

# Safety of contrast-enhanced ultrasonography in dogs and cats: 488 cases (2002–2011)

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**Objective**—To determine the incidence of adverse events within 24 hours after contrast-enhanced ultrasonography (CEUS) in dogs and cats and compare the risk of death within 24 hours after imaging for animals that underwent ultrasonography with and without injection of a contrast agent.

**Design**—Retrospective case-control study.

**Animals**—750 animals (411 case dogs, 238 control dogs, 77 case cats, and 24 control cats).

**Procedures**—At 11 institutions, medical records were reviewed of dogs and cats that had CEUS performed (cases) as were medical records of dogs and cats with clinical signs similar to those of case animals that had ultrasonography performed without injection of a contrast agent (controls). Information regarding signalment; preexisting disease; type, dose, and administration route of contrast agent used; immediate (within 1 hour after CEUS) and delayed (> 1 and ≤ 24 hours after CEUS) adverse events; and occurrence and cause of death (when available) was extracted from each medical record. Risk of death within 24 hours after ultrasonography was compared between case and control animals.

**Results**—Of the 411 case dogs, 3 had immediate adverse events (vomiting or syncope) and 1 had a delayed adverse event (vomiting). No adverse events were recorded for case cats. Twenty-three of 357 (6.4%) clinically ill case animals and 14 of 262 (5.3%) clinically ill control animals died within 24 hours after ultrasonography; risk of death did not differ between cases and controls.

**Conclusions and Clinical Relevance**—Results indicated that CEUS was safe in dogs and cats. (*J Am Vet Med Assoc* 2013;242:1255–1259)

Administration of a contrast agent to a patient will increase the amount of information that can be obtained from any method of diagnostic imaging. Iodinated contrast agents, barium sulfate, and gadolinium are routinely used for radiography, CT, and MRI in both human and animal patients. Although administration of any contrast agent may be associated with the development of adverse events, the benefits of administration are usually considered to exceed the risk.<sup>1–7</sup> In veterinary medicine, the use of CEUS is not as common as the use of other contrast-enhanced imaging techniques. Contrast agents for ultrasonography consist of microbubbles with a size approximately equal to

## ABBREVIATION

CEUS Contrast-enhanced ultrasonography

that of an RBC. These microbubbles typically contain a high-molecular weight gas core that is encapsulated in a lipid or polymer shell. The gas core makes the microbubble extremely echogenic such that individual bubbles can be detected ultrasonographically.<sup>8</sup> The microbubbles remain strictly within the vasculature and are used to highlight blood flow and tissue perfusion. The use of CEUS does not involve ionizing radiation and is not associated with nephrotoxicosis; therefore,

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it is commonly used in human patients in Europe and Asia.<sup>9,10</sup> In the United States, the FDA has not approved microbubble contrast agents for use in diagnostic imaging procedures except for cardiac imaging in people. In 2007, the FDA announced a black box warning for all ultrasonographic contrast agents following the death of 4 patients after injection of a microbubble contrast agent, although none of those deaths was proven to have been caused by injection of the contrast agent.<sup>11</sup> Since then, results of large, multicenter studies<sup>12,13</sup> indicate that CEUS is a safe diagnostic imaging method for human patients.

Ultrasonography is the most common cross-sectional diagnostic imaging method used in dogs and cats because it is readily available and does not require animals to be anesthetized. Results of multiple studies<sup>14–18</sup> in which CEUS was used in dogs and cats suggest that CEUS is a clinically valuable diagnostic procedure, and no adverse events associated with injection of various contrast agents were reported. However, the true incidence of adverse events associated with CEUS is unknown. Accurate information about potential adverse events associated with CEUS in dogs and cats is important for the education of pet owners and referring veterinarians. The purpose of the study reported here was to perform a retrospective multicenter survey to determine the incidence of adverse events within 24 hours after CEUS in dogs and cats and to calculate the risk for death within 24 hours after ultrasonography for dogs and cats that had CEUS performed, compared with that for dogs and cats that had ultrasonography performed without injection of a contrast agent. We hypothesized that the incidence of adverse events within 24 hours after CEUS would be low and that the risk of death in dogs and cats within 24 hours after CEUS would not differ from that in dogs and cats with similar clinical signs that had ultrasonography performed without injection of a contrast agent.

## Materials and Methods

**Case selection**—Medical records were reviewed of dogs and cats examined between February 2002 and June 2011 at 11 veterinary diagnostic imaging centers. A case was defined as a dog or cat that had CEUS performed and included clinically ill dogs and cats for which CEUS was performed for diagnostic purposes and healthy dogs and cats for which CEUS was performed for research purposes. A control was defined as a clinically ill dog or cat that had ultrasonography performed without injection of a contrast agent for diagnostic purposes. Control animals were matched to the clinically ill case animals on the basis of species and indication for ultrasonography as well as the institution where and the time period during which the animal was examined (within the same calendar year of performance of the CEUS for the case animal) so as to avoid potential bias in outcome caused by the evolution of treatment regimens or policies within or among institutions.

**Medical records review**—For each study animal, data obtained from the medical record included signalment, information about preexisting conditions

(cardiovascular, pulmonary, urinary, hepatobiliary, or neurologic abnormalities) that may have affected the development of adverse events, and indication for ultrasonography. For case animals, information was also obtained regarding the type, dose, and administration route of the contrast agent used; the number and type of CEUS examinations performed; and the occurrence of immediate (within 1 hour after CEUS) and delayed (> 1 hour and ≤ 24 hours after CEUS) adverse events. For all study animals, data regarding time and cause of death as well as survival time (if known) were retrieved from the medical records.

**Statistical analysis**—Descriptive statistics were generated. The risk ratio for death was calculated and compared between case and control animals. All statistical analyses were performed with statistical software,<sup>a</sup> and values of  $P < 0.05$  were considered significant.

## Results

**Animals**—Seven hundred fifty animals were enrolled in the study; 488 animals (411 dogs and 77 cats) had CEUS performed, and 262 animals (238 dogs and 24 cats) were enrolled as controls and had ultrasonography performed without injection of a contrast agent. Of the 411 case dogs, 314 were clinically ill and CEUS was performed for diagnostic purposes, whereas 97 were healthy and CEUS was performed for research purposes. Of the 77 case cats, 43 were clinically ill and CEUS was performed for diagnostic purposes, whereas 34 were healthy and CEUS was performed for research purposes. For some case animals, an appropriate control animal was not identified within the specified period of interest; therefore, more case animals were enrolled in the study than were control animals.

The median age of case dogs was 9 years (range, 1 to 20 years), and the median age of control dogs was 9 years (range, 2 to 16 years). The median weight of case dogs was 25 kg (55 lb; range, 2 to 98 kg [4.4 to 215.6 lb]), and the median weight of control dogs was 23.3 kg (51.3 lb; range, 3 to 86 kg [6.6 to 189.2 lb]). Of the 649 case and control dogs, 61 (9.4%) were sexually intact females, 256 (39.4%) were spayed females, 106 (16.3%) were sexually intact males, 196 (30.2%) were neutered males, and 30 (4.6%) were of unknown sex.

The median age of case cats was 10.5 years (range, 1 to 21 years), and the median age of control cats was 11.5 years (range, 2 to 17 years). The median weight of case cats was 4.5 kg (9.9 lb; range, 2 to 9.5 kg [4.4 to 20.9 lb]), and the median weight of control cats was 3.8 kg (8.4 lb; range, 2.1 to 9.3 kg [4.6 to 20.5 lb]). Of the 101 case and control cats, 4 (4%) were sexually intact females, 36 (35.6%) were spayed females, 9 (8.9%) were sexually intact males, 49 (48.5%) were neutered males, and 3 (3%) were of unknown sex.

**CEUS**—For each of the case animals, CEUS was performed via IV administration of 1 of 5 contrast agents; perflutren lipid microspheres,<sup>b</sup> galactose (99.9%) and palmitic acid (0.1%) microspheres,<sup>c</sup> perflutren protein type A microspheres,<sup>d</sup> phospholipid-stabilized sulphur hexafluoride microspheres,<sup>e</sup> or perfluorocarbon lipid microspheres.<sup>f</sup> The percentage of case animals that were administered each contrast agent

was summarized (Figure 1). The majority of case animals (316/411 [76.9%] dogs and 75/77 [97.4%] cats) had only 1 contrast-enhanced ultrasonographic examination performed, although 2 contrast-enhanced ultrasonographic examinations were performed on 63 of 411 (15.3%) dogs and 2 of 77 (2.6%) cats and 3 contrast-enhanced ultrasonographic examinations were performed on 32 of 411 (7.8%) dogs. A contrast-enhanced ultrasonographic examination most frequently (48.9% and 98.1% of examinations performed in dogs and cats, respectively) required 2 bolus injections of the contrast agent, although 35.7% and 2.6% of the examinations performed on dogs and cats, respectively, were performed with only 1 bolus injection of the contrast agent. Three bolus injections of the contrast agent were required for 14.5% and 1.3% of examinations performed on dogs and cats, respectively, and 4 bolus injections of the contrast agent were required for 1.0% of the examinations performed on dogs. In the case dogs, the spleen and liver were the organs most commonly examined via CEUS, whereas in the case cats, the pancreas was the most common organ examined via CEUS (Figure 2).

**Adverse events**—None of the case cats developed immediate or delayed adverse events after CEUS. Of the 411 case dogs, 3 (0.73%) developed an immediate adverse event (ie, vomiting [ $n = 2$ ] or syncope [1]) and 1 (0.24%) developed a delayed adverse event (vomiting). All adverse events occurred after the first contrast-enhanced ultrasonographic examination was performed on that dog; 1 dog subsequently had 2 additional contrast-enhanced ultrasonographic examinations performed without the development of an adverse event. Of the 3 immediate adverse events, 2 occurred after the first injection of the contrast agent and 1 occurred after the second injection of the contrast agent. Of the 4 adverse events, 2 (vomiting and syncope) occurred after administration of the perflutren lipid microsphere contrast agent, 1 (vomiting) occurred after administration of the perflutren protein A microsphere contrast agent, and 1 (vomiting) occurred after administration of the phospholipid-stabilized sulfur hexafluoride microsphere contrast agent. None of the 4 dogs that developed adverse events were sedated or anesthetized during CEUS.

The 3 case dogs that vomited after CEUS each had a preexisting disease condition; 1 dog had a heart murmur caused by mitral endocardiosis, 1 dog had hematuria, and 1 dog had liver enzyme activities increased from the reference interval. For each dog, the vomiting

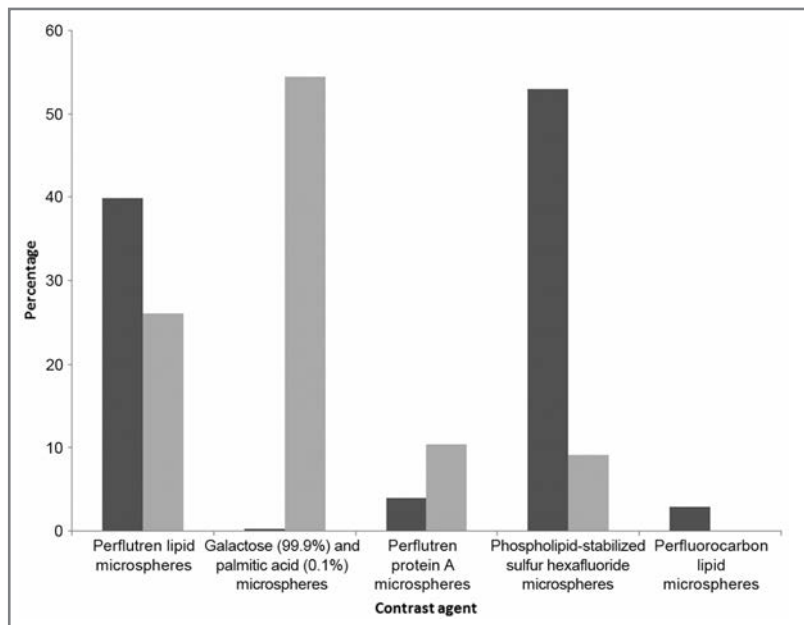


Figure 1—Percentage of case dogs (dark gray bars;  $n = 411$ ) and cats (light gray bars; 77) that were administered 1 of 5 contrast agents during CEUS in a retrospective case-control study conducted at 11 veterinary diagnostic imaging centers between February 2002 and June 2011.

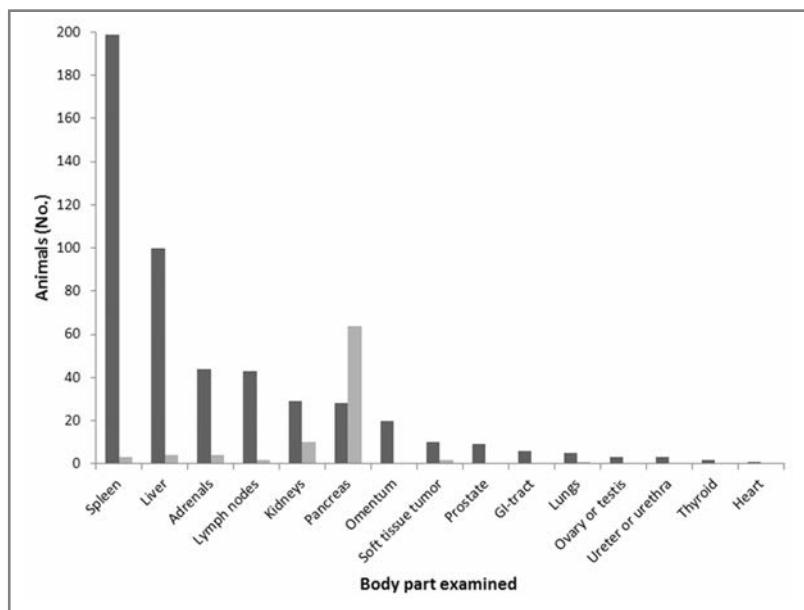


Figure 2—Frequency with which various body parts were examined via CEUS performed on the case dogs (dark gray bars;  $n = 411$ ) and cats (light gray bars; 77) of Figure 1. Some animals had multiple body parts evaluated via CEUS. See Figure 1 for remainder of key. GI = Gastrointestinal.

was an isolated incident that did not require treatment. All 4 dogs survived and were reported to be alive at 4 months ( $n = 3$ ) or 3 years (1) after CEUS.

Of the 357 clinically ill case animals (314 dogs and 43 cats), 23 (6.4%; 19 dogs and 4 cats) died within 24 hours after CEUS, whereas 14 of 262 (5.3%; 13 dogs and 1 cat) control animals died within 24 hours after the ultrasonographic examination. Of the 23 case animals that died, 21 were euthanized and the cause of death was not reported in the remaining 2 animals.

For the case animals that were euthanized, the reasons provided were poor prognosis (20/21 [95.2%]), progressive disease (3/21 [14.3%]), surgical complications (1/21 [4.8%]), and financial constraints (1/21 [4.8%]); multiple reasons were provided for some animals. All of the control animals that died within 24 hours after the ultrasonographic examination were euthanized, and the reasons provided for euthanasia included poor prognosis (14/14), financial constraints (2/14), and progressive disease (2/14); multiple reasons were provided for some animals. The risk of death for clinically ill case animals within 24 hours after the ultrasonographic examination did not differ significantly ( $P = 0.57$ ) from that for clinically ill control animals (risk ratio, 1.21; 95% confidence interval, 0.63 to 2.30). Necropsy was performed for 15 of the 23 case animals that died, and no evidence of disease associated with the administration of the contrast agent was detected in any of those 15 animals.

## Discussion

Results of the present study indicated that the prevalence of adverse events (excluding death) within 24 hours after CEUS was low for case dogs (0.2%), and none of the case cats developed adverse events following CEUS. Although 23 of 357 (6.4%) clinically ill case animals (19 dogs and 4 cats) died within 24 hours after CEUS, none of the deaths were believed to have been caused by injection of the contrast agent during CEUS (disease associated with injection of the contrast agent was definitively ruled out for 15 case animals during necropsy). Moreover, the risk of death at 24 hours after ultrasonography did not differ significantly between the case and control animals of the present study, which suggested that CEUS was as safe as ultrasonography without injection of a contrast agent for diagnostic purposes in dogs and cats.

In the present study, adverse events were classified as immediate (within 1 hour after CEUS) or delayed ( $> 1$  hour and  $\leq 24$  hours after CEUS), and immediate adverse events typically occurred promptly after injection of the contrast agent. In human patients, the most commonly reported adverse events following administration of a microbubble contrast agent are headache, nausea, and dizziness and generally affect  $< 1\%$  of patients.<sup>19</sup> Hypersensitivity reactions following administration of a microbubble contrast agent are rare. In human patients with a high cardiologic mechanical index and systolic triggering, CEUS can elicit premature ventricular contractions.<sup>20</sup> In the present study, only 1 animal (dog) had CEUS of the heart performed, and no adverse reactions were reported for that animal. At the cellular level, microbubble contrast agents cause microvascular rupture, which can be useful for delivery of the agent to particular parts of the body that are otherwise difficult to access (ie, across the blood-brain barrier); however, damage to endothelial cells caused by the contrast agents was not permanent.<sup>21,22</sup>

Investigators of only 1 other study<sup>23</sup> that involved dogs have reported adverse events following administration of a microbubble contrast agent. In that study,<sup>23</sup> 2 dogs that were administered a perflutren protein type A

microsphere contrast agent developed anaphylactoid reactions with severe self-limiting hypotension, which was believed to be the result of the dogs reacting to the human albumin component of that contrast agent. Although none of the case animals that were administered the perflutren protein type A microsphere contrast agent in the present study developed adverse events, the proportion of study animals that received that contrast agent was small, and on the basis of results of the other study,<sup>23</sup> administration of the perflutren protein type A microsphere contrast agent is not recommended in animals. Instead, only ultrasonographic contrast agents that do not contain human albumin should be used in veterinary species.<sup>23,24</sup>

The incidence of adverse events within 24 hours after CEUS for the case animals of the present study was comparable to that in various species after administration of other types of contrast agents.<sup>25–31</sup> In human patients, adverse reactions occur in 0.6% to 4% of patients following administration of nonionic iodinated contrast agents, and when ionic iodinated contrast agents are used, the incidence of adverse events increases 3 to 4 times that following administration of nonionic iodinated contrast agents.<sup>25–27</sup> Nephrotoxicosis secondary to administration of an iodinated contrast agent occurs in up to 10% of human patients with clinically normal kidney function.<sup>28</sup> Although the incidence of adverse events after administration of iodinated contrast agents has not been reported for dogs or cats, administration of an iodinated contrast agent resulted in moderate changes in heart rate and blood pressure in 4 of 91 (4%) dogs<sup>29</sup> and 4 of 60 (7%) cats.<sup>30</sup> Also, investigators of another study<sup>31</sup> reported severe adverse reactions in 2 anesthetized dogs following IV administration of an iodinated contrast agent.

In the present study, a temporal relationship was observed between administration of the microbubble contrast agents and the occurrence of adverse events; however, causality of that relationship could not be established because of the presence of confounding factors. One of the case dogs that vomited within 1 hour after injection of the contrast agent had also been administered chemotherapy, which can likewise cause vomiting. The case dog that was classified as having a delayed adverse event reportedly was very excited when it was discharged from the hospital; the owners took the dog home and fed it a large meal, after which it vomited. It is unlikely that injection of the contrast agent the previous afternoon caused that dog's vomiting.

Limitations of the present study include its retrospective nature and the lack of data such as results of CBCs, serum biochemical analyses, and heart rate and blood pressure monitoring before and after CEUS. For example, it is unknown whether the brief episode of syncope in 1 case dog was associated with hypotension. Also, many of the mild adverse events such as headache and dizziness that have been described in human patients following administration of a microbubble contrast agent may not be detectable in dogs and cats.

The risk of a case animal developing an adverse event could not be associated with any particular preexisting condition or contrast agent used because of the low incidence of adverse events within 24 hours after CEUS in

the animals of present study. In human patients, contraindications for the administration of microbubble contrast agents include pulmonary hypertension and impaired cardiopulmonary function,<sup>12</sup> neither of which was reported for any of the case animals of the present study. However, it is possible that dogs and cats with pulmonary hypertension or impaired cardiopulmonary function may be at increased risk for adverse events resulting from injection of a microbubble contrast agent, and caution should be used when CEUS is performed in those animals.

In the present study, the risk of death within 24 hours after ultrasonography was compared between clinically ill case and control animals to determine whether CEUS had a negative impact on patient outcome. The control group was smaller than the case group because of the matching criteria used. In some instances, a control animal could not be identified within the specified time period relative to the performance of CEUS on the case animal, and we did not want to match control animals to case animals outside of that time period because the evolution of diagnostic and treatment procedures may have biased the risk of death. Also, 131 of 488 (26.8%) case animals of the present study were healthy animals that had CEUS performed for research purposes. In the present study, CEUS was most frequently used as an aid for the diagnosis of hemangiosarcoma in dogs and pancreatitis in cats. Patients with either hemangiosarcoma or pancreatitis may have vasculitis, which may be exacerbated by injection of a microbubble contrast agent for CEUS; however, the risk of death did not differ significantly between the case and control animals of the present study.

Results of the present study indicated that CEUS was a safe method for diagnostic imaging in clinically ill dogs and cats. The incidence of adverse events within 24 hours after CEUS was low, and most adverse events were transient and mild (ie, vomiting or syncope). Most case animals that died within 24 hours after CEUS were euthanized because of a poor prognosis and not because of complications associated with the procedure. Moreover, the risk of death within 24 hours after ultrasonography did not differ between case and control animals.

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