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ORIGINAL ARTICLE

Gastroenterology

Gastric emptying and myoelectrical activity testing in children with esophageal atresia: A pilot study

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Abstract

Objectives: Abnormalities of gastric function in children with esophageal atresia (EA) could potentially contribute to gastrointestinal symptoms and reduced quality of life (QOL). Therefore, we aimed to determine the feasibility and clinical usefulness of gastric function testing in children with EA.

Methods: The validated PedsQL Gastrointestinal Symptoms Questionnaire (PedsQL-GI) was completed to assess gastrointestinal symptoms and symptom-related QOL. Gastric emptying and gastric myoelectrical activity were studied using ^{13}C-gastric emptying octanoic acid breath test (^{13}C-GEBT) and surface electrogastrography (EGG). Correlations between ^{13}C-GEBT and EGG parameters and PedsQL-GI scores were investigated.

Results: Fifteen patients (four males) were included (median age: 6 [3.0–8.5] years). Mean PedsQL-GI scores as reported by the children were comparable to the healthy population. However, parents reported a diminished QOL. Gastric function tests (gastric emptying and/or surface EGG) showed abnormalities in 12 patients (80%). Patients with abnormal slow waves showed abnormal gastric emptying coefficient more often. There was no significant association between ^{13}C-GEBT nor EGG results and PedsQL-GI scores.

Conclusions: ^{13}C-GEBT and EGG can be used to evaluate gastric function in patients with EA. Abnormal gastric function tests were present in 80% of our cohort. However, abnormal gastric function did not significantly correlate with reported gastrointestinal symptom-related QOL.

KEYWORDS

esophageal atresia, gastric function, octanoic gastric emptying breath test, quality of life, surface electrogastrography

1 | INTRODUCTION

Esophageal atresia (EA), is a rare congenital gastrointestinal malformation with an incidence of approximately 1 in 3500 births.[1] Its mortality has dropped in the last decades, which shifted the focus of care to common problems such as gastroesophageal reflux, dysphagia, feeding difficulties, nausea, early satiety, and bloating. Condition-specific quality of life (QOL) is known to be negatively affected by these symptoms in patients with EA.[2]

Although a clear role for esophageal dysfunction in the etiology of these symptoms is present, altered gastric function as an underlying cause for these problems was

Abbreviations: ^{13}C-GEBT, ^{13}C-octanoate gastric emptying breath test; EA, esophageal atresia; EGG, electrogastrography; GE-T1/2, gastric emptying half time; GE, gastric emptying; GEC, gastric emptying coefficient; PedsQL-GI, PedsQL Gastrointestinal Symptoms Module 3.0; QOL, quality of life.

not studied previously. Several mechanisms in EA can theoretically alter gastric function, including abnormal development of the enteric nervous system, iatrogenic damage to the vagal nerves during surgical repair, and the effect of fundoplication on vagal nerve integrity.[3–7] However, objective measurement of gastric function in children with EA has not been studied before.

We, therefore, aimed to evaluate the feasibility and clinical usefulness of gastric function testing in children with EA. To gain extended insight, the two tests evaluating different aspects of gastric function were correlated to symptoms and QOL.

What is Known

- Gastrointestinal symptoms are known to impair the quality of life in children born with esophageal atresia.
- Several mechanisms in esophageal atresia patients can theoretically alter gastric function, including abnormal development of the enteric nervous system, iatrogenic damage to the vagal nerves during surgical repair of the esophagus, and the effect of fundoplication on vagal nerve integrity.

What is New

- Gastric function in children with esophageal atresia can feasibly be evaluated using ^{13}C sodium octanoate gastric emptying breath test and surface electrogastrography.
- A large proportion of patients with esophageal atresia have altered gastric function.

2 | METHODS

2.1 | Patients

The study was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee. Children with repaired EA attending the multidisciplinary EA Clinic for standard follow-up between 2015 and 2016 were recruited. Patients with gastric pull-up and colonic or jejunal interposition were excluded. Patients and their parents/caregivers had the study explained to them, and written informed consent was obtained.

2.2 | Demographics and historical clinical data

Data on patient demographics and medical history were collected from the files. Files were searched for type of EA, current medication use, associated comorbidities, details of prior surgeries including fundoplication, gastrostomy, and aortopexy, and results of gastroesophageal reflux disease investigations (endoscopy and pH-impedance testing).

2.3 | Study protocol

Patients were recruited and asked to stop any prokinetic medication 2 weeks before the baseline visit. During this visit, a detailed clinical history, including questions regarding the presence of symptoms and current medication use, was completed. The PedsQL Gastrointestinal Symptoms Module (PedsQL-GI) was obtained and ^{13}C-sodium-octanoate gastric emptying test (^{13}C-GEBT) and electrogastrography (EGG) were performed.

2.4 | Feasibility and clinical usefulness

Feasibility was evaluated by the number of patients who completed the entire study protocol and the number of tests that generated a meaningful result. Clinical usefulness was evaluated by correlating the gastric function test results to the presence of symptoms and the PedsQL-GI scores.

2.5 | PedsQL-GI

This validated questionnaire for children with gastrointestinal symptoms is composed of 74 items.[8] In all children, questionnaires were proxy-reported by parents and additionally, children aged 5–18 years completed the age-appropriate self-reported questionnaire. The responses are reverse-scored and linearly converted to a 0–100 scale.[9] A lower score indicates more GI symptoms, hence a lower QOL. In this study, we evaluated the total score, as well as two subscales related to gastric function. These were (1) *stomach pain and hurt* and (2) *stomach discomfort when eating*. Patients with a score more than two standard deviations (SDs) below the healthy reference mean were considered abnormal.[10]

2.6 | ^{13}C-GEBT

The ^{13}C-GEBT test was performed to assess the GE of liquids as per previously published studies in children.[11–13] ^{13}C labeled sodium octanoate was added to the test meal (50 mg if aged <6 months and 100 mg if >6 months). Duplicate breath samples were collected via nasal prongs in children unable to blow through a straw. Samples were taken every

5 min for 30 min and afterward every 15 min for another 210 min.

The breath samples were analyzed using an ABCA isotope ratio mass spectrometer. Corrected gastric emptying half-time (GE-$T½$), T_{lag}, T_{max}, and gastric emptying coefficient (GEC) were calculated.[14] The GE-$T½$ was defined as normal by age and sex-matched historical control data.[11] GEC was considered normal if >3.1.[15,16]

2.7 | Surface EGG

Surface EGG was used to measure gastric myoelectrical activity. Patients <6 months fasted from their last feed; patients 6–12 months fasted for 4 h, and patients >12 months fasted overnight with a minimum of 8 h. We used EGG software (version 9.5; Medical Measurement Systems) to perform bipolar recording.[17]

After a baseline recording of 15 min, a 200 mL liquid test meal of either formula or breastmilk (if aged <1 year) or full cream milk was consumed within 10 min. For patients <6 months of age, the meal volume given was consistent with routine feeding habits (up to a maximum of 200 mL). During the postprandial period, the recording continued for 30 min. Motion artifacts were minimized by keeping the patient comfortable and supine.

The EGG signals were examined by computerized spectral analysis. Three well-established parameters were measured: (1) dominant frequency (cycle per minute [cpm]) including dominant frequency instability coefficient (DFIC), (2) percentage of normal slow waves, and (3) postprandial to fasting power ratio, which reflects an increase in gastric contractility if >1, whereas a ratio of <1 reflects a decrease in gastric contractility.[18–21]

The percentage of normal slow waves and the postprandial to fasting ratio were used to classify the EGG as normal or abnormal.[22]

2.8 | Statistics

Normally distributed data are described as a mean (± SD) and were compared using *t* tests. Nonparametric data are presented as median (interquartile range) and were compared using the Mann–Whitney *U* test. Fisher's exact test was used for proportional data. Spearman's rho correlation analysis was used to explore the existence of correlations. A p value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patients

A total of 15 patients (four males), with a median age of 6 (3.0–8.5), were recruited. Twelve (80%) patients had EA type C, two type A (13%), and one type D (7%). Nine (60%) patients had strictures needing dilations in the past. Of them, six were still on proton pump inhibitor (PPI) during the trial. At baseline, seven patients (47%) used prokinetic medication, which was ceased before testing. Five patients (33%) had a history of laparoscopic Nissen fundoplication. Median age at the time of fundoplication was 4 (0–6) years old. One patient had a refundoplication 9 months after the initial fundoplication. See Table 1 for an overview of all patient demographics.

3.2 | Feasibility of gastric function tests

All 15 patients completed gastric emptying and surface EGG. All tests were analyzable.

3.3 | Symptoms

A detailed history of clinical symptoms was completed in all 15 patients. Regurgitation, coughing, and gagging at meals were mentioned by two patients. Three patients stated they had occasional heartburn, and one patient had severe heartburn and daily chest pain. Three patients reported dysphagia. One patient choked on food 2–3 times a week. No patients reported symptoms of vomiting, hematemesis, melena, cyanotic spells, food bolus impaction, or recurrent chest infections.

3.4 | PedsQL-GI

Fourteen (93%) patients and their parents completed the PedsQL-GI questionnaires (File S1). When compared to reference ranges in healthy children, neither the child's self-reported score (difference 16 [confidence interval, CI: −44 to 11], $p = 0.220$) nor the parent-proxy reported score (difference 14 [CI: −16 to 44], $p = 0.337$) was significantly lower. Both, self-reported and proxy PedsQL-GI subscale scores for *stomach pain and hurt* (self-reported; proxy: $p = 0.936$; $p = 0.608$) as well as *stomach discomfort when eating* scale (self-reported; proxy: $p = 0.698$; $p = 0.578$), did not show a statistical difference. There was a significant correlation between the parent-proxy report and the child self-report for the total score (Rs = 0.867, $p = 0.001$) and *stomach pain and hurt* scale (Rs = 0.966, $p < 0.001$), but not *stomach discomfort when eating* scale (Rs = 0.424, $p = 0.22$). For the latter scale, children reported a slightly lower burden of their symptoms compared to their parents.

3.5 | ^{13}C-GEBT

Breath tests were successfully completed in all patients (Table 2). Eight (53%) patients had abnormal GE tests.

TABLE 1 Demographics of EA children ($n = 15$).

Age (years), med (IQR)	6 (3.0–8.5)
Age (years) distribution in groups, *n* (%)	
0–1	3 (20%)
2–4	2 (13%)
5–7	5 (33%)
8–12	4 (27%)
13–18	1 (7%)
Male, *n* (%)	4 (27%)
Gestational age (weeks), med (IQR)	36 (36.0–37.5)
Birth weight (g), med (IQR)	2485 (2220–2915)
Type of EA, *n* (%)	
A	2 (13%)
C	12 (80%)
D	1 (7%)
Median age at time of repair in days (IQR)	2 (0–12)
Laparoscopic repair procedure (yes), *n* (%)	15 (100%)
Foker procedure (yes), *n* (%)	2 (13%, both type A)
Fundoplication (yes), *n* (%)	5 (33%)
History of gastrostomy (yes), *n* (%)	6 (40%)
Strictures requiring dilations (yes), *n* (%)	9 (60%)
Eosinophilic esophagitis	5 (71%)
Acid suppressive medication (yes), *n* (%)	10 (67%)
Prokinetic use before inclusion (yes), *n* (%)	7 (47%)
Erythromycin, *n* (%)	2 (29%)
Domperidone, *n* (%)	5 (71%)
Weight at recruitment [*Z* score], med (IQR)	−0.4 (−1.3 to 0.7)
Height at recruitment [*Z* score], med (IQR)	−0.2 (−1.3 to 0.44)
Mode of feeding	
Oral	14 (93%)
Gastrostomy	1 (7%)
Symptoms	
Regurgitation	2 (13%)
Dysphagia	3 (20%)
Coughing	2 (13%)
Heartburn/chest pain	4 (27%)
Gagging at meals	2 (13%)
Choking	1 (7%)

Abbreviations: EA, esophageal atresia; IQR, interquartile range; med, median; *n*, number of patients.

TABLE 2 Results of gastric function tests.

^{13}C-GEBT		
Patient	**Corrected GE-*T*½**	**GEC**
1	41.8	3.0[a]
2	9.1	3.6
3	314.1	1.6[a]
4	163.3[a]	2.6[a]
5	16.6	3.6
6	35.3	3.4
7	62[a]	3.2
8	65.1[a]	2.9[a]
9	62.1[a]	3.2
10	49.3	3.3
11	68.8[a]	2.1[a]
12	188.4[a]	1.7[a]
13	−5.4	5.8
14	40.1	3.3
15	18.4	4.3
EGG	**Resting**	**Postprandial**
Dominant frequency, *n* (%)		
Normal	14 (93%)	13 (86%)
Bradygastria	1 (7%)	1 (7%)
Tachygastria	0 (0%)	1 (7%)
Percentage of normal slow waves, mean		
Normal	64.89%	68.20%
Bradygastria	26.87%	22.43%
Tachygastria	8.25%	9.37%
Fed-to-fasting power ratio, mean		
		1712

Note: GE-*T*½ results are compared to an age-matched historical cohort group without esophageal atresia and without symptoms. GEC is considered abnormal when <3.1.[20,22] Dominant frequency was considered normal when between 2–4 cpm; bradygastria <2 cpm; and tachygastria >4 cpm. The percentage of normal slow waves was normal >70%. A fed-to-fasting power ratio >1 was considered normal.[21]

Abbreviations: ^{13}C-GEBT, 13C-octanoate-gastric emptying breath test; EGG, electrogastrography; GE-T1/2, gastric emptying half time; GEC, gastric emptying coefficient.

[a]Considered abnormal.

Seven (47%) of them also had a GE-*T*½ above the upper limit compared to their matched controls. The mean GE-*T*½ was 75.27 min (SD: 84.63). Patients with abnormal gastric emptying had a significantly longer *T*½ (131.97 vs. 26.33; $p = 0.009$), a higher T_{max} ($p = 0.001$), and a longer T_{lag} ($p = 0.001$). Six patients (40%) had an abnormal GEC, five of whom also had abnormal GE-$T½$. The median GEC was 3.2 (1.57–5.76). Gastric emptying $T½$ correlated positively with GEC (Rs = −0.961; $p < 0.001$).

3.6 | Surface EGG

All 15 patients completed the EGG protocol. Overall, eight (53%) patients showed abnormal EGG results. See Table 2 for an overview of all results. In seven (47%), the proportion of abnormal slow waves was high in the postprandial period. The dominant frequency during the *fasting* period was abnormal in one patient who had bradygastria. It was abnormal in two patients during the *fed* period. One of them had bradygastria and the other tachygastria. The mean DFIC during the resting phase was 0.174 compared to a DFIC of 0.156 during the postprandial phase ($p = 0.226$). The patients with abnormal dominant frequency also showed an abnormal proportion of normal slow waves. The postprandial to fasting power ratio was abnormal in five (33%) patients. There was no association between the abnormal power ratio and abnormal postprandial slow wave proportion ($p = 0.119$).

3.7 | Correlations between clinical parameters, PedsQL-GI, ^{13}C-GEBT, and EGG

Patients with an abnormal EGG did not have delayed GE more often ($p = 0.573$). Patients with an abnormal ^{13}C-GEBT or EGG did not have an abnormal PedsQL-GI more often ($p = 0.736$ and $p = 0.569$). This lack of correlation was also seen between abnormal testing and PedsQL-GI subscores (stomach pain and hurt $p = 0.733$; stomach discomfort while eating $p = 0.691$). Patients with abnormal slow waves showed abnormal GEC more often ($p = 0.041$).

No significant correlation was found between delayed gastric emptying or abnormal EGG and type of EA, age, sex, PPI use, prior surgeries, strictures, and gastroesophageal reflux disease investigations.

4 | DISCUSSION

In children born with EA, gastrointestinal symptoms are known to impair QOL.[2] This is the first study showing that objectively measured gastric function (using gastric emptying and surface EGG) is feasible and proves abnormal in nearly all EA patients. Interestingly, no relation was found between gastric function abnormalities and symptoms or QOL.

In our study, both ^{13}C-GEBT and EGG were feasible in all participants. In line with our results, previous research indicates that ^{13}C-GEBT is safe, noninvasive, and an easy-to-perform measure to accurately evaluate gastric emptying in children and adults.[11,23] Furthermore, surface EGG is considered an attractive measurement as it is noninvasive and accurately reproducible with a standardized protocol.[21]

We found 80% of our cohort to have an abnormal gastric function by either delayed gastric emptying, abnormal EGG, or both. Gastric emptying was delayed in over half of our patients compared to historic age and sex-matched controls, which is consistent with previous studies in EA children and adults.[24–27] Abnormal gastric myoelectrical activity, especially in the postprandial period was present in the majority of our patients. These results are consistent with three previous studies reporting altered gastric function as measured by EGG in EA patients.[28–30]

While the gastric emptying results are suggestive of gastric dysmotility, we did not find correlations between ^{13}C-GEBT and EGG findings. This is likely caused by the variety of abnormalities found on EGG testing and the relatively small cohort. Larger studies are needed to identify the mechanisms of delayed gastric emptying on EGG, but hypotheses that may underlie the abnormal gastric function in EA patients are vagal damage during primary repair or abnormal development of the enteric nervous system beyond the esophagus.[26,27]

Although a reduced health-related QOL has been reported in other studies in EA patients we could not confirm this in our cohort.[31–33] Similar to our findings, a German–Swedish cohort of children between 8 and 18 years with repaired EA, rated their own health-related QOL significantly better compared to their parents.[32] This was also seen in a Dutch, Turkish, and Polish cohort of EA patients between 8 and 18 years old. However, none of them reported whether this difference was statistically significant.[34–36] One explanation for the discrepancy between patients and parents, could be the life-long presence of symptoms. Patients might have become used to their symptoms, while their parents compare their children to siblings or other children.

It is known that, apart from factors related to initial surgery and comorbidities, current gastrointestinal as well as respiratory symptoms influence patient-reported QOL in EA patients.[31,32] Specific gastrointestinal symptoms that are known to alter health-related QOL in children are vomiting, the need to eat small portions, and the inability to finish a full meal in 30 min.[37] Interestingly, we did not find correlations between abnormal gastric function testing and symptoms or QOL. These results are similar to those of previous studies assessing gastric function by scintigraphy or EGG.[25–30] They reported evidence of abnormal gastric function but were unable to determine whether gastric dysfunction exacerbates symptoms. However, a recent study, using high-resolution EGG, did find a correlation with gastrointestinal symptoms in adults with dyspepsia or gastroparesis.[38] In contrast, a study in children with gastroparesis revealed a significantly lower gastrointestinal QOL and increased upper gastrointestinal symptoms compared to healthy children.[39] However, even in this study, there was an overlap in symptoms reported by children with evidence of gastroparesis on scintigraphy with those with normal gastric emptying.

4.1 | Strengths and limitations

Our study is the first to combine an objective evaluation of gastric function and a validated QOL questionnaire. It does, however, have limitations that should be acknowledged. Similar to previous studies evaluating gastric function in EA patients, our study had a small sample size. This could be causing the lack of significance. Furthermore, it concerns a single-center study with a short observation time. Another limitation of our study is that patients enrolled were not homogenous for EA subtype and had a variable surgical history of prior fundoplication and gastrostomy, possibly altering gastric function. Future research should be powered to properly differentiate between the different EA types. Finally, only liquid test meals were used to evaluate gastric emptying. Future research should consider evaluating mixed or solid gastric emptying tests.

5 | CONCLUSION

In conclusion, ^{13}C-GEBT and EGG are feasible tests to evaluate gastric function in patients with EA. Our data suggest that a large proportion of patients with EA have altered gastric function. However, we did not find any relation with symptoms in this pilot study, so it remains unclear to what extent symptoms or QOL is related to this abnormal function. A large prospective trial further evaluating the gastric function in EA patients using ^{13}C-GEBT and EGG and studying its role in symptom generation and longitudinal symptom change is needed.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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