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Why to Use Intraluminal Impedance in the Evaluation of Children with Repaired Esophageal Atresia

Onarılmış Özofagus Atrezisi Olan Çocukların Değerlendirilmesinde Neden İntraluminal İmpedans Kullanılmalı

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Abstract

Introduction: Gastroesophageal reflux disease (GERD) and esophageal dysmotility are frequent in esophageal atresia (EA) patients. The aim of this study was to assess the role of intraluminal impedance (MII-pH) in the evaluation of GERD in children with repaired EA.

Materials and Methods: The medical records of 13 pediatric patients with repaired Gross type C EA were reviewed retrospectively. The MII-pH recordings were analyzed by software automatically and the results were then reviewed manually. The results of barium studies including upper gastrointestinal tract series and videofluoroscopic swallowing studies were also reviewed to evaluate dysmotility.

Results: The most common extra-esophageal and esophageal complaints were recurrent pulmonary infections (92%) and dysphagia (77%). pH measurements showed a median reflux index (RI) of 3.8% (0.1-35.4) with 38% (n=5) of patients having pathologic RI (RI >5%). In impedance analyses, 70% of the reflux episodes were non-acidic (4≤ pH). Percent of patients having non-acidic retrograde bolus movements (RBM) above 95th percentile of normal values was 38% (n=5). Five of the 8 patients with normal pH monitoring results had pathological non-acid RBM in impedance analyses. Esophageal motility problem was a common finding (n=10, 77%) followed by pharyngeal phase problems (n=5, 38.5%) in contrast studies.

Conclusion: Majority of the RBM in repaired EA patients were non-acidic which would have gone undetected with standard pH monitoring. Half of the patients with pathologic reflux indices could only be detected by impedance monitoring. MII-pH monitoring should be preferred over conventional pH monitoring in the surveillance of EA patients.

Öz

Giriş: Gastroözofageal reflü hastalığı (GÖRH) ve özofageal dismotilite özofagus atrezisi (ÖA) hastalarında sık görülür. Bu çalışmanın amacı, onarılmış ÖA'lı çocuklarda GÖRH'nin değerlendirilmesinde intraluminal impedansın (MII-pH) rolünü değerlendirmektir.

Gereç ve Yöntem: Onarılmış Gross tip C ÖA'lı 13 pediyatrik hastanın tıbbi kayıtları retrospektif olarak incelendi. MII-pH kayıtlarının yazılım tarafından otomatik olarak analiz edilmesiyle elde edilen sonuçlar manuel olarak tekrar gözden geçirildi. Dismotiliteyi değerlendirmek için, üst gastrointestinal sistem

kontrastlı çalışmalarını ve videofloroskopik yutma çalışmalarını içeren baryumlu tetkiklerin sonuçları gözden geçirildi.

Bulgular: En sık görülen ekstra-özofageal ve özofageal yakınmalar sırasıyla tekrarlayan akciğer enfeksiyonları (%92) ve disfajiydi (%77). pH ölçümlerinde ortanca reflü indeksi (RI) %3,8 (0,1-35,4) olarak saptanırken hastaların %38'i (n=5) patolojik RI (RI >%5) değerlerine sahipti. İmpedans ölçümlerinin analizinde, reflü epizodlarının %70'i non-asidik karakterdeydi (4≤ pH). Non-asidik retrograd bolus hareketlerinin (RBH) sayısı, normal değerlerin 95. persentilinin üzerinde olan hastaların oranı %38 (n=5) idi. pH monitörizasyonu sonuçları normal olan 8 hastanın 5'inin impedans analizinde patolojik non-asidik RBH saptandı. Özofageal motilite sorunu kontrastlı çalışmalarda en sık görülen bulguyken (n=10, %77), bunu faringeal faz sorunları (n=5, %38,5) izlemekteydi.

Sonuç: Onarılmış ÖA hastalarında görülen RBH'nin çoğunluğu non-asidik karakterdeydi ve standart pH monitörizasyonu kullanılsaydı saptanamayacaktı. Patolojik reflü indekslerine sahip hastaların yarısı ancak impedans monitorizasyonu ile tespit edilebildi. ÖA hastalarının sürveyansında MII-pH monitörizasyonu konvansiyonel pH monitörizasyonuna tercih edilmelidir.

Introduction

Esophageal atresia (EA), with or without a tracheoesophageal fistula (TEF), is the most common congenital anomaly of the esophagus with a prevalence of 2.4 per 10,000 births (1). Advances in pre- and postoperative care and surgical techniques have led to a better prognosis with reported survival rates of over 90% (2). This excellent survival outcome has shifted current focus from mortality to management of long-term complications in patients with repaired EA. Gastrointestinal and respiratory problems are not only common in the long-term follow-up but also related with significant post-surgical morbidity in these patients (3,4).

Gastroesophageal reflux (GER) and esophageal dysmotility occur frequently following surgical repair of EA (5). Gastroesophageal reflux disease (GERD) which is defined as GER leads to troublesome symptoms that affect daily functioning and/or complications is common after surgical repair of EA in children with a reported prevalence of 20% to 63% in different studies (6). Given the high prevalence and related complications, it is vital to appropriately monitor and treat GERD in this population (5). Combined multichannel intraluminal impedance and pH monitoring (MII-pH) is a sensitive tool in the objective evaluation of pediatric GERD (7). Detecting both acidic and non-acidic refluxate, differentiating intraesophageal content state (liquid or gas), determining the height of the reflux, distinguishing between swallow and reflux and making possible to establish a temporal association between symptoms recorded during the test and both non-acid and acid refluxate are the main advantages of MII-pH monitoring over conventional pH monitoring (8,9). Multiple studies have reported that GER in children with EA is mostly non-acid or weakly acid which can be missed with conventional pH monitoring (6).

The aim of this study was to assess the role of MII-pH monitoring in the evaluation of pediatric patients with repaired EA who had esophageal and/or extra-esophageal symptoms suggestive for GERD and to determine the reflux characteristics.

Materials and Methods

Study Design and Patients

This was a retrospective chart review study. Pediatric patients with repaired EA who underwent MII-pH monitoring between May 2016 and May 2018 were enrolled in the study. Patients who underwent MII-pH monitoring for the evaluation of symptoms suggestive of GERD (esophageal complaints like dysphagia, persistent vomiting and extra-esophageal complaints like recurrent pulmonary infections, chronic coughing, asthma/wheezing) were included in the study. Isolated TEF, esophageal replacement therapy and tube feeding were exclusion criteria. All available medical records of eligible patients were included in further data analysis. Demographic data (gender, birth weight, gestational age, age at primer repair, age at MII-pH monitoring), medication history at the time of impedance procedure, type of EA and performed surgical procedure, symptomatology necessitating MII-pH monitoring and swallowing characteristics of patients were collected from medical records. The reports of upper gastrointestinal tract (UGT) series were also reviewed when available. Recurrent pulmonary infections were defined as two or more pneumonia episodes in a 1-year period (10). Non-interventional Clinical Research Ethics Board of the hospital approved the study (GO 21/107, 2021/02-38). The study has been conducted in accordance with the principles set forth in the Helsinki Declaration.

MII-pH Monitoring Protocol

MII-pH monitoring was performed over a 24-hour period with age-appropriate MII-pH catheters. Catheter replacement was performed on an outpatient setting in the pediatric gastroenterology clinic. We used age-appropriate Greenfield (Dover, USA) single use pH-MII catheters (6.4 French, 6 impedance channels, 1 pH antimony channel) to perform 24-hour MII-pH studies. At the beginning of the procedure pH electrode was calibrated using pH 4.0 and 7.0 buffer solutions. The catheter was introduced nasally, and the approximate position of the probe was calculated according to Strobel's formula (11). The position of pH probe was confirmed with a chest X-ray and corrected if necessary. All acid suppressive and prokinetic therapies or drugs affecting lower esophageal sphincter function were discontinued at least 7 days before the procedure. Symptoms, body position (upright or recumbent), food/beverage intake, sleep periods and daily activities were asked to be recorded by parents during MII-pH monitoring.

The MII-pH recordings were analyzed by software (MMS, version 9.1w, Enschade, the Netherlands) automatically following an initial manual review to delete artifacts (acid/alkaline limits: pH 4.0 and 7.0; minimum reflux duration: 5 seconds; air threshold: 5,000Ω). Finally, all reflux events identified by software were reviewed manually for any misinterpretation. Parameters analyzed in this study were as follows: number of pH changes to <4; reflux index [(RI); percent time with esophageal pH <4]; number of long (>5 minutes) acid exposures; longest acid exposure (minutes); number of retrograde bolus movements (RBM); number of acidic (pH <4), weak acidic (4≤ pH <7) and weak alkaline (pH ≥7) RBM; number of liquid/mixed RBM; and number of proximal RBM (RBM reaching at least the second uppermost impedance channel); symptom index (SI) for reflux; and symptom association probability [(SAP); window of 2 minutes before and after a reflux event]. An RI >5% was considered to be abnormal (12). SI ≥50% and SAP ≥95% were considered positive.

Videofluoroscopic Swallowing Study

The swallowing functions of all patients were imaged and recorded during a videofluoroscopic swallowing study (VFSS) by a swallowing therapist and a radiologist as reported from our center before (13). Oral phase dysfunction, laryngeal penetration, aspiration, abnormal esophageal body function, and reflux were identified based on the previously proposed definitions (14). The results were reviewed particularly for aspiration and abnormal esophageal body function.

Data Analysis

All data were summarized in a descriptive fashion. No statistical testing was performed. Data were presented using descriptive statistics [mean ± SD, and median with range (minimum-maximum)] for continuous variables, and frequencies (n, %) for categorical variables].

Data Availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

There were 13 patients (5 females and 8 males) with repaired EA who underwent MII-pH monitoring for symptoms suggestive of GER. Patient demographics were summarized in Table 1. None of the patients had long gap EA. All the patients were Gross type C (EA with distal TEF). Repeated bougie dilations were performed in 3 patients (23%) due to post operative anastomotic strictures and 2 patients (15%) had a history of esophageal food impaction. The most common extra-esophageal and esophageal complaints among patients necessitating a MII-pH monitoring and VFSS were recurrent pulmonary infections (92%) and dysphagia (77%), respectively (Table 1). Refusal of feeding, history of food impaction, swallowing difficulties, coughing/chocking during meal and sensation of food stuck in the chest were accepted as signs of clinical dysphagia.

MII-pH Monitoring

The results of MII-pH monitoring are summarized in Table 2. pH measurements showed a median RI of 3.8% (0.1-35.4) with 38% (n=5) of patients having RI >5%. The total and median numbers of reflux episodes (pH <4) were 618 and 30 (3-233), respectively. Fifty-three episodes (8.6%) were pH-only reflux events which were defined as a decrease in pH to <4 in the absence of reflux detected by impedance monitoring.

Table 1. Demographic characteristics of study patients	
Number	13
Gender (female/male)	5/8
Age at MII-pH monitoring, years, median (minimum-maximum)	6.5 (1.3-13.5)
Age at primer repair, days, median (minimum-maximum)	2 (1-74)
Birth weight, grams, mean ± SD	2594 ± 1083
Gestational age, weeks, median (minimum-maximum)	38 (30-42)
*Acid suppressive therapy at the time of MII-pH monitoring	7 (54%)
Bronchodilator therapy at the time of MII-pH monitoring	11 (84.6%)
Symptoms, n (%)	
Dysphagia	10 (77%)
Persistent vomiting	2 (15%)
Recurrent pulmonary infections	12 (92%)
Asthma/wheezing	11 (85%)
Chronic coughing	6 (46%)

*Acid suppressive therapy was stopped in all patients one week before the procedure.
GERD: Gastroesophageal reflux disease, MII-pH: Combined multichannel intraluminal impedance and pH monitoring, SD: Standard deviation.

Table 2. Results of pH-impedance monitoring	
Recording duration, minutes, median (minimum-maximum)	1,453 (1,068-1,501)
pH monitoring results	
Total number of reflux episodes with pH <4	618
Reflux episodes, median (minimum-maximum)	30 (3-233)
Reflux episodes >5 minutes, n (%)	46/618 (13%)
Reflux index, median (minimum-maximum)	3.8 (0.1-35.4)
Reflux index >5%, n (%)	5 (38%)
Impedance results	
Total number of RBM	565
RBM, median (minimum-maximum)	43 (3-96)
Acidic RBM, median (minimum-maximum)	14 (0-38)
Non-acidic RBM, median (minimum-maximum)	31 (1-67)
Liquid RBM, median (minimum-maximum)	15 (0-39)
Mixed RBM, median (minimum-maximum)	24 (2-76)
*Total number of proximal RBM, n (%)	240 (42)

*RBM reaching at least the second uppermost impedance channel.
RBM: Retrograde bolus movements

In impedance analyses, a total of 565 RBM were detected of which 34% were liquid and 66% were mixed episodes. Forty-two percent (n=240) of the RBM were proximal reflux episodes reaching at least the second uppermost recording sensor while nearly one-fourth (n=136, 23%) reaching the uppermost impedance channel. Thirty percent of the reflux episodes were acidic (pH <4), 47.5% were weakly acidic (4≤ pH <7) and 22.5% were weakly alkaline (pH ≥7) episodes. Characteristics of RBM regarding reflux type, acidity and extent were shown in Figure 1. When normal values for children older than 1 year (15) were applied to our study group, percent of patients having non-acidic RBM above 95th percentile of normal values was 38% (n=5). Five of the 8 patients with normal pH monitoring results had pathological non-acid RBM in impedance analyses. Only 2 of the patients (15.4%) with esophageal symptoms had SI >50% and SAP >95%.

Videofluoroscopic Swallowing Study and Upper Gastrointestinal Tract Series

Radiographic findings of study patients including VFSS and UGT series were summarized in Table 3. The oral phase revealed normal findings in all but one of the patients. VFSS revealed aspiration in 5 patients (38.5%) all of whom also had a significant delay in swallowing response. Esophageal phase was impaired in most of the patients (n=10, 77%). The most common problem was varying degrees of esophageal motility problem which was particularly severe below the anastomosis. UGT series results were available in 12 patients (92%). Decreased peristalsis and slow passage of contrast below the anastomosis (n=8, 67%) were the most common findings followed by narrowing of the lumen at the site of anastomosis (n=3, 25%), mucosal irregularity (n=3, 25%) and gastric organo-axial malrotation (n=2, 16%). GER was detected only in 2 patients (16%) in UGT series.

Among those without clinical dysphagia (patients # 2, 3 and 9), all had radiologic findings suggestive of

Patient no:	Acid suppressive therapy at the time of procedure	Clinical dysphagia*	Extra-esophageal symptoms	UGT series	VFSS	MII-pH monitoring (pathologic reflux)	
						Acidic (RI >5%)	Non-acidic**
Table 3. Radiographic and pH-impedance monitoring findings of study patients							
1	-	+	RPI, chronic coughing	Normal findings	Aspiration with both liquids and solids, delay in swallowing response	-	-
2	-	-	RPI, asthma, chronic coughing	Mucosal irregularity at the site of anastomosis, decreased peristalsis and slow passage of contrast below the anastomosis, GER	Impaired esophageal motility	-	-
3	+	-	RPI	Decreased peristalsis and slow passage of contrast below the anastomosis, narrowing of the distal esophageal lumen	Severely impaired esophageal motility	+	-
4	+	+	RPI, asthma	Decreased peristalsis and slow passage of contrast below the anastomosis, GER	Aspiration with liquids, impaired esophageal motility	-	-
5	+	+	Asthma, wheezing	Mucosal irregularity, narrowing of the lumen at the site of anastomosis	Mild delay in swallowing response, severely impaired esophageal motility	-	+
6	+	+	RPI, wheezing	Normal findings	Aspiration with liquids, delay in swallowing response, normal esophageal motility	+	-
7	+	+	RPI, wheezing	n/a	Aspiration with liquids	+	-
8	-	+	RPI, wheezing, chronic coughing	Slow passage of contrast below the anastomosis	Aspiration with liquids, delay in swallowing response, impaired esophageal motility	-	+
9	-	-	RPI, asthma, chronic coughing	Decreased peristalsis and slow passage of contrast distal 2/3 of esophagus	Impaired esophageal motility	-	+
10	+	+	RPI, asthma	Decreased peristalsis and slow passage of contrast below the anastomosis	Severely impaired esophageal motility and GER	+	-
11	+	+	RPI, wheezing, chronic coughing	Gastric organo-axial malrotation, decreased peristalsis below the anastomosis	Aspiration with liquids, delay in swallowing response, mildly impaired esophageal motility	-	+
12	-	+	RPI, asthma, chronic coughing	Decreased peristalsis below the anastomosis, narrowing of the distal esophageal lumen	Severely impaired esophageal motility and GER	+	-
13	-	+	RPI, asthma	Mucosal irregularity at the site of anastomosis, gastric organo-axial malrotation	Impaired esophageal motility	-	+

MII-pH: Combined multichannel intraluminal impedance and pH, EA: Esophageal atresia, VFSS: videofluoroscopic Swallowing Study, UGT: Upper gastrointestinal tract, RPI: Recurrent pulmonary infections, RI: Reflux index, GER: Gastroesophageal reflux, n/a: not available

*Including refusal of feeding, history of food impaction, swallowing difficulties, coughing/chocking during meal, sensation of food stuck in the chest

**Reference values for impedance parameters per 24 h in healthy children older than 1 year were used [Mousa et al.(15)].
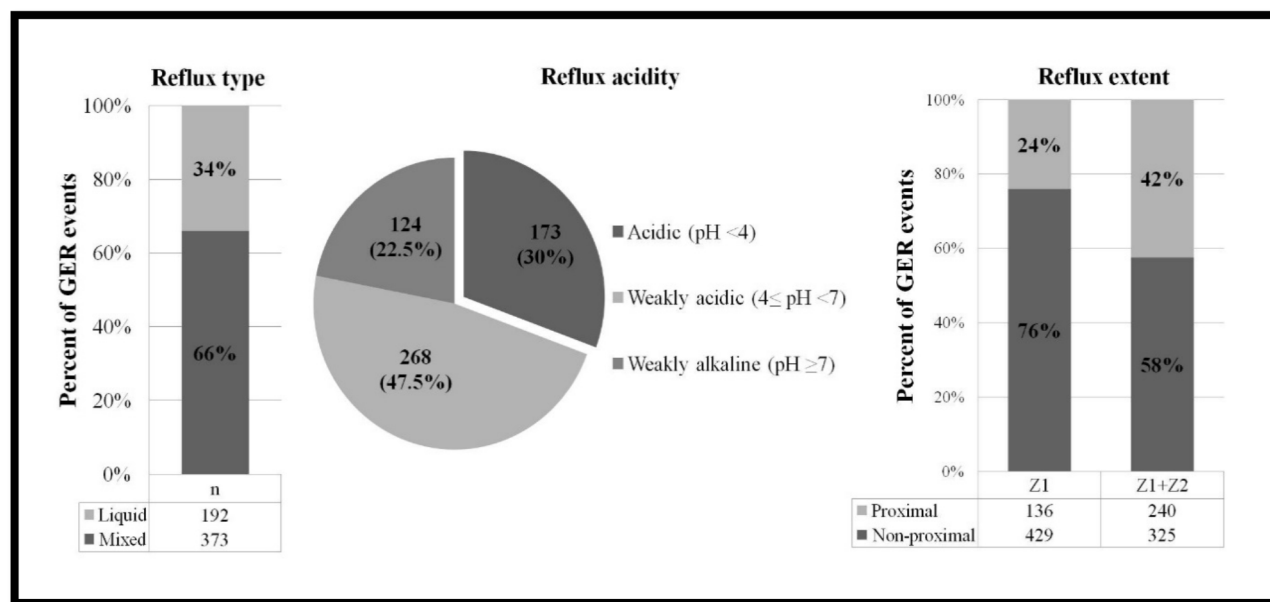
Figure 1. Characteristics of retrograde bolus movements regarding reflux type, acidity, and extent. Z1: Reflux episodes reaching the uppermost impedance channel, Z1+Z2: Reflux episodes reaching at least the second uppermost impedance channel, GER: Gastroesophageal reflux

esophageal dysmotility in both UGT series and VFSS (Table 3). Two of the 5 patients with acidic reflux (patients # 6 and 7) had aspiration with liquids without any sign of esophageal motility problem in radiologic evaluation while other 3 (patients #3, 10 and 12) had severely impaired esophageal motility and decreased peristalsis below the anastomosis. All but one patient with non-acidic reflux (patients # 5, 8, 9, 11 and 13) had clinical dysphagia. The common finding in VFSS of these patients was impaired esophageal motility. Two of these patients (patients # 11 and 13) also had gastric organo-axial malrotation detected in contrast series.

Anti-Reflux and Dietary Management of Patients

Seven patients (54%) were already on acid suppressive therapy with a proton pump inhibitor before MII-pH monitoring (Table 1). Anti-reflux treatment was continued in six as they had pathologic acidic (n=4) or non-acidic (n=2) reflux and discontinued in one with normal MII-pH monitoring. Proton pump inhibitor was started in one patient with pathologic RI and in 3 patients with pathologic non-acidic reflux. Two patients with clinical dysphagia and relatively normal esophageal motility were started domperidon as a prokinetic agent. Patients with oropharyngeal dysphagia (n=5) were included in a swallowing rehabilitation program. Beside rehabilitation, a diet modification including thickening of liquids was done in patients having aspiration with liquids. One patient aspirating both liquids and solid foods in VFSS was started to be fed through a nasogastric tube.

Discussion

Children with corrected EA continue to have significant morbidity related to GERD (16). In this study, we evaluated GER characteristics of 13 children with repaired EA using MII-pH monitoring. We also reviewed the results of contrast studies including VFSS and UGT series to evaluate swallowing and esophageal motility. Majority of RBM were non-acid (70%) and more than half of the patients with normal pH monitoring findings (5 out of 8 patients) had pathologic number of non-acid RBM in impedance analysis. Findings suggestive of esophageal dysmotility were common (approximately 70%) in both swallowing evaluation and UGT series.

GERD is one of the most frequent complications of repaired EA. The results of a long-term follow-up study reported a progressive increase in the incidence of GER during early childhood and concluded that spontaneous resolution is rare in this population (17).

The first study evaluating GER in EA patients with MII-pH monitoring revealed that EA patients with few or no symptoms may still have underlying severe GER and half of the GER events can be detected only by impedance analyses (18). In that study, 532 of 911 (58%) RBM in 24 patients with repaired EA were reported to be weakly acidic (18). Following studies have also reported similar findings (Table 4). Catalano et al. (19) reported that reflux episodes were mainly non-acidic (76.4% of total refluxes) in children with EA. They reported a pathologic bolus exposure index with normal pH RI in all patients younger than 1 year and concluded that the incidence of GER in children younger than 1 year would have been underestimated with conventional pH-meter (19). In a study where impedance results were interpreted in 10 infants and 10 adults with repaired EA, the percent of acidic reflux was only 20.6% in the infant group (20). Pedersen et al. (21) reported a similar median number of acidic and non-acidic reflux episodes in EA patients with a median age of 10.2 years. A higher incidence of non-acidic reflux (1,249 of the 1,457 episodes, 85.7%) was reported in 35 EA patients with a median age of 53 months which was probably related to more patients being on acid suppressive treatment at the time of procedure (22). In a more recent study, observed RBM were mainly non-acidic boluses (>60% of RBM) in 57 children with EA (23). In two other studies, although acidic reflux was observed more than non-acidic reflux in pediatric patients with EA by means of median number of refluxate or mean time of esophageal acid/non-acid exposure, there was still non-negligible amount or time of non-acidic reflux (24,25). In parallel to these literature findings, we also found that 70% of the reflux episodes were non-acidic, 47.5% being weak acidic and 22.5% being weakly alkaline. Anti-acid medication was not a contributing factor for high incidence of non-acidic reflux in our study as the use of acid suppressive treatment was stopped one week before the procedure. These results point a clear benefit of MII-pH monitoring in determining non-acidic reflux that cannot be evaluated with conventional pH-meter. It is of critical importance in EA patients as non-acidic reflux was reported to be associated with symptoms in these patients especially under 1 year of age (8,18,19).

In our study cohort median RI was 3.8% (0.1-35.4). Although it is comparable with the results of similar studies evaluating GER with MII-pH monitoring in repaired EA, median RI was reported in a wide range changing from 0.1 to 8.3% (Table 4) (18-25). Differences in pH-meter results were most likely due to differences in patient characteristics (age of patients, being symptomatic or asymptomatic) and study protocols (performing procedure under acid suppressive treatment). Feeding characteristics of infants younger than 1 year of age (more frequent feeding and milk feeding) and use of anti-acid treatments can be held responsible for the high incidence of non-acidic refluxes through buffering of gastric acid (19,22,26,27). However, our study cohort did not include infants younger than 16 months and the median age was 6.5 years (1.3-13.5). We discontinued acid suppressive treatment temporarily in our patients to eliminate the possible effect of treatment on reflux characteristics. We found a pathological RI in only 38% of the patients confirming the diagnosis of GERD which was much lower than we expected considering the clinical features of our patients and previously reported high incidence of GERD in children with repaired EA. However, 5 of 8 patients with normal pH recording results were found to have pathologic number of non-acidic reflux episodes in our study cohort. These non-acidic reflux events would be missed on sole pH monitoring which means half of the patients with pathologic GER episodes in our study cohort would have gone unrecognized. One important issue is that pediatric reference values of MII-pH monitoring are still an area of further research with only a few studies reporting normative data for pediatric population (15,28,29).

Correlation of persistent troublesome symptoms with GER events is one of the indications of MII-pH monitoring in the evaluation of GERD (8). In EA patients, respiratory complications related to GER are not rare (25). MII-pH monitoring allows symptom correlations between reflux episodes and respiratory symptoms including apnea, nocturnal/chronic coughing, wheezing, desaturation, asthma, and recurrent lower respiratory tract infections (30-33). Two different groups showed that more than half of the coughing episodes in children with repaired EA were associated with RBM (18,19). Respiratory symptoms were more prevalent than gastrointestinal symptoms

in our study cohort with all the patients having at least one respiratory complaint including having recurrent lower respiratory tract infections, asthma/wheezing and chronic coughing. However, only 2 of them (15%) had SI >50% and SAP >95% regarding coughing and wheezing. This finding was thought to be associated with inappropriate recording of symptom diaries as only a small number of symptoms were recorded in contrast to clinical complaints necessitating an impedance testing. Insufficient symptom recording has been reported previously (23,34). Among 12 EA patients with spontaneously reported symptoms before MII-pH monitoring, symptoms were absent during impedance testing in 83% of the patients making a symptom association analysis impossible (23). In another study, only half of the coughing episodes were recorded with a mean time lag of 11 seconds between the cough and the recording in the log (34). Proximal RBM were also reported to be associated with respiratory symptoms in children with persistent respiratory symptoms (30). However, another study from the same group did not find a significant association between cough production and the height of the refluxate (34). Percent of proximal RBM we found in our patients (23% reaching Z1 and 40% reaching Z1 and Z2) were comparable to literature findings. Frohlich et al. (18) reported that 37% of all reflux events ascended to the 2 most proximal channels without any correlation with respiratory symptoms. Catalano et al. (19) reported higher incidence up to 72.9% without any information regarding the relation between "high" refluxes and symptoms.

Esophageal dysmotility is considered as the main pathophysiological factor leading to significant digestive and respiratory morbidity via GER, aspiration, feeding disorders, and dysphagia in patients operated for EA. Studies have reported that dysphagia occurs in 21-84% of patients with EA at all ages after surgical repair (35). Food aversion, food impaction, difficulty in swallowing, odynophagia, choking, cough, pneumonia, alteration in eating habits, vomiting, and malnutrition were suggested as red flags for underlying dysphagia in children with EA (9). Our study cohort was evaluated for dysphagia with VFSS and UGT series as suggested by ESPGHAN/ NASPGHAN guideline (9). Abnormal esophageal

motility particularly distal to the anastomosis (77%) was the most frequent finding followed by aspiration (38.5%). In a previous study from our center, we evaluated deglutition in 32 EA patients by videofluoroscopy and found that 87.5% of the patients had moderate to severe esophageal phase problems (36). Higher frequencies for oral and pharyngeal phase problems were also reported. Forty seven percent of children with EA had aspiration or penetration during videofluoroscopic evaluation of deglutition (37). Coppens et al. (38) found oral phase abnormalities in 36% and pharyngeal phase abnormalities in 75% of patients. We could not find any specific correlation between radiologic findings and impedance results. Although esophageal dysmotility is present in 100% and 60% of patients with non-acidic and acidic reflux, respectively, the study cohort was too small to make a conclusion regarding the association of dysmotility with reflux acidity. Even patients without clinical dysphagia or with normal MII-pH monitoring had motility problems in VFSS or UGT series. Despite the high frequency of both GER and dysphagia in EA patients, MII-pH monitoring studies in children revealed that dysphagia is not consistently associated with reflux events (18,21,22). Treatment modalities for non-acidic GER and esophageal dysmotility in children are very limited and there are no specific recommendations in recent guidelines on this subject (8,23,35).

Study Limitations

There are some limitations of our study. Firstly, the retrospective nature of the study and small sample size were the main limitations. However, considering the limited number of studies regarding the use of MII-pH monitoring in the evaluation of children with repaired EA, our results contribute to the literature by confirming the high incidence of non-acidic reflux in repaired EA patients with GERD symptoms. Secondly, we only evaluated patients who were symptomatic, so the results regarding the characteristics of reflux episodes might be biased and cannot be generalized to whole EA patients. Thirdly, failure of appropriate symptom recording by the parents/patients made it impossible to make a symptom reflux correlation in our study.

Author	Study population	pH-meter results	Impedance results	Main findings

Table 4. Studies using MII-pH in the evaluation of patients with repaired EA

Author	Study population	pH-meter results	Impedance results	Main findings
Frohlich et al. (18)	24 patients Median age 3.5 years (4 months-23 years) off anti-acid treatment	Median RI 2.5% (0%-42.3%) 33% had pathologic RI (>5%)	Median BI 1.7% (0.4 -12.2%). 67% had abnormal BI (according to adult reference data). Non-acidic RBM 58%. High reflux 36.8% (Z1+Z2). Impaired bolus transit in impedance swallowing test	A higher tendency of non-acidic refluxes to be related to symptoms. Half of the reflux episodes only detected by impedance
Catalano et al. (19)	22 patients Median age 15 months (3-40 months) off anti-acid treatment	Median RI 6.1% (1.3% – 13.8%) •<1 y; 2.6% •>1 y; 8.1% 45.5% had pathologic RI (>4.2% for >1 y and >10% for ≤1 y) •All >1 y	Median BEI 7.2% (2.5-13.7%) •≤1 y; 6.1% •>1 y; 7.9% 100% had abnormal BEI (according to adult reference data) Non-acidic RBM 76.4% •≤1 y; 89.2% •>1 y; 70.4% High reflux 72.9% (Z1+Z2) EA vs. non-EA • Higher median BEI in EA • Longer MACT and MBCT in EA Symptomatic vs. asymptomatic • Longer MACT and MBCT in symptomatic	MII-pH monitoring detects more reflux episodes than pH-metry Underestimation of GER in children ≤1 y with pH-metry alone. A pathological bolus transit in children with EA
Di Pace et al. (39)	15 patients Mean age 7.5 years (5-10 years) Anti-acid treatment status n/a Patients with non-acidic reflux were excluded	RI >6% in all An average of 26.9 episodes were detected by pH probe alone	An average of 72.1 RBM were detected by impedance High reflux 95.6% (Z1+Z2) MACT 552.9±121.6 s MBCT 59.9±11.3 s EA vs. control (patients referred for suspicion of GERD) •Longer median BPT, median TBTT and median STT in EA	Significant GER with impaired bolus transit in EA patients compared to controls
Pedersen et al. (21)	59 patients Median age 10.2 years (7.1 – 13.3 years) off anti-acid treatment	Median RI 8.3% (4.8-14.9%) 55.2% had pathologic RI (>7%)	Median number of acidic and non-acidic episodes were similar in EA patients EA vs. control (patients referred for suspicion of GERD) •Higher number of acidic episodes in control •Lower baseline impedance in EA	More than half of the children with EA suffer from GERD and all have impaired peristalsis
van Wijk et al. (20)	10 infants and 10 adults Median age 0.67 years (0.23-3.42 years) in infants and 24.5 years (18.1-31.3 years) in adults off anti-acid treatment	n/a	In overall •Non-acidic RBM 68.3% •High reflux 18.6% (Z1) In infants •Non-acidic RBM 79.4% •High reflux 25.5% (Z1)	TLESR is the main mechanism underlying GER episodes in EA patients Impaired esophageal motility, delayed bolus clearance and delayed gastric emptying are present in majority of the study cohort

Table 4. Continued

Author	Study population	pH-meter results	Impedance results	Main findings
Tong et al. (22)	35 patients Median age 53 months (3-207 months) 30 patients were on anti-acid treatment	Median RI 0.1% (0 - 4.4%)	Non-acidic RBM 85.7% MACT 53 s (0-1386) MBCT 17 s (5-71) EA vs. control (patients referred for suspicion of GERD) •Lower acidic RBM in EA •Higher NARI in EA •Lower DBI in EA •Similar total number of RBM and proximal events •Similar MACT and MBCT 28% of reported symptoms associated with RBM Similar reflux parameters •Long gap vs. no long gap •Fundoplication vs. no fundoplication	Increased detection of non-acidic reflux events with MII-pH monitoring Significant universal dysmotility in EA patients
Tambucci et al. (24)	18 patients Median age 5.5 years (2.2-12 years) off anti-acid treatment	Mean AET 4.5±6 %	EA vs. GERD vs. control (patients with normal endoscopy and MII-pH monitoring results) •Greater percentage of AET and higher number of both long-lasting reflux and AR in GERD group •Median number of Wac and Walk episodes were similar •Lower values in both proximal and distal baseline impedance in EA	Strong relation of proximal and distal basal impedance with esophageal motor abnormalities and excessive acid reflux Possible role of baseline impedance assessment in deciding which patients would benefit from further investigations
Iwanczak et al. (25)	22 patients (19 had complete MII-pH procedure) Mean age 47.3 months (16-79 months) off anti-acid treatment	Mean RI 5.8±3.7	BEI 4.7±2.9 MACT 161.1±117.5 s MBCT 14.8±5.1 s GERD was diagnosed in 52.6% (pathological acid reflux in 9 and a non-acid reflux in one) Higher total number of reflux episodes, reflux index, bolus exposure index, esophageal exposure, esophageal acid exposure and acid clearance time in EA patients with GERD	High frequency of GERD in children with corrected EA
Vergouwe et al. (23)	57 patients Median age 0.6 years (0.2-1.5 years) in infants ≤18 months and 8.2 years (8-9 years) in school age children off anti-acid treatment	Median RI •Infants; 2.6% (0.1-28.5) •Older children; 0.3% (0-14.4) Abnormal pH results in •10% of infants •12.5% of older children	Non-acidic RBM •Infants; 62% •Older children; 64% Median number of RBM •Infants; 61 (0-134) •Older children; 21 (0-54) Four infants had >100 RBM/24 hours None of the older children had >70 RBM/24 hours 39% of all RBM were manually deleted (52% of all non-acidic and 8% of all acidic RBM)	Normal RI but significant number of nonacid RBM in most children with EA off medication Over-detection of reflux events in EA patients by automated analyses

RI: Reflux index, BI: Bolus index, BEI: Bolus exposure index, MACT: Mean acid clearing time, MBCT: Mean bolus clearing time, RBM: Retrograde bolus movements, EA: Esophagus atresia, GER: Gastroesophageal reflux, GERD: Gastroesophageal reflux disease, BPT: Bolus presence time, TBTT: Total bolus transit time, STT: Segmental transit time, Z1: Most proximal impedance channel, Z2: Second most proximal impedance channel, HREM: High resolution esophageal manometry, TLESR: Transient lower esophageal sphincter relaxation, NARI: Non-acid reflux index, DBI: Distal baseline impedance, AET: Acid exposure time, Wac: Weakly acidic, Walk: Weakly alkaline

Conclusions

Majority of the RBM was non-acidic in repaired EA patients with dysphagia or airway symptoms. MII-pH monitoring allowed the detection of pathologic non-acidic reflux events which would have gone undetected with standard pH monitoring. Half of the patients with pathologic reflux indices could only be detected by impedance monitoring. Appropriate and accurate recording of symptoms during impedance testing is of critical importance to evaluate symptom-reflux correlation. Esophageal motility disorder is a major problem among EA patients and can be documented with contrast studies including VFSS and UGT series. MII-pH monitoring should be preferred over conventional pH monitoring in the surveillance of EA patients. Further studies are warranted regarding the use and interpretation of MII-pH monitoring and the treatment of non-acidic GER and esophageal dysmotility in EA patients.

Ethics

Ethics Committee Approval: Non-interventional Clinical Research Ethics Board of the hospital approved the study (GO 21/107, 2021/02-38).

Conflicts of Interest: The authors declare no conflict of interest.

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