Mechanisms of burn-induced impairment in gastric slow waves and emptying in rats

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Sallam HS, Oliveira HM, Liu S, Chen JDZ. Mechanisms of burn-induced impairment in gastric slow waves and emptying in rats. Am J Physiol Regul Integr Comp Physiol 299: R298–R305, 2010.—Delayed gastric emptying is common following severe large cutaneous burns; however, the mechanisms of burn-induced delayed gastric emptying remain unknown. The aim of this study was to explore the possible involvement of hyperglycemia and cyclooxygenase-2 receptors in the burn-induced gastric dysrhythmias. Gastric slow waves and gastric emptying were assessed in rats 6 h following sham or burn injury. Animals were randomized to one sham-burn and seven burn groups: untreated; two groups of saline treated (control); insulin treated (5 IU/kg); cyclooxygenase-2 inhibitor treated (10 mg/kg); ghrelin treated (2 nmol/rat); and gastric electrical stimulation treated. It was found that 1) severe burn injury impaired gastric slow waves postprandially and delayed gastric emptying; 2) the impairment in gastric slow waves included a decrease in the slow-wave frequency and in the percentage of normal slow waves, and an increase in the percentage of bradygastria (P < 0.001, 0.01, and 0.01, respectively vs. preburn values). None of the gastric slow-wave parameters was significantly correlated with gastric emptying; 3) cyclooxygenase-2 inhibitor normalized burn-induced delayed gastric emptying (P = 0.3 vs. sham-burn), but not gastric dysrhythmias (P < 0.002 vs. sham), whereas insulin normalized both gastric emptying (P = 0.4 vs. sham-burn) and gastric dysrhythmias (P = 0.3 vs. sham-burn); 4) both gastric electrical stimulation and ghrelin accelerated burn-induced delayed gastric emptying (P = 0.002 and 0.04, respectively, vs. untreated burn). In conclusion, hyperglycemia alters gastric slow-wave activity and delayed gastric emptying, while cyclooxygenase-2 inhibition delays gastric emptying without altering gastric slow-wave activity.

cyclooxygenase inhibitor; gastric electrical stimulation; ghrelin; insulin

BURN INJURIES SIGNIFICANTLY alter the functions of many organ systems, including the gastrointestinal system (68). Upper gastrointestinal ulcerations, bleeding, feeding intolerance, abdominal distension, vomiting, ileus, bacterial translocation, and sepsis constitute major clinical problems in this unfortunate group of patients (2, 44).

It is known that, in severe cutaneous burn injury, aggressive nutritional support is required to meet the increased metabolic demands and prevent the depletion of body energy and nitrogen stores. Enteral route for nutritional support is generally preferred to parenteral route, especially if administered early, for its known benefits (3, 35, 57). However, early enteral feeding is hindered or may have to be delayed due to burn-induced gut dysmotility.

Delayed gastric emptying is common in patients with severe large cutaneous burns and is responsible for delayed enteral feeding (44). Inhibition of gastric motility has been reported in both animals (2, 9, 56, 59) and humans (34, 69) following burn. In a recent clinical study conducted in critically ill patients, 77% of burn patients on admission were diagnosed to have delayed gastric emptying (52).

Ghrelin is a 28-amino acid motilin-related peptide hormone, recently discovered. It is the endogenous ligand for the growth-hormone secretagogue receptor secreted by the oxyntic mucosa of the gastric fundus. Ghrelin possesses prokinetic properties and has been shown to accelerate gastric emptying in rats with gastrointestinal motility disorders or burn injuries (18, 64, 65, 59). In our preliminary experiments, ghrelin showed no ameliorating effects on postburn gastric dysrhythmia.

Cyclooxygenase (COX) enzyme is involved in the synthesis of prostaglandins. COX-2, in particular, has been shown to be inducible in response to tissue injury. In our laboratory’s recent studies on a scald-burn rat model, we have shown delayed colon transit and evidence of increased protein and mRNA expressions of COX-2 in both proximal and distal colon (21).

Gastric electrical stimulation (GES) or pacing entails the application of electrical stimulation to the stomach at a frequency slightly above the intrinsic frequency of the gastric slow waves. This type of stimulation is able to pace or entrain intrinsic gastric slow waves and is, therefore, capable of normalizing gastric dysrhythmias.

Mechanisms of burn-induced delayed gastric emptying remain largely unknown. We hypothesized that burn-induced delay in gastric emptying might be attributed to gastric slow-wave dysrhythmias induced by burn via the hyperglycemia and the prostaglandin pathway. This hypothesis was based on the following knowledge: 1) gastric slow waves determine the maximum frequency and propagation of gastric contractions (11a), and delayed gastric emptying has often been associated with gastric dysrhythmia (12); 2) gastric dysrhythmia is known to be associated with hyperglycemia (27), which is a common pathophysiological phenomenon encountered in burn patients (25, 26, 32); 3) gastric dysrhythmia is also known to be mediated via the prostaglandin pathway (27, 41) that our laboratory has shown recently to be involved in burn-induced gastric and colonic dysmotility (21, 56).

The aim of this study was to test our hypothesis, designed as follows: 1) gastric slow waves and gastric emptying were measured in burned rats for the analysis of a possible correlation between these two measurements; 2) insulin and COX-2 inhibitor (COX-2i) were used to study the involvement of hyperglycemia and COX-2 receptors, respectively; 3) to investigate the causative effect of gastric dysrhythmia on burn-induced delay in gastric emptying, gastric emptying was assessed in rats treated with either ghrelin or GES.
MATERIALS AND METHODS

Animals
A total of 75 rats were included in the study. Adult male Sprague Dawley rats (300–350 g, Harlan Sprague-Dawley, Houston, TX) were housed in a controlled environment. Rats had free access to regular chow pellets and drinking water. There was 1 wk of acclimatization, before the initiation of the study. The study was approved by the Animal Care and Use Committee of the University of Texas Medical Branch (Galveston, TX).

Experimental Design
Experimental design is shown in Fig. 1. All animals were subjected to surgery for placement of gastric electrodes, following 3 days later by recording of gastric slow waves (in both fasting and fed conditions). The next day, animals underwent sham or burn injury. Overnight-fasted animals were randomized into one sham-burn group (n = 11) and five burn groups as follows: untreated (n = 8), COX-2i-treated (n = 8), insulin-treated (n = 14), ghrelin-treated (n = 12), and GES-treated (n = 9) groups. In addition, we included two burned saline-treated groups: subcutaneous saline (n = 5) as a control for the insulin-treated group, and intraperitoneal saline (n = 5) as a control for COX-2i- and the ghrelin-treated groups. Six hours after sham or burn injury, we recorded the gastric slow waves (in both fasting and fed conditions), and killed the animals 30 min after feeding, to assess gastric emptying, as detailed below.

To study the involvement of COX-2 receptor pathway in the burn-induced gastric slow-wave changes, we studied two groups of burned rats (COX-2i treated and intraperitoneal-saline treated). For the COX-2i-treated animals, a selective COX-2i, nimesulide (NIM; Sigma-Aldrich, St. Louis, MO), 10 mg/kg (21, 55), was given as 1 ml intraperitoneally immediately after burn. Saline-treated rats were similarly treated with 1 ml saline intraperitoneally.

To study hyperglycemia as a possible mechanism for the burn-induced gastric slow-wave and emptying changes, we studied two groups of burned rats (insulin treated and subcutaneous-saline treated). For the insulin-treated animals, insulin Lispro (Humalog Lilly), 5 IU/kg, was given as 0.15–0.18 ml subcutaneously to rats just before the phenol red meal, 6 h after burn. We have selected this dose as Helton et al. (29) have reported that up to 3 IU/kg of insulin Lispro had no effect on gastrointestinal motility; so, in this study, we used a higher dose to improve burn-induced gastric emptying. The dose was also similar to the one used by Jeschke et al. (37) for intermediate dose to improve burn-induced gastric emptying. The dose was identical throughout the recorded tracing (47, 48). Based on these tests, we found that the optimum stimulation parameters to achieve complete entrainment of gastric slow waves. The pulse width selected ranged from 300 to 600 ms, and the pulse amplitude was from 1 to 10 mA. The complete entrainment was achieved if each of the intrinsic slow waves was found to be phase-locked with each of the stimuli, i.e., the distance between each stimulus artifact and the following gastric slow wave was identical throughout the recorded tracing (47, 48). Based on these tests, we found that the optimum stimulation parameters to induce entrainment were 5.5 pulses/min, 400 ms, and 5 mA. These parameters were applied to rats, 6 h after burn, for 30 min in the fasting state and 30 min postprandially.

Experimental Methods
Surgery and placement of recording electrodes. After an overnight fast (in wire-bottom cages without food after 5 PM), rats were given general anesthesia (2–3% isoflurane inhalation) and prepped for abdominal surgery. For the measurement of gastric slow waves, a pair of cardiac pacing wires was sutured to the stomach serosa 0.5 cm above the pylorus (recording electrode). In the GES-treated group, an additional pair of wires was sutured to the stomach serosa 1.5 cm from the distal pair and was used for GES application (stimulating electrode). The free ends of the wires were tunneled through the abdominal wall and exited at the neck skin. Buprenorphine (0.05–0.1 mg/kg) was given for all animals twice a day for 2 days. Rats were allowed 3 days to recover in their individual cages with food and water abundantly provided.

Recording of gastric slow waves before burn (baseline recording). On the third day after surgery, the rats were fasted overnight and housed in wire-bottom cages without access to food after 5 PM; water was removed just before recording. During the experiment, the rats were placed in Bollman cages, and gastric slow waves were recorded through the implanted serosal electrodes. Recordings were made for 30 min in the fasting state and 30 min in the fed state after a gavage feeding of 1.5 ml of a methylcellulose meal: 1.5% of aqueous methylcellulose meal (Fisher Scientific, Fair Lawn, NJ) was prepared, as previously described (59). Rats were then returned to their individual cages. They had abundant access to water and food. They were fasted 6 h later.

Gastric slow waves were recorded using a multichannel recorder (Acknowledge, Biopac Systems, Santa Barbara, CA), then low-pass filtered with a cutoff frequency of 1 Hz and down-sampled at 2 Hz. The percentage of normal gastric slow waves was computed using a validated computerized spectral analysis (11).

Dominant frequency represents the mean frequency of gastric slow waves, which, in rats, ranges from 4 to 6 cycles/min (cpm) (49).
Dominant power reflects the mean amplitude of the regular gastric slow wave. The percentage of normal gastric slow waves was defined as the percentage of time during which regular 4- to 6-cpm slow waves were presented over a specific analyzed period. It was computed using the adaptive spectral analysis method (14). In this method, each recording was divided into blocks of 1 min without overlap. The power spectrum of each 1-min recording was calculated and examined to see if the peak power was within the range of 4–6 cpm (normal range). The definition of normal slow-wave frequency range (4–6 cpm) was based on previous studies in our laboratory (49), while ≤4 and ≥6 cpm were considered bradygastria and tachygastria, respectively. Arrhythmia was established if the slow wave did not show any regular rhythm.

Burn injury. We used a modified Walker burn model in this study (31, 66). Animals, fasted overnight (housed in wire-bottom cages without food after 5 PM; water removed just before sham/burn injury), were anesthetized with 2–3% isoflurane inhalation (Abbott Laboratories, North Chicago, IL) before receiving burn injury. Intramuscular buprenorphine (0.1 mg/kg, once just before burn; Reckitt Benckiser Healthcare) was used as a pain-killer in all animals. Burn was inflicted as previously described (59). Briefly, the dorsum and ventrum of the rat were shaved, and the rat was placed on a Plexiglas plate, where only a delimited area was burned by immersion in 95°C water. The dorsum area was burned for 10 s, and the ventrum for 2 s, which resulted in a full-thickness burn involving 60% of the total body surface area. The burned rat was resuscitated immediately with Parkland formula (4 ml·kg⁻¹·%total body surface area⁻¹·24 h⁻¹), in which a total of 24 ml of Ringer lactate solution (for the first 8 h postburn) was given intraperitoneally. The rats in the sham group were treated identically, except for the burn injury, and they received 12 ml of Ringer lactate. They were returned to the cage for awakening. All experiments were done 6 h after burn/sham injury.

Recording of gastric slow waves after burn. Six hours after burn, rats were placed in Bollman cages, and the gastric slow-wave recording was repeated in the fasting and fed states with the same preburn protocol. The only difference was that the methylcellulose meal was mixed with phenol red [0.75 mg of phenol red (Sigma, St. Louis, MO) per 1.5 ml aqueous methylcellulose], so that gastric emptying could also be assessed.

Gastric emptying test. Thirty minutes after the phenol red methylcellulose meal, the rats were euthanized under general anesthesia with 5% isoflurane inhalation. For the assessment of gastric emptying, the stomach was carefully isolated, ligated just above the cardia and below the pylorus, and removed. The content of the stomach was collected for the calculation of the remaining phenol red. Phenol red analysis was done as previously described (20, 22, 59). Gastric emptying was determined as 100% minus the percentage of gastric emptying was calculated and examined to see if the peak power was within the range of 4–6 cpm (normal range). The definition of normal slow-wave frequency range (4–6 cpm) was based on previous studies in our laboratory (49), while ≤4 and ≥6 cpm were considered bradygastria and tachygastria, respectively. Arrhythmia was established if the slow wave did not show any regular rhythm.

Burn-induced Impairment in Gastric Slow Waves and Gastric Emptying

In the fasting state, the dominant frequency after burn showed a significant decrease compared with its preburn values (4.68 ± 0.2 vs. 4.93 ± 0.2; P < 0.05). Postprandially, main gastric slow-wave parameters were significantly changed after burn compared with their preburn values (see Fig. 2 for typical tracings). After burn, there was a significant decrease in the dominant frequency (4.51 ± 0.2 vs. 5.08 ± 0.2; P = 0.002, Fig. 3A) and in the percentage of normal slow waves (67 ± 7 vs. 85 ± 4%; P = 0.02, Fig. 3B) with a concomitant increase in the percentage of bradygastria (specifically, bradyarrhythmia, 25 ± 7 vs. 9 ± 4%; P = 0.02, Fig. 3C) and no change in the percentage of tachygastria (5 ± 2 vs. 3 ± 1%; P = 0.5, Fig. 3D).

Gastric emptying was significantly delayed in the rats after burn compared with the control sham rats. The percentages of gastric emptying were 77 ± 3% for the sham-burned rats and 40 ± 7% for the burned rats (P = 0.0002, Fig. 4). Gastric emptying was not correlated with any of the gastric slow-wave parameters before or after burn, neither in the fasting state nor in the fed state (P > 0.05 each, see Table 1).

The Effect of COX-2 Inhibition on Gastric Slow Waves and Gastric Emptying

The treatment of COX-2i showed no ameliorating effects on gastric slow waves, but normalized burn-induced delay in gastric emptying. Surprisingly, COX-2i did not improve burn-induced impairment in gastric slow waves; instead, it resulted in significant detrimental changes in slow waves in both fasting and fed conditions, including a decrease in dominant frequency (3.2 ± 0.3 for fasting and 3.2 ± 0.3 for postprandial, P = 0.01 each vs. sham, untreated burned or saline treated; Fig. 3A) and percentage of normal slow waves (36 ± 7% for fasting and 41 ± 12% for postprandial, P ≤ 0.04 each vs. sham, untreated burned or saline treated; Fig. 3B), an increase in the percentage of bradygastria (56 ± 7% for fasting and 59 ± 8% for postprandial, P ≤ 0.002 each vs. sham or untreated burned or saline treated; Fig. 3C), and no change in the percentage of tachygastria (4 ± 2% for fasting and 4 ± 3% for postprandial, P ≥ 0.3 vs. sham or untreated burned or saline treated; Fig. 3D).

Interestingly, however, gastric emptying was normalized following the COX-2i treatment. The percentages of gastric emptying were 46 ± 13 and 75 ± 5% for saline-treated and COX-2i-treated rats, respectively (P = 0.05, Fig. 4).

The Effect of Blood Glucose Concentration on Gastric Slow Waves and Gastric Emptying

Burn increased blood glucose, and the insulin treatment normalized the burn-induced impairment in gastric slow waves and emptying. In the insulin-treated and the saline-treated groups, a significant 50% increase in blood glucose was noted after burn (Table 2). Following insulin treatment, the mean blood glucose level (mg/dl) was dropped (P < 0.00002, ANOVA). The burned rats treated with insulin showed a significant improvement in gastric slow waves in the fed state and a decrease in blood glucose levels. The percentage of normal slow waves was 82 ± 4% in the insulin-treated burned rats, and this was significantly higher than that in the
burned rats treated with saline ($P < 0.04$) and comparable to that in the rats before burn ($P > 0.05$), suggesting a normalization of slow waves.

Gastric emptying was also normalized with the insulin treatment. The percentages of gastric emptying were $33 \pm 10$ and $78 \pm 6\%$ for saline-treated and insulin-treated rats, respectively ($P = 0.005$, Fig. 4).

There was a robust, negative correlation between the blood glucose level and gastric emptying ($r = -0.52; P = 0.003$, Fig. 5), and a marginal, negative correlation between the blood glucose level and dominant power ($r = -0.24; P = 0.08$).

**Effects of Ghrelin and GES on Gastric Emptying and Gastric Slow Waves**

In addition to the COX-2i data, findings from the treatment of ghrelin also indicated disassociation between gastric emptying and gastric slow waves: ghrelin showed no effects on gastric slow waves, but improved gastric emptying in burned rats. As shown in Fig. 3, ghrelin did not alter any of slow waves' parameters, neither in the fasting state, nor in the postprandial state. However, gastric emptying was normalized with the ghrelin treatment. The percentages of gastric emptying

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**Fig. 2. Example of postprandial tracings of gastric slow waves (GSW) after sham/burn and various treatments. A: sham; B: burn untreated; C: COX-2i treated; D: ghrelin treated; E: insulin treated.**
were 46 ± 13 and 91 ± 3% for saline-treated and ghrelin-treated rats, respectively \((P = 0.02; \text{Fig. 4})\). Interestingly, the percentage of gastric emptying with ghrelin treatment was even higher than that in the sham-burned control rats \((P = 0.002)\), indicating a potent prokinetic effect of ghrelin.

Gastric emptying was also normalized with the GES treatment. The percentages of gastric emptying were 77 ± 3, 40 ± 7, and 85 ± 3% for sham, burned untreated, and GES-treated rats, respectively \((P = 0.04 \text{ and } 0.00001, \text{respectively, for each compared with GES-treated rats}; P ≤ 0.0001, \text{ANOVA}; \text{Fig. 4})\).

**DISCUSSION**

This study shows six potentially important aspects of gastric slow waves and gastric emptying after severe burn injury: 1) severe burn injury impaired gastric slow waves mainly postprandially; 2) the percentage of gastric slow waves was increased in both fed and postprandial conditions; 3) the percentage of normal slow waves was decreased in both fasted and fed conditions; 4) there was a decrease in the percentage of bradygastria (%B) postprandially; 5) there was no significant change in the percentage of tachygastria (%T) postprandially; and 6) there was no significant correlation between any of the GSW parameters and gastric emptying (GE).

Table 1. *The correlation between GSW parameters and gastric emptying*

<table>
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<tr>
<th>State</th>
<th>Correlation with GE</th>
<th>DF</th>
<th>DP</th>
<th>N%</th>
<th>B%</th>
<th>T%</th>
<th>A%</th>
</tr>
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<tbody>
<tr>
<td>Before burn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>(r)</td>
<td>-0.17</td>
<td>0.22</td>
<td>-0.22</td>
<td>0.29</td>
<td>-0.03</td>
<td>-0.40</td>
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<tr>
<td>(P) value</td>
<td></td>
<td>0.66</td>
<td>0.58</td>
<td>0.57</td>
<td>0.46</td>
<td>0.94</td>
<td>0.29</td>
</tr>
<tr>
<td>Fed</td>
<td>(r)</td>
<td>-0.25</td>
<td>0.21</td>
<td>-0.20</td>
<td>0.22</td>
<td>-0.02</td>
<td>-0.12</td>
</tr>
<tr>
<td>(P) value</td>
<td></td>
<td>0.52</td>
<td>0.58</td>
<td>0.60</td>
<td>0.57</td>
<td>0.97</td>
<td>0.75</td>
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<tr>
<td>After burn</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fasting</td>
<td>(r)</td>
<td>-0.24</td>
<td>-0.18</td>
<td>-0.53</td>
<td>0.44</td>
<td>0.60</td>
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<tr>
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<tr>
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<td>0.41</td>
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</tr>
<tr>
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<td>0.22</td>
<td>0.27</td>
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The correlation coefficient \((r)\) and its corresponding \(P\) value are listed for all gastric slow-wave (GSW) parameters, including dominant frequency (DF), dominant power (DP), and percentage of normal slow waves (%N), bradygastria (%B), tachygastria (T), and arrhythmias (%A). There was no significant correlation between any of the GSW parameters and gastric emptying (GE).
impairment included a decrease in the slow-wave frequency and in the percentage of normal slow waves, and an increase in the percentage of bradygastria; 3) none of the gastric slow-wave parameters was significantly correlated with gastric emptying; 4) COX-2i normalized gastric emptying, but not gastric dysrhythmias; 5) insulin normalized gastric emptying and gastric dysrhythmias; 6) both GES and ghrelin normalized burn-induced delayed gastric emptying, and the normalization of gastric emptying with ghrelin was not associated with changes in gastric slow waves.

Severe burn injuries are known to inhibit gut motility. According to previous reports, gastric emptying and intestinal and colon transits are delayed in rats after burn (2, 9, 20, 21, 56, 59). The mechanisms of burn-induced GI dysmotility are not fully understood. However, it is generally known that the body response to the stress caused by burn injury involves the triggering of the sympathetic nervous system with an increase in catecholamine release and constriction of the mesenteric blood flow, with subsequent ischemic inhibition of the gut (30, 67).

No specific therapies are available for treating burn-induced gastric dysmotility. Clinicians have a limited choice of prokinetics to choose from: some are low in efficacy [e.g., metoclopramide (1, 40)], some have severe side effects that make them intolerable for many patients [e.g., erythromycin (36, 58)], some are not used in the USA (e.g., domperidone), and some have been withdrawn from the market because of their cardiac side effects (e.g., Cisapride). The need for new prokinetic agents and new modalities for treatment of burn-induced gastrointestinal dysmotility is undeniable. Thus, understanding the underlying mechanisms for the latter is a crucial step.

We hypothesized that burn-induced delay in gastric emptying might be attributed to gastric slow-wave dysrhythmias induced by burn via the hyperglycemia and the COX-2 receptor pathways. This hypothesis was explored in the present study. To the best of our knowledge, this study was the first to investigate the effects of burn injury on gastric slow waves and its possible association with, or causative effect on, gastric emptying in burn.

After burn, gastric slow waves showed detrimental changes, mainly postprandially. Dominant frequency was significantly decreased during fasting and postprandially after burn, but remained in the normal range of 4–6 cpm, rendering it of no clinical significance. However, such a decrease in the dominant frequency suggests an inhibition or a lower firing rate of the stomach pacemaker signal in burn injury. It is known that ischemic inhibition of the intestine has been associated with a decrease in the intestinal slow-wave frequency (45, 60). It is possible that the decrease in the gastric slow-wave frequency after burn observed in this study might be also attributed to gastric ischemia. Other gastric slow-wave parameters, including the percentage of normal gastric slow waves, was decreased postprandially after burn, attributed to an increase in bradygastria and bradyarrhythmia. The possibility that the burn-induced dysrhythmias might be mediated via the prostaglandin mechanisms and attributed to hyperglycemia was explored.

Based on the present results, burn-induced gastric dysrhythmias were not mediated via the COX-2 receptor pathway. The involvement of the COX-2 receptor pathway has been tested in this study by treating burned rats with a selective COX-2i. Interestingly, COX-2i failed to improve burn-induced gastric dysrhythmias. Although this finding was contradictory to what has been known about prostaglandin, a subsequent output for the production of COX-2 enzyme and a major mediator of slow-wave dysrhythmia (27, 41), it was in agreement with similar observations in dogs, in which neither selective nor nonselective COX-2i was able to improve glucagon-induced dysrhythmia (38, 70). On the other hand, the selective COX-2i normalized gastric emptying in the burned rats. This result was in agreement with our laboratory's previous findings (56). Prostaglandins have been reported to be increased after burn (10, 53) and have been related to burn-induced intestinal and colonic dysmotility (21, 56). Moreover, the selective COX-2i, NIM, has been proven to reduce intestinal tissue inflammation in rats after burn (55). It is possible that the NIM effect on burn-induced delayed gastric emptying observed in this study might be attributed to its ability to reverse burn-induced gastric tissue inflammation, rather than improve gastric dysrhythmia.

It was found, however, that burn-induced gastric dysrhythmias were mediated by hyperglycemia. Blood glucose is known to modulate gastric emptying, and hyperglycemia causes delayed emptying of the stomach (7, 15, 28, 33). Hyperglycemia has been also associated with gastric arrhyth-

![Fig. 5. The negative correlation between gastric emptying and postprandial blood glucose levels after burn in insulin-treated (n = 14) vs. saline-treated (n = 5) and untreated (n = 8) groups (r = −0.52; P = 0.003).](http://ajpregu.physiology.org/DownloadedFrom)
mias in diabetics (27) and is a common pathophysiological phenomenon in burn, usually associated with insulin resistance (16, 23). Hyperglycemia was evident in burned rats in the present study. Insulin treatment normalized the percentage of the normal slow waves. Moreover, insulin increased gastric emptying, a result consistent with the published literature in healthy and diabetic patients and/or rodents (6, 8, 24). Blood glucose levels were negatively correlated with gastric emptying and marginally correlated to the gastric slow-wave dominant power. This salutary effect of insulin on gastric slow waves is possibly due to its known effect as a vasodilator, exerting its effect by increasing the production of the potent vasodilator, nitric oxide (51), thus possibly counteracting the effect of burn-induced ischemic inhibition on the stomach.

To investigate the causative effect of gastric dysrhythmia on burn-induced delay in gastric emptying, we tested long-pulse GES, a known method for normalizing slow-wave dysrhythmia (13), and ghrelin, a known treatment for delayed gastric emptying in burn (59), but not gastric dysrhythmias. Ghrelin, a prokinetic hormone, normalized gastric emptying in burned rats. Ghrelin possesses prokinetic properties and has been shown to accelerate gastric emptying in healthy, postoperative, and septic ileus animal models (17–19, 39, 53, 64), as well as in healthy and gastroparetic subjects (42, 46, 62). The finding of this study was consistent with the literature and our laboratory’s previous findings, in which ghrelin at a dose of 2 nmol/rat normalized gastric emptying in burned rats (59). However, ghrelin was unable to improve gastric slow waves in burned rats.

Long-pulse GES with the parameters known to entrain gastric slow waves in rats normalized gastric emptying in burned rats. To the best of our knowledge, this was the first study investigating the effect of GES on burn-induced delay in gastric emptying, although improvement in gastric emptying with GES has been reported in a canine model of gastroparesis and a rodent model of diabetes, as well as in patients with gastroparesis (5, 49, 50, 61). The findings of the present study demonstrate that gastric dysrhythmias were not the cause of delayed gastric emptying in burn. First, although both slow waves and emptying were impaired with burn, no correlation was noted between these two measurements. Second, the COX-2i impaired gastric slow waves, but normalized gastric emptying in burned rats. Third, ghrelin improved gastric emptying, but showed no effects on gastric slow waves. Apparently, factors other than slow-wave dysrhythmias are involved in the burn-induced delay in gastric emptying, such as antral hypomotility or pyloric dysfunction, which were not investigated in the present study.

In conclusion, severe burn injury impairs not only gastric emptying, but also gastric slow waves, reflected as a substantial increase in gastric dysrhythmias. Burn-induced dysrhythmias and delayed gastric emptying are both manifestations of burn, and there is no correlation between these two measurements in the present study. Hyperglycemia is involved in burn-induced gastric dysrhythmia and thereby may lead to delayed gastric emptying, whereas both hyperglycemia and COX-2 receptor pathway may be involved in the mediation of delayed gastric emptying. Insulin and ghrelin, as well as GES, are effective in improving burn-induced delay in gastric emptying.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


MECHANISMS OF IMPAIRED GASTRIC MOTILITY IN BURN


