The term white-coat syndrome was coined to describe hypertension that develops in humans as a consequence of stress from visiting the hospital or their physician.\(^1-3\) In such stressful situations, sympathetic nervous activity increases and parasympathetic nervous activity decreases.\(^4,5\) This ANS response is an evolutionary reaction to prepare the body for fight and flight. Veterinarians have noticed a similar white-coat effect in dogs and cats, in which an increase in heart rate, blood pressure, respiratory activity, and rectal temperature can occur during veterinary visits.\(^6,7\) The proposed triggers for hospital-associated stress in dogs include separation from the owner, different environment from home, and confinement.\(^8\)

The ANS response to stress affects GIT function, given that the GIT is in part controlled by sympathetic and parasympathetic tone.\(^9\) Previous studies involving laboratory animals have shown that when sympathetic activity increases or parasympathetic activity decreases, GIT motility and function diminish.

Gastrointestinal tract motility is influenced by a combination of intrinsic and extrinsic nervous input. The intrinsic input acts as pacemaker and is responsible for producing coordinated phasic contractions of the smooth muscle throughout the GIT.\(^12-14\) The extrinsic nervous system, formed in part by the sympathetic and parasympathetic branches of the ANS, influences GIT motility by modulating the intrinsic nervous system.\(^9\) This enteric nervous system also generates MMCs to move large luminal contents through the GIT. These MMCs are composed of 4 phases. Phase I is a quiescent period with no contractions, phase II is characterized by irregular low-

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**Effect of hospitalization on gastrointestinal motility and pH in dogs**

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**OBJECTIVE**  
To determine the effect of hospitalization on gastrointestinal motility and pH in healthy dogs.

**DESIGN**  
Experimental study.

**ANIMALS**  
12 healthy adult dogs.

**PROCEDURES**  
A wireless motility capsule (WMC) that measured pressure, transit time, and pH within the gastrointestinal tract was administered orally to dogs in 2 phases. In the first phase, dogs received the WMC at the hospital and then returned to their home to follow their daily routine. In the second phase, dogs were hospitalized, housed individually, had abdominal radiography performed daily, and were leash exercised 4 to 6 times/d until the WMC passed in the feces. All dogs received the same diet twice per day in both phases. Data were compared between phases with the Wilcoxon signed rank test.

**RESULTS**  
Data were collected from 11 dogs; 1 dog was excluded because the WMC failed to exit the stomach. Median gastric emptying time during hospitalization (71.8 hours; range, 10.7 to 163.0 hours) was significantly longer than at home (17.6 hours; range, 9.7 to 80.8 hours). Values of all other gastric, small bowel, and large bowel parameters (motility index, motility pattern, pH, and transit time) were similar between phases. No change in gastric pH was detected over the hospitalization period. High interdog variability was evident for all measured parameters.

**CONCLUSIONS AND CLINICAL RELEVANCE**  
Hospitalization of dogs may result in a prolonged gastric emptying time, which could adversely affect gastric emptying of meals, transit of orally administered drugs, or assessments of underlying motility disorders. (J Am Vet Med Assoc 2017;251:65–70)

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**ABBREVIATIONS**  
ANS  Autonomic nervous system  
GIT  Gastrointestinal tract  
LBTT  Large bowel transit time  
MMC  Migratory motor complex  
SBTT  Small bowel transit time  
WMC  Wireless motility capsule
amplitude contractions, phase III consists of high-amplitude contractions and carries the large indigestible solid particles (> 2 mm in diameter) through the GIT, and phase IV is a transient quiescent period.\textsuperscript{15,16}

In addition to potential changes in GIT motility, emotional stress in humans can cause an increase in gastric acid secretions and decrease in gastric pH, both of which can contribute to the development of duodenal ulcers.\textsuperscript{17,18} To our knowledge, no study has been performed to examine the effect of hospitalization (a potentially stressful event) on gastric acid secretions and pH in dogs. The hypothesis of the study reported here was that GIT motility and pH would be altered in healthy dogs during hospitalization and would differ from values measured at home. To test this hypothesis, dogs were orally administered a WMC, which is a noninvasive device previously used to investigate GIT pH, pressure, and transit time in dogs.\textsuperscript{19–22}

**Materials and Methods**

**Animals**

Twelve privately owned adult dogs were enrolled in the present study from a group participating in a larger parallel clinical trial. For the studies, dogs were required to be healthy and > 1 year of age. Health status was assessed on the basis of medical history, physical examination, CBC, serum biochemical analysis, urinalysis, and fecal flotation test for parasites. Dogs were excluded if they had any previous or existing gastrointestinal disorders or had received any medications ≤ 8 weeks before the study began.

In the larger clinical trial, dogs had been categorized into 4 groups on the basis of body weight: ≤ 20.0 kg (44 lb), 20.1 to 30.0 kg (44.2 to 66.0 lb), 30.1 to 40.0 kg (66.2 to 88.0 lb), and > 40.0 kg. Dogs in the present study included 1 dog in the ≤ 20 kg category, 4 dogs in the 20.1 to 30.0 kg category, 4 dogs in the 30.1 to 40.0 kg category, and 2 dogs in the > 40.0 kg category. Protocols for both studies were approved by the institutional animal care and use committee. Owner consent was obtained for all dogs.

**Experimental design**

Measurement of GIT motility, transit time, and pH was performed in 2 phases. In phase 1, dogs were evaluated during hospitalization. In phase 2, dogs were evaluated in their home environment. The order of these 2 phases was not randomized because of the design of the parallel clinical trial from which dogs were enrolled. The first and second phases of the experiments were at least 10 days apart.

**Diet**

All dogs were fed a dry prescription gastroenteric formula diet\textsuperscript{*} at least 3 weeks before phase 1 began and until completion of phase 2. The amount of food offered for both phases to each individual dog remained the same throughout the study and was consistent with the amount the owners had been feeding prior to the study.

Food, but not water, was withheld the evening before each phase began (total duration of food withholding, approx 12 hours). On the first day of phase 1, dogs were brought to the hospital, where they were fed the prescription diet between 7:30 and 8:00 AM. On the evening before phase 2 began, dogs were admitted to the veterinary hospital. The following day, the dogs were fed between 7:30 and 8:00 AM.

**WMC administration**

On the first day of each phase, a WMC\textsuperscript{20} was orally administered to each dog following the morning meal. Immediately afterward, 20 to 30 mL of water was given to promote transit of the WMC into the stomach. Dogs were then fitted with a vest containing a pocket that held the receiver device used to collect and store the WMC data. In phase 1, dogs were returned home and the owners were instructed to keep the vest on the dog and follow their typical daily routine, with the exception of feeding the prescription diet, until the WMC passed in the feces or a technical problem was found, such as the WMC or receiver battery having run out. While dogs were hospitalized in phase 2, each was housed individually and exercised on a leash 4 to 6 times/d until the WMC passed in the feces or a technical problem was found, at which point they were allowed to return home. In addition, abdominal radiography (ventrodorsal and left lateral views) was performed 3 times/d while dogs were hospitalized to mimic a noninvasive but stressful procedure.

**WMC data collection**

The WMC used in the study consisted of a 13 X 27-mm wireless sensor that measured pH, temperature, pressure, and time within the GIT simultaneously. The wireless sensor capsule sent data to a receiver at specific points (eg, for pH data, every 5 seconds during the first 24 hours and then every 20 seconds), which stored the data until downloaded. Before administration of the WMC to each dog, the pH sensor was calibrated following the manufacturer-recommended calibration protocol. At the end of each phase, data from each dog were analyzed by use of proprietary software.\textsuperscript{21} The data included GIT pH, maximum and mean pressure amplitude, frequency of contractions, and motility index. Motility index was derived from the area under the pressure curve (motility index = ln[∑(sum of amplitudes X number of contractions + 1)]).\textsuperscript{22,23} Data collected for specific time points were averaged to represent a desired monitoring period (eg, while in the stomach) for analysis. Temperature data were not reported because these values are typically used only to indicate whether the WMC is inside or outside the body.

Data obtained by use of the WMC were subdivided to measure parameters specific to the gastric, small bowel (duodenum, jejunum, and ileum), and large bowel (cecum, colon, and rectum) sections of
the GIT. The pH data were used to determine the WMC location within the GIT. Gastric emptying time was measured from the point the WMC entered the stomach (pH < 4) until the point it exited the stomach (pH > 4). The SBTT was measured from the point the WMC exited the stomach (pH increased from < 4 to > 4) to the point it entered the large bowel. The transition from small to large bowel was identified as a decrease in pH of approximately 1 unit and a decrease in the amplitude of contractions. The LBTT was measured from the point of this transition to the point the WMC exited the body. The cluster of pressure contractions in the stomach of some dogs that were believed to represent phase III gastric MMCs was also analyzed.

**Statistical analysis**

The Shapiro-Wilk test was used to assess the data distribution, revealing a nonnormal distribution. Data are therefore reported as median (range). Values of WMC parameters were compared between phases by use of the Wilcoxon signed rank test. Statistical software was used for all analyses, and values of P < 0.05 were considered significant.

**Results**

**Animals**

Twelve dogs were originally enrolled in the study. However, during phase 1, the WMC failed to exit the stomach of 1 dog (a 10.8-kg [23.8-lb] mixed-breed dog) by 8 days after administration. Consequently, vomiting was induced by IV apomorphine administration to retrieve the WMC. Phase 2 was subsequently aborted for that dog, and data pertaining to it were excluded from the statistical analysis.

The 11 dogs included in the study consisted of 5 females and 6 males. Median age was 4 years (range, 1 to 10 years), and median body weight was 31.8 kg (70.0 lb; range, 19.4 to 63.8 kg [42.7 to 140.4 lb]). Breeds included mix (n = 3), Great Dane (2), Rottweiler (2), American Staffordshire Terrier (1), Vizsla (1), Australian Cattle Dog (1), and Labrador Retriever (1).

**WMC data**

Median GIT transit time for the WMC did not significantly (P = 0.07) differ between when dogs were at home (50.4 hours; range, 23.5 to 97.3 hours) and when they were hospitalized (53.3 hours; range, 47.5 to 177.5 hours; Table 1). Median gastric emptying

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Home</th>
<th>Hospital</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying time (h)</td>
<td>17.6 (9.7–80.8)</td>
<td>71.8 (10.7–163.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>SBTT (h)</td>
<td>4.2 (2.9–5.4)</td>
<td>3.4 (1.6–6.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>LBTT (h)</td>
<td>25 (1.1–49.1)</td>
<td>22 (7.2–37.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Total transit time (h)</td>
<td>50.4 (23.5–97.3)</td>
<td>53.3 (47.5–177.5)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Home</th>
<th>Hospital</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric maximum contraction pressure (mm Hg)</td>
<td>112 (68–315)</td>
<td>129 (36–261)</td>
<td>0.89</td>
</tr>
<tr>
<td>Gastric mean amplitude of contraction pressure (mm Hg)</td>
<td>0.2 (0.1–0.9)</td>
<td>0.2 (0.1–1.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Gastric motility index</td>
<td>20 (4.81–127.7)</td>
<td>29 (9.2–113.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Gastric frequency of contractions (contractions/min)</td>
<td>0.75 (0.2–2.8)</td>
<td>1 (0.3–2.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Gastric pH</td>
<td>1.7 (1.5–1.9)</td>
<td>1.8 (1.2–2.4)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

**Small bowel**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Home</th>
<th>Hospital</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum contraction pressure (mm Hg)</td>
<td>101 (60–121)</td>
<td>91.5 (63–137)</td>
<td>0.79</td>
</tr>
<tr>
<td>Mean amplitude of contraction pressure (mm Hg)</td>
<td>4.1 (1–11.0)</td>
<td>6.6 (3.1–11.3)</td>
<td>0.43</td>
</tr>
<tr>
<td>Motility index</td>
<td>306.2 (67.9–894.4)</td>
<td>367.8 (163.5–1067.8)</td>
<td>0.76</td>
</tr>
<tr>
<td>Frequency of contractions (contractions/min)</td>
<td>10.9 (0.7–16)</td>
<td>7.7 (3.8–16.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>pH</td>
<td>7.9 (7.3–8.8)</td>
<td>8.1 (6.8–9.9)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Home</th>
<th>Hospital</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum contraction pressure (mm Hg)</td>
<td>96 (62–158)</td>
<td>109 (47–143)</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean amplitude of contraction pressure (mm Hg)</td>
<td>0.6 (0.4–1)</td>
<td>1.1 (0.2–15)</td>
<td>0.29</td>
</tr>
<tr>
<td>Motility index</td>
<td>76.1 (43.5–160.9)</td>
<td>98.3 (20.5–128.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>Frequency of contractions (contractions/min)</td>
<td>0.6 (0.4–0.9)</td>
<td>1 (0.2–1.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>pH</td>
<td>6.2 (5.8–7.4)</td>
<td>6.4 (5.9–8.9)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Small bowel included the duodenum, jejunum, and ileum, and large bowel included the cecum, colon, and rectum.

Table 1—Median (range) values of GIT parameters measured by an orally administered WMC in 11 healthy dogs at home and during hospitalization until the capsule passed in the feces.

Table 2—Median (range) values of small and large bowel parameters measured by an orally administered WMC in 11 healthy dogs at home and during hospitalization until the capsule passed in the feces.
time during hospitalization (71.8 hours; range, 10.7 to 163.0 hours) was significantly ($P = 0.05$) longer than that at home (17.6 hours; range, 9.7 to 80.8 hours). No other measured gastric parameter, including pH, maximum contraction pressure, mean amplitude of contraction pressure, motility index, and frequency of contraction, differed significantly between study phases. Value ranges were wide in both phases, suggesting considerable intra- and interdog variability.

In 9 dogs at home and in 8 dogs during hospitalization, high-amplitude intraluminal pressure contractions (force of contraction) were detected when the WMC was exiting the stomach. These pressure patterns may have corresponded to phase III MMCs. The SBTT was comparable between study phases, with a value of 4.2 hours when dogs were at home and 3.4 hours during hospitalization ($P = 0.55$; Table 1). Values of no other measured small bowel parameter, including pH, maximum contraction pressure, mean amplitude of contraction pressure, motility index, and frequency of contractions, differed significantly between phases (Table 2). Similar to the small bowel, the LBTT was comparable between study phases, with a median value of 25 hours when dogs were at home and 22 hours during hospitalization ($P = 0.57$). Values of no other measured large bowel parameter differed significantly between phases.

**Discussion**

In the present study, no differences were identified in GIT pH, motility pattern, motility index, or total transit time between healthy dogs when monitored at home versus during hospitalization. However, a significant prolongation of gastric emptying time was identified when these dogs were hospitalized. This prolongation was not preceded by changes in the force of GIT contraction (amplitude of pressure contractions) or frequency of contractions, and the mechanisms underlying the prolongation remain to be elucidated. Similar prolongations of gastric emptying time during stressful conditions have been reported for rats, dogs, and humans.$^{11,24–26}$

During stressful situations, the body response is not limited to ANS activity and cortisol release. Hormones such as corticotropin-releasing factor, motilin, and ghrelin also play a role. In addition to cortisol regulation, corticotropin-releasing factor induces a decrease in plasma motilin concentration, which can disrupt MMCs.$^{27–29}$ Meanwhile, in response to stress, plasma ghrelin concentration can increase.$^{30}$ Both motilin and ghrelin contribute to modulation of GIT motility.$^{28–31}$ In the present study, ANS activity and circulating hormone concentrations were not assessed. Therefore, we can only speculate on potential causes and the pathophysiologic reasons for the prolonged gastric emptying time when dogs were hospitalized.

In human medicine, the presence of MMCs is considered important when the WMC is used for evaluation of GIT function. In such circumstances, gastric emptying time is dependent mainly on phase III of the MMCs.$^{32}$ In the present study, we noticed that in some dogs a cluster of high-amplitude pressure contractions (force of contraction) occurred when the WMC was exiting the stomach. However, these observations were poorly consistent within or between dogs, thereby limiting the ability to reliably draw conclusions regarding the importance of this finding.

A previous study$^{19}$ revealed good correlation between GIT findings in dogs obtained by use of a WMC and radioisotope scintigraphy. Radioisotope scintigraphy is considered the gold standard technique for assessment and measurement of gastric emptying time in dogs. Despite the good reported correlation between measurement techniques, large variability in gastric emptying times was identified within and between dogs in the present study.

The large size of the WMC is believed to reflect the passage of solid material through the GIT. However, in small dogs, the WMC may have been too large to allow normal passage through the narrower pylorus. Typically, gastric solid particles must be broken down to $< 2$ mm in diameter to exit the stomach. The WMC was larger than this (13 X 27 mm) and may have represented a larger solid-phase particle. We noticed radiographically that the WMC did not exit the stomach of some dogs following the first meal during the hospitalization phase of the study. Rather, the stomach emptied several times before the WMC eventually exited the stomach.

The large range in data obtained by use of the WMC in the present and other studies$^{15–21}$ suggests either large interdog variability or low technique sensitivity. Differences in body size could have contributed to the large range observed. However, a previous study$^{20}$ revealed no significant difference in GIT transit times in dogs of various body sizes when the same WMC technique was used.

In rats and humans, anxiety and stress result in not only a prolonged gastric emptying time but also a decrease in SBTT and increase in LBTT.$^{33}$ In the present study, no significant difference in SBTT or LBTT was identified when dogs were at home or hospitalized. The low sample size and large variability observed hindered our ability to detect any differences that might have actually existed.

The finding that gastric pH did not decrease when dogs were hospitalized in the present study was interesting. Observed gastric pH values were within previously reported ranges for healthy dogs.$^{34,35}$ In rats and humans, emotional and physical stress do not always induce changes in gastric pH.$^{17,36}$ It is possible that hospitalization of healthy dogs does not influence gastric acid secretion. However, in critically ill hospitalized patients, stress can result in increased gastric acid secretion and subsequent ulceration, suggesting that other factors such as splanchnic perfusion may play a role.$^{18,37}$

In the present study, hospitalization of healthy dogs resulted in a longer gastric emptying time than
when dogs were at home. The potential clinical implications of this finding include hindering of evaluations for GIT motility disorders, erratic intestinal drug absorption secondary to delayed gastric emptying time, and prolonged passage of gastric foreign material. Gastric dilatation–volvulus can spontaneously occur in dogs during hospitalization, and prolonged gastric emptying time could be a predisposing factor.\textsuperscript{38,39} Gastric luminal pH did not change significantly during hospitalization in the present study when noninvasive but potentially stress-inducing procedures (eg, restraint, individual confinement, and radiography) were performed. However, evaluation of dogs hospitalized for different clinical disorders may lead to different findings. Dogs hospitalized in an intensive care unit can develop hemorrhagic gastrointestinal disease,\textsuperscript{40} and additional research is needed to understand the role of gastric pH in the development of this disease. Also, the variability observed with the WMC technique in the present study was large and this should be considered when the technique is used for clinical purposes. We do not recommend use of the WMC for dogs weighing < 20 kg because the WMC may be retained in the stomach for an abnormally prolonged period.

**Acknowledgments**

Supported by Morris Animal Foundation (grant No. D10CA-016). The authors thank Dr. Kathryn Touran for editorial assistance.

**Footnotes**

1. Purina EN gastroenteric canine formula, Nestlé-Purina PetCare Co, St. Louis, Mo.
2. SmartPill, SmartPill Co, Buffalo, NY.
3. MotilG1 software, version 2.5, SmartPill Co, Buffalo, NY.

**References**


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**From this month’s *AJVR***

**Pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide in cats after oral, intravenous, and intraperitoneal administration of cyclophosphamide**

Katherine A. Stroda et al

**OBJECTIVE**
To characterize pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide (4-OHCP) in the plasma of healthy cats after oral, IV, and IP administration of cyclophosphamide.

**ANIMALS**
6 healthy adult cats.

**PROCEDURES**
Cats were randomly assigned to receive cyclophosphamide (200 mg/m²) via each of 3 routes of administration (oral, IV, and IP); there was a 30-day washout period between successive treatments. Plasma samples were obtained at various time points for up to 8 hours after administration. Samples were treated with semicarbazide hydrochloride to trap the 4-OHCP in stable form, which allowed for cyclophosphamide and trapped 4-OHCP to be simultaneously measured by use of tandem mass spectrometry. Pharmacokinetic parameters were determined from drug concentration-versus-time data for both cyclophosphamide and 4-OHCP.

**RESULTS**
Cyclophosphamide was tolerated well regardless of route of administration. Pharmacokinetic parameters for 4-OHCP were similar after oral, IV, and IP administration. Area under the concentration-time curve for cyclophosphamide was smaller after oral administration than after IV or IP administration.

**CONCLUSIONS AND CLINICAL RELEVANCE**
Cyclophosphamide can be administered interchangeably to cats as oral, IV, and IP formulations, which should provide benefits with regard to cost and ease of administration to certain feline patients. (*Am J Vet Res* 2017;78:862–866)

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