Gastric Dilation During Stimulation of Cardiac Sensory Receptors

U. James Johannsen, B.A., Robert Summers, M.D., and Allyn L. Mark, M.D.

SUMMARY Gastrointestinal symptoms are more common in patients with inferoposterior myocardial infarction than in patients with anterior infarction. These symptoms are often associated with bradycardia and hypotension, which may be caused by stimulation of sensory endings in the heart. The major goals of this study were to determine if stimulation of cardiac sensory receptors (the Bezold-Jarisch reflex) in dogs produces gastric responses, and if stimulation of receptors in the inferoposterior wall of the left ventricle produces larger gastric responses than stimulation of receptors in the anterior wall.

Gastric dilation was measured from increases in volume of a gastric balloon maintained at constant distending pressure. Cardiac sensory receptors in the inferoposterior wall (circumflex coronary artery) and in the anterior wall (anterior descending artery) were stimulated separately by intracoronary injection of veratridine in chloralose-anesthetized dogs.

Intracoronary injection of veratridine produced bradycardia, hypotension and gastric dilation. Decreases in heart rate and increases in gastric volume produced by injection of veratridine into the circumflex artery were greater than those that resulted from injection into the anterior descending artery (32 ± 10 ml vs 14 ± 5 ml, respectively; p < 0.05). Flow in these two beds and the weight of myocardium perfused by each vessel were not different.

Diaphragmatic vagotomy abolished the gastric response but not the bradycardic or hypotensive response to intracoronary injection of veratridine. Intracoronary administration of lidocaine and bilateral cervical vagotomy blocked all reflex responses to intracoronary veratridine.

Stimulation of cardiac receptors with vagal afferent pathways by veratridine in the dog evokes reflex gastric and circulatory responses in anesthetized dogs. These responses are greater during stimulation of cardiac receptors in the inferoposterior wall. A similar reflex may contribute to the nausea and vomiting in the early stages of inferoposterior myocardial infarction.

NAUSEA AND VOMITING are common symptoms in patients with acute myocardial infarction. They are more common in patients with inferoposterior infarction than in those with anterior infarction.1 Ahmed et al. reported that in 62 patients with documented myocardial infarction and gastrointestinal symptoms before administration of analgesics, 69% of the patients with inferoposterior infarction reported a history of nausea and vomiting, while only 27% with anterior infarction experienced these symptoms.1 This difference could not be explained by differences in severity of pain or the presence of shock. Thus, other mechanisms must play an important role in the pathogenesis of nausea and vomiting in these patients.

The gastrointestinal symptoms in patients with inferior infarction are often associated with bradycardia.1 The high frequency of bradycardia and hypotension during inferior infarction may result from stimulation of cardiac sensory receptors that mediate cardioinhibitory and vasodepressor responses.2 These sensory receptors may be preferentially distributed in the inferoposterior wall of the left ventricle.3,4 Abrahamsson and Thorén have reported that stimulation of cardiac receptors with vagal afferents by veratridine or ischemia in unanesthetized, decerebrate cats produces reflex gastric relaxation as
well as bradycardia and hypotension. With sustained electrical stimulation of these vagal afferents, retching movements and rapid decreases in gastric volume that occur with vomiting were regularly observed. Thus, Abrahamsson and Thorén concluded that gastric relaxation and eventually a vomiting response are an integral part of this cardioinhibitory, vasodepressor reflex in cats.

The major goals of this study were (1) to determine if gastric responses result from stimulation of cardiac receptors during intracoronary injection of veratrum alkaloid in dogs, (2) to determine if stimulation of cardiac receptors in the inferoposterior wall of the left ventricle produces greater gastric responses than does stimulation of receptors in the anterior wall, and (3) to identify the reflex pathways of the gastric dilation.

Methods

Mongrel dogs of either sex were anesthetized with sodium thiopental (25 mg/kg, i.v.) and alpha chloralose (10 mg/kg, i.v.). The dogs were intubated and ventilated with a respirator. Arterial PO2, Pco2, and pH were maintained within normal limits. Arterial pressure was measured via a brachial arterial catheter. Through a left thoracotomy, the pericardium was opened and short segments of the left circumflex coronary artery, which supplies the inferoposterior wall in the dog, and of the left anterior descending coronary artery, which supplies the anterior wall, were exposed. Careful dissection of the vessel does not interrupt afferent nerves coursing along the coronary artery.

Cardiac sensory receptors were stimulated by injecting veratridine (30 μg) into the left anterior descending and circumflex arteries via 22-gauge catheters inserted into these vessels within 1–2 cm of their bifurcation from the left main coronary artery. Veratridine is the classic stimulus for the Bezold-Jarisch reflex, a bradycardic, vasodepressor reflex which results from stimulation of cardiopulmonary sensory receptors with vagal afferent pathways.

Gastric volume was measured with a large flaccid balloon positioned in the stomach via the esophagus. The balloon was connected with wide-bore tubing to a water-filled reservoir suspended from a Grass force-displacement transducer. During the initial filling of the balloon, the height of the reservoir was adjusted to maintain a constant intragastric pressure of approximately 7 cm of water. The reservoir was large enough (1.5 l) so that changes in gastric volume were not associated with changes in pressure in the gastric balloon. At the end of the experiments, the abdomen was opened and the balloon, which was filled with water, was palpated to assure that it was contained within the stomach. The system was calibrated to give direct volume readings. Thus, with a constant gastric pressure, increases in gastric volume indicated gastric dilation.

In addition to observing the responses to veratridine, we performed additional experiments to identify afferent and efferent pathways. We obtained responses to veratridine before and after bilateral cervical vagotomy (n = 5); before and after administration of 10 mg of lidocaine into the circumflex coronary artery to anesthetize cardiac sensory receptors (n = 4); and before and after bilateral diaphragmatic vagotomy (n = 3). We also performed electrical stimulation of the cut central end of the left stellate ganglion (5 and 20 Hz, 2 msec, 10 V) to determine if activation of cardiac sympathetic afferent pathways (which are also stimulated by veratridine) results in reflex gastric responses (n = 4). In three other experiments, we measured the changes in gastric volume resulting from injection of 30 μg of veratridine into the circumflex coronary artery before and after bilateral stellate ganglionectomy; this was done to determine if sympathetic afferent pathways participate in the gastric responses to veratridine.

In five experiments we measured myocardial blood flow before and after inserting the coronary cannulas. This was performed to determine if insertion of the cannuulas altered flow and, more important, to compare flows through the anterior descending and circumflex coronary arteries. Flow was measured with radiolabeled microspheres using methods previously described. To estimate the amount of myocardium perfused by the anterior descending and circumflex arteries, we injected a different contrast material into each of the coronary cannuulas in six experiments. The two dyes were injected postmortem at a pressure of 100 mm Hg. The circumflex and anterior descending arteries were injected separately about 5 minutes apart distal to the site of cannulation of each vessel. The stained areas were separated from each other and from unstained tissue and weighed. This tissue was then used to estimate the amount of myocardium subserved by each vessel distal to the cannuula. Using the measurements of myocardial blood flow and the amount of myocardium subserved by each vessel, we could estimate the flow through each vessel at the point of injection.

Statistical analyses were performed using the t test for paired data and one-way analysis of variance. Values of p < 0.05 were considered statistically significant.

Results

Responses to Veratridine

Stimulation of cardiac receptors with veratridine produced bradycardia, hypotension and gastric dilation, indicated by the increase in gastric volume. Gastric responses to veratridine occurred with injection into each artery in all experiments. However, the decreases in heart rate and the increase in gastric volume produced by injection of veratridine into the circumflex artery were greater than those that resulted from injection into the anterior descending artery (figs. 1 and 2, table 1).

Reflex Pathways

Gastric responses to veratridine were abolished by bilateral cervical vagotomy. During circumflex inje-
Coronary injection of veratridine, gastric volume increased $84 \pm 34$ ml before and $0 \pm 0$ ml after cervical vagotomy. Bradycardia and hypotension produced by intracoronary injection of veratridine were also blocked by cervical vagotomy.

Bilateral diaphragmatic vagotomy abolished the gastric responses to intracoronary veratridine but did not alter the responses of heart rate and arterial pressure. Before diaphragmatic vagotomy, heart rate decreased $33 \pm 15$ beats/min and mean arterial pressure decreased $26 \pm 2$ mm Hg, and gastric volume increased $28 \pm 9$ ml with intracoronary veratridine. After diaphragmatic vagotomy, heart rate decreased an average of $31 \pm 10$ beats/min and mean arterial pressure decreased $24 \pm 6$ mm Hg, whereas the gastric response was abolished ($-3 \pm 3$ ml).

Intracoronary lidocaine also attenuated the gastric dilation during injection of veratridine. Gastric volume during circumflex injection of veratridine increased $24 \pm 11$ ml before and $4 \pm 2$ ml after circumflex injection of lidocaine. The heart rate and blood pressure responses to veratridine were also blunted by intracoronary lidocaine. This attenuation was not the result of a generalized depressant effect of the lidocaine because the gastric response to anterior descending coronary injection of veratridine was not blocked by circumflex administration of lidocaine ($18 \pm 4$ ml before and $16 \pm 5$ ml after lidocaine).

Electrical stimulation of cardiac sympathetic afferent pathways increased arterial pressure $8 \pm 2$ mm Hg and heart rate $15 \pm 3$ beats/min, but did not elicit gastric responses ($0 \pm 0$ ml).

Bilateral stellate ganglionectomy did not change the gastric dilation produced by intracoronary veratridine ($30 \mu g$). Intracoronary veratridine (circumflex coronary artery) increased gastric volume by $32 \pm 4$ ml before ganglionectomy and by $39 \pm 5$ ml after ganglionectomy.

**Myocardial Flow and Weight**

Analysis of flows showed that the blood flow to the two beds was not significantly different either before catheter insertion ($87 \pm 14$ ml/100 g/min circumflex vs $91 \pm 14$ ml/100 g/min left anterior descending) or after catheter insertion ($90 \pm 15$ ml/100 g/min circumflex vs $83 \pm 13$ ml/100 g/min left anterior descending). There was no significant difference in the weight of myocardium perfused by these two vessels ($47 \pm 4$ g circumflex vs $44 \pm 5$ g left anterior descending).

**Table 1. Gastric Responses to Intracoronary Injection of Veratridine (30 μg)**

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<thead>
<tr>
<th>Experiment no.</th>
<th>CX injection</th>
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Mean ± SEM $32^* \pm 10$ $14 \pm 5$

* $p < 0.05$, circumflex vs left anterior descending coronary artery.

Responses are increases in gastric volume (ml).

Abbreviations: CX = circumflex coronary artery; LAD = left anterior descending coronary artery.

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**Figure 1. Responses to injection of veratridine (30 μg) into the left anterior descending (LAD) and circumflex (CX) coronary arteries in one experiment.**

**Figure 2. Heart rate and gastric responses to intracoronary veratridine (30 μg). Entries are mean ± SEM. LAD = left anterior descending coronary artery; CX = circumflex coronary artery.**
**Discussion**

The principal new observations in this study are (1) stimulation of cardiac sensory receptors (Bezold-Jarisch reflex) evokes gastric dilation as well as circulatory responses in the dog; (2) the gastric responses are greater during stimulation of cardiac receptors in the inferoposterior wall than in the anterior wall of the left ventricle; and (3) the gastric responses result from stimulation of receptors with vagal afferent pathways and not from stimulation of receptors with sympathetic afferents.

The finding that gastric dilation is greater during stimulation of sensory endings in the inferoposterior wall is consistent with previous reports that cardiac sensory receptors that produce bradycardia and hypotension are preferentially distributed in the inferoposterior wall of the canine left ventricle. However, alternative explanations for the differences in responses to circumflex vs anterior descending injections of veratridine should be considered. First, if flow to the circumflex and anterior descending beds were not similar, the drug concentration reaching receptors in the two areas might differ. The microsphere measurements combined with estimates of myocardium perfused by each vessel indicated that flows to the circumflex and anterior descending beds did not differ. Therefore, the difference in responses cannot be explained by a difference in drug concentration reaching the two beds. Second, the amount of myocardium supplied by the two vessels might have differed. Walker et al. reported that the amounts of myocardium subserved by circumflex and anterior descending arteries were similar in the dog, and we have confirmed that observation in this study. Thus, the results cannot be explained by a difference in the amount of myocardium supplied by the two vessels. Third, one might suggest that exposure of the coronary arteries for cannulation would partially interrupt the afferent pathways, with this effect being more pronounced with the anterior descending artery. However, previous studies have demonstrated that exposure of the short segment of the anterior descending coronary artery does not interrupt afferent pathways. Because of the above considerations, we suggest that the difference in gastric responses to circumflex and anterior descending injections of veratridine cannot be explained by limitations of the methods and probably results from a preferential distribution of cardiac sensory receptors in the inferoposterior wall of the left ventricle.

The gastric dilation was not the result of gastric ischemia secondary to hypotension, since diaphragmatic vagotomy (which interrupts vagal efferent pathways to the stomach without interrupting cardiac vagal afferents) abolished the gastric dilation but did not attenuate the hypotension and bradycardia during intracoronary veratridine.

The gastric, heart rate, and arterial pressure responses were abolished by cervical vagotomy. Although this confirms the reflex nature of these responses, it does not precisely delineate the reflex pathways involved in the gastric dilation, because the cervical vagi contain both afferent fibers from the heart and efferent fibers to the gastrointestinal system. To delineate the afferent and the efferent pathways of the gastric response, we used intracoronary lidocaine, electrical stimulation of cardiac sympathetic afferent pathways and bilateral diaphragmatic vagotomy.

Blockade of the responses by intracoronary administration of lidocaine suggests origin in cardiac sensory receptors, but does not distinguish between vagal and sympathetic afferent pathways. However, direct electrical stimulation of sympathetic afferent pathways failed to cause gastric responses; in contrast, electrical stimulation of vagal afferent pathways produces gastric dilation. In addition, bilateral stellate ganglionectomy did not alter the gastric response to intracoronary veratridine. These observations support the view that the gastric responses result from stimulation of receptors with vagal afferents and suggest that sensory receptors with sympathetic afferents are not involved in the gastric dilation.

Interruption of the gastric response by diaphragmatic vagotomy indicates that the efferent pathway is vagal, because sectioning the vagi at the diaphragm does not interrupt cardiac afferents. This efferent mechanism appears to represent activation of an inhibitory noncholinergic, nonadrenergic vagal pathway because the response is not blocked by atropine or guanethidine. This inhibitory vagal pathway appears to play a role in the sequence of nausea and vomiting as well as the phenomenon of repetitive relaxation of the stomach during swallowing. The vomiting sequence is known to involve relaxation of the gastric fundus and lower esophageal sphincter.

We did not observe vomiting during intracoronary injection of veratridine. This may relate to the effects of anesthesia or to the duration of the stimulus. Abrahamsson and Thorén have reported that sustained electrical stimulation of vagal afferents in unanesthetized, decerebrate cats produces gastric dilation, which is followed by retching.

These data demonstrate that stimulation of cardiac sensory receptors in the dog evokes gastric dilation and circulatory responses. These responses are greater during stimulation of cardiac receptors in the inferoposterior wall. A similar reflex may contribute to the frequency of nausea and vomiting during the early stages of inferoposterior myocardial infarction.

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