Improvement of gastric motility by hemodialysis in patients with chronic renal failure

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Abstract

Background: Gastrointestinal (GI) symptoms are common in patients with chronic renal failure (CRF). We have previously demonstrated that patients with predialysis end-stage renal disease showed a high prevalence of GI symptoms and gastric hypomotility, and that gastric hypomotility appears to be an important factor in generating GI symptoms. However, it is not clear whether impaired gastric motor function would improve after hemodialytic treatment. Aims: To examine the relationship between gastric motor function and GI symptoms in CRF patients on hemodialysis. Methods: The study was performed in 19 patients with CRF treated with hemodialysis for more than six months and in 12 matched healthy controls. GI symptom severity was quantified in all patients. Gastric motility was evaluated with cutaneously recorded electrogastrography (EGG) and gastric emptying of semi-solid meals using the ^{13}C-acetic acid breath test. Results: Six patients had no symptoms, and 11 had slight GI symptoms with a total symptom score of less than 5. Compared with controls, CRF patients revealed no differences in gastric motility parameters, with the exception of a lower percentage of normogastria in EGG at fasting state. Eleven patients had normal gastric motor function (Group A), and eight showed abnormalities of either gastric myoelectrical activity or gastric emptying (Group B). There was no difference in symptom score between Group A and Group B. Conclusions: More than half of the patients with CRF on hemodialysis demonstrated normal gastric motility, and no or slight GI symptoms. Hemodialytic treatment may improve impaired gastric motility and reduce GI symptoms in patients with CRF.

Key words: gastrointestinal symptoms, gastric motility, chronic renal failure, hemodialysis

Introduction

Many gastrointestinal (GI) symptoms, such as anorexia, nausea, epigastric pain,

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postprandial fullness and constipation are common in patients with chronic renal failure (CRF). It is likely that various factors contribute to these symptoms, but no underlying mechanisms have been determined yet. Several reports (Brown-cartwright *et al.*, 1988; Dumitrascu *et al.*, 1995; Kao *et al.*, 1996; Van Vlem *et al.*, 2001; Hubalewska *et al.*, 2004; Wright *et al.*, 1984; McNamee *et al.*, 1985; Soffer *et al.*, 1987) evaluating gastric emptying in patients with CRF have yielded conflicting results. The discrepancies among these findings may be attributed to the methods used to measure gastric emptying or differences in the patients' conditions (*i.e.*, on hemodialysis, on continuous ambulatory peritoneal dialysis, or at the predialysis stage). In addition, some studies (Lin *et al.*, 1997; Ko *et al.*, 1998; Lee *et al.*, 2000) have investigated gastric myoelectrical activity in patients with CRF.

We have previously demonstrated (Hirako *et al.*, 2005) that the patients with predialysis end-stage renal disease showed a high prevalence of GI symptoms and gastric hypomotility, including impaired gastric myoelectrical activity and delayed gastric emptying, and that gastric hypomotility appears to be an important factor in the generation of GI symptoms. However, it is not clear whether impaired gastric motor function would improve after hemodialytic treatment.

In this study, to elucidate the effect of treatment on gastric motility in chronic hemodialysis patients, we simultaneously measured gastric myoelectrical activity by cutaneously recorded electrogastrography (EGG), and gastric emptying using the ^{13}C-acetic acid breath test. We then examined the relationship between these parameters of gastric motility and GI symptoms.

Subjects and methods

Subjects

The study was performed in 19 patients with CRF who were undergoing maintenance hemodialysis for more than six months. The control group comprised 12 asymptomatic, age- and sex-matched healthy volunteers with no history of GI or renal disease. Table 1 shows the characteristics of the subjects (Table 1). Written informed consent was obtained from all subjects prior to the study, in accordance with the Declaration of Helsinki (1977).

Table 1. Clinical Characteristics of Subjects

	Controls (n=12)	CRF Patients (n=19)	
Age (year)	54.8 ± 4.9	61.2 ± 3.3	
Sex (M/F)	8 / 4	13 / 6	
Etiology of Renal Disease		Diabetes Mellitus	7
		Chronic Nephritis	3
		RPGN	2
		IgA nephropathy	1
		Nephrosclerosis	1
		Polycystic disease	1
		Unknown	4

Values are mean ± SEM. CRF, Chronic Renal Failure; RPGN, Rapidly Progressive Glomerulonephritis.

Experimental procedure

Gastric motility was evaluated by cutaneously recorded EGG and by measurement of gastric emptying using the ^{13}C-acetic acid breath test. After fasting for at least 6 hr, the EGG was recorded for 60 min in the supine position. The subjects then ingested 100 mg of ^{13}C-acetic acid in the sitting position, mixed with a semi-solid test meal (Jerry Ace; 200 ml of jerry, containing 4.4 g of protein, 0.4 g of fat, 42.0 g of carbohydrate, and an energy content of 190 kcal; House Foods, Osaka, Japan). Immediately after consuming the test meal, the subjects returned to the supine position and EGG recording was continued for another 60 min.

Recording and analysis of EGG

The methodology has been previously published elsewhere (Hirako *et al.*, 2005). In brief, the EGG was measured using a portable EGG recorder (Digitrapper EGG; Synectics Medical, Stockholm, Sweden). Bipolar Ag-AgCl electrodes were placed on the right and left midclavicular lines along the long axis of the stomach over the surface of the upper abdomen. The obtained EGG data were digitalized by an analog-to-digital converter installed on the recorder and downloaded to a personal computer (Deskpower TIX 507; Fujitsu, Tokyo, Japan).

The following parameters were calculated using fast Fourier transformation and evaluated for each subject.

1. Percentage of normogastria: defined as the percentage of time during which normal 2–4 cycle per minute (cpm) slow waves were present over the entire observation period. This parameter reflects the regularity of the gastric myoelectrical activity.
2. Power ratio: defined as the ratio of the EGG dominant power values between after and before meal intake (*i.e.*, postprandial power/fasting power), where the dominant power refer to the power at the EGG dominant frequency. Since the absolute values of power are influenced by many factors (thickness of abdominal wall, distance between electrodes and the wall of the stomach, variable shape of the stomach and electrode-skin resistance, etc), EGG power can be evaluated only as relative changes. Changes in the EGG dominant power appear to reflect gastric contractility (Smout *et al.*, 1980; Hamilton *et al.*, 1986; Chen *et al.*, 1994; Sun *et al.*, 1995).

On the basis of control values, an abnormal EGG was defined as more than 2SD out with the mean at least one of any parameters either before or after the test meal.

Measurement of gastric emptying

Breath samples were collected in polyethylene storage bags before the test meal as a baseline, then at 15-min intervals during the first hour after the test meal, followed by samples taken every 30 min during the remaining 3 hr. The amount of ^{13}C in the breath storage bags was measured by infrared isotope spectrometry (UBiT-IR300; Otsuka Electronics, Osaka, Japan). Half-emptying time ($T_{1/2}$) and lag time (T_{lag}) were calculated as described by Ghoos *et al.* (1993): $y = m\,(1-e^{-kt})\beta$, where y is the percentage of cumulative ^{13}C excreted in breath; t is the time in hours; and m, k, and β are constants, m being the total cumulative ^{13}C recovery when time is infinite. The time parameters are defined as follows: $T_{1/2} = (-1/k) \times \ln\,(1-2^{-1/\beta})$ and $T_{lag} = (\ln\beta/k)$. $T_{1/2}$ is defined as the area under the fitted curve until half of the dose of the cumulative

^{13}C excretion has been excreted when time is infinite, and T_{lag} is the time corresponding to the maximum ^{13}C excretion of the fitted curve. These two parameters were used to assess the degree of gastric emptying. The criterion for delayed emptying was an either $T_{1/2} > 2.5$ hr or $T_{lag} > 1.6$ hr, greater than the 95th percentile of these parameters in 12 healthy subjects.

Assessment of GI symptoms

All patients completed a self-administrated questionnaire including seven symptoms (anorexia, nausea, heartburn, abdominal pain, bloating, diarrhea and constipation) to assess subjective GI symptoms. The severity of each of these symptoms was scored as absent (0), mild (1), moderate (2) or severe (3). In this study, four symptoms (anorexia, nausea, abdominal pain and bloating) that may be related to gastric motility were assessed. These symptom scores were summed in each patient, giving a total score ranging from 0 to 12.

Statistical analysis

Values of EGG and ^{13}C-acetic acid breath test parameters are expressed as mean ± SEM. Student's *t* test (paired or unpaired) was used as appropriate. GI symptom scores were presented as median (range) and evaluated by the Mann-Whitney test. The relationship between GI symptom scores and gastric motility parameters were analyzed by correlation and linear regression. A *P* value of less than 5% ($P<0.05$) was considered statistically significant.

Results

Electrogastrography and gastric emptying

The percentage of normal 2- to 4-cpm slow waves in CRF patients was significantly lower than that in healthy controls during the fasting state; however, no significant difference was observed between these two groups of subjects in EGG normogastria after the test meal (Fig. 1). The mean power ratio in the EGG in CRF patients was 2.3 ± 0.6 in patients, and 2.6 ± 0.2 in controls (not significant, Fig. 2). There were no significant differences in either $T_{1/2}$ and T_{lag} between CRF patients and healthy controls, indicating that gastric emptying was not delayed in the former (Fig. 3). Neither the percentage of EGG nor gastric emptying showed statistically significant differences between diabetic and nondiabetic patients (Table 2). Eight patients (42.1%) showed abnormalities of either gastric myoelectrical activity or gastric emptying.

We separated the patients into the following two subgroups according to the results of gastric motility:

Group A, with normal EGG and normal gastric emptying (11 patients).

Group B, with abnormal EGG and/or delayed gastric emptying (8 patients).

GI symptoms

Six patients (31.6%) had no symptoms, and 11 (57.9%) had slight GI symptoms with a total symptom score of less than 5. Only 2 (10.5%) demonstrated a score of more than 5. The 7 patients with diabetes presented a median score of 2 (range, 0–7), and the median score was 1 (range, 0–5) for the 12 patients without diabetes. No significant difference in symptom score

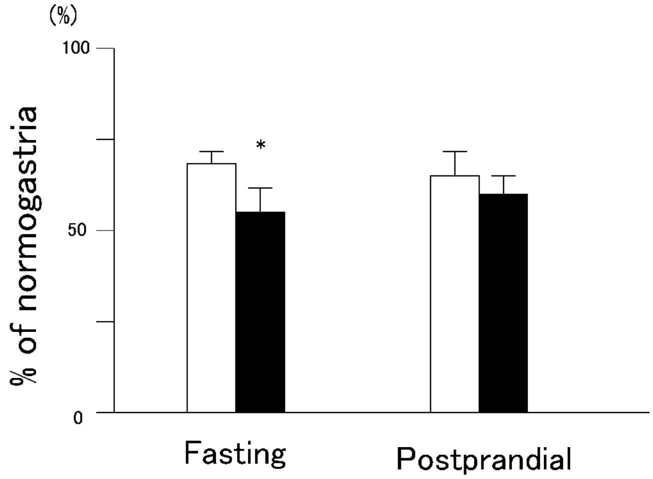

Fig. 1. Percentage of normogastria in Electrogastrogram for control subjects (open bars) and patients with chronic renal failure (CRF; solid bars). Data values are presented as mean ± SEM. CRF, chronic renal failure; *, P<0.05 *vs.* control (Control, n=12; CRF, n=19).

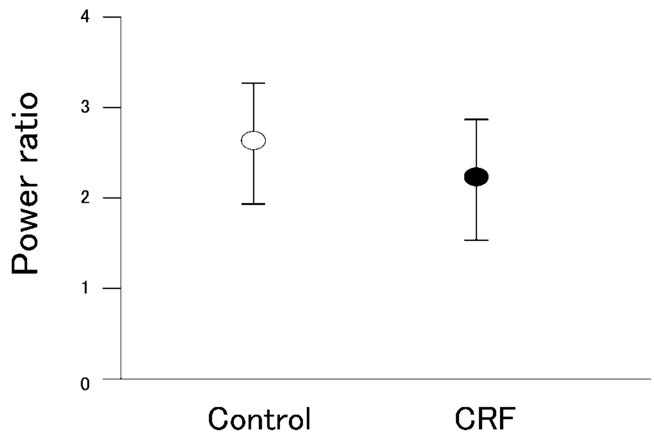

Fig. 2. Power ratio in Electrogastrogram for control subjects (open circle) and patients with chronic renal failure (CRF; solid circle). Data values are presented as mean ± SEM. CRF, chronic renal failure (Control, n=12; CRF, n=19).

was observed between diabetic and nondiabetic patients (Table 2).

The 11 patients with normal gastric motility showed a median score of 1 (range, 0–5), and the median score was 1 (range, 0–7) for 8 patients in Group B. There was no difference in symptom score between Group A and Group B. The total symptom score was positively correlated with the $T_{1/2}$ in the ^{13}C-acetic acid breath test (P<0.05, Fig. 4). There was no significant correlation between these symptom scores and the EGG values.

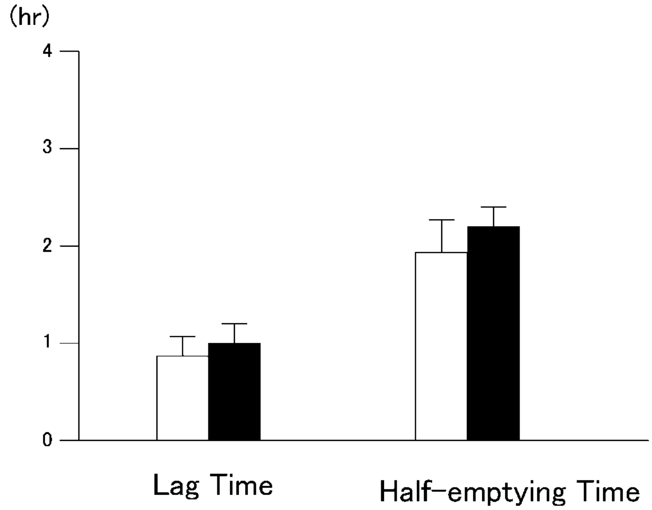

Fig. 3. Gastric emptying, expressed as lag time and half-emptying time, in ^{13}C-acetic acid breath test for control subjects (open bars) and patients with chronic renal failure (CRF; solid bars). Data values are presented as mean ± SEM. CRF, chronic renal failure (Control, n=12; CRF, n=19).

Table 2. Gastric Motility Parameters in Patients with CRF

	DM Patients (n=7)	Non-DM Patients (n=12)
Fasting EGG		
Normogastria (%)	61.1 ± 7.3	53.7 ± 9.9
Postprandial EGG		
Normogastria (%)	63.2 ± 6.2	65.6 ± 6.2
EGG Power Ratio	1.6 ± 0.3	2.0 ± 0.9
Gastric emptying		
Lag Time (hr)	0.92 ± 0.18	0.94 ± 0.15
Half-Emptying Time (hr)	2.02 ± 0.22	1.96 ± 0.18

Values are mean ± SEM. CRF, Chronic Renal Failure; DM, Diabetes Mellitus; EGG, Electrogastrogram.

Discussion

The findings of this study were as follows, (1) Compared with healthy controls, patients with CRF on hemodialysis revealed no significant differences in EGG parameters, with the exception of a lower percentage of normogastria during fasting state, (2) Patients with CRF did not show delayed gastric emptying, (3) Seventeen patients with CRF had no or slight GI symptoms, (4) Eleven patients had normal gastric motility and a significant correlation was observed only between GI symptom scores and $T_{1/2}$ values in the ^{13}C-acetic acid breath test, (5) There was no significant difference in gastric motility between patients with and without diabetes.

The most interesting finding of this study is that patients with CRF who were undergoing

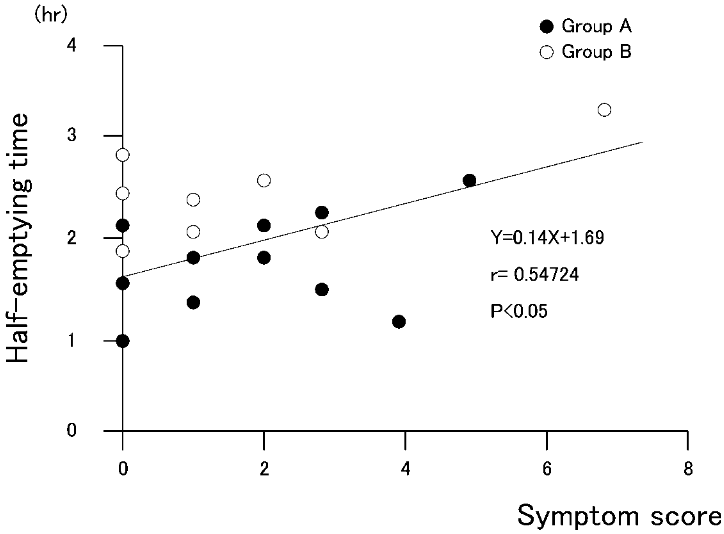

Fig. 4. Correlation between the total gastrointestinal symptom score and the half-emptying time in ^{13}C-acetic acid breath test in patients with CRF. CRF, chronic renal failure (Group A, solid circle, n=11; Group B, open circle, n=8). Group A, with normal EGG and normal gastric emptying. Group B, with abnormal EGG and/or delayed gastric emptying.

hemodialysis showed no significant differences in EGG parameters and gastric emptying compared with healthy controls, with the exception of a lower percentage of normogastria before the meal. Only a few studies (Lin *et al.*, 1997; Ko *et al.*, 1998; Lee *et al.*, 2000) have investigated gastric myoelectrical activity in patients with CRF. On the other hand, several studies evaluating gastric emptying in patients with CRF have yielded conflicting results; in some of these (Brown-cartwright *et al.*, 1988; Dumitrascu *et al.*, 1995; Kao *et al.*, 1996; Van Vlem *et al.*, 2001; Hubalewska *et al.*, 2004) gastric emptying was found to be delayed, while in others (Wright *et al.*, 1984; McNamee *et al.*, 1985; Soffer *et al.*, 1987) it remained unchanged. In most of these studies, it is not clear whether the patients were receiving dialysis. One reason for the discrepancies among these findings may be the differences in the patients' conditions (*i.e.*, on hemodialysis, on continuous ambulatory peritoneal dialysis, or at the predialytic stage).

The results of our present study show that hemodialytic treatment may improve impaired gastric motility in patient with CRF. We have previously reported (Hirako *et al.*, 2005) that patients with predialysis end-stage renal disease with severe uremia showed a significanty lower percentage of normogastria in the postprandial states and a lower power ratio in EGGs with delayed gastric emptying compared with healthy controls. In this study, we measured gastric motility in CRF patients undergoing hemodialysis for more than six months to evaluate the effect of maintenance dialysis, and we found no differences in the parameters of gastric motility between these patients and healthy controls. Gastric hypomotility including impaired gastric myoelectrical activity and delayed gastric emptying in CRF patients may be reversible and restorable after the hemodialysis.

Various factors affect gastric motility in patients with CRF. Among these may be the increased levels of some GI hormones (Taylor *et al.*, 1980; Wesdorp *et al.*, 1981; Sirinek *et al.*, 1984), several kinds of uremic toxin retention (Jones *et al.*, 1969; Nakamura *et al.*, 1990; De-Deyn *et al.*, 1995; Anderstam *et al.*, 1996), and a number of cytokines (Herbelin *et al.*, 1991; Brockhaus *et al.*, 1992; Kimmel *et al.*, 1998; king *et al.*, 1998) that appear in CRF patients. Some kinds of uremic toxin that can induce GI symptoms such as anorexia and bloating is excluded after the hemodialysis. Furthermore, hemodialytic treatment improves disturbance in the balance of electrolytes and metabolic acidosis, which may affect the autonomic nervous system (Heidbreder *et al.*, 1985; Jassal *et al.*, 1998). These factors may contribute to the improvement of impaired gastric motility in patients with CRF who are receiving hemodialysis.

In the present study, there was a significant correlation between GI symptom scores and the gastric emptying value. Our previous study showed that predialytic end stage CRF patients with both abnormal gastric myoelectrical activity and delayed gastric emptying had a significantly higher prevalence of GI symptoms than other patients. Several studies (Jian *et al.*, 1989; Kerlin *et al.*, 1989; Geldof *et al.*, 1986; Stanghellini *et al.*, 1996; Quartero *et al.*, 1998; Tack *et al.*, 1998) have addressed the role of gastric motility in generating dyspeptic symptom in some proportion of patients with functional dyspepsia (FD). Two large studies (Perri *et al.*, 1998; Sarnelli *et al.*, 2003) demonstrated that patients with delayed gastric emptying for solids are more likely to report postprandial bloating, nausea and epigastric pain. One report (Van Vlem *et al.*, 2000) showing that there was a significant difference in gastric emptying between dyspeptic and nondyspeptic hemodialysis patients has been published. These data support our results.

Our results suggest that in CRF patients with impaired gastric motility, restoring gastric motility is likely to improve GI symptoms. In this study, most CRF patients on hemodialysis had no or slight GI symptom, and more than half of these patients had normal gastric motility. GI symptoms associated with disturbed gastric motility reported by patients with CRF may substantially improve by treatment with hemodialysis. On the other hand, Strid *et al.* (2003) showed that delayed gastric emptying was more common in peritoneal dialysis patients than in predialysis patients, and they observed no correlation between gastric emptying and GI symptoms. Our findings associated with the gastric emptying differ from these results for unknown reasons, which may include the differences in the dialysis methods (*i.e.*, hemodialysis or peritoneal dialysis). In the case of peritoneal dialysis, gastric motility may be affected by dialysis fluid in the peritoneal cavity.

We did not find a significant difference in gastric motility and GI symptoms between CRF patients with and without diabetes, similar to the findings in our previous study. In general, diabetic CRF patients have severe autonomic nervous system dysfunction. Dumitrascu *et al.* (1995) reported that CRF patients with parasympathetic plus sympathetic autonomic neuropathy had a greater delay in gastric emptying than those with no autonomic neuropathy. Unfortunately, we did not assess the severity of neuropathy, which may be related to gastric smooth muscle contractility, in CRF patients. In addition, the number of diabetic CRF patients included in our study may be too small to allow a definitive evaluation.

In summary, more than half of the patients with CRF who were on hemodialysis demonstrated normal gastric motility, and most of CRF patients had either no GI symptoms or only slight ones. This indicates that hemodialytic treatment might improve impaired gastric motility and reduce GI symptoms in patients with CRF.

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