Tissue Doppler and strain imaging of left ventricle in Beagle dogs with iatrogenic hypercortisolism

Heejin Oui, Sunghoon Jeon, Gahyun Lee, Seungjo Park, Kyoung-Oh Cho, Jihye Choi*

College of Veterinary Medicine, Chonnam National University, Gwangju 500-757, Korea

Changes in radial and longitudinal left ventricular (LV) function were investigated in beagles with iatrogenic hypercortisolism. A total of 11 normal dogs were used, and 2 mg/kg prednisone was administered per oral q12 h for 28 days to 7 out of 11 dogs to induce iatrogenic hypercortisolism. Body weight, blood pressure, conventional echocardiography and tissue Doppler imaging (TDI) of normal and iatrogenic hypercortisolism groups were conducted. The myocardial wall velocity of the LV was measured using color TDI and myocardial deformation was determined by the strain and strain rate. Conventional echocardiography revealed that the diastolic LV free wall and interventricular septum in the hypercortisolism group were thickened relative to those in the normal group. The peak early diastolic myocardial velocity and early to late diastolic myocardial velocity ratio of TDI in the hypercortisolism group were significantly lower than those in the normal group. The strain values in the hypercortisolism group were significantly lower than those in the normal group, particularly for longitudinal wall motion. The lower values of myocardium from TDI and strain imaging could be used to investigate subclinical LV systolic and diastolic dysfunction in dogs with the iatrogenic hypercortisolism.

Keywords: dog, hypercortisolism, left ventricle, strain, tissue Doppler imaging

Introduction

Tissue Doppler imaging (TDI) quantitatively assesses global and regional systolic function and abnormal relaxation of the heart by measuring tissue velocity, strain and strain rate [24,27]. Tissue velocity directly describes wall motion, which is a tethering motion of the heart regardless of whether regional myocardium movement is active or passive. Strain is an index of the length change in a myocardial segment during the cardiac cycle, and strain rate is calculated as the time-derivative of strain [5]. If two adjacent points in one myocardial segment show different lengths of change with respect to time, the myocardial segment shows a change in its own shape. Using this property, strain and strain rate reflect myocardial deformation and deformation rate, respectively. However, these two parameters are less affected by the tethering movement of the heart and may discriminate between passive and active cardiac motion.

Hypercortisolism is one of the most common endocrine diseases in geriatric dogs [26]. This disorder can cause various side effects such as steroid hepatopathy, hypertension, impaired glucose tolerance of diabetes, and hypercoagulability [1,18,26]. The effects of hypercortisolism on cardiac function have been investigated in humans, and hypertrophy and concentric remodeling of the left ventricle (LV) and systolic and diastolic dysfunction have been suggested by conventional echocardiography and TDI studies [2,3,8,13,17]. In particular, impairment of LV systolic dysfunction, which is not clearly identified in conventional echocardiography, can be detected by TDI. Moreover, the association between hypercortisolism and cardiac function has not yet been studied in dogs using conventional echocardiography or TDI.

In this study, intra-observer within- and between-day TDI variability was assessed and LV function was investigated in dogs with iatrogenic hypercortisolism using TDI, including strain imaging, and the reliability of these methods for LV function was determined.

Materials and Methods

This study protocol was approved by the Institutional Animal Care and Use Committee of Chonnam National University and the animals were cared for in accordance with the Guidelines...
Eleven 3-year-old healthy male beagles (weight, 7.7–11.9 kg; median weight, 10.5 kg) were used in this study. The clinical state of every dog was determined by physical examination, systemic arterial blood pressure measured indirectly using a standard Doppler method, complete blood count, biochemistry, electrolytes, adrenocorticotropic hormone (ACTH) stimulation with injection of 5 μg/kg of synthetic ACTH (Synacthen; Dalim BioTech, Korea), urinalysis, heartworm occult antigen test, thoracic and abdominal radiographs, abdominal ultrasonography, conventional echocardiography and TDI. These data were used for the normal group. Seven dogs were then randomly selected for the iatrogenic hypercortisolism group and one dog was used for myocardium sampling for histopathologic examination. Dogs in the iatrogenic hypercortisolism group received 2 mg/kg prednisolone (Solondo; Yuhan Medica, Korea) per oral q12 h for 28 days. On day 28, body weight, blood pressure, conventional echocardiography, and TDI were repeated in the iatrogenic hypercortisolism group.

Echocardiography was performed with a ProSound α7 instrument (Hitachi-Aloka Medical, Japan) using a 3 to 7.5 MHz phased-array transducer according to the recommendations of the American Society of Echocardiography [23]. Echocardiographic measurements were carried out by one veterinarian (OHJ), and mean values from three separate cardiac cycles were used. In M-mode of the LV taken from the right parasternal short-axis view, LV internal dimension and the thicknesses of the LV free-wall (LVFW) and the interventricular septum (IVS) were measured at the end-diastole and end-systole, after which these parameters were normalized using Cornell’s equation to compare with prediction intervals [4]. The diameters of the aorta (Ao) and left atrium (LA) were measured.

**Fig. 1.** Examples of radial velocity and strain (A–D) assessment on right parasternal short-axis view at the level of papillary muscles and longitudinal velocity and strain assessment (E–H) of left ventricle (LV) on left apical four chamber view in a healthy beagle dog. (A and B) For radial velocity, 2 × 2 mm samples were placed on the endocardial (yellow circle) and epicardial (pink circle) segments between the papillary muscles. Peak velocities in systole (Sm), early diastole (Em) and late diastole (Am) were measured in the endocardium (yellow curve) and epicardium (pink curve). (C and D) Strain and strain rate variables were determined for a 3.5 × 3.5 mm region of interest and 1.5 mm strain length on the same frame. Maximum positive systolic strain was obtained in the end-systole. (E–G) The basal (yellow circle) and apical (pink circle) segments of the left ventricular free wall and interventricular septum with a 2 × 2 mm region of interest were used in the velocity analyses. (H–J) Peak velocities in systole (Sm), early diastole (Em) and late diastole (Am) were measured. Using the same region of interest with 5 mm strain length, strain and systolic strain rate were determined on the same frame. Negative systolic strain reflects longitudinal compression.
at the level of the aortic valve during diastole in two-dimensional mode. LV inflow velocities in early (E) and late (A) diastoles were measured using pulsed-wave Doppler mode in the left apical four-chamber view.

Two-dimensional color TDI was performed in the right parasternal short-axis view to evaluate the radial motion of the LV and left apical four-chamber view for the longitudinal motion (Fig. 1). The gray scale gain setting was adjusted to optimize wall boundaries of the LVFW and IVS, the Doppler velocity range was set as low as possible to avoid aliasing artifacts, and the frame rate was ≥ 150 frames/sec. The recorded TDI images were reviewed using a software program (SOP-ALPHA7-13; Hitachi-Aloka Medical). The region of interest (ROI) in the diastole was determined based on the wall width and length (Table 1). The peak velocities of LV myocardium were measured at systole (Sm), early diastole (Em), and late diastole (Am). The systolic strain rate (SRS), early diastolic (SRE) and late diastolic strain rates (SRA) of the radial motion were measured from LVFW. Strain and SRS of the longitudinal motion from LVFW and IVS were measured.

Before the study, within- and between-day variabilities of the TDI-derived variables were determined to evaluate the technical factors influenced by statistics. Six beagles were examined using TDI on three different days. On a given day, TDI examination was performed three different times. A total of 30 echocardiographic variables were measured using the same method as described above and mean values and standard deviations were used to determine the coefficient of variation using a variance component analysis. A significant interaction was considered when the coefficient of variation value was > 15%.

Myocardial tissues were collected from one dog each in the normal and iatrogenic hypercortisolism groups, then fixed in 10% buffered formalin for histopathological examination. The LVFW was processed and paraffin embedded. Serial 3 μm sections were cut, and routine histological staining was performed with hematoxylin and eosin. A standard protocol of Masson’s trichrome staining was used to assess fibrosis. Sections were also examined for arteriosclerosis and inflammatory infiltrates.

Statistical analysis was performed using the SPSS statistical program (IBM SPSS Statistics 21; IBM, USA). Groups were compared by the Mann-Whitney nonparametric test. All data are presented as median and ranges and a \( p < 0.05 \) was considered significant.

**Results**

Intra-observer within- and between-day coefficient of variation values are given in Table 2. Most within-day coefficient of variation values \( (23/30) \) were < 15\% (range: 4.2–25\%), except SRE and SRA at the radial LVFW, Em at the apex of the longitudinal LVFW, Am at the base and the apex of the longitudinal LVFW, and Am at the apex of longitudinal IVS. Most between-day coefficient of variation values \( (24/30) \) were also < 15\% (range: 4.3–28.2\%), except peak SRA at the radial LVFW, Em at the apex of longitudinal LVFW, Am at the base and apex of longitudinal LVFW and IVS, and SRS at the apex of longitudinal LVFW.

Dogs in the iatrogenic hypercortisolism group had higher concentrations of basal cortisol, serum alkaline phosphatase, and alanine aminotransferase than those of dogs in the normal group (data not shown). On day 28, serum cortisol concentrations were significantly higher than baseline values on day 0, and the ACTH-stimulated cortisol concentration was lower than the reference range (basal cortisol concentration: 2.0–6.0 μg/dL, ACTH-stimulated cortisol concentration: 5.0–18.0 μg/dL) in the hypercortisolism group. Blood pressure in the hypercortisolism group was significantly higher than that of the normal group \( (p < 0.05) \) (Table 3). No significant differences in body weight or heart rate were observed between groups.

No abnormal blood flow was detected in any of the groups by color Doppler conventional echocardiography. The normalized echocardiographic parameters of the two groups were within normal reference ranges (Table 4). The diastolic thicknesses of LVFW and IVS in the hypercortisolism group were significantly higher than those in the normal group \( (p < 0.05) \). No significant difference in the diastolic LV internal dimension was observed between groups. The E/Em ratio of the hypercortisolism group was significantly lower than that of the normal group.

### Table 1. Size and position of region of interest (ROI) for tissue Doppler imaging-derived parameters in left ventricle (LV)

| LV motion | Parameters                  | Size (mm) | Position                                      |
|-----------|-----------------------------|-----------|-----------------------------------------------|
| Radial    | Velocities                  | 2 × 2     | Endocardial and epicardial segments between the papillary muscles in LVFW |
|           | Strain and strain rate      | 3.5 × 3.5 × 1.5 | LVFW segment between the papillary muscles |
| Longitudinal | Velocities                  | 2 × 2     | The basal and apical segments of the LVFW and IVS |
|           | Strain and systolic strain rate | 2 × 2 × 5 | The basal and apical segments of the LVFW and IVS |

ROI for strain and strain rate; size × length. LVFW, left ventricular free wall; IVS, interventricular septum.
Table 3. Median values and ranges of clinical parameters in the normal and iatrogenic hypercortisolism groups

| Median (range)          | Normal (n = 11) | Hypercortisolism (n = 7) |
|-------------------------|-----------------|--------------------------|
| Body weight (kg)        | 10.5 (7.7–11.9) | 10.9 (9.8–11.2)          |
| Blood pressure (mmHg)   | 130 (115–140)   | 150 (140–158)*           |
| Heart rate (beats/min)  | 86 (73–91)      | 86 (76–93)               |

*Indicates significantly different at p < 0.05.

The TDI results for the radial LVFW variables are given in Table 5. Table 6 shows the longitudinal LVFW variables, and Table 7 shows the longitudinal IVS variables. No significant differences in the radial LVFW variables such as Em or Am velocities of endocardial and epicardial segments were observed, or in the Em/Am ratio in the epicardial segment of the two groups. Conversely, several diastolic alterations were observed in the endocardial segment of the hypercortisolism group. The Em velocity and the Em/Am ratio of the hypercortisolism group were significantly lower (p < 0.05), and the Am velocity was significantly higher (p < 0.05) than those in the normal group. Most longitudinal LVFW variables...
Table 4. Conventional echocardiographic parameters related to left ventricle in normal and iatrogenic hypercortisolism groups

| Parameter          | Normal (n = 11)       | Hypercortisolism (n = 7) |
|--------------------|-----------------------|--------------------------|
| IVSd (mm)          | 6.73 (4.73–8.37)      | 7.96 (7.55–11.02)*       |
| Normalized (%)     | 0.39 (0.30–0.48)      | 0.46 (0.41–0.62)*        |
| LVIDd (mm)         | 30.61 (27.55–33.06)   | 31.63 (28.1–32.86)       |
| Normalized (%)     | 1.53 (1.45–1.66)      | 1.54 (1.43–1.62)         |
| LVFWd (mm)         | 6.94 (5.31–8.16)      | 8.16 (7.53–9.16)*        |
| Normalized (%)     | 0.40 (0.31–0.48)      | 0.47 (0.42–0.52)*        |
| IVSs (mm)          | 8.98 (7.96–12.24)     | 10.41 (9.18–12.65)*      |
| Normalized (%)     | 0.51 (0.47–0.75)      | 0.57 (0.51–0.71)         |
| LVIDs (mm)         | 21.22 (18.52–25.51)   | 19.80 (17.55–24.29)      |
| Normalized (%)     | 1.03 (0.88–1.24)      | 0.94 (0.80–1.13)         |
| LVFWs (mm)         | 9.59 (6.73–11.43)     | 10.82 (9.39–13.06)       |
| Normalized (%)     | 0.57 (0.40–0.68)      | 0.63 (0.55–0.75)         |
| EF (%)             | 59.80 (50.80–75.50)   | 60.80 (52.90–79.50)      |
| FS (%)             | 30.70 (32.20–43.10)   | 29.70 (27.20–44.90)      |
| LA (mm)            | 15.40 (12.42–18.68)   | 14.82 (13.14–16.70)      |
| Aorta (mm)         | 16.31 (14.29–17.90)   | 15.76 (14.30–17.80)      |
| LA/Ao              | 0.93 (0.86–1.11)      | 0.92 (0.83–1.06)         |
| E (m/s)            | 0.71 (0.55–0.9)       | 0.69 (0.51–0.79)         |
| A (m/s)            | 0.35 (0.25–0.63)      | 0.41 (0.36–0.50)         |
| E/A                | 1.82 (1.37–2.81)      | 1.58 (1.38–1.68)         |
| E/Em               | 12.99 (11.27–13.73)   | 16.72 (12.0–18.27)*      |

*Indicates significantly different at p < 0.05. IVSd, interventricular septal diastolic thickness; LVIDd, left ventricular end-diastolic diameter; LVFWd, left ventricular free wall diastolic thickness; IVSs, interventricular septal systolic thickness; LVIDs, left ventricular end-systolic diameter; LVFWs, left ventricular free wall systolic thickness; EF, ejection fraction; FS, fractional shortening; LA, left atrium; LA/Ao, left atrial to aortic diameter ratio; E, peak early left ventricular inflow velocity; A, peak late left ventricular inflow velocity; E/A, ratio of peak early to peak late left ventricular inflow velocities; E/Em, ratio of peak early left ventricular inflow velocities to peak radial left ventricular free wall velocity in early diastole.

Discussion

A quantitative assessment of TDI in beagles with iatrogenic hypercortisolism showed subclinical systolic and diastolic dysfunction of LV myocardium, whereas conventional echocardiography could not determine myocardial dysfunction. Although the exact mechanism has not been clearly identified, excessive glucocorticoids impair conversion of cortisol to an inactive form, thereby allowing glucocorticoid-mediated mineralocorticoid effects on the heart such as increased myocardial fibrosis [9,28]. Atherosclerosis with intimal thickening in coronary arteries occurs during hypercortisolism and may cause an imbalance between tissue oxygen requirements and supply, resulting in cardiac ischemia [19,22]. However, fibrosis or arteriosclerosis was not found in myocardial tissues of dogs with iatrogenic hypercortisolism in this study. The discrepancy between our results and those of previous studies [9,10,19,22,28] may be attributed to the short duration of glucocorticoid treatment. Cardiac fibrosis of this study was evaluated subjectively upon microscopic examination, not...
Table 5. Tissue Doppler imaging-derived variables of radial left ventricular free wall in the normal and iatrogenic hypercortisolism groups

|                      | Median (range) Normal (n = 11) | Hypercortisolism (n = 7) |
|----------------------|--------------------------------|--------------------------|
| **Endocardial velocity (cm/s)** |                                |                          |
| Sm                   | 4.77 (4.4-5.46)                | 4.77 (3.7-5.24)          |
| Em                   | 6.34 (5.1-7.68)                | 5.33 (4.15-5.95)*        |
| Am                   | 2.86 (2.03-3.72)               | 3.5 (2.01-4.1)           |
| **Epicardial velocity (cm/s)** |                                |                          |
| Sm                   | 2.66 (2.45-2.84)               | 2.7 (2.37-3.58)          |
| Em                   | 2.5 (2.32-2.86)                | 2.1 (1.79-2.99)          |
| Am                   | 1.7 (1.32-2.1)                 | 1.85 (1.51-2.16)         |
| **Endocardial Em/Am** | 2.40 (1.69-2.87)               | 1.42 (1.05-2.65)*        |
| **Epicardial Em/Am**  | 1.50 (1.17-1.89)               | 1.25 (1.02-1.61)*        |
| **Radial strain (%)** | 56.26 (54.25-57.1)             | 53.09 (52.43-55.31)      |
| **Radial strain rate (s⁻¹)** |                             |                          |
| SRS                  | 4.36 (3.89-4.91)               | 4.45 (3.87-4.91)*        |
| SRE                  | -4.99 (-4.21 - -6.1)           | -3.88 (-3.59 - -5.79)*   |
| SRA                  | -2.41 (-1.92 - -3.52)         | -2.59 (-2.02 - -3.89)    |

*Indicates significantly different at p < 0.05.

Table 6. Tissue Doppler imaging-derived variables of longitudinal left ventricular free wall in the normal and iatrogenic hypercortisolism groups

|                      | Median (range) Normal (n = 11) | Hypercortisolism (n = 7) |
|----------------------|--------------------------------|--------------------------|
| **Basal variables**  |                                |                          |
| Sm (cm/s)            | 5.16 (4.68-5.53)               | 4.93 (4.31-5.64)         |
| Em (cm/s)            | 5.9 (4.66-6.89)                | 4.27 (3.04-5.66)*        |
| Am (cm/s)            | 3.77 (2.51-4.01)               | 3.21 (2.26-4.09)         |
| Em/Am                | 1.58 (1.23-2.42)               | 1.35 (1.01-1.6)*         |
| Strain (%)           | -24.31 (-23.4 - -25.99)        | -20.26 (-19.5 - -21.26)* |
| SRS (s⁻¹)            | -2.78 (-2.65 - -3.16)         | -2.25 (-1.94 - -2.66)*   |
| **Apical variables** |                                |                          |
| Sm (cm/s)            | 2.33 (1.92-2.66)               | 1.98 (1.34-2.31)         |
| Em (cm/s)            | 2.99 (2.39-3.23)               | 1.95 (1.6-2.36)*         |
| Am (cm/s)            | 0.99 (0.78-1.37)               | 1.21 (0.88-1.8)          |
| Em/Am                | 2.99 (1.83-3.56)               | 1.69 (1.31-1.84)*        |
| Strain (%)           | -22.93 (-21.99 - -23.88)       | -19.95 (-18.59 - -20.88)*|
| SRS (s⁻¹)            | -2.32 (-1.92 - -2.67)         | -2.02 (-1.85 - -2.21)*   |

*Indicates significantly different at p < 0.05.

Conventional echocardiography revealed that the diastolic LVFW and IVS were significantly thicker in the hypercortisolism group than in the normal group, although these parameters in the hypercortisolism group were also within the reference range [4]. Specifically, the hypercortisolism group showed quantitatively as in previous studies [10]; thus, mild alterations could have been missed. However, other factors that might play crucial roles in the development of fibrosis and atherosclerosis with exogenous treatment of glucocorticoids in dogs need to be investigated.
Table 7. Tissue Doppler imaging-derived variables of longitudinal interventricular septum in the normal and iatrogenic hypercortisolism groups

|                      | Median (range)                                      |             |
|----------------------|----------------------------------------------------|-------------|
|                      | Normal (n = 11)                                     | Hypercortisolism (n = 7) |
| **Basal variables**  |                                                    |             |
| Sm (cm/s)            | 5.01 (4.72–5.85)                                   | 4.84 (4.1–5.85) |
| Em (cm/s)            | 5.55 (4.51–5.99)                                   | 3.78 (2.65–4.12)* |
| Am (cm/s)            | 3.85 (2.49–4.55)                                   | 3.58 (2.89–4.14) |
| Em/Am                | 1.37 (1.22–2.27)                                   | 1.04 (0.82–1.38)* |
| Strain (%)           | −22.93 (−21.36–−24.12)                             | −18.52 (−17.35–−19.7)* |
| SRS (s⁻¹)            | −2.07 (−1.88–−2.34)                                | −1.86 (−1.5–−2.33) |
| **Apical variables** |                                                    |             |
| Sm (cm/s)            | 2.12 (1.83–2.33)                                   | 2.04 (1.65–2.41) |
| Em (cm/s)            | 1.98 (1.66–2.13)                                   | 1.66 (1.35–2.01)* |
| Am (cm/s)            | 0.95 (0.66–1.31)                                   | 1.05 (0.76–2.12) |
| Em/Am                | 2.17 (1.42–2.61)                                   | 1.29 (0.95–2.05)* |
| Strain (%)           | −20.65 (−19.33–−22.6)                              | −18.8 (−17.44–−20.46)* |
| SRS (s⁻¹)            | −2.03 (−1.68–−2.77)                                | −1.89 (−1.05–−2.48) |

*Indicates significantly different at p < 0.05.

symmetrically concentric LV hypertrophy with normal fractional shortening. In humans, a positive correlation was detected between relative wall thickness and duration of the hypercortisolism [8]. In light of the short duration of this study, this tendency for thicker LVFW and IVS might indicate that LV concentric remodeling was in progress in the hypercortisolism group.

Previous human studies [3,8,13] demonstrated that systolic and diastolic dysfunction in patients with Cushing’s syndrome develops independent of hypertension. Systemic hypertension can cause significant myocardial hypertrophy and myocardial dysfunction. In dogs with systemic hypertension, myocardial dysfunction, particularly for the LVFW longitudinal diastolic motion, occurred independently of the presence of myocardial hypertrophy [12]. The effects of blood pressure on cardiac function in dogs with hypercortisolism could not be excluded in this study because the systemic blood pressure of the hypercortisolism group was significantly higher than that of the normal group. However, the effects of systemic hypertension on the myocardium depend on the degree of systemic hypertension [11]. Since the absolute value in the hypercortisolism group was smaller than the criteria for systemic hypertension (> 160 mmHg), the effects of blood pressure on myocardial dysfunction of the hypercortisolism group may be minimal.

The E/A ratio is a useful parameter for evaluating LV filling pressure [15]. However, this ratio may not be accurate in patients with a preserved LV ejection fraction [14,21]. Em velocity and the E/Em ratio are more reliable indices of LV relaxation, and the E/Em ratio reflects LV filling pressure, independent of LV ejection fraction [14,21]. In the present study, Em, Em/Am, and E/Em in were significantly lower the hypercortisolism group than in the normal group. Increased LV filling pressure was observed in the hypercortisolism group because of the occurrence of abnormal myocardial relaxation. Human patients with hypercortisolism show TDI-derived diastolic parameter alterations, as well as decreased E velocity and E/A ratio on conventional echocardiography, while conventional echocardiographic changes may be related to the long duration and stages of hypercortisolism [17]. LV hypertrophy and ischemia are strongly associated with progression of diastolic dysfunction [20].

Dogs with hypercortisolism showed a significant decrease in systolic strain values, similar to a human study [16]. Sm can be used to assess LV contractile function, but the parameter depends on preload and afterload [6,16]. Strain can demonstrate local dysfunction and detects the regional contractile function more precisely than Sm velocity [7,25]. In the present study, Sm velocity did not differ between two groups, suggesting that myocardial dysfunction occurred locally and Sm velocities in the affected segments were unchanged by passive movement of the adjacent normal tissue. The degree of decreased strain was more remarkable in longitudinal values than in radial values, and was compatible with the result of study in human [17]. Longitudinal fibers are more sensitive to ischemia and fibrosis than radial fibers [20].

It should be noted that the present study had some limitations. First, TDI variables with a coefficient of variation > 15% may have interacted with the technical aspect of this method. The
TDI-derived variables obtained from the apical segment had relatively higher coefficients of variation than those in the basal segment. This may have occurred because TDI is angle-dependent and sensitive to noise. A second limitation is that only intra-observer repeatability was evaluated. Finally, this study was performed in a relatively small population of adult dogs for a short period. Despite these limitations, we demonstrated the effects of iatrogenic hypercortisolism on myocardial function in dogs.

The LV showed diastolic and systolic dysfunction in dogs with iatrogenic hypercortisolism. These changes were detected more clearly with TDI-derived variables, particularly in longitudinal motion before becoming prominent on conventional echocardiography. The results presented herein will serve as fundamental data for investigating the effects of cortisol effect on myocardial changes in a larger population of dogs with hypercortisolism.

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Conflict of Interest

There is no conflict of interest.

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