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A disturbance of the gastric myoelectric activity in post-operative patients with biliary atresia

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Abstract *Background* Abnormalities in gastrointestinal motility have been reported in adult patients with advanced liver disease. However, there have so far been no reports on the gastric myoelectric activity in post-operative patients with biliary atresia (BA).

Aim The purpose of this study was to evaluate the gastric myoelectric activity in post-operative patients with BA in relation to liver fibrosis.

Patients and methods Twenty-one post-operative patients with BA, consisting of 6 boys and 15 girls with a mean age of 8.0 years and 6 healthy children (control group) were included in the study. The gastric myoelectric activity was measured by electrogastrography (EGG). The patients with BA were divided into two groups according to the serum hyaluronic acid (HA) level as a marker of liver fibrosis: the fibrotic group (FG, $n=11$), HA > 50 ng/ml and the non-fibrotic group (NF, $n=10$), HA ≤ 50 ng/ml. All recorded data were spectrally analyzed and any parameters related to changes in the dominant peak frequency (DPF) and its power were investigated. Furthermore, the gastrointestinal symptom scores (GSS) were calculated in patients with dyspeptic symptoms according to the degree of advanced liver fibrosis.

Results The results showed that 1) the postprandial DPF in the FG tended to be higher than that in the NFG ($p=0.051$), 2) the postprandial variability index of the DPF in the FG and NFG were significantly

higher than those in the controls ($p<0.05$), and 3) the preprandial percentage of normal waves (PNW) in the FG tended to be lower than that in the controls ($p=0.089$). The postprandial PNWs in the FG and NFG were significantly lower than those in the controls ($p<0.05$). Especially, the postprandial PNW in the FG was significantly lower than that in the NFG ($p<0.05$). 4) The power ratio in the FG and NFG were significantly lower than those in the controls ($p<0.05$), and 5) the GSSs in the FG were significantly higher than those in the NFG ($p<0.05$).

Conclusions The gastric myoelectric activity appeared to be disturbed in BA patients associated with portal hypertension and neurohormonal changes due to liver fibrosis.

Keywords Biliary atresia · Post-operative patients · Gastric myoelectric activity · Dyspepsia

Introduction

Post-operative patients with biliary atresia (BA) have several complications, including ascites, encephalopathy, and gastrointestinal bleeding due to portal hypertension as the liver dysfunction progresses to liver cirrhosis. These patients often complain of symptoms suggesting the presence of dyspepsia, such as postprandial vomiting, regurgitation, bloating, fullness, and early satiety. Some of these symptoms may be related to gastritis or peptic ulcer, but abnormal gastric motility has also been noted in patients with liver fibrosis including cirrhosis. Delayed gastric emptying of solid or liquid components of a meal has also been noted in patients with liver cirrhosis [6, 12, 29]. The mechanisms responsible for such an abnormal gastric motility in liver cirrhosis patients are still not well understood, but the microcirculation in the gastric walls and neural and hormonal factors may play essential roles in the regulation of gastric emptying [1, 6, 12, 22, 29]. A simple,

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non-invasive test such as electrogastrography (EGG) would enable a further investigation of these mechanisms. It is worth noting that a number of reports have described abnormalities in the gastric electrical activity in patients with unexplained upper gastrointestinal symptoms and gastric dysmotility [7, 32].

Hyaluronic acid (HA), a glycosaminoglycan distributed in the connective tissue, is a component of the liver extracellular matrix which is synthesized and degraded in liver sinusoidal cells [25]. The high serum HA levels observed in patients with liver disease, particularly in those with fibrosis, have been reported to be related to a decreased function of the endothelial sinusoidal cells [8]. Some studies have suggested that the circulating levels of HA reflect the liver function. HA may also reflect ongoing liver fibrosis, because this component is synthesized by Ito cells [9]. The serum levels of HA tend to be high in patients with liver cirrhosis [15, 20].

The aim of this study was to measure and evaluate both the preprandial and postprandial gastric myoelectric activity in post-operative patients with BA, especially regarding the relationship between the serum HA level and the dyspeptic symptom score.

Patients and methods

Patients and controls

A total of 21 post-operative patients with BA (including 6 boys and 15 girls) were examined, and 6 healthy children without any clinical symptoms (2 boys and 4 girls) were used as control subjects. The ages ranged from 1 to 21 years (mean 8.0 years) in the BA group and from 7 to 20 years (mean 10.7 years) in the controls. The patients with BA were treated by the Kasai operation with Suringa's transient enterostomy [19]. After ensuring the presence of a sufficient bile flow, the transient enterostomy was closed at 0.5–1 year after the initial operation. No patients were taking any medication such as prokinetic drugs that could affect the EGG results.

The serum HA level correlates to the degree of liver fibrosis in liver disease [15, 20] and the cut-off level for the serum HA was set at 50 ng/ml. The patients with BA were divided into two groups according to their serum HA level: the fibrotic group (FG, $n=11$) with HA > 50 ng/ml and the non-fibrotic group (NFG, $n=10$) with HA ≤ 50 ng/ml. The patients' laboratory data were discussed by comparing the serum HA levels between the FG and NFG. The items investigated regarding the patients' laboratory data were as follows: T.Bil (total bilirubin), GOT, GPT, γ -GTP, Alp, ChE (cholinesterase), TP (total protein), Alb (albumin), TBA (total bile acid), RBP (retinol binding protein), PA (prealbumin), TF (transferrin), Vit-A (vitamin A), Vit-E (vitamin E).

Methods

Symptom evaluation (gastrointestinal symptom scores GSS)

The gastrointestinal symptoms of post-operative patients with BA (nausea, vomiting, anorexia, early satiety, bloating, and abdominal pain) were evaluated according to Riezzo's criteria [23]. The severity of symptoms was graded from 0 (none) to 3 (severe) [23].

The final score represented the total of all individual scores with a total possible score of 18.

Electrogastrography (EGG) recording

The gastric myoelectric activity was recorded using a non-invasive method, by means of surface electrodes attached to the epigastric abdominal wall along the axis of the distal stomach which had been previously localized by ultrasonography [10, 18, 30]. The electrodes were connected to a polygraph. The high cut-off filter and time constant were set at 0.5 Hz and 5 s, respectively. Because of interindividual anatomic variations, various recording sites were tried to find the best combination of leads which generated the best signal-to-noise ratio for the analysis. The EGG signal was simultaneously recorded on the polygraph and on a magnetic data recorder. This was later digitized (real time sampling rate: 2 Hz) and fed into a personal computer for a spectral analysis, namely a method by which the wave form data is broken down into various frequency components and the relative contribution of a given frequency band to the entire signal is called the 'power' of the frequency band. This analysis shows the greatest contribution of frequencies to range from 2.4–4.0 cycles per minute (cpm) and thus demonstrates its highest 'power' to be at that frequency range.

The EGG recordings were performed for 30 min during the preprandial period and for 30 min after feeding the test meal. A low-residue diet (Clinimeal, Eizai Co., Japan) was used with a calorie density of 1 kcal/ml and 10 kcal/kg body weight. The children were examined in the supine position after an overnight fast [10, 18, 30]. Informed consent was given by the patients and the families before they were enrolled in this study.

EGG data analysis

A visual analysis of the EGG wave forms is neither possible nor objective. Therefore, a spectral analysis was used to compute the power of the EGG signal as a function of its frequency components. Running spectral analyses were represented by pseudo three-dimensional plots, where the electrical frequencies (0–15 cpm) were plotted on the horizontal axis and time (in 128 s intervals) on the vertical axis. This procedure generates a series of overlapping spectra and makes both a frequency and time analysis possible [10, 18, 30]. A quantitative and statistical analysis of the EGG data was performed to investigate the frequency, amplitude, and regularity of the EGG after the spectral analysis using the maximum entropy method (MEM) in the preprandial and postprandial state. The calculated parameters were as follows: i) dominant peak frequency (DPF), ii) variability index of the DPF (VI), iii) percentage of normal gastric slow waves (PNW), and iv) peak power ratio (PR). The parameters closely corresponded to those already described in previous reports in humans [3, 10, 18, 23, 29, 30, 31]. After these analyses we determined what factors might influence the GSS in order to identify any evaluative parameters for the gastric myoelectric activity in post-operative patients with BA.

1. Dominant peak frequency (DPF) was defined as the frequency at which the EGG power spectrum has its maximum peak power. The DPF usually falls in the range of 0.5–15 cycles per minute (cpm) [10, 18, 30]. The normal range of DPF remains controversial [4, 7, 32], but we considered the range to be abnormal if it was not between 2.4 and 4 cpm in our study series [31]. Tachygastria was defined as a dominant frequency of greater than 4 cpm. Bradygastria was defined as a dominant frequency of less than 2.4 cpm. A dysrhythmic episode had to be present for at least 2 min with the absence of the normal gastric signal. The dominant frequency and the corresponding power were computed with each EGG tracing, using the maximum entropy method (MEM) [10, 18, 30].
2. Variability index of the DPF (VI) was defined as the ratio (standard deviation of DPF)/DPF.

3. Percentage of normal slow waves (PNW): After the ensemble mean of the spectra (EMS) was calculated in the preprandial and postprandial states, the area enclosed between the curve of the EMS and baseline was defined as the total area of the spectra (TAS). PNW was defined as the percentage of area enclosed between 2.4 and 4.0 cpm (normal wave area: NWA) in TAS, i.e. $PNW = (NWA/TAS) \times 100$.
4. Peak power ratio (PR). The power at the DPF in the power spectrum is the EGG peak power. The PR was defined as a the relative difference (the postprandial power/the preprandial power) in the peak power (in microvolts squared) at the DPF between the fasted and postprandial states [10, 18, 30].

Statistical analysis

Student's *t*-test, Fisher's protected least significant difference test (Fisher's PLSD test), χ^2 -test and Pearson's correlation coefficient were used where appropriate for a comparison of GSS, EGG parameters, and the serum laboratory data as a statistical analysis. The data were expressed as the mean \pm SD. Probability values were considered to be statistically significant at a level of 0.05 or less.

Results

Comparison of laboratory data between FG and NFG

There were significant differences in GOT, γ -GTP, Alp, Alb, TBA, RBP, PA, and Vit-A between the FG and the NFG ($p < 0.05$) (Table 1). Furthermore, ChE and TP in the FG also tended to be lower than those in the NFG ($p < 0.1$) (Table 1).

EGG studies and GSS

Clear episodes of gastric dysrhythmias were recognized by a visual inspection of the raw EGG signals in some post-operative patients in the FG. Figure 1 shows an example of an EGG running spectral array in the post-operative BA patients, a clear example of dysrhythmia is shown in one post-operative patient in the FG.

Table 2 summarizes the data of DPF, VI, and PNW in the controls and post-operative patients with BA. Postprandial DPF in the FG tended to be higher than that in the NFG ($p = 0.051$). Although postprandial VIs in the FG and NFG were significantly higher than those in the controls ($p = 0.018$ and 0.02 , respectively), there was no significant difference between the FG and NFG in VI. The preprandial PNW in the FG tended to be lower than that in the controls ($p = 0.089$). The postprandial PNWs in the FG and NFG were significantly lower than those in the controls ($p = 0.0001$ and 0.0067 , respectively), and especially, the postprandial PNW in the FG was significantly lower than that in the NFG ($p = 0.029$). The PRs in the FG and NFG were significantly lower than those in the controls ($p = 0.023$ and 0.023 , respectively) (Fig. 2).

The GSSs in the FG, the NFG, and the controls were 6.73 ± 2.49 points, 1.90 ± 1.37 points and 0 points, respectively. The GSSs in the FG were significantly

higher than those in the NFG ($p < 0.0001$). The postprandial VIs in the patients with GSS above 3 points were significantly higher than in the controls ($p = 0.002$) and they tended to be higher than those in the patients with GSS under 3 points ($p = 0.07$). The postprandial PNWs in the patients with GSS above 3 points were significantly lower than those in the controls ($p = 0.0001$) and tended to be lower than those in patients under 3 points ($p = 0.06$). There was a significant negative correlation between the postprandial PNWs and GSS in postoperative patients with BA ($r = -0.633$, $p = 0.0003$).

Discussion

Recent advances in operative techniques and in the pre-operative and post-operative management of BA have greatly increased the life expectancy of patients who undergo a Kasai's hepatic portoenterostomy [17, 19]. Although several patients have survived after a hepatic portoenterostomy with good bile flow and a clearing of jaundice in infancy, some tend to demonstrate complications, such as cholangitis, ascites, bleeding secondary to portal hypertension, and liver dysfunctions such as cirrhosis. Even in anicteric post-operative patients, a cholestatic tendency, as revealed by an increase in the serum total bile acids or γ -GTP, is common [14]. Furthermore, the serum HA level correlates to the degree of liver fibrosis in patients with liver cirrhosis [15, 16, 20]. Regarding the serum HA cut-off level (50 ng/ml), most of the parameters of liver function, especially the cholestatic markers described above, were reflected in the present grouping of liver fibrosis in this study.

Abnormalities of gastrointestinal motility have been reported to be associated with end-stage liver disease in adults, complaining of dyspeptic symptoms by electrogastrography (EGG) [3, 29]. The electrical activity of the stomach consists of the cyclic depolarization of the membrane potential of smooth muscle cells electric control activity (ECA) or slow-wave activity. ECA emanates from a pacemaker area located along the greater curvature and is propagated in an aboral direction toward the pylorus at a frequency of 3 cpm in humans. When ECA shows an increase in plateau depolarization with superimposed spike potentials, then the stomach exhibits motor contractions that are involved in the mechanical trituration and propulsion of ingested food [27]. Electrical abnormalities related to the frequency of gastric activity are usually called gastric dysrhythmias. It is believed that the gastric threshold for dysrhythmias increases postprandially due to the effects of mechanical and neurohormonal changes on gastric smooth muscle [13]. Normal slow-wave frequency in the EGG was related to normal gastric motility and abnormal slow-wave frequencies were associated with motility disorders. When comparing EGG rhythm irregularity, we defined VI and PNW as the parameters. In this study, the postprandial VIs in the FG and NFG

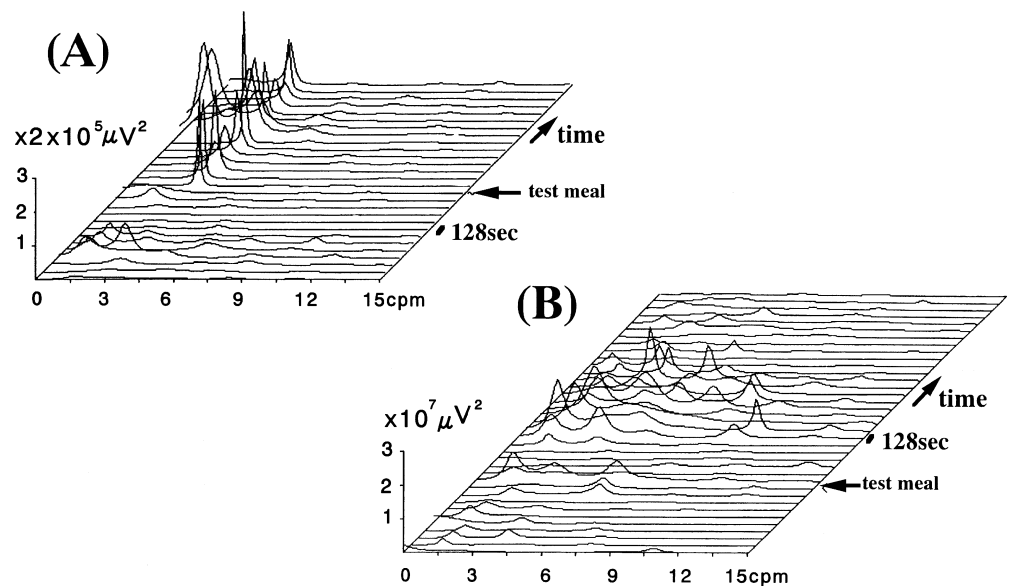
Table 1 Comparison of laboratory data between FG and NFG

Parameter	T.Bil	GOT	GPT	Gamma-GTP	Alp	ChE	TP
Normal range	0.3–1.1	10–29	4–41	7–66	103–217	213–496	6.6–8.0
FG (n = 11)	3.6 ± 5.8	122 ± 73	88 ± 45	303 ± 137	1104 ± 473	221 ± 95	6.46 ± 0.74
NFG (n = 10)	0.62 ± 0.28	56 ± 61	60 ± 69	121 ± 103	545 ± 262	291 ± 75	6.89 ± 0.26
<i>p</i> -value	0.13	0.038	0.27	0.0029	0.0037	0.079	0.094
Parameter	Alb	TBA	RBP	PA	TF	Vit-A	Vit-E
Normal range	4.1–5.7	< 10	2.2–7.4	21–41	237–423	65–276	0.75–1.41
FG (n = 11)	3.9 ± 0.71	128 ± 105	1.5 ± 0.67	11.7 ± 4.9	304 ± 71	59 ± 37	0.86 ± 0.30
NFG (n = 10)	4.6 ± 0.26	16 ± 12	2.4 ± 0.97	18.6 ± 5.3	286 ± 49	104 ± 26	0.89 ± 0.28
<i>p</i> -value	0.0064	0.0035	0.017	0.0059	0.54	0.0054	0.84

NFG non-fibrotic group (n = 10)
FG fibrotic group (n = 11)
T.Bil Total bilirubin (mg/dl)
ChE Cholinesterase (IU/l)
TP Total protein (g/dl)
Alb Albumin (g/dl)

TBA Total bile acid (nmol/ml)
RBP Retinol binding protein (mg/dl)
PA Prealbumin (mg/dl)
TF Transferrin (mg/dl)
Vit-A Vitamin A (IU/dl)
Vit-E Vitamin E (mg/dl)

Fig. 1A, B An example of the EGG running spectral array. **A** The NFG: a 6-year-old female patient without jaundice: GSS 2 points, serum HA level 18 ng/ml, EGG rhythm regular, PR 6.15. **B** The FG: a 1.5-year-old female patient without jaundice who complained of anorexia: GSS 7 points, serum HA level 162 ng/ml, EGG rhythm irregular, PR 1.27. *FG* fibrotic group, *NFG* non-fibrotic group, *GSS* gastrointestinal symptom score, *HA* hyaluronic acid, *PR*: power ratio



were significantly higher than those in the controls. Preprandial PNW in the FG tended to be lower than those in the controls. Postprandial PNWs in the FG and NFG were significantly lower than those in the controls, and especially, the postprandial PNW in the FG was significantly lower than that in the NFG. Furthermore, a significant negative correlation was observed between postprandial PNWs and GSS in post-operative patients with BA. The GSS partly reflected the rhythm of the gastric myoelectric activity. From these results, PNW and VI appeared to be key markers of gastric dysrhythmias.

Although the increased amplitude in the postprandial EGG reflects an increased contractile strength, there is no one-to-one correlation between EGG amplitude and the strength of contractions in adults [30]. The relative increase in the EGG amplitude provides information about the contractions of the stomach [26]. As a result,

we used PR as a marker reflecting the gastric contractile activity. The PRs of FG and NFG were significantly lower than those of the controls. Therefore, the gastric contractile activities of the post-operative BA patients might be lower than those of the controls. Furthermore, the degree of liver fibrosis partly reflected the EGG abnormalities, such as the postprandial DPF and PNW.

The mechanism responsible for an abnormal gastric motility in liver fibrosis or cirrhosis is still not well understood. Autonomic dysfunction is common in patients with cirrhosis of the liver. This may be secondary to the deranged liver function or a consequence of portal hypertension itself. Other factors such as an impaired vascular hyporesponsiveness (possibly related to a circulating vasodilator) or the presence of false neurotransmitters or a true neuropathy may also contribute to this condition [2, 21, 24, 28]. Increased sympathetic nerve activity has been reported in patients with cir-

Table 2 Dominant peak frequency (DPF), variability index of the DPF (VI), and percentage of normal slow waves (PNW) in the NFG and FG in comparison to the controls

	Preprandial						Postprandial					
	Controls	Patients		<i>p</i> -value			Controls	Patients		<i>p</i> -value		
		NFG	FG	<i>P</i> _{CN}	<i>P</i> _{CF}	<i>P</i> _{NF}		NFG	FG	<i>P</i> _{CN}	<i>P</i> _{CF}	<i>P</i> _{NF}
DPF (cpm)	3.33 ± 0.25	3.31 ± 0.36	3.52 ± 0.27	0.88	0.23	0.12	3.32 ± 0.21	3.23 ± 0.27	3.45 ± 0.25	0.51	0.29	0.051
VI	0.12 ± 0.08	0.13 ± 0.06	0.15 ± 0.03	0.70	0.26	0.38	0.081 ± 0.04	0.14 ± 0.05	0.14 ± 0.04	0.018	0.02	0.90
PNW (%)	44.1 ± 23.2	38.7 ± 16.8	28.6 ± 13.7	0.55	0.089	0.20	62.3 ± 12.6	44.9 ± 9.2	33.5 ± 12.4	0.0067	0.0001	0.029

*P*_{CNP}-value (Controls vs NFG patients)

*P*_{CFP}-value (Controls vs FG patients)

*P*_{NFP}-value (NFG patients vs FG patients)

NFG Non-fibrotic group

FG Fibrotic group

rhosis on direct intraneural recording [5]. Furthermore, subjects who experience nausea and other symptoms of motion sickness in the rotating drum show an initial increase in the sympathetic nervous system activity and a decrease in the parasympathetic nervous system activity, followed by a change in the gastric myoelectric activity in EGG from a regular 3 cpm activity to a dysrhythmic 4–9 cpm activity, or tachyarrhythmia [11]. From the view point of dysrhythmia examined in this study, an autonomic dysfunction might occur in post-operative patients with BA due to liver fibrosis. Furthermore, the spinal evoked potentials in post-operative icteric patients with BA have been reported to be disturbed even with a normal serum vitamin E status [14]. These facts suggest that post-operative patients with BA might have potential risk of developing various kinds of neural disturbances. Screening by EGG and early treatment of the potential gastric motility disorders in post-operative patients with BA may thus be able to effectively improve the quality of life in these patients as well as help to investigate the mechanisms of the dysrhythmias. However, it may be impossible to distinguish any substantial differences in the dysrhythmias between post-operative

patients after gastrointestinal surgery and post-operative patients with BA. Some post-operative patients with gastric ruptures and esophageal atresia were found to have a disturbed gastric pacemaker and/or gastric motor activity related to the stomach itself or the esophagus [18, 31]. However, the incidence of dysrhythmias was significantly higher in the patients with liver fibrosis than in those without liver fibrosis. This fact suggests that metabolic and hemodynamic changes associated with liver fibrosis seemed to affect the gastric motility in the post-operative patients with BA. Whenever dysrhythmias or gastrointestinal symptoms are identified in these patients, possible gastric myoelectric activity disorders should be taken into consideration. Future goals might be to prevent dysrhythmias using prokinetic drugs and other methods.

In conclusion, the gastric myoelectric activity appeared to be disturbed in BA patients associated with portal hypertension and neurohormonal changes due to liver fibrosis.

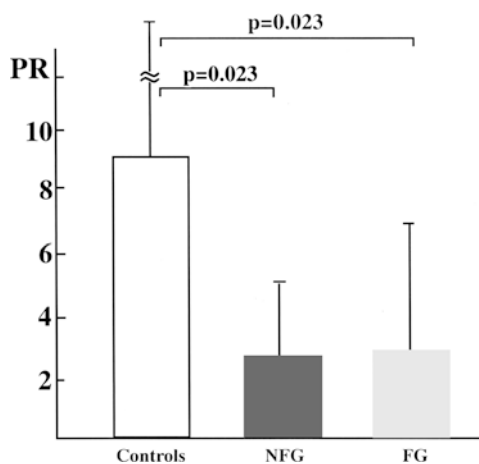


Fig. 2 Power ratio (PR). The PRs in the FG and NFG were significantly lower than those in the controls ($p=0.023$ and 0.023 , respectively). Controls ($n=6$), NFG non-fibrotic group ($n=10$), FG fibrotic group ($n=11$)

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