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Ultrasonographic Evidence of the Gut-Heart Axis: Increased Colon Wall Thickness in Dogs with Congestive Heart Failure: Case Control Research

Kalp-Bağırsak Ekseninin Ultrasonografik Kanıtı: Konjestif Kalp Yetersizliği Bulunan Köpeklerde Artan Kolon Duvar Kalınlığı: Olgu Kontrol Araştırması

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ABSTRACT Objective: The potential role of the intestine in the pathophysiological process of heart diseases is a matter of curiosity due to the bidirectional interaction between the intestinal microbiota and the cardiovascular system, called the gut-heart axis. In our study, intestinal ultrasonographic evaluation was performed in dogs with congestive heart failure (CHF), under the name of heart-gut axis; It was aimed to evaluate the correlation between CHF severity and colon wall thickness (CoWt). **Material and Methods:** Eight dogs with CHF were used to evaluate CoWt, using intestinal ultrasonography. In addition to calculating the left atrium/aorta ratio in echocardiographic examination, visual evaluation, systolic and diastolic function evaluations, and regurgitation evaluation with color Doppler were also performed. Intestinal ultrasonography was performed and CoWt was measured from the beginning of the mucosa to the end of the serosa excluding the lumen. **Results:** We found that the CoWt in dogs with heart failure increased between 3.3 and 3.8 mm. CoWt measurements obtained from a limited number of dogs showed a statistically insignificant correlation with E/A and ejection fraction (%) at r=0.80 and r=-0.65, respectively. **Conclusion:** Our research shows a noticeable increase in CoWt in dogs suffering from CHF. More comprehensive studies with a larger data pool are needed to truly understand the link between CoWt elevation and diastolic dysfunction in dogs with CHF.

Keywords: Colon wall thickness; congestive heart failure; diastolic dysfunction; dog

ÖZET Amaç: Bağırsak mikrobiyotası ile bağırsak-kalp ekseni adı verilen kardiyovasküler sistem arasındaki çift yönlü etkileşim nedeniyle bağırsağın kalp hastalıklarının patofizyolojik sürecindeki potansiyel rolü merak konusudur. Çalışmamızda konjestif kalp yetersizliği (KKY) olan köpeklerde intestinal ultrasonografik değerlendirme yapılarak, kalp-bağırsak ekseni adı altında; KKY şiddeti ile kolon duvar kalınlığı [colon wall thickness (CoWt)] arası korelasyonun değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bağırsak ultrasonografisi kullanılarak CoWt'yi değerlendirmek için KKY olan 8 köpek kullanıldı. Ekokardiyografik incelemede, sol atriyum/aort oranının hesaplanmasına ek olarak görsel değerlendirme, sistolik ve diyastolik fonksiyon değerlendirmeleri ve renkli Doppler ile regürjitasyon değerlendirmesi de yapıldı. Bağırsak ultrasonografisi yapıldı ve CoWt, mukozanın başlangıcından lümen hariç serozanın sonuna kadar ölçüldü. **Bulgular:** Kalp yetersizliği olan köpeklerde CoWt'nin 3,3-3,8 mm arasında değişen düzeylerde arttığını tespit ettik. Sınırlı sayıda köpekten elde edilen CoWt ölçümleri, E/A ve ejeksiyon fraksiyonu (%) ile sırasıyla r=0,80 ve r=-0,65 düzeylerinde istatistiksel olarak anlamsız bir korelasyon gösterdi. **Sonuç:** Araştırmamız KKY'den muzdarip köpeklerde CoWt'de gözle görülür bir artış olduğunu göstermektedir. KKY'li köpeklerde CoWt yükselmesi ile diyastolik fonksiyon bozukluğu arasındaki bağlantıyı gerçekten anlamak için daha geniş bir veri havuzunu içeren daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kolon duvar kalınlığı; konjestif kalp yetersizliği; diyastolik disfonksiyon; köpek

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The potential role of the gut in the pathophysiological process of heart diseases is a matter of curiosity due to the bidirectional interaction between the gut microbiota and the cardiovascular system, called the gut-heart axis. The gastrointestinal system (GIS) is colonized by several different microorganisms. This community of microorganisms is called the intestinal microbiota and its homeostasis is important because of its key role in physiological and pathological conditions.[1] There is only one layer that controls the passage between the intestinal lumen and the systemic circulation, which is the intestinal barrier.[2] This barrier, formed by intercellular tight junctions between mucosal cells, allows selective passage of substances in the lumen.[2,3] In heart failure (HF), microcirculation disorders occur in the intestine due to i) decreased perfusion, ii) increased congestion and sympathetic vasoconstriction, and iii) functional damage to the intestinal epithelium as a consequence of ischemia.[4,5] Mucosal malabsorption, intestinal barrier disorder and edema in the intestinal wall may occur due to decreased perfusion, low blood pressure and impaired microcirculation in the intestine.[6,7]

Elevated intestinal permeability via disruption of intestinal barrier integrity causes toxic, pathogenic, inflammatory and immunogenic agents to enter the systemic circulation and trigger chronic inflammation.[8] Chronic inflammation also plays a role in the pathogenesis of cardiovascular diseases.[9] Inflammatory cytokines (tumor necrosis factor α, ST2, interleukin-6, C-reactive protein and galectin-3) produced by the triggering of endotoxins in HF patients play a role in the process of cardiomyocyte hypertrophy, fibrosis and apoptosis, and also cause exacerbation of inflammatory responses by disrupting the intestinal barrier function.[6,10-12]

There are many factors that can cause dysbiosis in patients with HF, such as insufficient oxygen supply due to decreased intestinal perfusion and consequently increased colonization of pathogenic anaerobic bacteria, sudden changes in fluid balance, GI dysmotility and nutrient deprivation.[13,14] All these factors cause bacterial overgrowth and bacterial translocation.[14] Lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, has an inflammatory effect on cardiomyocytes and cardiac fibroblasts.[6] High levels of LPS were detected in the plasma of patients with congestive heart failure (CHF), suggesting that severe venous occlusion is an important factor for bacterial overgrowth and increased intestinal permeability during the edematous decompensation process.[15]

The aim of this study is to ultrasonographical reveal the increase in colon wall thickness (CoWt), which is caused by inflammatory and ischemic changes in dogs with HF.

MATERIAL AND METHODS

ANIMALS

Eight dogs who applied to Aydın Adnan Menderes University, Faculty of Veterinary Medicine, Department of Internal Medicine with symptoms of CHF were subjected to radiographic, echocardiographic and ultrasonographic evaluation after clinical examination. Exercise intolerance, cough, dyspnea, cardiac murmur, ascites, pulmonary effusion, edema and cardiomegaly were considered as signs of HF. The study group included 4 females and 4 males, in the 2-15 age group, 2 terrier, 2 Cavalier King Charles Spaniel, 2 mongrel dog, Golden Retriever and Pekingese. The clinical findings of these dogs with suspected CHF ranged from 3 weeks to 9 months. The patient owners were informed about the research and they signed a consent form. This study was approved by the local ethics committee of Aydın Adnan Menderes University Ethics Committee on August 24, 23 with reference number 64583101/2023/129. In experimental studies, all animals were subjected to humane treatment in accordance with the "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html).

ECHOCARDIOGRAPHY

Echocardiography of dogs was performed using a Mindray M5 Color Doppler device with a 3.5-4 MHz convex probe and a table suitable for echocardiography. The 4th to 6th intercostal spaces were shaved, and cardiac evaluation was performed

in the right and left parasternal long and short-axis views, using alcohol and ultrasound gel. Echocardiographic examination involved a visual assessment (for valvular abnormalities, pericardial effusion, and chordo tendinea lesions) in addition to the calculation of the left atrium to aorta (LA/Ao) ratio, systolic and diastolic function assessments, and regurgitation evaluation via color Doppler. For the systolic function assessment, Teichholz measurements in the M-mode view at the right parasternal short-axis left ventricle (LV) level were utilized. Right parasternal short-axis heart base level imaging was performed for LA/Ao evaluation. For diastolic function evaluation, the E/A ratio was determined by placing the PW/CW cursor on the mitral valve in the right parasternal long-axis view.[16]

ULTRASONOGRAPHY

After shaving the dogs' abdomens, intestinal ultrasonographic evaluation was conducted using a 7 MHz probe (Esaote-MyLab 30 CV Ultrasound Device, USA) in the dorsal recumbency position, with the aid of ultrasound gel. The descending colon, located dorsally to the bladder, was identified using the urinary bladder as a reference point, as reported by Huynh and Berry.[17] From the center to the periphery, the intestinal layers are visualized as follows: lumen (hyperechoic), mucosa (hypoechoic), submucosa (hyperechoic), muscularis (hypoechoic), and serosa (hyperechoic) (Figure 1). The CoWt was measured from the beginning of the mucosa to the end of the serosa, excluding the lumen (Figure 1). The CoWt reference value for healthy dogs, as stated by Huynh and Berry, is between 2-3 mm.[17]

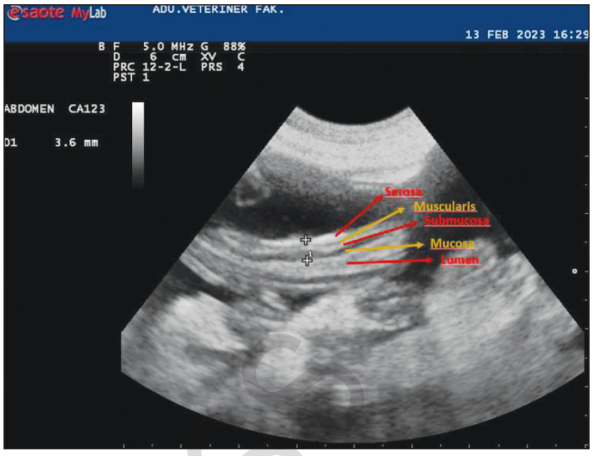

FIGURE 1: Colon wall thickness measurement and visualization of intestinal layers in case 6.

STATISTICAL ANALYSIS

Correlation coefficients of CoWt and echocardiographic measurements were determined using the Spearman correlation test. All analysis and graphical presentation were performed using the GraphPad Prism® 9.0 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

All eight dogs admitted to the animal hospital with the suspicion of HF had exercise intolerance, cough, dyspnea and cardiac murmur varying in severity. In addition, taking breed variations into account, every dog was found to exhibit cardiomegaly based on the evaluation of the Vertebral Heart Score through radiographic examination (Figure 2, Figure 3). Through the evaluation via radiography and ultrasonography, pulmonary edema was discerned in

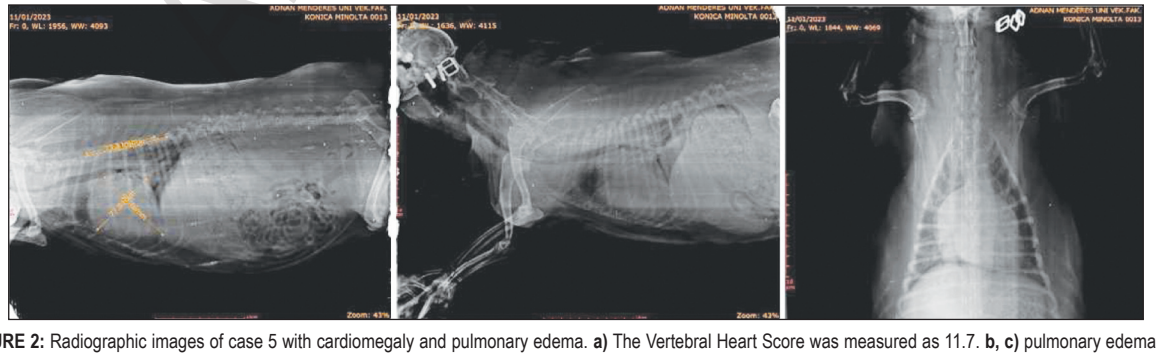

FIGURE 2: Radiographic images of case 5 with cardiomegaly and pulmonary edema. **a)** The Vertebral Heart Score was measured as 11.7. **b, c)** pulmonary edema and cardiomegaly.

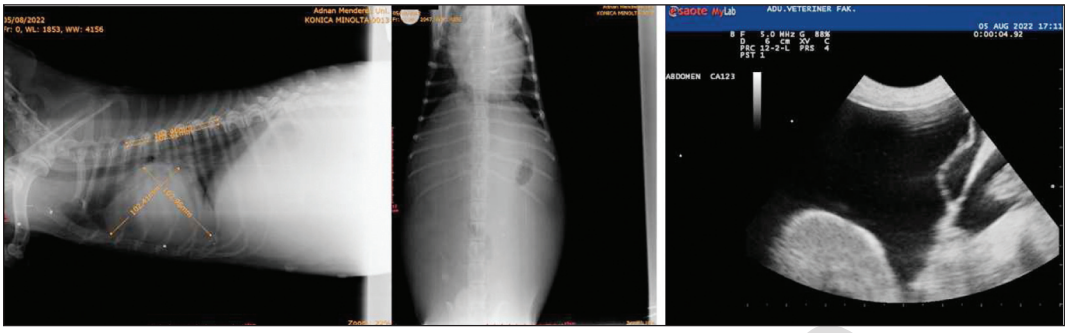

FIGURE 3: Radiographic and ultrasonographic images of case 6 with cardiomegaly and ascites. **a)** The Vertebral Heart Score was measured as 11.2. Radiographic **b)** and ultrasonographic **c)** appearance of ascites.

five (cases 1, 2, 5, 7, 8; Figure 2) of the eight dogs, while ascites was identified in three dogs (cases 3, 4, 6; Figure 3). Along with these findings, we noted the presence of subcutaneous edema in the second case and detected cyanosis in the eighth case.

Through echocardiographic examination, mitral regurgitation of varying degrees was identified in every dog. The LA/Ao ratio, an indicator of atrial enlargement, exceeded the reference value of 1.3 cm in all cases. Indices of cardiac function, such as the ejection fraction (EF) and fractional shortening (FS), were found to be elevated in some dogs, whereas others displayed values within normal limits.[18] The E/A ratio, which signifies diastolic function, was ascertained in six of the eight dogs. Of these, two exhibited a ratio greater than 2, and three demonstrated a ratio exceeding 1.5.

Colon ultrasonography revealed measurements surpassing the 2-3 mm benchmark value in all patients.[16] The details of the echocardiography and ultrasonography evaluations are displayed in Table 1. An illustrative case, presenting the CoWt measurement and echocardiographic evaluations (Figure 4).

The effect of echocardiographic measurements on CoWt was determined by subjecting the Spearman correlation test and this evaluation is visualized on the heatmap (Figure 5). A positive insignificant correlation (r=0.80) was determined between CoWt and E/A values. Furthermore, it was determined that the relationship between CoWt, EF (%) and FS (%) was at levels of r=-0.65 and r=-0.49, respectively.

DISCUSSION

The gut's possible contribution to HF pathophysiology has started gaining interest. HF patients experience diminished cardiac output and increased tissue congestion, which can compromise gut function, leading to malnutrition and cachexia. This can also facilitate the translocation of bacteria-derived endotoxins across the gut barrier, triggering systemic inflammation.[19-22] HF patients experience

TABLE 1: Echocardiography and ultrasonography measurements of the heart failure patients.

Case	Colon wall thickness	Mitral regurgitation (%)	Left atrium to aorta	Ejection fraction (%)	Fractional shortening (%)	E/A
1	3.3	60	2.45	82.2	50.0	1.70
2	3.7	80	2.48	71.2	40.3	-
3	3.8	30	1.84	56.5	29.2	2.12
4	3.8	90	5.06	80.0	48.9	2.24
5	3.6	30	2.18	81.0	48.0	1.77
6	3.6	85	1.88	63.2	33.8	1.80
7	3.6	50	1.47	85.5	53.3	1.45
8	3.4	20	1.33	88.2	55.6	-

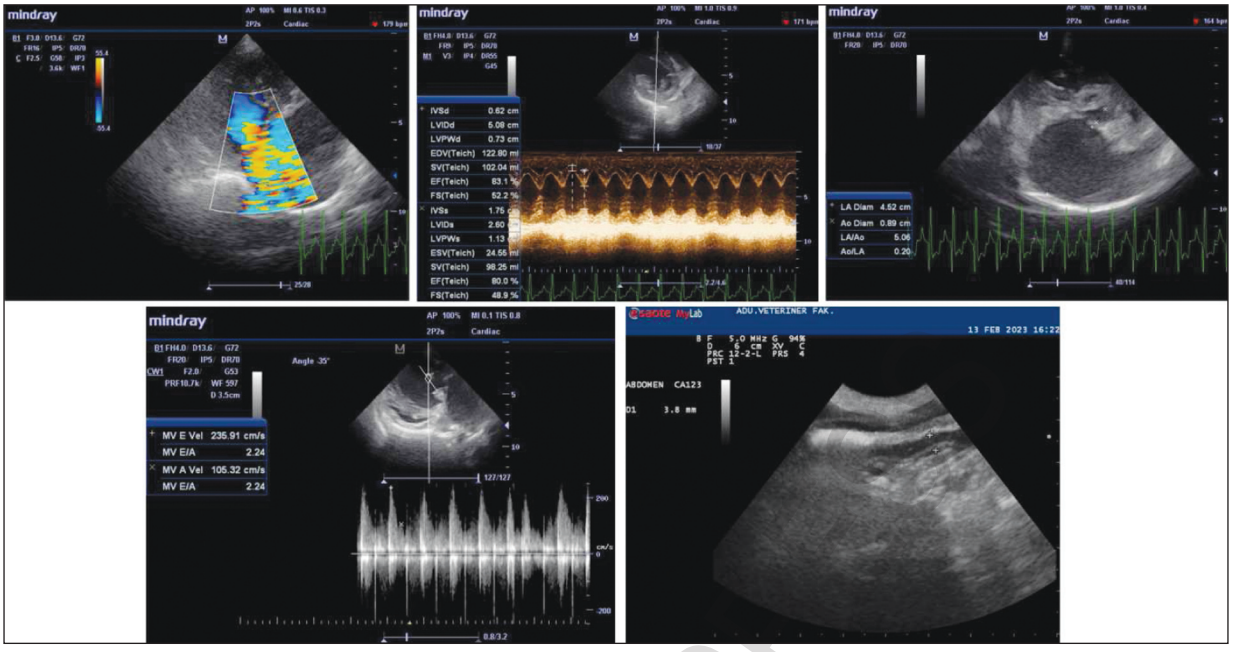

FIGURE 4: Echocardiographic measurements and CoWt measurement in case 4. **a)** severe mitral regurgitation. **b)** Dilated cardiomyopathy was diagnosed as a result of the increase in left ventricular internal diameter values and ejection fraction values according to the Teicholz method. **c)** Severe left atrial enlargement is present in the patient with an left atrium to aorta ratio of 5.06. **d)** Restrictive pattern of diastolic dysfunction was determined in the patient whose E/A ratio was measured as 2.24. **e)** Thickening was observed in CoWt with a measurement of 3.8 mm.
CoWt: Colon wall thickness.

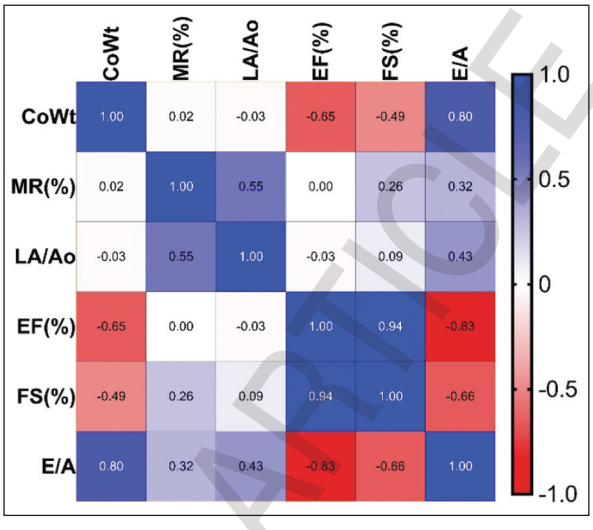

FIGURE 5: Correlation coefficients between echocardiographic values and colon wall thickness values.
MR: Mitral regurgitation; LA/Ao: Left atrium to aorta; EF: Ejection fraction; FS: Fractional shortening.

significant changes in gut structure and function. Notably, these patients see a reduction in intestinal blood flow, a condition that intensifies with the progression of HF. Particularly in cachectic patients, there's a marked decrease in blood flow to the celiac trunk and mesenteric arteries, as identified via ultrasonography.[13] HF patients exhibit alterations in gut morphology, such as thickening of the terminal ileum and colon walls, possibly due to bowel edema. Additionally, these patients show increased collagen deposits in biopsies taken from the mucosa of the small intestine.[7,23] The hemodynamic changes in HF patients can intensify hypoxia, particularly at the tips of the intestinal villi. This condition may lead to functional impairment of intestinal epithelial cells due to bowel ischemia associated with HF.[19] In our study, we determined that in dogs with HF, CoWts increased in accordance with the levels indicated in the above-mentioned literature, ranging between 3.3 and 3.8 mm. This situation confirms the association of intestinal epithelial cells with ischemia due to HF. Furthermore, measurements of the CoWt, obtained from a limited number of dogs, demonstrated a statistically insignificant correlation with E/A and EF (%) at levels of r=0.80 and r=-0.65 respectively. Further studies involving a larger number of cases, as well as investigations evaluating inflammatory

cytokines, could potentially shift the direction of clinical approaches to survival times by determining the impact of HF in dogs on bowel wall thickness. Specifically, the entry of LPS and endotoxins, produced by Gram-negative bacteria, into the systemic bloodstream can stimulate inflammatory reactions that amplify the severity of HF.

As a result of the literature review, GIS ultrasonography study could not be determined in dogs with HF or CHF, even in animals. Therefore, our study is the first data.

Clinical observations suggest that chronic HF patients exhibit increased intestinal permeability and colon wall thickening due to edema compared to healthy individuals.[6,23] Furthermore, a study involving 224 HF patients established a link between elevated portal congestion and intestinal edema with both the severity of HF and poor prognosis, associating these gastrointestinal changes with right-sided heart dysfunctions.[24] In light of the literature reviews, our study is the first to evaluate CoWt in dogs with HF from the perspective of GIS ultrasonography.

A study by Ikeda et al. found a significant link between colon wall thickening and the progression of left ventricular diastolic dysfunction.[25] Another research by Sandek et al. showed increased intestinal wall thickness and permeability in chronic HF patients compared to controls, using transcutaneous sonography and permeability tests.[6] Higher levels of adhesive bacteria were also found. These findings imply that increased intestinal wall thickness in chronic HF may be linked to heightened intestinal permeability and edema. This relationship was also suggested by Sundaram and Fang.[22] The connection between blood flow to intestinal arteries, bacterial overgrowth, gastrointestinal symptoms, and cachexia was explored in 65 HF patients.[13] They found a decline in intestinal arterial blood flow in these patients, which appeared to contribute to increased cardiac cachexia, inflammation, gastrointestinal symptoms, and juxtamucosal bacteria. Furthermore, they noted that intestinal wall thickness of the sigmoid and descending colon was greater in cachectic patients than non-cachectic ones, but the wall thickness of the terminal ileum and ascending colon was consistent across both groups. Although they found no direct correlation between reduced intestinal blood flow and increased intestinal wall thickness, they suggested this could be indicative of venous congestion. A positive association was observed between the levels of microbial metabolites and the extent of diastolic dysfunction in patients with HF.[26] In our preliminary study, the inability to determine dysbiosis formed in the intestines can be regarded as limiting factors of the research. In light of the data obtained in our study, evaluating microbial dysbiosis along with the changes in CoWt will yield much more useful clinical data in dogs with HF.

We found an increased CoWt value in dogs suffering from CHF, which aligns with human literature data. Echocardiographic data reveal that many CHF patients might in fact retain normal systolic function, as seen in our study too. Diastolic failure stems from increased resistance to filling and heightened LV filling pressure, with elevated ventricular end-diastolic pressure being paramount for CHF diagnosis. In CHF, a restrictive filling pattern is noted, where increased E wave velocity and reduced E deceleration time lead to a higher E/A ratio (>2). In our investigation involving dogs with CHF, there exists a positive correlation between CoWt value and the elevated E/A value, a marker of diastolic dysfunction, which is in line with the existing literature. Although the statistical evaluation identified an 80% positive correlation between CoWt and E/A values, it was not statistically significant with a p value of 0.054, as it didn't meet the $p<0.05$ assurance. This lack of significance likely stems from the limited number of cases evaluated. Our study serves as a preliminary investigation for a more comprehensive study aiming to amass a larger data pool.

CONCLUSION

In conclusion, our research indicates a noticeable rise in CoWt in canines suffering from CHF. To truly understand the connection between CoWt elevation and diastolic dysfunction in dogs with CHF, more extensive studies involving a larger pool of data are required. This would allow for more robust statistical analyses, which in turn would provide a more definitive insight into the complexities of these relationships.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Kerem Ural;* ***Design:*** *Kerem Ural, Cansu Balıkçı, Hasan Erdoğan, Songül Erdoğan;* ***Control/Supervision:*** *Kerem Ural, Cansu Balıkçı, Hasan Erdoğan, Songül Erdoğan;* ***Data Collection and/or Processing:*** *Kerem Ural, Cansu Balıkçı, Hasan Erdoğan, Songül Erdoğan;* ***Analysis and/or Interpretation:*** *Kerem Ural, Cansu Balıkçı, Hasan Erdoğan, Songül Erdoğan;* ***Literature Review:*** *Kerem Ural, Cansu Balıkçı, Hasan Erdoğan, Songül Erdoğan;* ***Writing the Article:*** *Kerem Ural, Cansu Balıkçı, Hasan Erdoğan, Songül Erdoğan;* ***Critical Review:*** *Kerem Ural, Hasan Erdoğan, Songül Erdoğan;* ***References and Fundings:*** *Kerem Ural, Hasan Erdoğan, Songül Erdoğan;* ***Materials:*** *Kerem Ural, Cansu Balıkçı, Hasan Erdoğan, Songül Erdoğan.*

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