Gastric Emptying of Solids but Not Liquids Is Decreased in Rats with Chronic Renal Failure

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Severe gastric complications occur in uremic patients, yet few studies have addressed the effect of chronic renal failure (RF) on gastric physiology. In the present study, we investigated: (1) the effect of RF on gastric emptying of liquids and solids in awake rats, (2) the motor function in the gastric corpus, and (3) the role of nitric oxide in any alterations in gastric motor function in uremic rats. RF was induced by partial kidney infarction. RF had no effect on gastric emptying of liquids but significantly inhibited gastric emptying of solids by 68%. N-Nitro-L-arginine, an inhibitor of nitric oxide (NO) synthesis, had no effect on the reduced gastric emptying of solids in RF rats. RF rats showed an altered pattern of gastric motility compared to sham-operated rats. These data suggest that RF induced an inhibition of gastric emptying of solids, but not liquids. However, NO does not seem to play a role in this inhibition.

KEY WORDS: renal failure; nitric oxide; gastric motility; L-NAME; uremia.

Alterations in gastric function occur in uremic patients (1), yet few studies have addressed the mechanisms of chronic renal failure (RF) on gastric physiology. Nausea and emesis is common in patients with chronic renal failure (1), and a delay in gastric emptying has been suggested to be responsible for these symptoms (2). Delayed gastric emptying has been reported in uremic patients (3, 4), yet there is no systematic study on gastric emptying in patients or in animal models of chronic renal failure.

In a model of RF in rats that mimics chronic renal disease in many respects, we have found that there is an increased susceptibility to gastric mucosal lesions and gastric hyperemia (5, 6). This increased gastric mucosal blood flow is dependent on nitric oxide (NO) synthesis since gastric mucosal blood flow decreases to normal levels after administration of Nω-nitro-L-arginine methyl ester (5). Nitric oxide has recently been shown to be a nonadrenergic noncholinergic (NANC) inhibitory neurotransmitter of smooth muscle in the gastrointestinal tract (7). Evidence for such a role was largely based on inhibition of relaxation in response to various stimuli by use of specific inhibitors of NO synthesis. For example, receptive relaxation, the ability of the stomach to reflexly relax with increases in volume, is mediated by NANC nerves; this reflex is blocked...
by L-NMMA (N\textsuperscript{G}-monomethyl-L-arginine) and reversed by the precursor for NO, L-arginine, in the isolated guinea pig stomach (8). In strips of rat gastric muscle, L-NNA increased basal tension, suggesting that tonic release of NO may regulate tone in the proximal stomach (9). Thus, if there is an increased production of NO in chronic renal failure (5), this may alter gastric motor function.

In the present study, we examined the effects of renal failure on gastric motor function in a well established model in rats (10). We assessed the rate of gastric emptying of liquids and solids in awake rats and examined the pattern of motility of the proximal stomach in urethane-anesthetized rats. We also investigated a role for nitric oxide in the alterations of function that we observed.

MATERIALS AND METHODS

Animal Preparation. Male Sprague-Dawley rats weighing 200–300 g were used in this study. Since RF rats gain weight more slowly than sham-operated rats, the initial weight for sham-operated rats was 207 ± 10 g and for renal failure rats was 280 ± 21 g. The surgical procedures for chronic renal failure have been described previously (10). Rats were anesthetized with pentobarbitone (50 mg/kg intraperitoneally). The animals underwent a two-stage flank incision. Renal insufficiency was induced by ligation of two or three extrarenal branches of the main left renal artery. This procedure was followed one week later by contralateral nephrectomy. Sham-operated rats underwent flank incision and manipulation of kidneys. Rats were allowed to recover for four weeks on standard laboratory rat chow and water ad libitum and housed under conditions of controlled light (6 AM to 6 PM) and temperature (20 ± 2 °C). Rats were fasted for 24 hr but allowed free access to water before experiments.

Renal failure was assessed by measuring serum creatinine four weeks after surgery.

Drugs. N\textsuperscript{W}-nitro-L-arginine methyl ester (L-NAME) was obtained from Sigma (St. Louis, Missouri) and dissolved in physiological saline.

Measurement of Gastric Emptying of Solids. This method has been described elsewhere (11). Briefly, at 7:00 AM fasted rats were fed rat chow ad libitum for 3 hr. The food was removed and the rats were euthanized after 5 hr. The gastric contents and the stomachs were weighed.

In addition, the amount of food eaten in RF rats (N = 6) and sham-operated rats (N = 7) was measured by weighing the food before feeding and the food and spill at the end of the three hour feeding period.

Measurement of Gastric Emptying of Liquids. Gastric emptying was measured as described previously (12). Briefly, the emptying of 1.5 ml of a 1.5% solution of methylcellulose in distilled water containing phenol red (60 mg/100 ml) was measured 20 min after its oral administration. Animals were euthanized by CO\textsubscript{2} inhalation, and the stomach was clamped at the pylorus and cardio, removed, and homogenized in 100 ml of 0.1 N NaOH. Proteins in 5 ml of homogenate were precipitated with 0.5 ml of trichloroacetic acid (20% w/v) and centrifuged. The supernatant was added to 5 ml of NaOH and the concentration of phenol red measured by spectrophotometry at an absorbance wavelength of 560 nm. Phenol red recovered from stomachs of rats euthanized immediately after administration of the methylcellulose solution served as the standard. Gastric emptying was calculated according to the following formula: gastric emptying % = (1 – concentration of phenol red recovered from test stomach/ concentration of phenol red recovered from standard stomach) x 100.

Measurement of Proximal Gastric Motility. Rats were anesthetized with urethane (1.25 g/kg intraperitoneally). Cannulae were placed in the exterior jugular vein for the administration of drugs and into the femoral artery for measurement of arterial blood pressure. Intraluminal pressure in the gastric corpus was measured manometrically using a fluid-filled catheter placed into the corpus via the forestomach (13). The pylorus was occluded. After 60 min, the stomach was placed under 4–5 cm H\textsubscript{2}O pressure to ensure a consistent baseline intraluminal pressure. Intraluminal pressure was measured via Gould Statham P23D pressure transducers and displayed on a chart recorder.

Gastric Emptying of Solids. At the time of food removal, rats (control, N = 14; sham operated, N = 13; renal failure, N = 13) were anesthetized with enflurane. Either saline or L-NAME (3 mg/kg) was administered intravenously. Rats were maintained under general anesthesia for 5 min after which they were returned to home cages for 5 hr.

Gastric Emptying of Liquids. In control (N = 6), sham-operated (N = 6), and RF (N = 6) rats, methylcellulose solution was administered orally by gavage. At the end of the 5-hr period of gastric emptying, two groups of rats (sham and RF; N = 7 in each group) were anesthetized with pentobarbitone (50 mg/kg intraperitoneally) to measure arterial blood pressure. A midline incision was made and the pylorus clamped so that no further emptying of gastric contents could occur. A catheter (PE 50) was placed in the carotid artery and blood pressure measured for 5–10 min.

Gastric Motility Studies: After at least a 30- to 40-min basal period, L-NAME was given intravenously (3 mg/kg). Data was analyzed for five 1-min periods immediately before and 10 min after administration of L-NAME.

Statistical Analysis. The results are expressed as mean ± SEM. Comparison of the mean values was carried out by factorial ANOVA. Statistical probabilities after ANOVA were calculated by multiples comparisons using the Fisher test. Differences were considered significant if P < 0.05.

RESULTS

Serum creatinine was significantly increased in rats with renal insufficiency (0.3 ± 0.2 mg/dl vs 1.8 ± 0.2 mg/dl; P < 0.001; N = 8 and 7, sham and RF rats, respectively).