell layer hyperplasia: Measure thickness of basal cell layer in micrometers and express as a proportion (%) of total epithelial thickness (× 10). The severity score defined as 0 (< 15%), 1 (15%-30%), and 2 (> 30%); (2) Papillary elongation: measure papillary length in micrometers and express as a proportion (%) of total epithelial thickness (×10). The severity score defined as 0 (< 50%), 1 (50%-75%), and 2 (> 75%); (3) Dilatation of

intercellular spaces: identified as irregular round dilatations or diffuse widening of intercellular space (×40). The severity score defined as 0 (absent), 1 (small; diameter < 1 lymphocyte), and 2 (large; diameter ≥ 1 lymphocyte); (4) Intraepithelial eosinophils: Counted in the most affected high-power field (×40). The severity score defined as 0 (absent), 1 (1-2 cells), and 2 (> 2 cells); (5) Intraepithelial neutrophils: Counted in the most affected high-power field (×40). The severity score defined as 0 (absent), 1 (1-2 cells), and 2 (> 2 cells); and (6) Intraepithelial mononuclear cells: counted in the most affected high-power field (×40). The severity score defined as 0 (0-9 cells), 1 (10-30 cells), and 2 (> 30 cells).

The sum of severity scores divided by the number of lesion types assessed can be stratified into degree of esophagitis. Score 0-0.25 were indicated normal, score 0.5-0.75 were regarded as mild esophagitis, and score 1 or higher qualified for severe esophagitis.

Statistical analysis

Data were analysed with IBM SPSS statistics 22.0. Demographic data were reported as median (IQR) for numerical variables while percentage or proportion for categorical variables. Diagnostic test was calculated and presented as sensitivity, specificity, accuracy, positive predictive value, and negative predictive value by using esophageal histopathology as the gold standard. Statistical significance between paired continuous variables were calculated by Wilcoxon signed ranks test. χ^2 or Fisher's exact test for categorical variables. Clinically significance were defined as P-value < 0.05. The statistical review of the study was performed by a biomedical statistician at Department of Statistics Science, Kasetsart University, Thailand, Bangkok, Thailand.

The primary outcome is to study the prevalence of GERD in children with EA using combined Video MII-pH study. The secondary outcome is to evaluate the specific symptom association of GERD in children with EA.

RESULTS

Patient characteristics

There were 15 patients diagnosed with EA recruited into the present study. The median age was 3.08 (range from 1.4 to 12.9) years (40%, male) and the most common type was C (93.3%). Ten (33.3%) patients had at least one comorbidity [cardiac malformations (n = 9), renal malformations (n = 3), anorectal malformations (n = 2), musculoskeletal malformations (n = 2), lung hypoplasia (n = 1), vertebral anomalies (n = 1), others (skin tags, growth hormone deficiency) (n = 3)]. Eleven (73.3%) patients underwent esophageal anastomosis since neonate and 4 (26.7%) underwent delayed esophageal anastomosis within the first year of life. Ten patients underwent EGD with esophageal biopsy before and seven of them had reflux esophagitis. Five patients were using PPIs (33%) (omeprazole 1-2 mg/kg per day; n = 2, lanzoprazole 2-3 mg/kg per day; n = 3) and two of these were using prokinetic drugs (13.3%) (domperidone 0.3-0.5 mg/kg/dose every 6-8 h) at the time of recruitment. The medication was continued before MII-pH monitoring due to esophagitis finding from previous endoscopy and histopathology. Fundoplication was performed in two patients because of the pharmacological failure. The most common previously symptom reported were recurrent regurgitation with or without vomiting (60%) and cough (60%). Dental screening was performed in six patients and founded dental erosion in three patients (50%). The most common previously signs documented were esophagitis (53%) and recurrent respiratory tract infection (53%) (Table 2). In these 15 children diagnosed with EA, we got 17 records from Video MII-pH study due to two patients were performed for two times for reassessment during pharmacological therapy.

GERD diagnosed by gross and histopathology

Gross appearance on endoscopic view showed abnormality in 52.9% while esophageal histopatholgy demonstrated esophagitis in 64.7% of them. Three (37.5%) patients with normal gross appearance had histopathology of reflux esophagitis (Table 3).

GERD diagnosed by combined Video MII-pH study and the symptom association

The median of monitoring period excluding fed periods (hours) was 21.2 (19.3-22.1). The median RI (%), and esophageal clearance (minutes) were 2.7 (0.5-9.5) and 1.4 (0.6-2.5), respectively. There was no statistical significance of the symptom recorded by caregivers and video monitoring that was recorded by primary investigators [2.5 (1-

Table 2 Patient demographic data and characteristics (*n* = 15)

Characteristics	Median (IQR) or *n* (%)
Male sex	6 (40)
Age (yr)	3.1 (2.2-9.8)
Weight for height (%)	100 (89.4-104.6)
Previous symptoms	
General	
Discomfort/ Irritability in infants	3
Failure to thrive or weight loss	8
Feeding refusal	3
Total	10 (66.7)
Gastrointestinal	
Recurrent regurgitation with or without vomiting	9
Heartburn or chest pain	1
Epigastric pain	1
Hematemesis	1
Dysphagia, odynophagia	6
Total	11 (73.3)
Airway	
Wheezing, stridor	4
Cough	9
Hoarseness	2
Total	10 (66.7)
Previous signs	
General	
Dental erosion	4
Anemia	2
Total	4 (26.7)
Gastrointestinal	
Esophagitis	8
Esophageal stricture	7
Barret's esophagus	2
Total	12 (80)
Airway	
Asthma	1
Recurrent respiratory tract infection	8
Recurrent otitis media	2
Total	8 (53.3)

EA: Esophageal atresia; GER: Gastroesophageal reflux; IQR: Interquartile range.

4.5) *vs* 3 (1-5), $P = 0.282$]. Using the cut-off value from EURO-PIC for the RI and/ or total reflux time, 47.1% of them considered acid/weakly acid related GERD diagnosis. Other MII-pH study parameters are shown in Table 4. In subgroup analysis, there was no significantly different result of combined Video MII-pH monitoring between using and non-using acid suppression therapy during the monitoring (Table 5).

Table 3 Esophagogastroduodenoscopy findings and biopsy results of children with esophageal atresia after esophageal anastomosis (*n* = 17)

Classification	*n* (%)
Los Angeles Classification	
Normal[1]	8 (47.1)
A[2]	2 (11.8)
B[3]	4 (23.5)
C[4]	3 (17.6)
Pathology	
Normal	6 (35.3)
Mild esophagitis	2 (11.8)
Severe esophagitis	9 (52.9)

[1]One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.
[2]One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds.
[3]Mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference.
[4]Mucosal breaks which involve at least 75% of the esophageal circumference.

Table 4 Parameters used and the analysis result of combined multichannel intraluminal impedance and pH study in children diagnosed esophageal atresia after esophageal anastomosis (*n* = 17)

Parameters	Median (IQR)
Monitoring period excluding fed periods (h)	21.2 (19.3-22.1)
RI (%)	2.7 (0.5-9.5)
Longest reflux period (min)	20 (5-29)
Esophageal clearance (min)	1.4 (0.6-2.5)
Total reflux (times)	19 (11-36)
Acid	9 (4-14)
Weakly acid	10 (6-15)
Weakly alkaline	0 (0-0)
mean bolus clearance time (s)	14.9 (10.4-19.2)

RI: Reflux index.

The total symptoms recorded from video of all 17 combined Video MII-pH monitoring were cough (67.3%), vomiting (17.3%), irritability or unexplained crying (13.4%) and dysphagia (1.9%). In aspect of symptom association, vomiting was the symptom that mostly associated with reflux followed by irritability or unexplained crying and cough (Table 6).

Diagnostic value of combined Video MII-pH study compared to esophageal histopathology

Using esophageal histopathology as the gold standard for GERD, combined Video MII-pH has high diagnostic value with the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 72.7%, 100%, 100%, 67% and 82.4%, respectively.

DISCUSSION

The present study demonstrated the high prevalence of GERD in children with EA

Table 5 Parameters used and results from the analysis of combined Video Multichannel Intraluminal Impedance and pH study in children diagnosed esophageal atresia after esophageal anastomosis between using and non-using acid suppression therapy (*n* = 17)

Parameters	Acid suppression therapy (*n* = 7)	No acid suppression therapy (*n* = 10)	*P* value
Monitoring period (h)	21.2 (18.1-24.5)	21.3 (19.5-22.1)	0.696
RI (%)	7.1 (1.4-10)	1.45 (0.3-4.2)	0.24
Longest reflux period (min)	29 (5-96)	16 (4-24)	0.143
Esophageal clearance (min)	2.0 (1.0-3.6)	1.0 (0.5-1.7)	0.261
Total reflux (times)	19.0 (11-46)	19.0 (11-29)	0.66
Acid	10.0 (4-16)	6.5 (3-11)	0.558
Weakly acid	13.0 (4-32)	9.0 (6-14)	0.733
Weakly alkaline	0.0 (0-0)	0.0 (0-1)	0.123
Mean bolus clearance time (s)	11.9 (9.3-16.5)	17.3 (10.4-21.7)	0.242
Number of symptoms (times)	3.0 (1.0-5.0)	4.0 (1.0-7.0)	0.452
SI (%)	25 (0.0-50)	10.5 (0-66.7)	0.84
SSI (%)	1.4 (0-5.3)	3.7 (0.0-17.6)	0.419
SAP (%)	73.9 (0-90.9)	83.9 (0-99.1)	0.649

Present as median (IQR). RI: Reflux index; SAP: Symptom association probability; SI: Symptom index; SSI: Symptom sensitivity index.

Table 6 Symptoms and symptom correlation from video recording in children with esophageal atresia (*n* = 17)

Symptom	Symptoms	Symptom-reflux correlation	Acid	Weakly acid	Non acid	SI	SSI	SAP
Cough	35	16 (45.7)	9	7	0	58.5 (6.2-100)	2.9 (0.3-7.1)	95 (18.9-99.2)
Vomit	9	8 (89)	5	3	0	75 (50-100)	3.9 (2.3-60.7)	99.6 (87.8-99.9)
Irritability or unexplained crying	7	5 (71)	4	1	0	50 (25-50)	3.8 (2.5-3.8)	92.8 (72.9-92.8)
Dysphagia	1	0 (0)	0	0	0	0	0	0
Total	52	29 (55.7)	18	11	0	58.4 (27-100)	3.9 (1.3-7.1)	92.3 (77.4-99.6)

Present as *n* (%) or median (IQR). SI: Symptom index; SSI: Symptom sensitivity index; SAP: Symptom association probability.

based on the gold standard tools, esophageal histopathology and/or combined MII-pH study. Most of them had the previous symptoms suspected GERD in aspect of general, gastrointestinal and respiratory system (Table 1). In this study, combined Video MII-pH study could depict a trend of symptom-reflux association of vomiting, irritability or unexplained crying and cough.

Previous studies supported the high incidence of GERD in children with EA though the different diagnostic tools[3,4,9,14,15]. Esophageal histopathology is considered the gold standard to detect the early reflux esophagitis while MII-pH study, previous gold-standard test for GERD[16], had the main limitation in aspect of normal value for age. The strength of MII-pH study is its high accuracy if there is the specific symptom correlation during monitoring. The present study found most children with EA had histopathology result compatible with reflux esophagitis and MII-pH study had high specificity to this reflux esophagitis. Moreover, there is a trend of symptom-reflux correlation of vomiting, irritability or unexplained crying and cough. However, symptom recorded during Video MII-pH study per person was too small to extrapolate that GERD was the cause of these symptoms. Reevaluation of these clinical symptoms with Video MII-pH study after adequate treatment might strongly confirm that the symptom-reflux association for further study. As the prevalence of GERD and

it's complications tended to increase very early, the ESPGHAN-NASPGHAN guidelines for children with EA recommended using PPIs in all EA patients in the neonatal period and should be longer, depending on persistence of GERD. As a result all EA patients should undergo MII-pH study, at least, at the time of discontinuation of PPIs and during long-term follow-up. Furthermore, significant esophageal morbidity in adult with EA is evidenced. The prevalence of Barrett esophagus is at least 4-fold higher among adult population with EA[17] and the cumulative incidence of esophageal squamous cell carcinoma at fourth decade was 50 times[18] when compared with general population. Consequently, regular surveillance and follow-up patients with EA and GERD should be included not only MII-pH study but also EGD and esophageal biopsy to optimize therapy so that Barrett esophagus and esophageal carcinoma, hopefully, could be avoided.

In theory, combined Video MII-pH study should provide the accurate symptoms that could be confidently correlated with the reflux from the tracer. We could confirm the more numbers and specificity of the symptom recorded by video monitoring compared to the record from caregivers even though it did not reach statistical significance that might because of low number of subjects. Moreover, the precise time of symptom recorded could increase the symptom association as the machine will count the 2-min window period before a reflux event. However, this precise recording consumes time (more than 3-h recording by a pediatrician per patient) that makes it impossible in routine clinical practice. In the future, real-time Video MII-pH monitoring machine should be developed for children suspected GERD so that clinician will manually correlate the reflux with the real-time symptoms from video monitoring. For the overall symptoms during the MII-pH study, we could use the symptom record from caregivers and manually analyze the suspected symptom correlation by checking the video in case that caregiver might delay recording more than the 2-min window period.

Pathological mechanism of GERD in EA was postulated in many studies. Disruption of vagal denervation, vascular interruption, or traction on the lower esophagus occurred after esophageal corrective procedure could be the risk factors of GERD in children with EA[19] However, children with isolated tracheoesophageal fistula could have severely esophageal motility before surgical repair that might imply the congenital esophageal dysmotility rather than acquired from surgical correction[20] Esophagus per se might be the main risk factor of GERD in children with EA. Although the MII-pH study could not evaluate the esophageal motility, the long duration of esophageal clearance and mean bolus clearance time from the present study might reflect the esophageal dysmotility of children with EA. Apart from esophageal dysmotility, the present study demonstrated that mainly GERD in these children was acid reflux in etiology that 3 and 2 of them has no response with PPIs therapy and fundoplication, respectively. More aggressive management could be considered and esophageal motility should be evaluated before surgical fundoplication as this surgery could impair esophageal clearance and worsening the reflux esophagitis.

The strength of the present study is the evaluation of both esophageal histopathology and combined MII-pH study in the meantime. To the best of our knowledge, this is the first study that integrate video recording into the MII-pH study and a pediatrician was the person recording the symptom that might associate with reflux event. These methods lead to the most reliable symptom recorded albeit consuming time. However, the small number and inhomogenous characteristic of the subjects are the main limitation of this pilot study. Further large study that highlights the accurate symptom association using real-time video or developed artificial intelligence MII-pH machine for children suspected of GERD should be more meritorious.

ARTICLE HIGHLIGHTS

Research background

Esophageal atresia (EA) is a common digestive malformation with increasing risk of esophageal complications even after successful surgical correction. Gastroesophageal reflux disease (GERD) is the frequent gastrointestinal co-morbidity causing serious long-term consequences namely esophageal stricture and esophageal carcinoma. Hence, early detection and prompt treatment are crucial.

Research motivation

This research aimed to study the prevalence of GERD using esophageal histopathology and the novel tool, combined Video Multichannel Intraluminal Impedance and pH (MII-pH) study, in children diagnosed with EA. We believe that symptoms from video monitoring should be recorded more precisely with time reflux than by caregivers and make the interpretation of reflux-symptom association more meaningful.

Research objectives

To investigate the prevalence of GERD and the symptom association in children diagnosed EA by combined Video MII-pH study.

Research methods

Seventeen investigations that included esophagogastroduodenoscopy with biopsy and combined Video MII-pH study were performed in 15 children diagnosed EA. All signs and symptoms of GERD from video were recorded during MII-pH monitoring. MII-pH study was manually analysis including the symptom-reflux association using the symptoms from video record. Diagnostic value of combined Video MII-pH study was calculated using the result of esophageal histopathology as the gold standard to diagnose GERD.

Research results

The total symptoms recorded from video of all 17 combined Video MII-pH monitoring were cough (67.3%), vomiting (17.3%), irritability or unexplained crying (13.4%) and dysphagia (1.9%). In aspect of symptom association, vomiting was the symptom that mostly associated with reflux followed by irritability or unexplained crying and cough. Using esophageal histopathology as the gold standard for GERD, combined Video MII-pH has high diagnostic value with the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 72.7%, 100%, 100%, 67% and 82.4%, respectively.

Research conclusions

Prevalence of GERD in children with EA was high. Combined Video MII-pH study to detect GERD in children with EA had high diagnostic value with the trend of specific symptom association.

Research perspectives

MII-pH study has limitation to be the gold-standard test for GERD as the data of the reflux value in each age group are scarce. To improve the utility and diagnostic value of this machine, we synchronized the video recording during the study. The precise time of symptom recorded from video could increase symptom-reflux association albeit its time consuming. In the future, real-time Video MII-pH monitoring machine should be developed to improve the accuracy and clinical utility of MII-pH study.

ACKNOWLEDGEMENTS

The author would like to thank Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University (Grant No RA62/001), the Pediatric Liver Diseases and Immunology STAR (Special Task Force for Activating Research), Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University for research funding.

REFERENCES

1 **Onyeador N**, Paul SP, Sandhu BK. Paediatric gastroesophageal reflux clinical practice guidelines. *Arch Dis Child Educ Pract Ed* 2014; **99**: 190-193 [PMID: 24722652 DOI: 10.1136/archdischild-2013-305253]

2 **Krishnan U**, Mousa H, Dall'Oglio L, Homaira N, Rosen R, Faure C, Gottrand F. ESPGHAN-NASPGHAN Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Esophageal Atresia-Tracheoesophageal Fistula. *J Pediatr Gastroenterol Nutr* 2016; **63**: 550-570 [PMID: 27579697 DOI: 10.1097/MPG.0000000000001401]

3 **Somppi E**, Tammela O, Ruuska T, Rahnasto J, Laitinen J, Turjanmaa V, Järnberg J. Outcome of patients operated on for esophageal atresia: 30 years' experience. *J Pediatr Surg* 1998; **33**: 1341-1346 [PMID: 9766349 DOI: 10.1016/s0022-3468(98)90003-3]

4 **Deurloo JA**, Ekkelkamp S, Schoorl M, Heij HA, Aronson DC. Esophageal atresia: historical evolution of management and results in 371 patients. *Ann Thorac Surg* 2002; **73**: 267-272 [PMID: 11834021 DOI: 10.1016/s0003-4975(01)03263-5]

5 **Koivusalo A**, Pakarinen M, Rintala RJ, Lindahl H. Does postoperative pH monitoring predict complicated gastroesophageal reflux in patients with esophageal atresia? *Pediatr Surg Int* 2004; **20**: 670-674 [PMID: 15372290 DOI: 10.1007/s00383-004-1270-z]

6 **Koivusalo A**, Pakarinen MP, Rintala RJ. The cumulative incidence of significant gastrooesophageal reflux in patients with oesophageal atresia with a distal fistula--a systematic clinical, pH-metric, and endoscopic follow-up study. *J Pediatr Surg* 2007; **42**: 370-374 [PMID: 17270551 DOI: 10.1016/j.jpedsurg.2006.10.010]

7 **Legrand C**, Michaud L, Salleron J, Neut D, Sfeir R, Thumerelle C, Bonnevalle M, Turck D, Gottrand F. Long-term outcome of children with oesophageal atresia type III. *Arch Dis Child* 2012; **97**: 808-811 [PMID: 22753768 DOI: 10.1136/archdischild-2012-301730]

8 **Saito T**, Uesato M, Terui K, Nakata M, Komatsu S, Yoshida H. Acid and bolus exposure in pediatric reflux disease according to the presence and severity of esophageal mucosal lesions. *Pediatr Surg Int* 2019; **35**: 887-893 [PMID: 31144005 DOI: 10.1007/s00383-019-04490-5]

9 **Rosen R**, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **66**: 516-554 [PMID: 29470322 DOI: 10.1097/MPG.0000000000001889]

10 **Mutalib M**, Rawat D, Lindley K, Borrelli O, Perring S, Auth MKH, Thapar N. BSPGHAN Motility Working Group position statement: paediatric multichannel intraluminal pH impedance monitoring-indications, methods and interpretation. *Frontline Gastroenterol* 2017; **8**: 156-162 [PMID: 28839903 DOI: 10.1136/flgastro-2016-100796]

11 **Wenzl TG**, Benninga MA, Loots CM, Salvatore S, Vandenplas Y; ESPGHAN EURO-PIG Working Group. Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. *J Pediatr Gastroenterol Nutr* 2012; **55**: 230-234 [PMID: 22711055 DOI: 10.1097/MPG.0b013e3182592b65]

12 **Lundell LR**, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172-180 [PMID: 10403727 DOI: 10.1136/gut.45.2.172]

13 **Schneider NI**, Plieschnegger W, Geppert M, Wigginghaus B, Hoess GM, Eherer A, Wolf EM, Rehak P, Vieth M, Langner C. Validation study of the Esohisto consensus guidelines for the recognition of microscopic esophagitis (histoGERD Trial). *Hum Pathol* 2014; **45**: 994-1002 [PMID: 24746203 DOI: 10.1016/j.humpath.2013.12.013]

14 **Montgomery M**, Frenckner B. Esophageal atresia: mortality and complications related to gastroesophageal reflux. *Eur J Pediatr Surg* 1993; **3**: 335-338 [PMID: 8110713 DOI: 10.1055/s-2008-1066039]

15 **Pedersen RN**, Markøw S, Kruse-Andersen S, Qvist N, Hansen TP, Gerke O, Nielsen RG, Rasmussen L, Husby S. Esophageal atresia: gastroesophageal functional follow-up in 5-15 year old children. *J Pediatr Surg* 2013; **48**: 2487-2495 [PMID: 24314192 DOI: 10.1016/j.jpedsurg.2013.07.019]

16 **Vandenplas Y**, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG, North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009; **49**: 498-547 [PMID: 19745761 DOI: 10.1097/MPG.0b013e3181b7f563]

17 **Sistonen SJ**, Koivusalo A, Nieminen U, Lindahl H, Lohi J, Kero M, Kärkkäinen PA, Färkkilä MA, Sarna S, Rintala RJ, Pakarinen MP. Esophageal morbidity and function in adults with repaired esophageal atresia with tracheoesophageal fistula: a population-based long-term follow-up. *Ann Surg* 2010; **251**: 1167-1173 [PMID: 20485152 DOI: 10.1097/SLA.0b013e3181c9b613]

18 **Jayasekera CS**, Desmond PV, Holmes JA, Kitson M, Taylor AC. Cluster of 4 cases of esophageal squamous cell cancer developing in adults with surgically corrected esophageal atresia--time for screening to start. *J Pediatr Surg* 2012; **47**: 646-651 [PMID: 22498376 DOI: 10.1016/j.jpedsurg.2011.09.065]

19 **Di Pace MR**, Caruso AM, Catalano P, Casuccio A, Cimador M, De Grazia E. Evaluation of esophageal motility and reflux in children treated for esophageal atresia with the use of combined multichannel intraluminal impedance and pH monitoring. *J Pediatr Surg* 2011; **46**: 443-451 [PMID: 21376190 DOI: 10.1016/j.jpedsurg.2010.08.012]

20 **Lemoine C**, Aspirot A, Morris M, Faure C. Esophageal dysmotility is present before surgery in isolated tracheoesophageal fistula. *J Pediatr Gastroenterol Nutr* 2015; **60**: 642-644 [PMID: 25493344 DOI: 10.1097/MPG.0000000000000667]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com