

# A randomized crossover study of compounded liquid sildenafil for treatment of generalized megaesophagus in dogs

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## OBJECTIVE

To determine whether delivery of compounded liquid sildenafil directly to the stomach of dogs with megaesophagus (ME) would affect esophageal clearance, regurgitation frequency, body weight, or quality of life.

## ANIMALS

10 client-owned otherwise healthy dogs with stable ME.

## PROCEDURES

A randomized crossover study was performed. Dogs received either sildenafil (1 mg/kg, PO, q 12 h) or a placebo for 14 days, followed by a 7-day washout period, then the opposite treatment for 14 days. Esophageal clearance time was assessed by means of videofluoroscopy prior to treatment and on day 1 of each treatment period. Owners maintained logs of regurgitation episodes and quality of life.

## RESULTS

Compounded liquid sildenafil moved into the stomach during 21 of 30 (70%) videofluoroscopy sessions. Sildenafil resulted in a significant reduction in the number of regurgitation episodes (median, 3.5 episodes/wk; range, 0 to 14.5 episodes/wk), compared with baseline (median, 6.5 episodes/wk; range, 1.5 to 19.5 episodes/wk) and the placebo (median, 4 episodes/wk; range, 0 to 28 episodes/wk), and a significant increase in body weight (median, 22.05 kg; range, 6 to 26.3 kg), compared with baseline (median, 21.55 kg; range, 5.1 to 26.2 kg) and the placebo (median, 22.9 kg; range, 5.8 to 25.9 kg). There were no differences in esophageal clearance times or quality-of-life scores between sildenafil and placebo.

## CLINICAL RELEVANCE

Although significant differences with placebo administration were identified, clinically relevant improvements were not seen with the use of compounded liquid sildenafil in dogs with ME.

**M**egaesophagus (ME) is characterized by reduced to absent esophageal motility resulting in dilation of the esophagus and accumulation of ingesta in the esophageal lumen; it is the most common cause of regurgitation in dogs.<sup>1-3</sup> In dogs with generalized ME, regardless of the underlying cause, complications such as esophagitis, weight loss, malnourishment, dehydration, and aspiration pneumonia are commonplace and lead to a guarded to poor prognosis.<sup>1-8</sup> Previous studies<sup>3,7</sup> have estimated survival times of 1 to 3 months after diagnosis with an overall case mortality rate of 74%. Death or euthanasia is often the result of complications or owner frustration with the management that is required, which is lifelong and primarily focuses on feeding strategies to reduce retention of ingesta and subsequent regurgitation.<sup>2,8</sup> To improve management, treatments to reduce the retention of solids and liquids in the

esophagus would be ideal to prevent regurgitation and development of life-threatening complications.

In humans, ME most often develops secondary to achalasia, a primary esophageal motor disorder that results in reduced to absent peristalsis, hypertonicity of the gastroesophageal sphincter (GES), and subsequent failure of the sphincter to open in response to swallowing, resulting in ingesta accumulation, esophageal dilation, and hypomotility if not addressed.<sup>9</sup> This causes clinical signs similar to those seen in dogs with ME, in which there also appears to be a lack of synchrony between swallowing and relaxation of the GES, although hypertonicity of the GES is not a common finding in affected dogs. One pharmacologic intervention for achalasia that has been investigated in people is sildenafil, a phosphodiesterase-5 inhibitor that relaxes smooth muscle, including the GES. Various studies<sup>10-16</sup> have found

that sildenafil resulted in a significant reduction in GES tone, reaching maximum effect approximately 10 minutes after administration and with effects lasting approximately 1 hour following administration. The use of sildenafil to relax the GES may be relevant in dogs with ME, even though these dogs do not specifically have achalasia, because relaxing the GES may allow food material to pass into the stomach more quickly and consistently. A recent study<sup>17</sup> evaluated the effects of liquid sildenafil (1 mg/kg) in puppies with congenital ME, using radiographic changes in esophageal dilation and regurgitation frequency as outcome measures. This study found that liquid sildenafil was well tolerated and that there were improvements in the number of regurgitation episodes recorded by owners.

To our knowledge, no studies to date have evaluated changes in GES tone in dogs with ME in response to sildenafil administration or assessed the real-time effects of the drug on the movement of ingested material. The purpose of the study reported here was to determine whether compounded liquid sildenafil could reduce clinical signs and complications in dogs with ME. Specific aims were to determine whether liquid sildenafil was able to reach the stomach in dogs with ME; to compare clearance times of liquids and solids in dogs with ME with and without prior administration of compounded liquid sildenafil; and to compare frequency of regurgitation and owner perceptions of quality of life before and during daily administration of compounded liquid sildenafil at home.

## Materials and Methods

### Case selection

Ten client-owned dogs > 1 year of age in which ME had been previously diagnosed were recruited to participate in the study. Dogs were eligible for inclusion in the study only if they had stable disease, defined as having no new clinical signs or changes in signs reported by the owners within the 3 months prior to study enrollment. Owners of all dogs included in the study provided informed consent.

Testing for ME prior to study enrollment included measurement of serum total thyroxine concentration, baseline serum cortisol concentration (with ACTH stimulation testing if baseline serum cortisol concentration was < 2.0 µg/dL), creatine kinase activity, and acetylcholine receptor antibody titer. All dogs underwent complete evaluations to determine an underlying cause for their ME. The presence of regurgitation was necessary for inclusion in the study.

Health status was confirmed at the time of study enrollment by reviewing medical records and performing a complete physical examination, CBC, serum biochemistry panel, urinalysis, and thoracic radiography to screen for evidence of aspiration pneumonia. Dogs were excluded from the study if they had any concurrent diseases not directly associated with their ME diagnosis, had received medications that could interfere with the function of the

GES (eg, metoclopramide, cisapride, or sildenafil) within the 3 weeks prior to enrollment, had evidence of aspiration pneumonia on screening radiographs, or would not tolerate handling or sitting upright in a Bailey chair for a prolonged period of time. The study protocol was approved by the Washington State University Institutional Animal Care and Use Committee.

### Study design

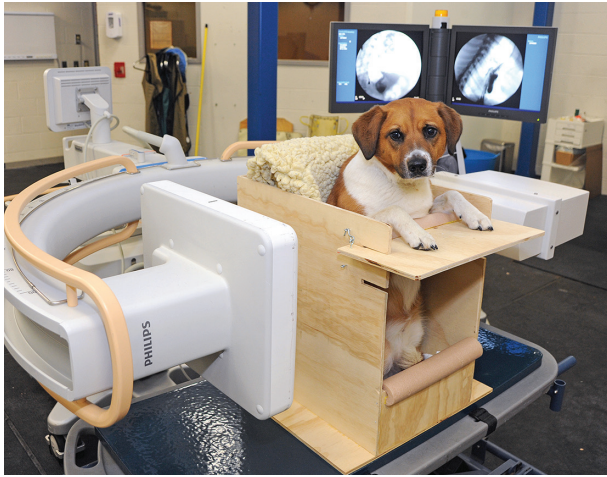
The study was designed as a randomized crossover study with compounded beef-flavored liquid sildenafil (Northwest Pharmacy Services Inc) as the test treatment. Liquid sildenafil was compounded from commercial bulk sildenafil powder (sildenafil citrate powder; Medisca) suspended in an almond oil fixed oil suspension vehicle (PCCA) and formulated to contain 20 mg of sildenafil/mL. A placebo (Northwest Pharmacy Services Inc) was made in the same manner by substituting calcium carbonate (Fagron) for the sildenafil. The sildenafil and placebo solutions were made in batches and had a shelf life of 6 months at room temperature. Dispensing instructions included shaking the bottle well before administering each dose.

Dogs were randomly assigned to receive either compounded liquid sildenafil (1 mg/kg, PO, q 12 h) or an equivalent volume of the placebo for 14 days, followed by a minimum washout period of 7 days, and then the opposite treatment for 14 days. Randomization was performed by an individual with no other involvement in the study who labeled the medications as A or B and then assigned dogs to an A-B or B-A sequence on the basis of a coin flip. The liquid sildenafil and placebo for both in-hospital and at-home use was dispensed by the hospital pharmacy; researchers and owners were blinded to which medication was being administered.

For the 2 weeks prior to the first study visit, owners were required to keep a log of their dog's regurgitation episodes (**Supplementary Appendix S1**). Log sheets provided instructions for recording the information and included the following description of regurgitation: "A regurgitation episode would consist of a passive expulsion of material out of the mouth or into the mouth."

During the first study visit, information was collected from the owners detailing disease history and management, such as the typical frequency, timing, and nature of regurgitation; feeding strategies; ability to tolerate water; and current diet (including consistency of the food), along with any other medical history, including any previous episodes of aspiration pneumonia (**Supplementary Appendix S2**).

Baseline videofluoroscopy was then performed with dogs sitting upright in a Bailey chair (**Figure 1**). The same fluoroscopy unit (OEC 9600 C-Arm Unit; GE Healthcare) was used for all dogs. Bailey chairs were constructed of thin plywood so as to not affect image resolution. All dogs were fasted for 12 hours prior to videofluoroscopy, and none of the dogs were sedated. For baseline videofluoroscopy, dogs were seated upright in the Bailey chair and given 5 mL of a 25% iohexol solution diluted with



**Figure 1**—Photograph of a dog with megaesophagus positioned in a Bailey chair for videofluoroscopic evaluation of esophageal clearance of liquids and solids.

broth.<sup>18</sup> This volume was selected to ensure an adequate amount of contrast medium would reach the GES without excessive retention in the rostral portion of the esophagus and was intended to mimic liquid sildenafil administration. Videofluoroscopic images were collected at a rate of 30 frames/s for 5 to 10 seconds after administration of the contrast medium and then at 5-minute intervals until all the contrast medium had passed from the esophagus or 30 minutes had passed.

The dog was then offered a slurry of canned food, water, and iohexol (20 mL of iohexol/1 cup of food). In all cases, a canned gastrointestinal diet (Purina Pro Plan EN Gastroenteric; Nestlé Purina) was used, and the amount of food was calculated as 10% of the dog's resting energy requirement (calculated as  $[30 \times \text{body weight in kilograms}] + 70$ ), so as to standardize volumes for the variably sized dogs. Dog were allowed to eat voluntarily. Videofluoroscopic images were again obtained at a rate of 30 frames/s for 5 to 10 seconds after administration of the slurry and then at 5-minute intervals until all the contrast medium had passed from the esophagus or 30 minutes had passed.

On the second day of the first study visit, dogs were randomized to a treatment sequence, and depending on the treatment sequence, dogs received either compounded sildenafil liquid (1 mg/kg) or the same volume of the placebo. Both articles were diluted to a total volume of 5 mL with broth and 25% iohexol. Videofluoroscopy was performed as on the previous day immediately after administration of the liquid. Then, to better mimic at-home administration, once 5 minutes was reached or all contrast medium had cleared from the esophagus, the slurry was offered, and videofluoroscopy was performed again.

Following the second videofluoroscopy procedure, dogs were discharged, and the liquid sildenafil or placebo was dispensed. Owners were instructed to dilute the medication to a volume of 5 mL with liquid to increase the total volume and match the method of delivery used during videofluoroscopy and to

offer the liquid to the dog to drink freely or carefully syringe it into the dog's mouth.

Dogs were given the liquid sildenafil or placebo at the time of feeding for 14 days, and administration was then discontinued to allow for a minimum 7-day washout period.<sup>19</sup> Owners were requested to maintain the log of their dog's regurgitation episodes throughout this period.

Following the initial treatment and washout periods, dogs were returned for a second study visit. At this time, dogs were given the alternative treatment, and videofluoroscopy was performed as described previously. Dogs were then discharged, and the alternative treatment was dispensed. Owners were instructed to administer the medication for 14 days and to continue to log all regurgitation episodes for 3 weeks (ie, for the 14-day treatment period and a 7-day washout period). At the completion of each treatment period and prior to the 7-day washout period, each dog was weighed, and body weight was recorded.

### Quality-of-life assessment and treatment prediction

Owners were asked to provide an assessment of their dog's quality of life prior to enrollment in the study and at the end of each treatment period. Quality of life was graded as poor, fair, good, or excellent (Supplementary Appendix S2) on the basis of variables such as attitude, energy level, and general perception of ability to perform normal daily activities. At the end of the study, owners were asked to indicate whether they thought their dog was receiving sildenafil or the placebo during each treatment period.

### Statistical analysis

Data from a previous study<sup>20</sup> were used to determine the number of dogs required in the study. With a power of 80% and  $\alpha$  of 0.05, a sample size of 8 dogs was required to detect at least a 5-minute difference in esophageal clearance between placebo versus sildenafil with an SD of at least 3.5 minutes.

Descriptive statistics (mean, median, range, and interquartile [75th percentile minus 25th percentile] range [IQR]) were calculated. Quality-of-life scores were coded as ordinal data (excellent = 2, good = 1, fair = -1, and poor = -2) for calculation of descriptive statistics. The Shapiro-Wilk test, frequency histograms, and skewness and kurtosis statistics were used to determine that data for number of regurgitation episodes per week, body weight, and quality-of-life scores were not normally distributed. For number of regurgitation episodes per week and body weight, the Wilcoxon signed rank test for paired data was used to compare pre-treatment (baseline) values with values obtained at the end of each treatment (sildenafil or placebo) period. The Wilcoxon signed rank test for related samples was used to compare quality-of-life scores between baseline and the end of each treatment period. Linear regression was used to determine whether body weight was associated with number of regurgitation episodes per week.

All statistical analyses were performed with standard software (SPSS version 27; IBM Corp). Values of  $P \leq 0.05$  were considered significant.

## Results

### Animals

All 10 dogs completed the study. There were 4 spayed females and 6 neutered males. Four of the dogs were German Shepherd Dogs, 1 was a Labrador Retriever, 1 was a West Highland White Terrier, and 4 were mixed-breed dogs. Median weight of the dogs at the start of the study was 21.55 kg (range, 5.1 to 40.1 kg), and median age was 3 years (range, 1 to 8.8 years). Three dogs had congenital ME and 7 had idiopathic acquired ME.

None of the owners expressed any concerns regarding administration of the solutions, and no missed doses were reported. All but 1 dog consumed the beef-flavored liquid freely, with 1 dog requiring syringing for both the sildenafil and placebo solutions. No animals showed any adverse effects while receiving sildenafil or the placebo. All dogs had a minimum washout period of 7 days between treatments (median, 15 days; range, 7 to 37 days). All dogs ate the entire slurry mixture freely. Two dogs were receiving concurrent medications, with one dog receiving omeprazole once daily and a second dog receiving famotidine and oclacitinib.

### Regurgitation episodes

There was no significant ( $P = 0.385$ ) difference between number of regurgitation episodes per week at baseline (median, 6.5 episodes/wk; range, 1.5 to 19.5 episodes/wk; IQR, 12.75 episodes/wk) and number of regurgitation episodes per week during the 2 weeks of placebo treatment (median, 4 episodes/wk; range, 0 to 28 episodes/wk; IQR, 12 episodes/wk). In contrast, there was a significant ( $P = 0.05$ ) difference between number of regurgitation episodes per week at baseline and number of regurgitation episodes per week during the 2 weeks of sildenafil treatment (median, 3.5 episodes/wk; range, 0 to 14.5 episodes/wk; IQR, 6.6 episodes/wk). Numbers of regurgitation episodes per week during the washout period after the placebo treatment (median, 3 episodes/wk; range, 0 to 17 episodes/wk; IQR, 6.5 episodes/wk) and during the washout period after sildenafil treatment (median, 4 episodes/wk; range, 0 to 12 episodes/wk; IQR, 11 episodes/wk) did not differ significantly from each other or from numbers of regurgitation episodes per week at baseline or during either treatment period.

Three dogs had an increased frequency of regurgitation episodes and 7 dogs had a decreased frequency of regurgitation episodes when the baseline period was compared with the placebo treatment period. Three dogs had an increased frequency of regurgitation episodes, 5 dogs had a decreased frequency of regurgitation episodes, and 2 dogs had no change in frequency of regurgitation episodes when the baseline period was compared with the sildenafil treatment period.

### Body weight

Body weight at baseline (median, 21.1 kg; range, 5.1 to 26.2 kg; IQR, 6.3 kg) was not significantly ( $P = 0.11$ ) different from body weight at the end of the placebo treatment period (median, 22.9 kg; range, 5.8 to 25.9 kg; IQR, 7.13 kg). However, body weight at baseline was significantly ( $P = 0.05$ ) different from body weight at the end of the sildenafil treatment period (median, 22.05 kg; range, 6 to 26.3 kg; IQR, 6.48 kg). For 1 dog, body weight at the end of the placebo treatment period was not recorded; therefore, significant testing was performed by excluding this dog.

For the placebo treatment period, median percentage change in body weight from baseline was 2.38% (range, -2.48% to 15.64%; IQR, 14.7%). For the sildenafil treatment period, median percentage change in body weight from baseline was 2.35% (range, -0.52% to 17.65%; IQR, 6.25%). Median percentage change in body weight during the placebo treatment period was not significantly ( $P = 0.866$ ) different from median percentage change in body weight during the sildenafil treatment period. There was no significant linear relationship between body weight and number of regurgitation episodes during either the sildenafil or placebo treatment period.

### Clearance time

During baseline videofluoroscopy, median time for clearance of the 5 mL of 25% iohexol solution diluted with broth (measured in increments of 5 minutes) was 30 minutes (range, 5 to 30 minutes; IQR, 21.25 minutes). There was a total of 30 videofluoroscopy episodes (3 episodes/dog) during which liquid was administered followed by a slurry of canned food, water, and iohexol. During 5 of these episodes, the liquid had moved into the stomach prior to subsequent slurry meal administration. Conversely, during 16 of these episodes, the liquid initially remained in the esophagus, but subsequent administration of the slurry resulted in most or all of the liquid moving into the stomach. During the remaining 9 episodes, the liquid did not move into the stomach and simply mixed with the slurry. Six of these 9 episodes occurred in just 2 dogs, with the remaining 3 episodes occurring in an additional 2 dogs.

Median clearance time of the slurry was 25 minutes at baseline (range, 5 to 30 minutes; IQR, 17.5 minutes), 25 minutes after placebo administration (range, 5 to 30 minutes; IQR, 12.5 minutes), and 22.5 minutes after administration of sildenafil (range, 5 to 30 minutes; IQR, 16.25 minutes). There were no significant differences in time of clearance of the slurry between placebo and baseline ( $P = 0.671$ ) or between sildenafil and baseline ( $P = 0.798$ ).

### Quality of life

At baseline and at the end of each treatment period, quality of life was assessed by the owners of all 10 dogs as good, good-excellent, or excellent. There were no significant differences in quality-of-life scores between baseline and the end of the placebo treatment period ( $P = 0.705$ ), between baseline and



the end of the sildenafil treatment period ( $P > 0.999$ ), or between the end of the placebo treatment period and the end of the sildenafil treatment period ( $P = 0.785$ ). During the placebo treatment period, quality of life decreased from good-excellent to good in 3 dogs, was unchanged in 6 dogs, and increased from good to excellent in 1 dog. During the sildenafil treatment period, quality of life decreased from excellent to good in 1 dog and from good-excellent to good in 1, was unchanged in 6 dogs, and increased from good-excellent to excellent in 1 dog and good to excellent in 1 dog.

### Owner treatment prediction

Five owners correctly guessed when their dog was receiving sildenafil versus the placebo, 2 owners could not distinguish a difference, and 3 owners guessed incorrectly.

## Discussion

Results of the present study indicated that in dogs with ME, administration of sildenafil immediately prior to feeding resulted in significantly fewer episodes of regurgitation and increased body weight, compared with baseline values and values recorded when administering a placebo. However, the degree of change was minimal and may not represent clinically relevant improvements. There were no significant changes in owner-perceived quality of life or significant differences in videofluoroscopic clearance time of food from the esophagus into the stomach. In some dogs, compounded liquid sildenafil did not reach the stomach prior to subsequent feeding. These results suggested that sildenafil could be beneficial in reducing the number of regurgitation episodes experienced by some dogs with ME, but that efficacy could vary substantially between dogs owing to variations in the ability to deliver sildenafil to the stomach.

Because of frequent regurgitation, malnourishment and poor body condition are common complications of ME. If the number of regurgitation episodes can be reduced, more food would be expected to reach the stomach and body weight would be expected to increase. In the present study, body weight was measured at baseline and at the end of each treatment period, and there was a significant increase in body weight following sildenafil treatment but not placebo. This suggests that in patients in which sildenafil does reduce the number of regurgitation events or the volume of regurgitated material, weight gain could occur. This is an important consideration given that chronic malnutrition is a reason why some owners elect euthanasia for dogs with ME.

In the present study, no difference was found among videofluoroscopic clearance times at baseline, after sildenafil administration, and after placebo administration. Several factors could account for this, including failure of the compounded liquid sildenafil to pass into the stomach with sufficient time to become effective. Clearance of liquid was variable in the present study, and in most dogs, liq-

uid did not pass into the stomach before dogs were fed the slurry. Once the slurry was given, the liquid moved into the stomach in a number of dogs. Of the 9 episodes during which the liquid did not move into the stomach before or after slurry administration, 6 of them occurred in 2 dogs. This suggests there may be a patient-dependent component to GES relaxation and the ability of a meal slurry to effectively initiate esophageal transit of an administered liquid. It may also have been associated with individual patient retention of other liquids (eg, saliva or water) in the esophagus between meals, which may cause the liquid to be retained cranial to the GES and prevent passage into the stomach. In addition to variable transit times through the esophagus, absorption may be variable in individual dogs, and the 30 minutes during which videofluoroscopy was performed may not have been sufficient to allow for absorption and the onset of action of the medication. The time to reach maximum concentration of sildenafil in dogs after oral administration is approximately 1 to 2 hours, with therapeutic concentrations likely being achieved within 10 to 30 minutes on the basis of onset of action in humans after oral administration.<sup>10-12,21,22</sup> The half-life of sildenafil in dogs is 3 to 5 hours,<sup>19,21</sup> and there does not appear to be a lasting effect of sildenafil given that there was no significant difference in the number of regurgitation episodes during the washout period versus baseline in our study. This was an important finding, in that prolonged relaxation of the GES could in fact be detrimental if it increases the incidence of gastroesophageal reflux. Upright positioning, as was used in this study, may prevent some reflux events from occurring and may not have been visualized during the imaging period.

As mentioned previously, in some dogs, liquid remained in the esophagus and then mixed with the subsequently administered slurry. This might have prevented passage of a sufficient dose of sildenafil into the stomach, potentially resulting in dose variability. Dogs with ME have a wide variation in clinical severity of their disease. In the present study, some dogs did have marked differences between the sildenafil and placebo treatments both clinically and videofluoroscopically, but this was not reflected in the group findings. This may suggest that sildenafil will prove useful in select individuals, but that a larger population of dogs would be needed to determine whether there is a clear group effect.

One aim of our study was to determine whether liquid sildenafil could be delivered successfully to the stomach of dogs with ME. Liquid medication was chosen owing to concerns that pills or tablets would become trapped in the esophagus, which would be ineffective and could potentially lead to an overdose if multiple doses accumulated and then reached the stomach at the same time. A previous study<sup>20</sup> found that liquids were able to reach the GES but did not clear well in most dogs with ME unless followed by a meal. The reason for this is unknown but could relate to changes in hydrostatic pressure. Given that many of the dogs that did not clear the

liquid at baseline did still clear it following administration of the slurry, all owners were instructed to give the medication in an upright position and then feed their dogs shortly (2 to 5 minutes) after giving the medication, allowing the medication time to reach the GES. Previous studies<sup>21,23</sup> reported that giving sildenafil with a meal did not significantly affect absorption, maximum concentration, or half-life. However, these studies were done using tablets in healthy dogs, and differences in esophageal transit time in dogs with ME as well as the use of a liquid formulation of sildenafil in the present study could affect these variables.

For all dogs in the present study, quality of life at baseline was assessed by the owners as good, good-excellent, or excellent, and quality of life was, on average, unchanged following both the sildenafil and placebo treatment periods. These findings were not consistent with findings of the only other study<sup>17</sup> that has evaluated the effects of sildenafil in dogs with ME. Although that study did not evaluate real-time clearance of ingested material, there was clinical improvement in the number of regurgitation episodes recorded by owners. Additionally, in the present study, only 5 of the 10 owners correctly guessed when their dog was receiving sildenafil versus the placebo. One consideration is that many dogs were already rated as having good or excellent quality of life at baseline, leaving little room for improvement. In dogs with mild ME, small changes will be difficult to detect, whereas dogs with severe disease could potentially show marked improvement. However, in dogs with severe disease, liquid medication might not consistently reach the stomach, resulting in a failure to detect a difference. No dogs were excluded from the present study on the basis of disease severity. However, dogs were required to have regurgitation as one of their clinical signs so that a response to treatment could be detected. It may have been useful to characterize the severity of ME in each dog prior to enrollment, given that the severity of ME may have contributed to the lack of a measurable response to sildenafil treatment.

Importantly, quality of life was not perceived as worse during treatment with sildenafil in the present study, and sildenafil was well tolerated at a dose of 1 mg/kg every 12 hours, with none of the dogs having adverse effects when receiving sildenafil. This was consistent with findings of other studies<sup>17,24,25</sup> in which the same dose of sildenafil in dogs did not result in any reported adverse effects. Dogs with ME already have increased risks of regurgitation, aspiration pneumonia, and malnutrition, so medications that cause nausea, vomiting, or a reduced appetite can be especially detrimental to their quality of life and health. A possible downside of compounded liquid sildenafil is the potential for changes in absorption, bioavailability, and efficacy attributable to the compounding process.

The present study had several limitations, one of which was the use of a bulk sildenafil powder to compound the liquid formulation. The authors were not aware until after completion of the study that a

bulk agent was used instead of the FDA-approved finished drug product, which falls outside of legal compounding standards. The purity, potency, and, ultimately, safety of a bulk agent cannot be guaranteed. This type of veterinary compounding is unfortunately quite common, and given the difficulties in giving pills to dogs with ME, the high cost to owners of even generic sildenafil, and the fact that only a grape-flavored brand name liquid formulation is available, it is likely that many owners are electing to purchase compounded liquid sildenafil formulations. Given the widespread use of bulk agents by compounding pharmacies, it is also likely that many veterinarians are prescribing a formulation similar to the one used in the present study. Thus, although the present study's results may have been different if a formulation compounded from a finished drug product had been used, our results were likely representative of findings in clinical practice. Veterinarians should be cautious when prescribing compounded sildenafil formulations for their patients and should ensure that these formulations are being compounded from FDA-approved drug products. The absorption of a compounded liquid made from a bulk powdered agent may be highly variable, which could help explain the lack of efficacy seen in the present study.

Another important limitation of the present study was the small sample size. Future studies enrolling a larger number of dogs would be beneficial to clarify the effects found in our study. The study relied heavily on owner compliance, as owners had to medicate their dogs and record regurgitations for a total of 2 months. However, logs from the owners of enrolled dogs were suggestive of high compliance. Of course, determining whether an episode of regurgitation has occurred can be somewhat subjective. Although this subjectivity could not be eliminated, owners were blinded as to whether their dog was receiving sildenafil or a placebo.

The gold standard for evaluating the GES is measuring pressures by means of manometry.<sup>26,27</sup> This involves passing a catheter down the esophagus and can be challenging in dogs that are awake. For safety reasons, dogs with ME were not sedated. In addition, manometry is expensive and has limited availability. Videofluoroscopy has been shown to be a safe and effective method of assessing esophageal function in dogs with ME without requiring sedation. For these reasons, videofluoroscopy was chosen for our study.

In conclusion, compounded liquid sildenafil may benefit some dogs with ME by reducing the frequency of regurgitation and thereby promoting weight gain. The true clinical impact of sildenafil overall could not be determined in the present study. The lack of a significant difference in owner-perceived quality of life or clearance time of food suggested that any positive effects may be influenced by the severity of ME and individual responses. Future studies with a larger number of dogs would be beneficial to continue to assess use of this medication.

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The authors declare that there were no conflicts of interest.

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## Supplementary Materials

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