Received: 14 March 2018 | Accepted: 12 December 2018

DOI: 10.1111/jvim.15414

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

STANDARD ARTICLE

Incidence and risk factors associated with development of clinical cardiotoxicity in dogs receiving doxorubicin

Briana E. Hallman[1] | **Marlene L. Hauck**[1] | **Laurel E. Williams**[2] | **Paul R. Hess**[1] | **Steven E. Suter**[1]

[1]Department of Clinical Sciences, North Carolina State University, College of Veterinary Medicine, Raleigh, North Carolina

[2]Veterinary Specialty Hospital of the Carolinas, Cary, North Carolina

Correspondence
Steven E. Suter, Department of Clinical Sciences, North Carolina State University, 1051 William Moore Drive, CVM Research 308 Raleigh, NC 27607.
Email: sesuter@ncsu.edu

Background: Doxorubicin (DOX) can cause cumulative cardiotoxicity in dogs, but the incidence of clinical cardiotoxicity in dogs receiving DOX has not been determined.

Hypothesis/Objectives: To determine if the duration of DOX infusion influences the incidence of cardiotoxicity, to characterize the incidence of clinical cardiotoxicity in dogs during or after DOX chemotherapy, and to identify any risk factors associated with cardiotoxicity.

Animals: Four-hundred ninety-four dogs that received at least 1 dose of DOX for the treatment of cancer.

Methods: Retrospective study of dogs that received DOX from 2006 to 2015.

Results: Of 494 dogs, 20 (4.0%) developed clinical cardiotoxicity. The duration of DOX infusion was not significantly associated with clinical cardiotoxicity, whereas a higher cumulative dose of DOX, higher body weight, decreases in fractional shortening after 5 doses of DOX, and development of ventricular premature contractions were significantly associated with clinical cardiotoxicity. High-risk breeds for developing dilated cardiomyopathy had an incidence of 15.4%, whereas low-risk breeds had an incidence of 3.0%.

Conclusions and Clinical Importance: Although the duration of DOX infusion did not influence the incidence of cardiotoxicity, premature contractions and decreases in fractional shortening should raise concern for the development of clinical cardiotoxicity. Overall, the incidence of clinical DOX-induced cardiotoxicity is low, but Boxers and other breeds at high risk for dilated cardiomyopathy may be at an increased risk.

KEYWORDS

canine, cardiology, cardiomyopathy, chemotherapy, echocardiography, oncology

1 | INTRODUCTION

Doxorubicin (DOX) is an anthracycline antitumor antibiotic used to treat many malignancies in dogs and people, including lymphoma, osteosarcoma, soft tissue sarcoma, histiocytic sarcoma, and carcinomas.[1,2] Repeated doses of DOX can result in potentially life-threatening cardiotoxicity in both species.[3,4] Clinical findings of cardiotoxicity include arrhythmias and decreased systolic function, resulting in a disease resembling dilated cardiomyopathy (DCM). However, electrocardiographic abnormalities do not correlate with the severity of cardiomyopathy.[5,6] Moreover, not all individuals with echocardiographic or electrocardiographic abnormalities will develop clinical signs of cardiac disease, such as syncope or congestive heart failure.[5,7–9] Acute arrhythmias during administration also can be seen and do not correlate with chronic toxicity.[5,7] Histopathologic findings of chronic irreversible cardiotoxicity include myofibrillary atrophy and degeneration, interstitial edema and fibrosis, swelling of the sarcoplasmic reticulum, and cytoplasmic vacuolation, although these findings are difficult to distinguish from other cardiac diseases.[2,7,10]

Abbreviations: 2DE, 2-dimensional echocardiography; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; DOX, doxorubicin; MST, median survival time; VPC, ventricular premature contraction.

In humans, factors known to increase risk of cardiotoxicity include cumulative doses of DOX greater than 300 mg/m^2, advanced (>70 years old) or young (<15 years old) age.[11,12] Before radiation to the chest wall, coadministration with other cytotoxic agents (particularly cyclophosphamide), hypertension, diabetes mellitus, active congestive heart failure, preexisting cardiac disease, history of myocardial infarction within 1 year, and previous anthracycline administration all increase the risk of DOX cardiotoxicity.[11] Cardiotoxicity typically develops within 6 months after completion of treatment but has been observed several years after DOX treatment.[13–15] Measures to prevent cardiotoxicity include administering the drug over a longer duration of time (>6 hours) or coadministering the cardioprotective drug dexrazoxane.[16,17]

Known risk factors that predispose dogs receiving DOX to development of clinical cardiotoxicity are less well defined. Although cardiotoxicity in dogs is uncommon at cumulative doses <240 mg/m^2, most institutions rarely exceed 180 mg/m^2. Administration of DOX over a 1-hour time period resulted in a lower incidence of ECG abnormalities (12%) as compared to a historical population of dogs that received the drug over a 10-minute time period (17.7%).[18] In this study, 63% of the ECG abnormalities were ventricular premature contractions (VPCs), which usually did not require medical treatment, whereas 2 and 3 dogs developed Grade II and III arrhythmias, respectively. These abnormalities were noted during the course of treatment (5.3%) and from 94 to 1339 days after treatment (6.7%). However, the effect of a 1-hour infusion on the development of clinical cardiotoxicity (congestive heart failure or other clinical signs) was not described. Historically, at our institution, DOX has been administered either as a short 10-15 minutes infusion or as a longer 1-hour infusion, depending on clinician preference or if the dogs were considered high-risk breeds for DCM (Boxers, Doberman Pinschers, Great Danes, Irish Wolfhounds, Newfoundlands, or Cocker Spaniels).[19] In addition, because dexrazoxane is safe and well tolerated when coadministered with DOX in dogs and decreases the severity of histopathologic heart lesions in dogs receiving DOX,[10,20,21] we coadminister it based on clinician preference.

The aims of this retrospective study were to determine if the duration of DOX infusion influenced the incidence of cardiotoxicity, to characterize the incidence of clinical cardiotoxicity in dogs during or after DOX chemotherapy, and to identify any risk factors associated with cardiotoxicity.

2 | MATERIALS AND METHODS

Medical records of client-owned dogs that received at least 1 dose of DOX for treatment of a variety of malignancies from 2006 to 2015 at North Carolina State University Veterinary Hospital were reviewed. Patient characteristics collected included breed, body weight, sex, age, tumor type and stage if appropriate, any prior, concurrent, or subsequent treatments (including dexrazoxane), date of diagnosis, date of death, cause or suspected cause or death, and necropsy results if available. Dogs were considered to have developed clinical signs related to cardiac disease if they developed syncope or collapse, weakness or lethargy, exercise intolerance, respiratory difficulty because of congestive heart failure, or sudden death, and if they had no other identifiable cause for those clinical signs. Data collected pertaining to DOX treatment include date of DOX initiation, interval between DOX treatments, infusion duration, individual dose per treatment, number of treatments, and cumulative dose (mg/m^2). Data pertaining to cardiac evaluation collected included dates of echocardiographic and ECG evaluations, fractional shortening, presence and type of arrhythmias, presence and type of heart murmur, and any preexisting cardiac disease. Change in fractional shortening between serial echocardiograms also was calculated as a measure of change in systolic function. Because of to the wide variable range in normal fractional shortening in dogs, change in fractional shortening was calculated as proportional change from each individual's baseline value. Cause of death or euthanasia was noted when available, and necropsy findings of the heart were documented.

2.1 | Doxorubicin and dexrazoxane administration

Doxorubicin was administered at a starting dosage of 30 mg/m^2 for dogs weighing ≥15 kg and 1 mg/kg for dogs weighing <15 kg. All dogs with systolic function abnormalities (eg, low fractional shortening), regardless of breed, noted on prescreening echocardiography and ECG were given DOX using a 1-hour infusion. For these dogs, DOX was diluted in 25, 50, or 100 mL of 0.9% sodium chloride (volume determined by patient weight and attending clinician discretion). The infusion was administered over 1 hour via a long IV catheter placed in the jugular or saphenous vein. For dogs receiving DOX over a shorter time period, DOX was administered by syringe via a short IV catheter placed in a peripheral vein over 10-15 minutes. Dexrazoxane was given at 10 times the dosage of DOX over 15 minutes, immediately before the start of DOX treatment. Dogs were pretreated 15-30 minutes before DOX administration with 1 mg/kg diphenhydramine IM.

2.2 | Cardiac evaluation

All clients were offered cardiac evaluation by echocardiography and ECG with the North Carolina State Veterinary Hospital Cardiology Service, although this was not required for treatment. All echocardiographic and ECG data were collected and assessed by a cardiologist or a cardiology resident whose findings then were reviewed by a board-certified cardiologist. The most consistently documented measurement of systolic function throughout the study period was fractional shortening in M-mode echocardiography, and this variable was used to assess systolic function. Electrocardiographic evaluations typically were performed at 5-minute intervals. Dogs whose owners elected cardiac evaluation underwent evaluations before their first dose of DOX, then again after their 3rd and 5th doses. Additional evaluations were performed at the clinicians' discretion based on development of new murmurs or arrhythmias, concerning findings on previous evaluations warranting more frequent monitoring, or development of clinical signs suspected to be cardiac-related.

2.3 | Statistical evaluation

Chi-square analysis was used to compare the incidence of clinical cardiotoxicity in dogs receiving a 1-hour infusion of DOX with development of cardiotoxicity in dogs receiving a short infusion of DOX.

Similarly, Chi-square analysis also was used to determine potential risk factors in dogs that developed clinical cardiotoxicity. Dogs that were lost to follow-up or had unknown causes of death were presumed to have experienced noncardiac events and were censored. Risk factors evaluated included interval between treatments, coadministration with dexrazoxane, administration of other chemotherapy drugs, radiation therapy, tumor type, age, breed, and preexisting heart disease. A 2-sided Student's *t* test was used to compare differences in mean body weight, mean cumulative dose, and mean fractional shortening change between dogs that developed clinical cardiotoxicity and those that did not. Factors found to be significant in univariate analysis were evaluated using logistic regression for multivariate analysis. Analysis was performed by JMP 12 Software. A *P*-value of <.05 was considered significant for all comparisons.

3 | RESULTS

3.1 | Patient characteristics

A total of 494 cases met the inclusion criteria. Ages ranged from 1 to 17 years (mean, 8.27 years). Sex was evenly distributed with 233 females (6 intact and 227 spayed) and 261 males (30 intact and 231 neutered). Body weight ranged from 2.03 to 86.3 kg (mean, 24.48 kg). A total of 93 breeds was represented, with the most common being Labrador Retriever (n = 75), Golden Retriever (n = 48), mixed breed (n = 35), and Boxers (n = 16). High risk breeds for development of DCM included Boxers (n = 16), Cocker Spaniels (n = 14), Great Danes (n = 6), Doberman Pinschers (n = 1), Irish Wolfhound (n = 1), and Newfoundland (n = 1). There were 28 different tumor types represented, with lymphoma (n = 316), hemangiosarcoma (n = 45), soft tissue sarcoma (n = 41), and osteosarcoma (n = 24) being the most common.

3.2 | Doxorubicin treatment

The total number of doses ranged from 1 to 9 within the intended maximum cumulative dose (180 mg/m^2). The mean number of doses was 3.9. The interval between doses ranged from 2 to 4 weeks, depending on the treatment protocol. The mean cumulative dose among all dogs was 121.9 mg/m^2 (range, 35.8-220 mg/m^2). One-hundred fifty-five dogs received DOX as a single agent, and of these dogs, 105 received DOX at a dosing interval of every 3 weeks, whereas 50 received DOX every 2 weeks. Two dogs received only 1 dose of DOX. Two-hundred two dogs received the drug over a 1-hour time period, whereas 292 received the drug over a 10-15-minute time period. Only 9 dogs received dexrazoxane before each dose of DOX. Eight of these 9 dogs received dexrazoxane because of low systolic function seen on echocardiogram or the presence of arrhythmias on ECG during pretreatment evaluation, and 1 dog received dexrazoxane because of a mass compressing the right atrium. A total of 399 dogs had at least 1 other chemotherapy drug administered either concurrently, before, or after DOX treatment (including L-asparaginase, vincristine, cyclophosphamide, lomustine, mechlorethamine, procarbazine, dacarbazine, carboplatin, chlorambucil, toceranib phosphate, mitoxantrone, ifosfamide, and melphalan). Eighty-four dogs also received radiation therapy, all of which received half-body radiation therapy for lymphoma after chemotherapy.

3.3 | Cardiac evaluation

Ninety-five (19%) dogs had heart murmurs noted during their first examination, including grade I (n = 21), grade II (n = 28), grade III (n = 21), grade IV (n = 12), and grade V (n = 13). No grade VI heart murmurs were documented, and 9 murmurs were not graded in the record. A total of 327 (66%) dogs had at least 1 echocardiogram and concurrent ECG, and 304 (61%) of these were baseline evaluations performed before the first dose of DOX. Of the 304 dogs with first evaluations done before the first DOX dose, 130 (43%) had at least 1 abnormality noted, with the most common being mitral valve regurgitation (110/130, 85%). The remainder of abnormalities included tricuspid valve regurgitation (21/130, 16%), pulmonic insufficiency (9/130, 7%), impaired left ventricular filling (4/130, 3%), low fractional shortening (10/130, 8%), and arrhythmias, including VPCs (9/130, 7%) or atrial premature contractions (2/130, 2%) and accelerated idioventricular rhythm (1/130, 1%). Dogs that did not have a pretreatment ECG or echocardiograms performed did not have these cardiac variables evaluated during treatment because we were assessing clinical cardiotoxicity. Two-hundred twenty-one dogs had at least 1 reevaluation echocardiogram and ECG after starting DOX chemotherapy.

3.4 | Clinical cardiotoxicity

A total of 31/494 (6.3%) dogs developed cardiac clinical signs during or after DOX treatment. Eleven of these dogs had preexisting cardiac abnormalities based on an echocardiogram before initiation of DOX. Two dogs had right atrial masses suspected to be hemangiosarcoma, and progression of tumor size assessed on echocardiogram was suspected to be the cause of these dogs' clinical signs. The remaining 9 dogs had preexisting mitral valve disease that progressed on subsequent echocardiograms, and led to development of clinical signs. These 11 dogs were excluded from the group with clinical DOX-induced cardiotoxicity. For 1 dog, sudden death was the only cardiac-related clinical sign, and because this dog was not necropsied, the actual cause of death could not be determined. This dog was included because sudden death previously has been reported as the only clinical sign of DOX cardiotoxicity.[22] As such, 20/494 (4.0%) dogs remained that developed clinical signs related to cardiotoxicity. Of these dogs, 16 had echocardiograms and ECGs before DOX treatment. The median time to development of clinical signs was 194 days from the start of treatment (range, 50-928 days), with a median survival time (MST) after development of clinical signs of 29 days (range, 0-913 days). Syncope or collapse was the most common clinical sign (Table 1). Affected breeds in this population included 4 Boxers, 2 each of Labrador Retrievers, Golden Retrievers, and mixed breeds, and 1 each of American Cocker Spaniel, Pembroke Welsh Corgi, Bullmastiff, American Staffordshire Terrier, Hound, Chesapeake Bay Retriever, Great Dane, Weimeraner, Giant Schnauzer, and Boston Terrier. These dogs had a higher mean total cumulative dose of DOX (144.78 versus 121.9 mg/m^2, P = .01; Figure 1). Body weight was significantly associated with the development of clinical cardiotoxicity, with affected dogs

TABLE 1 Reported clinical signs of clinical cardiotoxicity. One dog had more than 1 clinical sign (respiratory difficulty and subsequent cardiac arrest)

	Number of dogs
Syncope/collapse	12
Weakness/lethargy	2
Exercise intolerance	2
Respiratory difficulty cause by congestive heart failure	3
Sudden death	2

having higher mean body weight (32.41 kg) compared to unaffected dogs (24.21 kg; P = .007; Figure 2). Both higher body weight and higher cumulative dose were found to be significant in multivariate analysis (P = .005 and .007, respectively). In addition, Boxers were more likely to develop clinical cardiotoxicity (P < .001) than other breeds in multivariate analysis. The primary clinical sign for each of the 4 Boxers was syncope. Seven affected dogs received DOX as a single agent treatment, 1 received the drug every 2 weeks and 6 received the drug every 3 weeks. The interval between treatments was not associated with development of cardiotoxicity (P = .30). In addition, the dose intensity per dog also was not associated with cardiotoxicity (P = .44). Finally, the number of doses, patient age, administration of other chemotherapy drugs, and administration of radiation therapy were not associated with development of cardiotoxicity. None of these 20 dogs received dexrazoxane treatment. More dogs received DOX over a 1-hour time period (n = 12) compared to a 10-15-minute time period (n = 8), although no association with infusion time and development of cardiotoxicity was found (P = .07). In the cardiotoxicity group, 15/20 had lymphoma (LSA) or lymphoid leukemia (14 LSA, 1 lymphoid leukemia), and in the no cardiotoxicity group, 304/475 dogs had LSA or lymphoid leukemia. This difference was not significant (P = .31).

Sixteen of the 20 dogs with clinical DOX-induced cardiotoxicity had a cardiac evaluation with an echocardiogram and an ECG before starting DOX treatment, with all of these dogs also having at least 1 subsequent evaluation. Thirteen of the 16 dogs had their 2nd

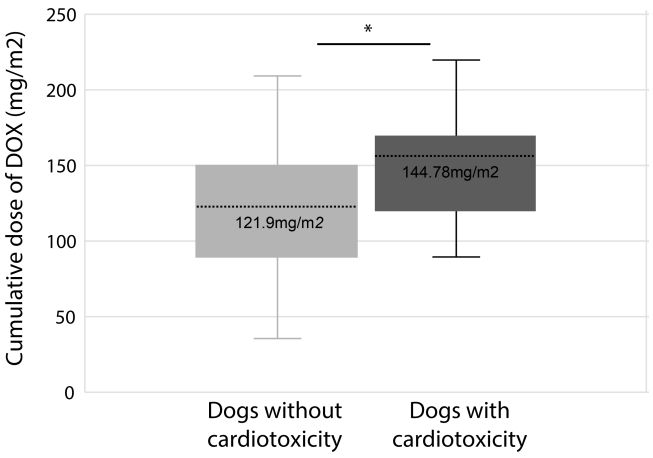

FIGURE 1 Comparison of cumulative doxorubicin (DOX) dose between dogs with cardiotoxicity (mean 144.78 mg/m^2, n = 20) and dogs without cardiotoxicity (mean 121.9 mg/m^2, n = 474) (P = .01). Horizontal dotted lines indicate means. *Statistically significant difference

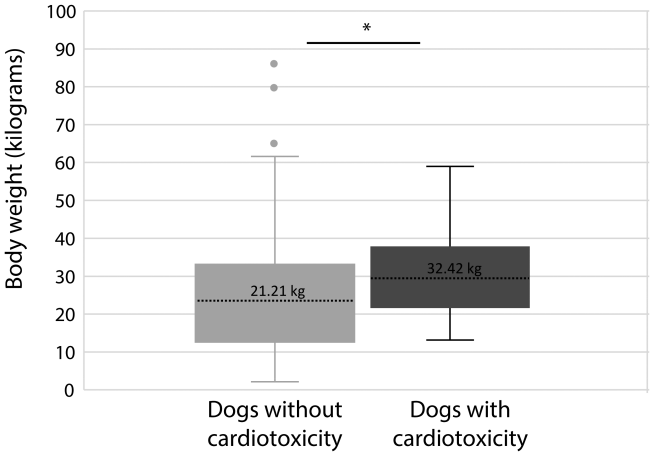

FIGURE 2 Comparison of body weights between dogs with cardiotoxicity (mean 32.41 kg, n = 20) and dogs without cardiotoxicity (mean 21.21 kg, n = 474) (P = .001). Horizontal dotted lines indicate means. *Statistically significant difference

echocardiogram and ECG performed after 3 doses of DOX when they were presented for their 4th dose of DOX. Mean fractional shortening change from first to the 2nd echocardiogram (before the 4th dose of DOX) was an increase of 1.7% from baseline in unaffected dogs and a 5.0% decrease from baseline in affected dogs (P = .25). For dogs that developed cardiac clinical signs, the mean absolute value of the fractional shortening measurement at baseline was 35.8% (range, 27%-44.7%), and after 3 doses of DOX the mean absolute value was 33.6% (range, 27.5%-43.4%). For dogs that did not develop cardiac clinical signs that could be related to cardiotoxicity, the mean absolute value of the fractional shortening measurement at baseline was 36.7% (range, 22.0%-66.4%), and after 3 doses of DOX the mean absolute value was 36.2% (range, 20.5%-58.8%). Six dogs had a 3rd echocardiogram and ECG performed before the 6th dose of DOX, and the mean change in fractional shortening from the 1st echocardiogram was a 31.4% decrease from the baseline value. This result was significantly different from the fractional shortening decrease of 2.1% from the 1st to the 3rd echocardiogram seen in unaffected dogs (P = .02; Figure 3). The mean absolute value for fractional shortening in these 6 dogs after 5 doses of DOX was 22.9% (range, 12.3%-31%), which was significantly different from the mean absolute fractional shortening value of 34.26% (range,16.8%-57%) in dogs that did not develop cardiac clinical signs (P = .04). Seven (44%) dogs developed new arrhythmias during or after treatment (all VPCs), and this development was significantly associated with clinical cardiotoxicity (P < .001). Of these 7 dogs, 5 had 3 echocardiograms during treatment. Three of these dogs had decreases in systolic function and 2 had VPCs without decreased systolic function. Seven dogs (5 with clinical signs and 2 without clinical signs but with echocardiographic evidence of systolic dysfunction) were treated with pimobendan in combination with angiotensin converting enzyme inhibitors (enalapril or benazepril) or antiarrhythmic agents (atenolol, diltiazem, or sotalol). Decreased fractional shortening after 5 doses of DOX and development of VPCs were significantly associated with cardiotoxicity in multivariate analysis (P = .04 and .008, respectively). Of the 16 dogs with pretreatment cardiac evaluations, 6 had mitral valve regurgitation noted. These

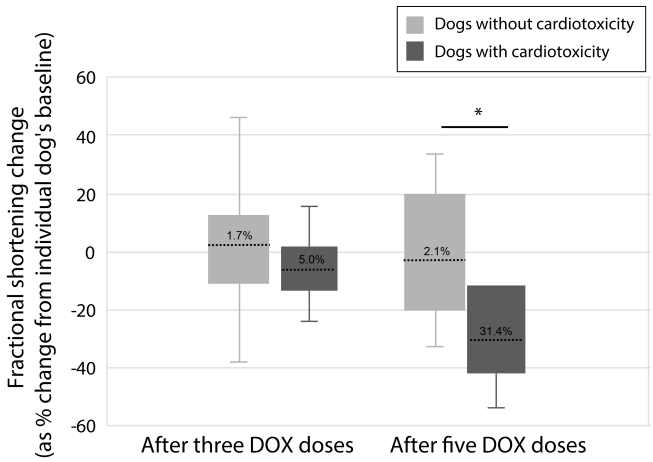

FIGURE 3 Comparison of changes in fractional shortening after 3 and 5 doses of doxorubicin between dogs with cardiotoxicity (n = 20) and dogs without cardiotoxicity (n = 474). After 3 doses, dogs with cardiotoxicity had a mean 5.0% decrease and dogs without cardiotoxicity had a mean 1.7% increase) (P = .25). After 5 doses, dogs with cardiotoxicity had a mean 31.4% decrease and dogs without cardiotoxicity had a mean 2.1% decrease (P = .02). Horizontal dotted lines indicate means. *Statistically significant difference

6 dogs all had echocardiograms and ECGs performed after development of cardiac clinical signs that confirmed a DCM-like phenotype rather than progression of mitral valve disease. The incidence of mitral valve regurgitation diagnosed on echocardiography was not higher in dogs with cardiotoxicity compared to dogs without cardiotoxicity (P = .39). Six dogs had heart murmurs, and this incidence was not different between dogs with and without cardiotoxicity (P = .21). All dogs, except 1 that experienced sudden death and had no antemortem clinical signs, had an echocardiogram and ECG after developing clinical signs to confirm cardiac disease (defined as either development of VPCs or decreased fractional shortening below the normal minimum of 28%) as the cause of the clinical signs, regardless of whether or not they had these baseline tests before treatment began.

Sixteen dogs received 1-hour infusions of DOX specifically because of low or low-normal systolic function seen on a pretreatment echocardiogram. Two of these dogs developed cardiac clinical signs, but the infusion time was not associated with development of cardiotoxicity for these dogs (P = .11). Additionally, 14 dogs developed ECG or echocardiographic findings (VPCs or decreases in fractional shortening) suggestive of DOX toxicity but did not develop any clinical signs. The MST for dogs with and without cardiotoxicity (from the time of treatment initiation) was not significant (272 days versus 276 days; P = .63).

TABLE 2 Frequency of cardiac findings in the 22 dogs with heart pathology on necropsy

Histopathologic finding	Number of cases
Mitral valve endocardiosis	10
Myocardial fibrosis	3
Ventricular dilatation	3
Cardiomyocyte fragmentation	3
Myocardial necrosis	1
Arterial/arteriolar amyloidosis	1
Small arteriolar tunica media thickening	1

Thirty-nine dogs, including 4 dogs that developed clinical cardiac signs, were necropsied. The cause of death or euthanasia was considered as secondary to DOX toxicity in 3 of the 4 dogs. One dog went into cardiac arrest and was found to have severe ventricular dilatation, and 2 dogs had cardiomyocyte fragmentation (1 euthanized because of refractory congestive heart failure and 1 euthanized for refractory atrial fibrillation). The 4th dog was a Boxer that was suspected to have arrhythmogenic right ventricular cardiomyopathy (ARVC) based on antemortem test results (ventricular bigeminy and syncope), and the cardiac findings at necropsy consisted of presumed amyloid deposits within the arteries and arterioles. In total, 22/39 (56%) dogs had some form of heart pathology (Table 2). Six additional dogs had cardiac findings on necropsy (all were euthanized because of progressive noncardiac disease) that were compatible with DOX cardiotoxicity (3 with myocardial fibrosis and 3 with moderate to severe ventricular dilatation) but none had antemortem clinical signs. Seven of the 20 affected dogs were suspected to have experienced DOX cardiotoxicity-related death or euthanasia because of clinical signs or findings on echocardiogram or history of arrhythmias, but no necropsy was performed.

3.5 | Breeds at high risk for DCM

Given the overlap of clinical signs and diagnostic findings between DCM and DOX cardiotoxicity, dog breeds known to be predisposed to DCM (American Cocker Spaniels, Boxers, Great Danes, Irish Wolfhound, Doberman Pinscher, and Newfoundland) were analyzed as a risk factor together. Thirty-nine dogs in the study population were breeds at high risk for DCM: 33 dogs in the unaffected group (13 American Cocker Spaniels, 12 Boxers, 5 Great Danes, and 1 each of Irish Wolfhound, Doberman Pinscher, and Newfoundland) and 6 dogs in the group that developed cardiac clinical signs (4 Boxers, 1 Great Dane, and 1 American Cocker Spaniel). Dog breeds at high risk for DCM had a clinical cardiotoxicity incidence of 15.4%. No association was found among body weight, cumulative dose, number of doses, dose intensity, or duration of infusion time and the development of clinical cardiotoxicity. Development of VPCs in these high-risk breeds was associated with cardiotoxicity (P < .001), but no association with fractional shortening change between the 3rd (7.06% decrease for dogs without cardiotoxicity versus 3.85% decrease for dogs with cardiotoxicity; P = .62) or the 5th (5.65% decrease in dogs without cardiotoxicity versus 26.9% decrease in dogs with cardiotoxicity, P = .21; Table 3) dose was found.

Cases were analyzed again excluding dog breeds at high risk for DCM, resulting in an incidence of 3.0% (14/455). This was significantly lower than the incidence of 15.4% seen in high-risk DCM dog breeds (P < .001). Higher body weight and higher cumulative dose of DOX were associated with clinical cardiotoxicity (P = .02 and .02, respectively). Decrease in fractional shortening after 5 doses of DOX (but not after 3), when compared to baseline results, was also a risk factor (P = .02) for dogs not at high risk for DCM. These factors also were found to be significantly associated in multivariate analysis. Development of VPCs was not associated with cardiotoxicity in this

TABLE 3 Selected factors evaluated for association with clinical cardiotoxicity. A *P*-value <.05 was considered significant. Dogs that did not develop cardiac clinical signs are classified as "unaffected," and dogs that developed clinical signs are classified as "affected"

	All dogs	*P* value	Excluding breeds predisposed to DCM	*P* value	Including only breeds predisposed to DCM	*P* value
Total	494		455		39	
Unaffected	474		441		33	
Affected	20		14		6	
Mean cumulative DOX dose (mg/m^2)						
Unaffected	121.9	.01	121.81	.02	128.24	.51
Affected	144.78		146.46		140.83	
Mean number of DOX doses						
Unaffected	3.9	.32	3.8	.39	4.5	.55
Affected	5		5.1		4.8	
Mean body weight (kg)						
Unaffected	24.21	.001	23.9	.02	30.46	.74
Affected	32.41		32.15		33.01	
Mean fractional shortening (FS) change after 3 DOX doses (% change from baseline)						
Unaffected	+1.7	.25	+2.3	.30	−7.06	.62
Affected	−5.0		−3.6		−3.85	
Mean FS change after 5 DOX doses (% change from baseline)						
Unaffected	−2.1	.02	−4.03	.02	−5.65	.21
Affected	−31.4		−25.8		−26.9	
Developed VPCs						
Unaffected	40	.001	37	.43	3	.001
Affected	7		2		5	
1-hour infusion time (versus 10-15-minute infusion time)						
Unaffected	190	.08	7	.45	22	.38
Affected	12		7		4	

Abbreviations: DCM, dilated cardiomyopathy; DOX, doxorubicin; VPC, ventricular premature contraction.

group (*P* = .43). No other risk factor was identified. Table 3 compares the different groups.

4 | DISCUSSION

In our study population, administration of DOX over 1 hour did not decrease the risk of clinical cardiotoxicity compared to a 10-15-minute infusion. In humans, a 6-hour infusion has been shown to decrease the risk of cardiotoxicity, as evidenced by a decrease in left ventricular ejection fraction, compared with a 15-20-minute infusion.[23] The 1-hour infusion, rather than a 6-hour infusion, was selected at our institution because it is the longest duration of administration chosen to balance the aim of extended administration while minimizing the risk of extravasation with extended chemotherapy administration, and a 1-hour infusion previously was shown to decrease the development of ECG signs of toxicity in dogs.[18] This duration of infusion may not be sufficient to prevent clinical cardiotoxicity in this patient population. Not enough dogs received dexrazoxane treatment to assess this treatment as a preventative measure.

The overall incidence of clinical cardiac disease secondary to confirmed or presumed DOX-induced cardiotoxicity in all patients receiving DOX was 4.0%. This incidence of clinical cardiac disease is similar to the reported incidence of 2.2% to 5.1% in people receiving DOX.[24,25] Previous studies evaluating cardiotoxicity in dogs have found incidences of 2.3% to 17.7%, but the incidence has been reported to be as high as 29.8%.[9,18,26,27] However, when examining the incidence of clinical cardiotoxicity, as manifested by the development of signs consistent with congestive heart failure, the results (4%-6.8%) are very similar to ours. The incidence of confirmed and suspected cardiotoxicity-related deaths in this population of dogs was 2.0% (10/494), although only 0.6% (3/494) could be confirmed on necropsy. The MST for patients after developing clinical signs in our study (29 days) was similar to the previously reported result of 26.5 days.[28] Other reported survival times include 48 hours and 90 days.[8,9]

The finding that dogs with clinical cardiotoxicity received a higher cumulative dose of DOX is not surprising given that the cardiotoxic effects of this drug are cumulative. The mean cumulative dose of 150 mg/m^2 of the affected dogs was similar to what has previously been reported.[9] Additionally, higher body weight was significantly associated with the development of clinical cardiotoxicity. Higher body weight previously has been suggested as a risk factor,[29] and therefore, larger dogs may be more likely to develop cardiotoxicity. Because smaller dogs were dosed at 1 mg/kg, this finding also may be because of the fact that smaller dogs received lower cumulative doses, although multivariate analysis showed both higher body weight and higher cumulative dose to be significantly associated with cardiotoxicity. Doxorubicin-induced cardiomyopathy has many similarities with DCM, a disease that also has a higher incidence in large breed dogs.

The exact causes of DCM are still unknown, but the underlying factors that predispose dogs to DCM also may increase the risk of DOX cardiotoxicity.[19]

Boxers were found to have a higher incidence of clinical cardiotoxicity compared to other breeds, and collectively, dog breeds known to be at high risk for DCM (American Cocker Spaniels, Boxers, Great Danes, Irish Wolfhounds, Doberman Pinschers, and Newfoundlands) did have a higher incidence of cardiotoxicity. The only risk factor identified for these dogs was the development of VPCs and a decrease in fractional shortening after 5 doses of DOX. However, 2/12 (16.6%) Boxers in the nonclinical group had VPCs, suggesting that development of VPCs is not a useful marker for the development of clinical cardiotoxicity. Given the overlap of clinical signs, echocardiographic and ECG findings, and histopathology results between DCM and DOX cardiotoxicity, some of the dogs that developed clinical cardiac disease instead may have had primary DCM or ARVC.[19] Boxers can develop DCM, most commonly thought to be secondary to ARVC, and 1 dog in our study was suspected of having ARVC.[19,30] However, this dog's clinical signs developed after the 1st dose of DOX, and given the similarities in echocardiographic and ECG findings, this dog was included to avoid overlooking DOX as a contributing factor to clinical signs from ARVC. Occult DCM or ARVC may be independent risk factors for DOX cardiotoxicity. Although currently no single genetic test exists for DCM, a genetic test for a mutation in the striatin gene associated with ARVC in Boxers is available, and therefore further investigation could include striatin gene mutation analysis in Boxers receiving DOX to determine if a correlation exists between DOX administration in Boxers with this mutation and development of cardiotoxicity.[30]

A decrease in fractional shortening from baseline was associated with the development of cardiac clinical signs, which is consistent with previous reports of decreased systolic function in DOX cardiotoxicity.[3,9,13] The significant decrease in fractional shortening was noted after 5 doses of DOX. For most of these dogs, the change in fractional shortening was considered a contraindication for treatment, and a 6th dose was not administered. These dogs still progressed to develop clinical cardiac disease, which indicates that irreversible cardiotoxicity had already taken place by the time the change in fractional shortening was detected. Interestingly, no significant change in fractional shortening was noted between the 1st and 2nd cardiac evaluations (before the 4th DOX dose). A repeat echocardiogram before the 5th dose may have detected signs of cardiotoxicity earlier. Given the potential for interobserver variability in obtaining fractional shortening measurements, the magnitude of the decrease in fractional shortening seen in this patient population may not be as important as noting trends over repeated echocardiographic evaluations. As a single measurement, a decrease in fractional shortening may not be diagnostic for clinically relevant decreased systolic function, but if the result is part of a downward trend, as it was for the majority of dogs in our study that developed clinical cardiotoxicity, concern for cardiac dysfunction is warranted. In the dogs that developed cardiotoxicity, the absolute value for the change in fractional shortening from baseline to that after 5 doses varied from 12.3% to 31%, with the majority of dogs having results below 28%, which is the cutoff for normal at our institution. Although it is difficult to determine an exact cutoff, decreases in fractional shortening of >15% from the baseline warrant concern for cardiotoxicity. In addition to decreases in fractional shortening, development of VPCs also was associated with clinical cardiotoxicity, and although this resulted in discontinuation of DOX treatment for the majority of dogs when detected, they still eventually developed clinical signs. More frequent ECG monitoring may be warranted.

Earlier detection methods are needed to help identify patients most at risk for cardiotoxicity. Given the finding that VPCs were associated with cardiotoxicity in this patient population, an ECG can be considered before each dose. Echocardiography also should be used, particularly in breeds at risk for developing DCM, to obtain a baseline fractional shortening and monitor for decreases. In humans, patients can be monitored for cardiotoxicity using echocardiography and ECG, and more advanced techniques such as radionuclide angiocardiography, phased-tracking methods, and endomyocardial biopsy also have been reported.[14,26,31,32] The preferred echocardiographic method of monitoring left ventricular function in humans is 3-dimensional echocardiography, as opposed to 2-dimensional echocardiography (2DE), which is used in most veterinary hospitals. Three-dimensional echocardiography is more accurate at detecting changes in ejection fraction and systolic function and also has been associated with better reproducibility than 2DE.[33] Although detectable deterioration in heart function, such as decreases in left ventricular ejection fraction or decreases in velocity of the ventricular septum myocytes, and histopathologic changes consistent with cardiotoxicity typically result in the recommendation to discontinue DOX, there unfortunately is insufficient data to develop evidence-based recommendations for DOX-induced cardiotoxicity even in humans.[26,32,33] Serum cardiac troponin I concentration has been used as a marker in humans for myocardial damage secondary to DOX.[15,34] Cardiac troponin I also has been evaluated in dogs as a screening tool for myocardial damage.[35,36] Serum troponin I concentrations were shown to increase in some dogs receiving DOX in a retrospective study, but this increase did not correlate with clinical signs of DOX-induced cardiotoxicity.[27] Too few dogs in our population had serum troponin I concentration measured for any statistical evaluation.

Limitations of our study include its retrospective design, which resulted in inconsistent follow-up for patients. The inconsistent follow-up may have resulted in underreporting of the development of cardiac-related clinical signs. For 1 dog, sudden death was the only cardiac-related clinical sign, and because this dog was not necropsied, the actual cause of death could not be determined. Cardiac reevaluations with echocardiography and ECG also were not required for all patients receiving DOX, and patients with subclinical cardiotoxicity may have been missed. However, the aim of our study was to characterize the incidence of cardiac clinical signs that affected quality of life, and thus the incidence of nonclinical heart disease identifiable only by echocardiography or ECG was irrelevant. Only 4 of the dogs with clinical cardiotoxicity were necropsied, and we may have erroneously attributed some of the other dogs' cardiac disease to DOX-induced cardiotoxicity when it may have been caused by other factors. The incidence of cardiac disease in our population was similar to what has previously been reported, however, and all dogs that developed cardiac clinical signs, other than the dog that experienced

sudden death, had at least 1 cardiac evaluation after development of clinical signs to confirm cardiac origin. With the exception of those cardiac diseases actually representing unrelated DCM or ARVC and misdiagnosed as DOX induced, it is unlikely that a substantial portion of these documented clinical signs was incorrectly attributed to DOX-induced cardiotoxicity. Finally, because the decision to administer DOX over 1 hour or to give dexrazoxane concurrently was based on clinician preference, bias, leading to a type II error, could have been introduced.

5 | CONCLUSIONS

Administration of DOX over a 1-hour time period did not decrease the incidence of clinical cardiotoxicity compared to a 10-15 minute infusion. The median time to development of cardiac clinical signs was 194 days after the 1st DOX treatment, and thus the risk for cardiotoxicity may be less clinically important in patients with aggressive tumors that already have a poor prognosis and short expected survival times. Doxorubicin-induced cardiotoxicity was suspected to be a direct contributor to the cause of death in only 2.0% of cases and clinically affected only 4.0% of dogs, although breeds at high risk for DCM had a clinical cardiotoxicity incidence of 15.4%. Therefore, for most canine cancer patients, the risk of cardiotoxicity is likely to be outweighed by the potential benefit of treatment. However, for dogs that have tumors that could have a more favorable long-term prognosis, the risk must be carefully weighed. Although the current standard of cardiac monitoring at our institution (performing an echocardiogram and ECG before to the 1st, 4th, and 6th dose of DOX) is likely to be adequate for most dogs, cardiac reevaluation should be offered before every dose of Dox for Boxers, large dogs, and dog breeds at high risk for DCM. Although too few dogs in our study received dexrazoxane to detect any benefit, coadministration with DOX also should be offered for high-risk dogs, particularly if a good prognosis is expected.

CONFLICT OF INTEREST DECLARATION

Steven E. Suter serves as Associate Editor for the *Journal of Veterinary Internal Medicine*. He was not involved in review of this manuscript.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Steven E. Suter https://orcid.org/0000-0002-4972-3571

REFERENCES

1. Page RL, Macy DW, Ogilvie GK, et al. Phase III evaluation of doxorubicin and whole-body hyperthermia in dogs with lymphoma. *Int J Hyperthermia*. 1992;8:187-197.
2. Susaneck SJ. Doxorubicin therapy in the dog. *J Am Vet Med Assoc*. 1983;182:70-72.
3. Billingham ME, Mason JW, Bristow MR, Daniels JR. Anthracycline cardiomyopathy monitored by morphologic changes. *Cancer Treat Rep*. 1978;62:865-872.
4. Venable RO, Saba CF, Endicott MM, Northrup NC. Dexrazoxane treatment of doxorubicin extravasation injury in four dogs. *J Am Vet Med Assoc*. 2012;240:304-307.
5. Kehoe R, Singer DH, Trapani A, Billingham M, Levandowski R, Elson J. Adriamycin-induced cardiac dysrhythmias in an experimental dog model. *Cancer Treat Rep*. 1978;62:963-978.
6. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for DOX-induced congestive heart failure. *Ann Intern Med*. 1979;91:710-717.
7. Lefrak EA, Pitha J, Rosenheim S, et al. A clinicopathologic analysis of Adriamycin cardiotoxicity. *Cancer*. 1973;32:302-314.
8. Loar AS, Susaneck SJ. Doxorubicin-induced cardiotoxicity in five dogs. *Sem Vet Med Surg (Small Anim)*. 1986;1:68-71.
9. Mauldin GE, Fox PR, Patnaik AK, Bond BR, Mooney SC, Matus RE. Doxorubicin-induced cardiotoxicosis – clinical features in 32 dogs. *J Vet Intern Med*. 1992;6:82-88.
10. Vejpongsa P, Yeh ETH. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. *J Amer Coll Cardiol*. 2014;64:938-945.
11. Abeloff MD, Armitage JO, Niederhuber JE, et al. Cardiac effects of cancer therapy. In: Meloni D, ed. *Clinical Oncology*. 3rd ed. Philadelphia, PA: Churchill Livingstone; 2004:1251-1263.
12. Ugoretz RJ. Cardiac effects of doxorubicin therapy of neoplasms. *J Amer Med Assoc*. 1976;236:295-296.
13. Haq MM, Legha SS, Choksi J, et al. Doxorubicin-induced congestive heart failure in adults. *Cancer*. 1985;56:1361-1365.
14. Bristow MR, Mason JW, Billingham ME, Daniels JR. Doxorubicin cardiomyopathy: evaluation by phonocardiography, endomyocardial biopsy, and cardiac catheterization. *Ann Int Med*. 1978;88:168-175.
15. Moazeni S, Cadeiras M, Yang EH, et al. Anthracycline induced cardiotoxicity: biomarkers and "Omics" technology in the era of patient specific care. *Clin Trans Med*. 2017;6:1-12.
16. Legha SS, Benjamin RS, Mackay B, et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med*. 1982;96:133-139.
17. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. *Cancer*. 2003;97:2869-2879.
18. Gillings SL, Johnson J, Fulmer A, Hauck M. Effect of a 1-hour IV infusion of doxorubicin on the development of cardiotoxicity in dogs as evaluated by electrocardiography and echocardiography. *Vet Ther*. 2009;10:46-58.
19. Dukes-McEwen J, Borgarelli M, Tidholm A, et al. Proposed guidelines for the diagnosis of canine idiopathic dilated cardiomyopathy. *J Vet Cardiol*. 2003;5:7-19.
20. FitzPatrick WM, Dervisis NG, Kitchem BE. Safety of concurrent administration of dexrazoxane and doxorubicin in the canine cancer patient. *Vet Comp Oncol*. 2010;8:273-282.
21. Imondi AR, Della Torre P, Mazué G, et al. Dose-response relationship of dexrazoxane for prevention of doxorubicin-induced cardiotoxicity in mice, rats, and dogs. *Cancer Res*. 1996;56:4200-4204.
22. Banco B, Grieco V, Servida F, Giudice C. Sudden death in a dog after doxorubicin chemotherapy. *Vet Pathol*. 2011;48:1035-1037.
23. Shapira J, Gotfried M, Lishner M, Ravid M. Reduced cardiotoxicity of doxorubicin by a 6-hour infusion regimen: a prospective randomized evaluation. *Cancer*. 1990;65:870-873.
24. Kane RC, McGuinn WD, Dagher R, et al. Dexrazoxane (Totect™): FDA review and approval for the treatment of accidental extravasation following intravenous anthracycline chemotherapy. *Oncologist*. 2008;13:445-450.
25. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *New Engl J Med*. 1998;339:900-905.
26. Nousiainen T, Vanninen E, Jantunen E, et al. Comparison of echocardiography and radionuclide ventriculography in the follow-up of left

ventricular systolic function in adult lymphoma patients during doxorubicin therapy. *J Int Med*. 2001;249:297-303.
27. Selting KA, Lana SE, Ogilvie GK, et al. Cardiac troponin I in canine patients with lymphoma and osteosarcoma receiving doxorubicin: comparison with clinical heart disease in a retrospective analysis. *Vet Comp Oncol*. 2004;2:142-156.
28. Ratterree W, Gieger T, Pariaut R, et al. Value of echocardiography and electrocardiography as screening tools prior to doxorubicin administration. *J Am Vet Med Assoc*. 2012;48:89-96.
29. Postorino NC, Susaneck SJ, Withrow SJ, et al. Single agent therapy with adriamycin for canine lymphosarcoma. *J Am Anim Hosp Assoc*. 1989;24:221-225.
30. Meurs KM. Arrhythmogenic right ventricular cardiomyopathy in the Boxer dog: an update. *Vet Clin North Am Small Anim Pract*. 2017;7:1103-1111.
31. Bristow MR, Lopez MB, Mason JW, Billingham ME, Winchester MA. Efficacy and cost of cardiac monitoring in patients receiving doxorubicin. *Cancer*. 1982;50:32-41.
32. Saito Y, Susukida I, Uzuka Y, Kanai H. Noninvasive early detection of anthracycline-induced cardiotoxicity in patients with hematologic malignancies using the phased tracking method. *Cancer Med*. 2016;5:2276-2285.
33. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27:911-939.
34. Herman EH, Zhang J, Rifai N, et al. The use of serum levels of cardiac troponin T to compare the protective activity of dexrazoxane against doxorubicin- and mitoxantrone-induced cardiotoxicity. *Cancer Chemother Pharmacol*. 2001;48:297-304.
35. Bertinchant JP, Polge A, Juan JM, et al. Evaluation of cardiac troponin I and T levels as markers of myocardial damage in doxorubicin-induced cardiomyopathy rats, and their relationship with echocardiographic and histological findings. *Clin Chim Acta*. 2003;329:39-51.
36. DeFrancesco TC, Atkins CE, Keene BW, et al. Prospective clinical evaluation of serum cardiac troponin T in dogs admitted to a veterinary teaching hospital. *J Vet Intern Med*. 2002;16:553-557.

How to cite this article: Hallman BE, Hauck ML, Williams LE, Hess PR, Suter SE. Incidence and risk factors associated with development of clinical cardiotoxicity in dogs receiving doxorubicin. *J Vet Intern Med*. 2019;33:783–791. https://doi.org/10.1111/jvim.15414