

# Metabolic Acidosis and Respiratory Acidosis Impair Gastro-Pyloric Motility in Anesthetized Pigs

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Acidosis impairs smooth muscle function in various organs. However, the effects of acidosis on the gastroduodenal tract are unknown while its dysfunction has potential perioperative harmful consequences. We investigated the effects of metabolic (MA) and respiratory acidosis (RA) on upper gut motility in tracheally ventilated pigs whose anesthesia was induced with halothane and maintained with  $\alpha$ -chloralose-urethane administration (IV). Increased dead space and perfusion of hydrochloric acid 1 N (150 mL over 30 min) were used to induce RA and MA, respectively. Measurements of fundic tone using an electronic barostat, antro-pyloroduodenal phasic motility with perfused manometry and antro-duodenal electric control activity by electromyography were used to evaluate gastroduodenal function. Acidosis increased the fundic tone

as reflected by a decrease in barostat volumes from  $275 \pm 83$  to  $194 \pm 88$  mL for MA and from  $278 \pm 93$  to  $236 \pm 106$  mL for RA. Pyloric and duodenal basal tones were not affected by either acidosis. A decrease in pyloric contraction amplitude from  $95 \pm 24$  to  $62 \pm 26$  mm Hg during MA and from  $94 \pm 26$  to  $64 \pm 20$  mm Hg during RA was observed. Both acidosis altered antral control activity that became dysrhythmic. Acidosis could be implicated in perioperative complications, such as gastroparesis, emesis, and regurgitation of gastric contents. **Implications:** Metabolic and respiratory acidosis mainly affects gastric antral rhythms and has a major effect on fundic tone. Acidosis could be implicated in perioperative complications, such as gastroparesis, emesis, and regurgitation of gastric contents.

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**A**cute gastroduodenal motor dysfunction resulting in gastric stasis could contribute to perioperative morbidity and complications. The resultant gastric distension could enhance nausea and vomiting induced by anesthetics and could lead to regurgitation with an increased risk of pulmonary aspiration (1).

A number of factors could affect upper gastrointestinal motor activity in the perioperative period. Drugs, such as thiopental, opioids, muscle relaxants, and benzodiazepines, reduce lower esophageal sphincter function, and volatile anesthetics and morphine reduce gastric and small intestinal motility (2,3). Metabolic changes are also likely to cause dysmotility but, with the exception of hyperglycemia, there is limited information about the effects of these on gastrointestinal motor activity (4).

Acidosis occurs commonly during surgery as a result of respiratory compromise and in patients with

reduced tissue perfusion. *In vitro* studies have shown that acidosis depresses myoelectric and contractile activity in gastric and esophageal smooth muscle, but the *in vivo* effects are largely unknown in animals and humans (5).

We examined the effects of acidosis on the electrical and mechanical activity of the stomach and duodenum using an animal model. In addition, we assessed whether the mechanism responsible for producing acidosis, i.e., respiratory or metabolic, influenced motor activity and gastric volume.

## Method

The study was approved by the animal care committee of the University of Lyon. Studies were performed in five White pigs weighing  $41 \pm 3$  kg. The animal preparation and anesthesia have been previously described and take approximately 2 h in each animal (6,7). Briefly, after a 12-h fast, ketamine 7 mg/kg was given IM as premedication. Suppression of the pharyngotracheal reflex was obtained by the administration of 5% halothane via a face mask immediately

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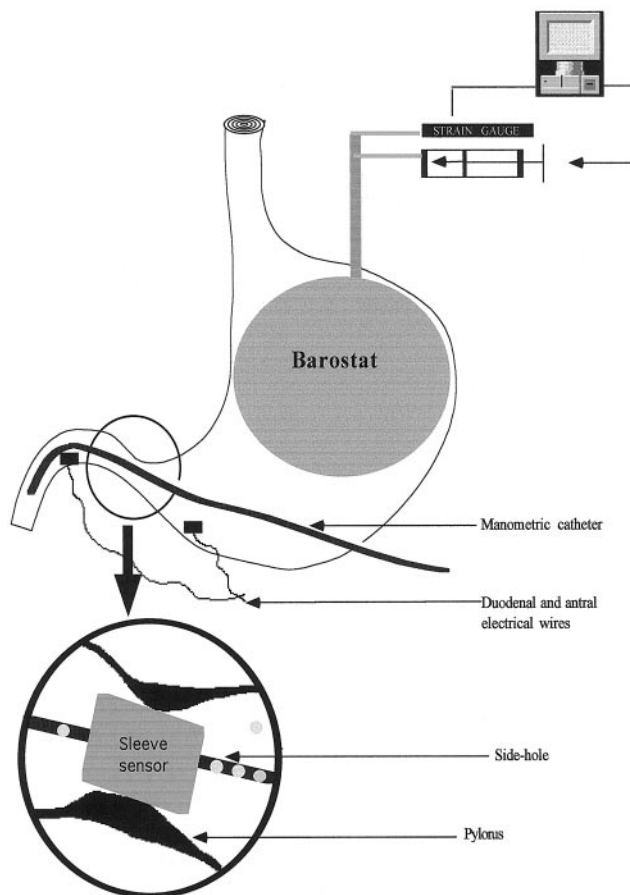
before tracheal intubation. After intubation, no further halothane was administered. Artificial respiration was provided with a mechanical ventilator set to a tidal volume of 15 mL/kg at a respiratory rate of 15–18 breaths/min. Ventilation was adjusted to obtain normocapnia at baseline, the fractional inspired concentration of oxygen was set at 0.60.

A surgical level of anesthesia (absent eye lid reflex, no change in blood pressure or heart rate in response to painful stimuli) was maintained by a 10-mL injection of a mixture of  $\alpha$ -chloralose (60 mg/kg) and urethane (500 mg/kg) every 2 h at rate of 4 mL/min via a venous cannula inserted into the marginal vein of the ear.

Rectal temperature was continuously monitored and maintained at  $38.5 \pm 0.5^\circ\text{C}$  by a heating element placed below the animal. The right carotid artery was cannulated for sampling of arterial blood.  $\text{SpO}_2$  was continuously monitored throughout the study by using an oxymeter (Ohmeda 3700, Louisville, CO) attached to the animal's tail.

After a 60-min recovery period following surgery and instrumentation, baseline pressures and electrical activity were measured for 30 min. The dead space of the respirator was then increased for 30 min (100 mL of dead space added at the Y-piece) to produce a stable respiratory acidosis (RA). Data were then collected for 45 min, after which time there was a 30-min recovery period (during which blood gas values and gastroduodenal manometric measurements returned to baseline). A metabolic acidosis (MA) was then induced by IV infusion of 150 mL hydrochloric acid (HCl) in 500 mL saline (1 N) over 30 min and data collected for a further 45 min before the animals were killed by using IV thiopental. Repeated arterial blood pH,  $\text{PaO}_2$ , and  $\text{PaCO}_2$  analyses (corrected for body temperature) (each 5 min) were performed during each phase of the study using an ABL TM 5 blood gas analyzer (Radiometer, Copenhagen, Denmark).

*Antro-pyloroduodenal manometry.* Access to the abdominal cavity was obtained via a midline incision. A four-multi-lumen manometric assembly (3.5-mm diameter, each lumen connected to a pressure transducer) incorporating three side holes and a 4-cm sleeve sensor was introduced into the stomach through a 1-cm incision. The catheter was positioned so that one side hole was located in the distal and another in the terminal antrum, 5 cm and 2 cm proximal to the sleeve respectively (6,7). The sleeve was placed across the pylorus using the pyloric artery as an external marker. A further sidehole was positioned in the duodenal bulb 5 mm distal to the sleeve. When the manometric assembly was correctly placed, its proximal and distal ends were fastened by sutures to prevent loss of position. (Fig. 1).



**Figure 1.** Apparatus used in anesthetized pigs to test the effect of acidosis on gastroduodenal motility.

Side holes were perfused with degassed distilled water using a low-compliance pneumohydraulic pump (IP 8000, Gould, Ballanvillier, France) at a flow rate of 0.3 mL/min. The sleeve channel was perfused at 0.5 mL/min (7). Pressures were recorded. Sudden occlusion of each orifice of the catheter resulted in a pressure increase rate in excess of 400 mm Hg/s. All pressures were measured with the pigs supine and with transducer zero set to the midchest position.

*Proximal gastric motility.* A gastric barostat (Synetics, Stockholm, Sweden) was introduced through a small incision of the lateral side of the stomach (Fig. 1). This barostat was based on that developed by Aspiroz and Malagelada (8). This device measures the fundic tone. The barostat consists of an air injection-aspiration system and an electronic feedback mechanism that keeps the pressure in the system constant. The system was designed to measure the volume of air within an intragastric polyethylene bag maintained at a preselected pressure of 4 mm Hg, a value which does not affect gastric motility (8). The barostat was connected with a single-lumen catheter (14F) to a polyethylene

bag (capacity of 500 mL). The system was checked to ensure there were no leaks before recording.

**Electrical recordings.** Six NiCr electrodes (120  $\mu\text{m}$  diameter, Microfil Industries SA, Lausanne, Switzerland), arranged in two groups of three, were implanted into the antral and duodenal muscular layers as described previously (9) (Fig. 1). The electrode lead wires together with the connectors for the manometric catheter and the barostat were brought out through the abdominal incision and the wound was closed.

**Signal acquisition.** Pressure data were acquired onto a microcomputer using a propose-built system based on Labview 2.0 (National Instruments, Austin, TX). After low-pass filtration (10 Hz), pressures were digitized at 15 Hz on a microcomputer by using an analog to digital converter card (NB MIO 16, National Instruments) and recorded onto the computer disk for later analysis. Barostat volumes were displayed by using commercial software Acqknowledge 2 (Biopac Systems, Santa Barbara, CA). Myoelectric potentials (100–500  $\mu\text{V}$ ) were amplified, filtered, and stored for later analysis (Fig. 1).

Automated analysis of antral, pyloric, and duodenal bulb pressures was performed by using a computerised software package (MAD Synetics, Stockholm, Sweden) to determine the amplitude of all pressure waves. Only pressure waves with an amplitude greater than 10 mm Hg were analyzed, to avoid confusion with respiratory artifacts. Basal antral, pyloric, and duodenal bulb pressures were also determined automatically by the software as the mean of all the data points between two pressures waves. Barostat data were analyzed manually.

All data were presented as mean  $\pm$  SD. Data analysis was performed by using commercially available software (Statistica 5.0; Stasoft Inc, Tulsa, OK). Statistical significance was tested by using a repeated measures analysis of variance. Before analysis, the normality of the data was determined by a  $\chi^2$  test. The correlation between blood gas values and motor events was determined by using Fischer' exact test. A  $P$  value  $<$  0.05 was accepted as significant in all analyses.

## Results

Respiratory dead space induced a significant decrease in pH (from  $7.43 \pm 0.03$  at baseline to  $7.25 \pm 0.03$ ;  $P <$  0.02) and an increase in  $\text{Paco}_2$  values (from  $37.1 \pm 4.5$  mm Hg at baseline to  $61.2 \pm 6.8$  mm Hg;  $P <$  0.02). Before the metabolic challenge, arterial blood gas tensions and pH returned to within normal range and were not different from their initial values. The acid infusion induced a significant decrease of pH from  $7.41 \pm 0.03$  to  $7.25 \pm 0.03$  ( $P <$  0.02) without significant change for  $\text{Paco}_2$  values (from  $39.7 \pm 3.8$  mm Hg at

baseline to  $44.4 \pm 1.3$  mm Hg during acid infusion). Throughout the whole study,  $\text{Spo}_2$  remained above 0.98 and  $\text{Pao}_2$  was always above 150 mm Hg.

Fundic tones recorded before each set of acidoses were not statistically different (Fig. 2). MA and RA decreased the volume of the barostat, i.e., increased the fundic tone (Fig. 3). The decrease occurred within the first 5 min of acid infusion, a time in which the mean value for arterial blood pH was  $7.31 \pm 0.01$ . The decrease in fundic tone was negatively correlated with the decrease in pH ( $r = 0.63$ ;  $P <$  0.05). MA and RA did not alter pyloric tone with minimal and maximal values, respectively, ranged from 8.31 to 28.3 mm Hg throughout the whole protocol.

Amplitude of pyloric contractions decreased significantly during MA and RA (Table 1) ( $P <$  0.05). These changes were not correlated with changes in arterial blood pH values ( $P <$  0.05,  $r = 0.35$ ). The frequency and duration of pyloric pressure waves were not affected by RA and MA (Table 1). During the course of the whole experimental protocol, the basal tone, the amplitude, and propagation of duodenal pressure waves were not affected by the changes in acid status.

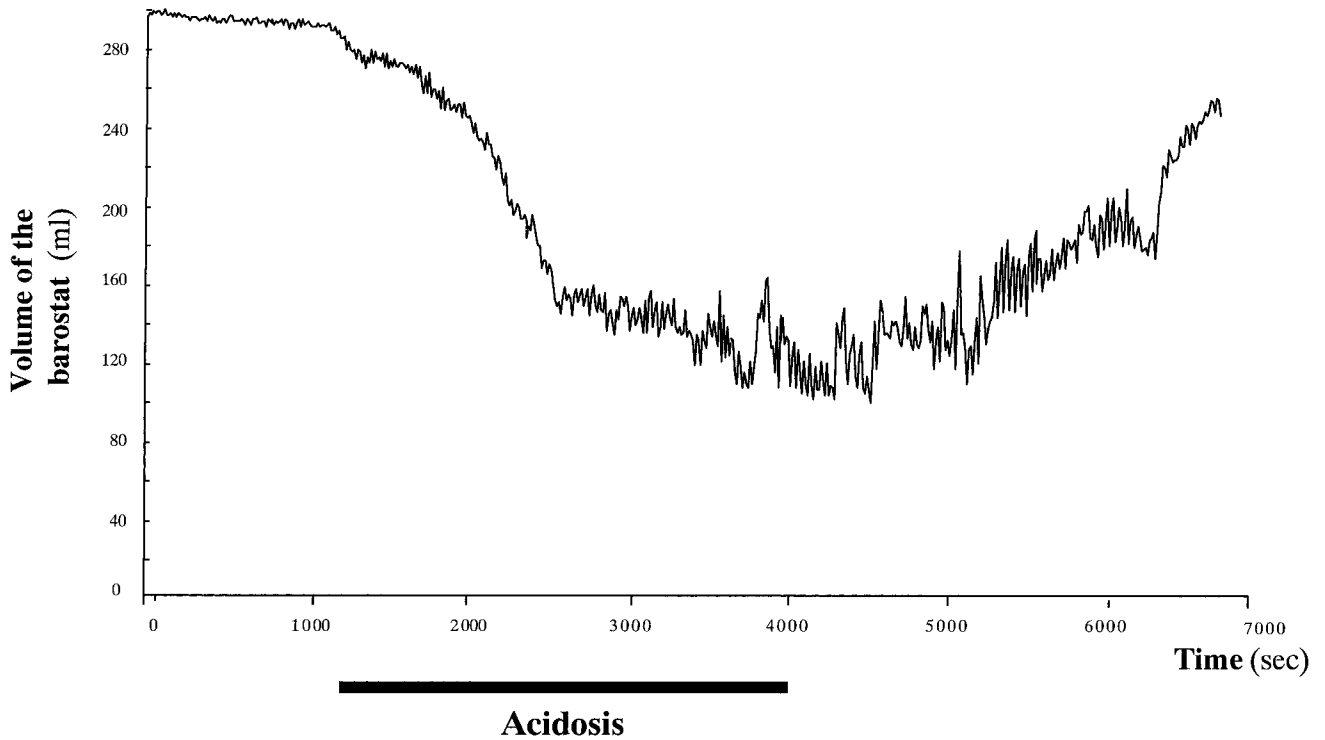
Both MA and RA altered antral electrical activity in all the cases. Dysrhythmic episodes appeared at the end of the acid infusion: the interval between slow-waves began irregular and silences longer than 180 s, followed by slow-wave bursts that were observed after acidosis (Fig. 4).

In contrast, the duodenal region elicited few dysrhythmic episodes during acidosis.

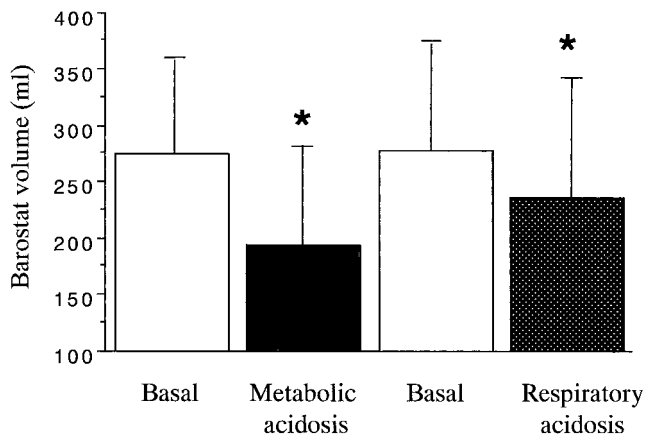
## Discussion

This is the first study to assess the effect of arterial blood pH and  $\text{Paco}_2$  on gastroduodenal motility. We found that MA and RA increase fundic tone, alter pyloric contractions, and antral control activity that become arrhythmic. There are no differences between MA and RA for all the data analyzed, suggesting that the pH value is the most important factor involved in the gastrointestinal motility variations induced by acidosis.

The predominant motor activity of the fundus is the accommodation of ingested materials. The gastric barostat we used maintains a constant pressure level within the air-filled intragastric bag. Hence, the barostat measures gastric tone as isobaric volume variations: any decrease in the volume of barostat reflects an increase in fundic tone. During both MA and RA, an increase in fundic tone was observed, demonstrating that acidosis induces a contraction of fundic smooth muscle. This result confirms a previous *in vitro* study that found an increase in the baseline tension of



**Figure 2.** Typical barostat volume change obtained in one pig during acidosis. The barostat is placed in the fundus. It measures changes in the volume of air necessary to maintain a preselected pressure of 4 mm Hg within the barostat (polyethylene bag, capacity of 500 mL). Thus, any decrease in barostat volume corresponds to an increase in fundic tone.



**Figure 3.** Effect of acidosis on barostat volume. Increased dead space and perfusion of hydrochloric acid 1 N (150 mL over 30 min) were used for respiratory acidosis and metabolic acidosis, respectively. \* $P < 0.05$ .

isolated animal stomach strips exposed to acidosis (5). Smooth cells usually dilate during acidosis, but a constriction has also been described depending on the organ studied. Studies in animals and humans reported both vascular smooth muscle vasodilatation or vasoconstriction in the pulmonary artery (10). Hypocapnia directly contracts airways smooth muscle (11), whereas hypercapnia has no effect on the lower esophageal sphincter (12).

Study design differences (mainly differences in arterial pH,  $Paco_2$  blood range values, and smooth muscles differences) may explain these discrepancies. It is unlikely that the infusion of HCl, instead of lactic acid, to create the acidosis explains our results. Lactic acid is usually the end result of widespread metabolic disorders in clinical situations. However, under low infusion rate conditions, HCl does not produce smooth muscular cells effects unrelated to the circulating arterial blood pH (13).

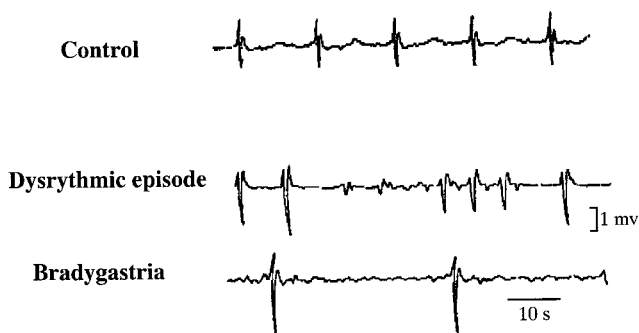
We found that acidosis increases fundic tone without any antropyloric tone change. The differences in functional and electrophysiological properties between these two parts of the stomach may explain these results. Muscle strips from the fundus exposed to a fixed tension undergo a larger elongation than those from the antrum tested under similar conditions. Electrophysiological studies have shown that the fundus can generate this tonic contraction because its membrane potential is above the threshold of contraction (14). These previous studies also showed that the resting potential of fundic smooth cells was lower than that of the antrum ( $-48$  vs  $-71$  mV) (15). Nevertheless, we cannot guarantee that more acidotic conditions or higher  $Paco_2$  than those obtained in our study could not have any effect, particularly on the antroduodenal contractility.

Our study showed that acidosis decreased the amplitude of pyloric contractions. This decrease is another

**Table 1.** Electrical and Mechanical Responses of the Stomach, Antrum, and Duodenum After Metabolic and Respiratory Acidosis in Anesthetized Pigs ( $n = 5$ )

	Metabolic acidosis		Respiratory acidosis	
	Baseline	Acidosis	Baseline	Acidosis
Pyloric contraction amplitude (mm Hg)	95 ± 24	62 ± 26*	94 ± 26	64 ± 20*
Pyloric contraction rate (number/min)	1.7 ± 0.5	2.0 ± 0.8	2.2 ± 0.5	2.0 ± 0.8
Duration of pyloric contraction (ms)	11.3 ± 0.8	10.9 ± 1.7	11.4 ± 0.7	11.6 ± 1.2
Duodenal contraction amplitude (mm Hg)	4.4 ± 4.4	5.9 ± 3.2	5.1 ± 3.7	7.2 ± 1.9
Duodenal contraction rate (number/min)	1.0 ± 1.0	0.6 ± 0.2	1.1 ± 1.1	1.3 ± 0.8
Duration of duodenal contraction (ms)	6.3 ± 3.1	5.2 ± 3.2	6.1 ± 3.6	7.3 ± 2.6
Antral slow waves (time (s) between 2 waves)	22.8 ± 6.7	20.8 ± 6.2	22.7 ± 6.3	18.0 ± 3.5
Duodenal slow waves (Time (s) between 2 waves)	15.0 ± 0.8	15.2 ± 0.5	14.7 ± 0.5	14.2 ± 0.5

Data are mean ± sd.

\*  $P < 0.05$  versus baseline.**Figure 4.** Typical electrical tracings obtained from duodenal and antral electrical wires in one pig during acidosis. The control tracing becomes dysrhythmic and bradygastria appears during acidosis.

known factor leading to retardation of gastric emptying and gastroparesis (16). This result, using an intact organism, confirms Shulze-Delrieu and Lepsien's (5) results; they assessed the effect of acidosis on nerve-muscle strips preparations of opossum stomach and esophagus and found a decrease in amplitude of spontaneous contraction in stomach strips. Although we found no decrease in frequency of spontaneous contractions, the degree of acidosis was lower in our study.

However, we found no significant change in duodenal contraction amplitude, which may reflect a Type II error as a result of the small sample size. Calculation of power for our experiment revealed a power of 0.75, suggesting that there was a Type II error of 0.25 in our study.

Peristaltic contractions in the stomach are coordinated by the gastric slow wave (basic electric rhythm), a wave of depolarization of smooth muscle proceeding from the fundus to the pylorus approximately every 20 s. This wave commands antral peristalsis and plays a major role in the control of gastric emptying. In our study, acidosis induced antral arrhythmia. Gastric dysrhythmias are commonly induced by activation of the emetic reflex in experimental animals as well as in humans (17) and have been found in different disorders characterized by nausea, particularly vomiting in

postoperative states (18). Dysrhythmia leads to gastroparesis and delay in gastric emptying associated with an increase of gastroesophageal reflux, nausea, and vomiting (19). Moreover, the increase in fundic tone, described above, increases intragastric pressure. Thus, it is possible that acidosis status inducing these motility disorders may favor esophageal regurgitations during the perioperative period.

Interpretation of our results must consider the experimental model used. Basal antro-pyloric and duodenal pressure recorded in our anesthetized animals was close to that reported by others in conscious pigs (20). Although it is possible that anesthesia influences gastroduodenal motility, basal pyloric and duodenal tone has been recorded in fasted, chloralose-urethane anesthetized dogs (21). Furthermore, unlike a similar anesthetized canine preparation, the pigs exhibit antro-pyloroduodenal events as well as isolated pyloric pressure events. The model used also reproduces the pattern of gastric and duodenal occlusive motor events observed in awake animals (22). In addition, ketamine, in doses similar to those we used, does not provoke any change in gastrointestinal motility (23).

Finally, our ability to translate our findings to clinical application is also hindered by the fact that we did not study the long-term consequences of acidosis. However, chronic acidosis as encountered in chronic renal failure causes nausea and vomiting, and delays gastric emptying, suggesting that gastrointestinal motility abnormalities remain present in long-term acidosis (34). Moreover, a recent study by Laussen et al. (25) reported an increased frequency of vomiting in postoperative patients who had respiratory acidosis.

In conclusion, we showed that acute acidosis impairs gastroduodenal motility. All the changes observed may contribute to gastroparesis, emesis, ileus, and delayed gastric emptying during the perioperative period. Therefore, acid-base status must be carefully evaluated in anesthetic or critical care studies assessing the gastroduodenal function

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