Layer-specific myocardial function in asymptomatic cats with obstructive hypertrophic cardiomyopathy assessed using 2-dimensional speckle-tracking echocardiography

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Background: Hypertrophic cardiomyopathy (HCM), a primary disorder of the myocardium, is the most common cardiac disease in cats. However, determination of layer-specific myocardial function with 2D speckle-tracking echocardiography in cats with asymptomatic HCM has not yet been reported.

Objectives: To quantitatively measure layer-specific myocardial function of asymptomatic cats with HCM.

Animals: Ten client-owned, asymptomatic cats with obstructive HCM and 13 healthy cats.

Methods: A retrospective, case-control study. Cats underwent assessment of layer-specific myocardial function (whole, endocardial, and epicardial) in the longitudinal and circumferential directions by using 2D speckle-tracking echocardiography.

Results: Longitudinal strains were significantly lower in cats with HCM than controls in the whole (−15.5% vs −19.1%), endocardial (−18.3% vs −21.8%), and epicardial (−13.1% vs −16.8%) layers. Circumferential strains in whole and epicardial layers also were significantly lower in cats with HCM as compared with controls (−15.0% vs −20.2% and −4.4% vs −9.4%, respectively). However, no significant difference was found between cats with HCM and controls in the global circumferential strain in the endocardial layer (−31.2% vs −34.2%). The circumferential endocardial-to-epicardial strain ratio was significantly higher in cats with HCM than in controls (6.1 vs 3.5).

Conclusions and Clinical Importance: Layer-specific myocardial function assessed by 2D speckle-tracking echocardiography differed in asymptomatic cats with obstructive HCM compared to controls despite their apparently normal systolic function, as determined by conventional echocardiography. The maintained endocardial circumferential strain and higher circumferential endocardial-to-epicardial strain ratio may reflect compensation for occult systolic dysfunction in cats with obstructive HCM.

KEYWORDS
cat, endocardial strain, epicardial strain, feline, myocardium, strain

1 | INTRODUCTION

Hypertrophic cardiomyopathy (HCM), a primary disorder of the myocardium, is the most common cardiac disease in cats. Histopathologically, HCM is associated with myocardial hypertrophy, fiber
disarray, increased loose connective tissue, intramural coronary arterial narrowing, myocardial ischemia, and fibrosis, all of which are believed to interfere with the generation of force and relaxation of the cardiac muscle. However, detailed assessment of myocardial function in cats with HCM has not been fully evaluated.

Recently, 2D speckle-tracking echocardiography (2D-STE) has been used for the diagnosis and assessment of HCM in humans and cats. This technique has enabled the assessment of myocardial variables that provide better quantification of regional and global myocardial deformations and might have higher sensitivity than conventional echocardiographic parameters for detecting subtle myocardial functional abnormalities. Furthermore, the novel multi-layer 2D-STE technique enables detailed assessment of layer-specific myocardial function (whole, endocardial, and epicardial). However, layer-specific assessment of myocardial function with 2D-STE has not been reported previously in cats. Our study was designed to quantitatively measure layer-specific myocardial function in cats with asymptomatic HCM. We hypothesized that myocardial functional abnormalities would correspond to the severity and pathogenesis of HCM, and that myocardial function assessed with 2D-STE would be a sensitive marker of systolic dysfunction in cats with asymptomatic HCM.

2 | MATERIALS AND METHODS

2.1 | Animals

Our study population consisted of 10 client-owned cats with HCM and 13 healthy cats serving as controls. These cats were presented for cardiac screening and their clinical findings were analyzed retrospectively. The breeds of cats with HCM were Scottish Fold (n = 4), Domestic Shorthair cat (n = 2), Maine Coon (n = 2), Munchkin (n = 1), and Exotic Shorthair (n = 1). Cats were diagnosed with HCM if the echocardiographic left ventricular (LV) wall thickness was ≥6 mm, measured by 2D methods. Left ventricular thickness was measured from the short-axis view, and the mean value of 3 consecutive cardiac cycles of the thickest segment was used. We excluded cats that had systolic blood pressure >160 mmHg (using noninvasive oscillometric methods) or systemic and other cardiovascular diseases known to cause LV hypertrophy. There was no evidence of dehydration in any of the cats. All cats with HCM had echocardiographic evidence of dynamic LV outflow obstruction and systolic cranial motion of the mitral valve. Left ventricular outflow obstruction was defined as turbulent LV outflow of high velocity (>2.0 m/s) based on continuous-wave Doppler ultrasound examination. None of the cats with HCM had received any medication or had a history of clinical signs of cardiac disease.

We identified cats as controls if they had normal findings on complete physical examination, ECG, thoracic radiography, and transthoracic echocardiography. All control cats had an echocardiographically symmetric left ventricular wall and non-hypertrophied papillary muscle and wall thickness. Control cats did not have systolic cranial motion of the mitral valve and did not have 2D or Doppler evidence of cardiac disease as assessed from either right- or left-sided imaging views. None of the control cats were on medication or had a history of clinical signs of cardiac disease.

2.2 | Standard echocardiography

Conventional 2D and Doppler examinations were performed by a single trained investigator using a Vivid 7 or Vivid E95 echocardiographic system (GE Healthcare, Tokyo, Japan); ECG limb lead II was recorded simultaneously and displayed on the images. All data were obtained for at least 3 consecutive cardiac cycles in sinus rhythm from nonsedated cats that were manually restrained in the right and left lateral recumbent positions. A single trained observer analyzed the images using an offline workstation (Echopac PC, version 201; GE Healthcare). The left atrial-to-aortic root ratio was obtained from the right parasternal short-axis view using the B-mode method. End-diastolic interventricular septal thickness, end-diastolic LV free-wall thickness, end-diastolic LV internal diameter, end-systolic LV internal diameter, and fractional shortening were measured using the B-mode method from the right parasternal short-axis view of the LV. As indicators of LV hypertrophy, the relative wall thickness (RWT) was calculated as the ratio of the sum of the end-diastolic interventricular septal thickness and end-diastolic LV free-wall thickness to the end-diastolic LV internal diameter. Transmitral flow was obtained from the left apical 4-chamber view, and the peak velocity of the early diastolic wave (E-wave), deceleration time of the E-wave, and peak velocity of the late diastolic wave (A-wave) were measured. In cats in which the E and A waves were fused, values for those waves were not used. For all analyses, the mean values of 3 consecutive cardiac cycles in sinus rhythm from high-quality images were used.

2.3 | 2D speckle-tracking echocardiography

The 2D-STE protocols that we previously reported for dogs and cats were applied. High-quality images for 2D-STE analysis were carefully obtained by the same investigator. To evaluate circumferential deformation by 2D-STE, we used a right parasternal short-axis view of the LV at the level of the papillary muscles. A left apical 4-chamber view was used to analyze longitudinal deformation. Images again were analyzed by a single observer using an offline EchoPAC workstation, as described previously. We selected 1 cardiac cycle (from 1 QRS complex to the next QRS complex) from the high-quality images and manually traced the endocardial borders of the myocardium in the end-diastole to select the appropriate region of interest. Each region of interest then was adjusted to incorporate the entire myocardial thickness and checked by the observer to ensure that it was visually synchronized with cardiac movement throughout the entire cardiac cycle. The computer software automatically traced the myocardium, created 6 segments in each image, and evaluated whether it reliably followed myocardial motion. If the initial evaluation failed because of an inability to trace the region of interest during myocardial movement, the endocardial borders were retraced and manually corrected as needed. Finally, we measured the peak systolic strain of the endocardial, whole, and epicardial layers in the longitudinal (Figure 1) and circumferential directions (Figure 2). We calculated the endocardial-to-epicardial strain ratio to determine the endocardial dependency of the myocardium. We also measured the end-diastolic segmental LV wall thicknesses by the 2D method corresponding to segments created by the 2D-STE analysis. The mean values of the measurements from 3 consecutive cardiac cycles from high-quality images were used in all analyses.
2.4 Statistical analysis

Data are expressed as medians and interquartile ranges. All statistical analyses were performed using R software version 2.8.1. (The R Foundation for Statistical Computing, Vienna, Austria). We used the Shapiro-Wilk test to check for normal distribution of the variables. We used a Mann-Whitney $U$ test to compare the variables between HCM and control cats. Linear regression analysis was performed to examine correlations of 2D-STE strains with LV wall thicknesses of the corresponding myocardium. Values of $P < .05$ were considered significant. Intra-observer reproducibility was assessed by determining the coefficients of variation by having the observer repeat the measurements 3 times for 3 cats selected at random on different days. The studies also were analyzed by a second blinded observer to assess inter-observer reproducibility.

3 RESULTS

3.1 Clinical profiles and standard echocardiography

The clinical characteristics and conventional echocardiographic data in healthy controls and cats with asymptomatic HCM are summarized in Table 1. Age, body weight, heart rate, and systolic blood pressure did not differ significantly between HCM and control cats. The cats with HCM had significantly higher RWT and peak velocity of the LV outflow than did controls ($P < .001$ and $P < .001$, respectively). Also, they had significantly higher segmental LV wall thicknesses compared to controls (Table 2) in the long-axis (basal septum, $P < .001$; middle septum, $P = .04$; apical septum, $P = .009$; apical lateral, $P < .001$; middle lateral, $P < .001$; basal lateral, $P < .001$) and short-axis assessment ($P$ of all segments <.001).

3.2 2D speckle-tracking echocardiography

All views for the analysis of 2D-STE were recorded at an average rate of 142 (range, 116-214) frames per second, which is adequate for evaluation of cats.8,9,24 The average SD and average coefficients of variation for intra-observer and inter-observer reliability for layer-specific longitudinal and circumferential strains are summarized in Table 3.

The global 2D-STE data for healthy cats and cats with HCM are summarized in Table 4. Global longitudinal strain was significantly lower in cats with HCM than in controls in whole, endocardial, and epicardial layers (whole, $P = .03$; endocardial, $P = .04$; epicardial,
The global circumferential strain in the whole and epicardial layers also was significantly lower in cats with HCM than in controls (P < .001 and P = .001, respectively). However, no significant difference was found between cats with HCM and controls for global circumferential strain in the endocardial layer (P = .17). Furthermore, the circumferential endocardial-to-epicardial strain ratio was significantly higher in cats with HCM than in controls (P = .006).

The segmental 2D-STE data for healthy cats and cats with HCM are summarized in Table 5 (longitudinal assessment) and Table 6 (circumferential assessment). The basal lateral segment of longitudinal strain in whole, endocardial, and epicardial layers was significantly lower in cats with HCM than in controls (whole, P = .01; endocardial, P = .006; epicardial, P = .006, respectively). In addition, middle lateral segments of longitudinal strain in whole and epicardial layers also were lower (whole, P = .01; epicardial, P = .02). Cranial septum and septum segments of circumferential strain in whole, endocardial, and epicardial layers were significantly lower in cats with HCM than in controls (whole, P = .008 and P < .001; endocardial, P = .02 and P = .01; epicardial, P = .01 and P < .001, respectively). The lateral segment of circumferential strain in the whole layer also was lower (P = .04).

The peak systolic longitudinal strain was significantly correlated with the corresponding segmental LV wall thicknesses (Figure 3; whole, ρ = −0.58, P = .01; endocardial, ρ = −0.62, P = .01; epicardial, ρ = −0.60, P = .02, respectively). In contrast, circumferential strains in any layers were not significantly correlated with LV wall thicknesses.

4 | DISCUSSION

We found that layer-specific myocardial deformations could be assessed with 2D-STE to evaluate the myocardial function of cats with adequate repeatability. Our study also indicated that longitudinal function in all layers and circumferential function in whole and epicardial layers allow noninvasive detection of abnormal systolic deformations in asymptomatic cats with obstructive HCM, despite an apparently normal contractile state of the LV based on conventional echocardiography. These deformations may have been altered by the pathological myocardial changes of HCM, even in the occult (asymptomatic) state. Furthermore, maintained endocardial circumferential strain and a higher circumferential endocardial-to-epicardial strain ratio may contribute to the preservation of pump function and prevent the development of cardiac clinical signs in cats with HCM.
TABLE 1 Characteristics and conventional echocardiographic data for healthy cats and cats with asymptomatic hypertrophic cardiomyopathy

|                  | Control                  | Asymptomatic HCM            |
|------------------|--------------------------|-----------------------------|
| Number of cats (male) | 13 (5)                  | 10 (5)                      |
| Age (mo)         | 25 (11–41)               | 16 (10–71)                  |
| Body weight (kg) | 4.1 (3.8–4.7)            | 4.1 (3.6–5.1)               |
| HR (bpm)         | 180 (172–183)            | 179 (167–186)               |
| SBP (mm Hg)      | 135 (119–150)            | 133 (125–148)               |
| LA/Ao            | 1.1 (1.0–1.2)            | 1.2 (1.1–1.3)               |
| LVIDd (mm)       | 15.1 (13.7–15.8)         | 14.2 (13.2–14.7)            |
| LVIDs (mm)       | 9.5 (7.6–10.0)           | 8.5 (7.6–8.9)               |
| RWT              | 0.50 (0.44–0.64)         | 0.82 (0.73–0.98)            |
| FS (%)           | 37.4 (35.8–43.6)         | 39.3 (34.7–42.7)            |
| E wave velocity (m/s) | 0.79 (0.71–0.83)     | 0.70 (0.67–0.96)            |
| Deceleration time of E wave (ms) | 85.3 (80.5–88.2) | 65.8 (55.2–74.0)            |
| A wave velocity (m/s) | 0.66 (0.58–0.77)      | 0.57 (0.45–0.72)            |
| E/A ratio        | 1.1 (1.0–1.4)            | 1.6 (1.0–2.3)               |
| Peak velocity of LVOT (m/s) | 0.9 (0.9–1.0)  | 4.5 (3.6–4.7)               |

Data are expressed as medians (25%-75% interquartile ranges). Abbreviations: FS, fractional shortening; HR, heart rate; LA/Ao, left atrial to aortic root ratio; LVIDd, end-diastolic left ventricular internal diameter; LVIDs, end-systolic left ventricular internal diameter; LVOT, left ventricular outflow tract; RWT, relative wall thickness; SBP, systolic blood pressure.

In our study, cats with HCM had adequate systolic function compared to controls, as indicated by similar end-systolic LV internal diameter and fractional shortening values. However, global longitudinal strain was significantly lower in cats with HCM than in controls.

In cats with obstructive HCM, myocardial function differed according to the layer of the myocardium. Therefore, determination of layerspecific myocardial function may facilitate detailed assessment of systolic function in cats with HCM.

In our study, cats with HCM had adequate systolic function compared to controls, as indicated by similar end-systolic LV internal diameter and fractional shortening values. However, global longitudinal strain was significantly lower in cats with HCM than in controls.

In our study, longitudinal strain in whole, endocardial, and epicardial layers was significantly lower in cats with HCM than in controls. Previous 2D-STE studies of cats indicated that global and segmental longitudinal strain in the whole layer was lower in asymptomatic cats with HCM than in healthy cats. These changes may have been altered by global and regional myocardial dysfunction and histopathological changes. Although layer-specific longitudinal strain was not assessed in studies of cats, studies of humans previously had indicated that patients with HCM had lower endocardial and epicardial longitudinal strains compared to control subjects. These findings may suggest occult systolic dysfunction in cats with HCM. Histopathological changes, alterations in myocardial fiber orientation, and myocardial compensatory mechanisms may be related to these functional abnormalities. Because the diagnosis of HCM in asymptomatic cats is sometimes difficult, assessment of the myocardium using 2D-STE may be useful to distinguish between asymptomatic cats with HCM and healthy cats.

In our study, longitudinal strain in whole, endocardial, and epicardial layers was significantly correlated with segmental LV wall thicknesses. Similarly, a previous study of cats indicated that tissue Doppler-derived longitudinal strain was decreased with increasing LV concentric hypertrophy. These relationships may be explained by an association of the extent of myocardial changes and ischemia with the severity of wall thickening. Furthermore, the relationship between the amount of myocardial fibrosis and speckle-tracking-derived strain variables has been described. Although histopathological characteristics were not assessed in our study, layer-specific myocardial strains might provide additional insights regarding the extent and distribution of LV fibrosis.

In our study, the global circumferential strain in whole and epicardial layers was significantly lower in cats with HCM than in controls, which is consistent with previous studies of humans. The more inner wall is influenced not only by active contraction but also by passive contraction (layer-to-layer compensatory interaction). Therefore, a decrease in the epicardial (outer) circumferential strain would reflect impaired myocardial function in cats with HCM.

In contrast, no significant difference was found in the global circumferential strain in the endocardial layer between asymptomatic cats with HCM and controls. Furthermore, the circumferential endocardial-to-epicardial strain ratio was significantly higher in cats.
with HCM than in controls. These findings are in agreement with previous studies involving human patients with HCM. Circumferential deformations play an important role in cardiac pump function in people with cardiac disease, and LV myocardial contractions that are impaired in the longitudinal direction are compensated for by circumferential shortening in subclinical patients with cardiovascular risk factors. Furthermore, because of the above-mentioned layer-to-layer compensatory mechanism, endocardial circumferential strain tended to be passively maintained by the epicardial layer and actively enhanced as compensatory contraction for epicardial myocardial dysfunction. The circumferential endocardial-to-epicardial strain ratio may reflect endocardial dependency for compensation of the myocardium. Accordingly, maintained circumferential strain in the endocardial layer and higher circumferential endocardial-to-epicardial strain ratio in asymptomatic cats with HCM may be compensatory mechanisms for impaired myocardial function and may allow

### TABLE 4 Peak systolic global layer-specific strains assessed by 2-dimensional speckle-tracking echocardiography for healthy cats and cats with hypertrophic cardiomyopathy

| Strain Type | Control | Asymptomatic HCM |
|-------------|---------|------------------|
| Whole layer | 19.1 (−16.6 to −21.5) | 15.5 (−14.7 to −18.4) |
| Endocardial layer | 21.8 (−20.1 to −25.2) | 18.3 (−16.9 to −21.6) |
| Epicardial layer | 16.8 (−14.5 to −19.0) | 13.1 (−12.3 to −15.4) |
| Endo/epi | 1.3 (1.3 to 1.4) | 1.4 (1.3 to 1.4) |

Data are expressed as medians (25%-75% interquartile ranges). Abbreviation: Endo/Epi, endocardial to epicardial ratio. Within a row, values differed significantly (P < .05) from controls.

### TABLE 5 Peak systolic segmental layer-specific longitudinal strains assessed by 2-dimensional speckle-tracking echocardiography for healthy cats and cats with hypertrophic cardiomyopathy

| Strain Type | Control | Asymptomatic HCM |
|-------------|---------|------------------|
| Whole layer | 12.1 (−8.5 to −15.7) | 12.5 (−9.9 to −14.4) |
| Basal septum | 20.0 (−19.5 to −23.5) | 20.7 (−16.6 to −22.9) |
| Middle septum | 28.1 (−23.5 to −32.8) | 26.7 (−23.6 to −29.4) |
| Apical septum | 22.4 (−20.6 to 27.0) | 19.2 (−17.8 to −22.9) |
| Middle inferior | 15.9 (−14.5 to −19.3) | 11.8 (−8.1 to −13.0) |
| Basal inferior | 10.9 (−9.6 to −16.2) | 7.7 (−6.6 to −8.6) |
| Endocardial layer | 13.2 (−10.2 to −18.1) | 12.4 (−11.5 to −16.1) |
| Basal septum | 22.5 (−20.1 to −24.3) | 22.0 (−16.1 to −24.9) |
| Middle septum | 34.8 (−28.5 to −39.0) | 31.6 (−28.7 to −38.3) |
| Apical septum | 28.7 (−26.1 to −34.5) | 26.3 (−23.5 to −30.8) |
| Middle inferior | 18.8 (−17.3 to −22.2) | 15.5 (−11.1 to −17.1) |
| Basal inferior | 11.0 (−9.6 to −17.1) | 8.2 (−6.8 to −8.6) |
| Epicardial layer | 11.2 (−7.0 to −14.6) | 11.4 (−8.8 to −14.5) |
| Basal septum | 19.7 (−17.1 to −23.0) | 19.6 (−16.7 to −21.6) |
| Middle septum | 24.7 (−19.7 to −27.4) | 22.6 (−20.3 to −24.6) |
| Apical septum | 19.4 (−14.4 to −22.3) | 14.4 (−13.2 to −16.8) |
| Middle inferior | 13.7 (−10.8 to −16.8) | 7.1 (−5.5 to −10.4) |
| Basal inferior | 11.9 (−9.4 to −15.4) | 7.3 (−6.0 to −8.6) |

Data are expressed as medians (25%-75% interquartile ranges). Within a row, values differed significantly (P < .05) from controls.

### TABLE 6 Peak systolic segmental layer-specific circumferential strains assessed by 2-dimensional speckle-tracking echocardiography for healthy cats and cats with hypertrophic cardiomyopathy

| Strain Type | Control | Asymptomatic HCM |
|-------------|---------|------------------|
| Whole layer | −27.9 (−21.6 to −29.7) | −16.6 (−13.4 to −18.3) |
| Cranial septum | −20.2 (−15.6 to −22.8) | −9.3 (−5.0 to −13.0) |
| Lateral | −15.5 (−11.8 to −19.1) | −9.8 (−6.7 to −14.4) |
| Caudal | −19.2 (−13.4 to −23.5) | −20.0 (−16.9 to −24.9) |
| Inferior | −19.9 (−14.9 to −25.9) | −21.2 (−17.4 to −23.5) |
| Septum | −25.8 (−22.9 to −27.9) | −19.5 (−14.8 to −20.3) |
| Endocardial layer | −35.6 (−33.8 to −41.7) | −30.2 (−25.8 to −36.1) |
| Cranial septum | −35.8 (−31.2 to −38.7) | −26.6 (−16.9 to −28.4) |
| Lateral | −31.0 (−28.6 to −35.5) | −24.1 (−21.7 to −31.4) |
| Caudal | −31.4 (−24.9 to −39.8) | −34.9 (−32.2 to −39.6) |
| Inferior | −34.3 (−26.2 to −38.2) | −39.1 (−31.0 to −42.0) |
| Septum | −38.3 (−33.6 to −42.4) | −35.8 (−28.0 to −38.1) |

Data are expressed as medians (25%-75% interquartile ranges). Within a row, values differed significantly (P < .05) from controls.
preservation of pump function and prevent the development of clinical signs of cardiac disease.

Dynamic obstruction of the LV outflow tract is observed frequently in cats with HCM. The LV outflow tract obstruction causes pressure overload in the myocardium and mitral regurgitation because of systolic cranial motion of the mitral valve. These abnormalities may induce additional hypertrophy, delayed ventricular relaxation, increased LV diastolic pressure, myocardial ischemia, and decreased cardiac output. A previous 2D-STE study of humans indicated that patients with obstructive HCM had lower longitudinal strain than did patients with nonobstructive HCM. Left ventricular outflow tract obstruction may degrade myocardial function in patients with HCM. In human patients with HCM, deterioration of myocardial strain was identified as an independent predictor of adverse outcomes. Although clinical outcome was not assessed in our study, evaluation of myocardial deformation has the potential to allow the early identification of cats at risk for progression to symptomatic HCM. The clinical importance of myocardial deformations as assessed by 2D-STE and their relationship to survival time should be investigated.

Our study had several limitations. First, because our study was a noninvasive clinical investigation, we could not definitively measure myocardial contractility using the invasive assessment that is the gold standard for assessing LV function. Second, we did not perform the histopathological examination to make a definitive diagnosis and assess myocardial histopathological changes. Some control cats, however, may have had occult myocardial disease. Third, 2D-STE analysis requires high-quality B-mode images that are sometimes difficult to obtain, especially in the feline heart. Some 2D-STE segmental strains were not sufficient for repeatability in clinical examinations, although layer-specific global strains had adequate measurement variability. Standardization of the 2D-STE protocol as reported in a consensus paper in human medicine may help improve repeatability in veterinary medicine. Finally, the small number of cats in our study may have had an influence on statistical power and limits extrapolation of our findings to larger populations. However, we obtained detailed and precise myocardial functional data in cats with HCM in our study. These limitations should be addressed in future investigations.

CONCLUSIONS

Layer-specific myocardial function assessed by 2D-STE differed in asymptomatic cats with obstructive HCM compared to controls despite their apparently normal systolic function as determined by conventional echocardiography. Decreased longitudinal myocardial strains in all layers, and circumferential in whole and epicardial layers, may reflect myocardial dysfunction in asymptomatic HCM. Maintained endocardial circumferential strain and a higher circumferential endocardial-to-epicardial strain ratio may reflect compensation for occult systolic dysfunction in cats with HCM. Measurement of layer-specific myocardial function using 2D-STE may provide more detailed assessment of contractile function in cats with HCM. Nevertheless, the clinical importance of these strains and their relationship to survival time require further investigation.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

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.

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