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Cardiac and Metabolic Variables in Obese Dogs

M. Tropf, O.L. Nelson, P.M. Lee, and H.Y. Weng

Background: The etiology of obesity-related cardiac dysfunction (ORCD) is linked to metabolic syndrome in people. Studies have indicated that obese dogs have components of metabolic syndrome, warranting evaluation for ORCD in obese dogs.

Objectives: To evaluate cardiac structure and function and metabolic variables in obese dogs compared to ideal weight dogs.

Animals: Forty-six healthy, small-breed (<25 pounds), obese dogs (n = 29) compared to ideal weight dogs (n = 17).

Methods: A cross-sectional study of cardiac structure and function by standard and strain echocardiographic measurements and quantification of serum metabolic variables (insulin:glucose ratios, lipid analysis, adiponectin, inflammatory markers).

Results: Compared to the ideal weight controls, obese dogs had cardiac changes characterized by an increased interventricular septal width in diastole to left ventricular internal dimension in diastole ratio, decreased ratios of peak early to peak late left ventricular inflow velocities, and ratios of peak early to peak late mitral annular tissue velocities, and increased fractional shortening and ejection fraction percentages. The left ventricular posterior wall width in diastole to left ventricular internal dimension in diastole ratios were not significantly different between groups. Systolic blood pressure was not significantly different between groups. Obese dogs had metabolic derangements characterized by increased insulin:glucose ratios, dyslipidemias with increased cholesterol, triglyceride, and high-density lipoprotein concentrations, decreased adiponectin concentrations, and increased concentrations of interleukin 8 and keratinocyte-derived chemokine-like inflammatory cytokines.

Conclusions and Clinical Importance: Compared to ideal weight controls, obese dogs have alterations in cardiac structure and function as well as insulin resistance, dyslipidemia, hypoadiponectinemia, and increased concentrations of inflammatory markers. These findings warrant additional studies to investigate inflammation, dyslipidemia, and possibly systemic hypertension as potential contributing factors for altered cardiac function.

Key words: Obesity-related cardiac dysfunction; Metabolic syndrome.

In people, obesity is an independent risk factor for development of obesity-related cardiac dysfunction (ORCD).[1–3] Characteristics of ORCD include systolic dysfunction, diastolic dysfunction, and vascular endothelial dysfunction independent of coronary artery disease.[3–6] Additionally, obese people have structural cardiac changes including increased left ventricular mass and hypertrophy.[7]

Obesity-related cardiac dysfunction has been identified both as a component of metabolic syndrome and as an independent disease process in people. Components of metabolic syndrome, most recently defined as a combination of obesity, insulin resistance, dyslipidemia, and hypertension, are believed to play an important role in

Abbreviations:

BCS	body condition score
CRP	C-reactive protein
E:A	ratio of peak early to peak late left ventricular inflow velocities
E:E′	ratio of peak early left ventricular inflow to mitral annular tissue velocities
E′:A′	ratio of peak early to peak late mitral annular tissue velocities
EF	ejection fraction
FS	fractional shortening
GM-CSF	granulocyte-macrophage colony-stimulating factor
HDL	high-density lipoprotein
IL	interleukin
INF	interferon
IP	interferon-gamma-induced protein
IVSd/LVIDd	ratio of interventricular septal width in diastole to left ventricular internal dimension in diastole
KC	keratinocyte-derived chemokine
LA:Ao	left atrial to aortic ratio
LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
MCP	monocyte chemoattractant protein
ORCD	obesity-related cardiac dysfunction
PWd/LVIDd	ratio of left ventricular posterior wall width in diastole to left ventricular internal dimension in diastole
SBP	systolic blood pressure
SNS	sympathetic nervous system
TG	triglyceride
TNF-alpha	tumor necrosis factor-alpha
TNF	tumor necrosis factor

From the Department of Small Animal Clinical Sciences, Washington State University, Pullman, WA (Tropf, Nelson, Lee); and the Department of Comparative Pathobiology, Purdue University, West Lafayette, IN (Weng).

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Corresponding author: M. Tropf, DVM, ACVIM Cardiology, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, 625 Harrison Street, West Lafayette, IN 47907-2026; e-mail: mtropf@purdue.edu.

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the pathophysiology of ORCD.[6,8] The presence of metabolic syndrome has implications in both the pathophysiologic mechanisms and treatment of ORCD.[9] As such, assessment for subclinical cardiac dysfunction and metabolic derangements in obese people has become the standard of care in human medicine.

Both ORCD and metabolic syndrome are greatly influenced by complex endocrine signaling pathways and altered substrate metabolism. Adipokines produced by adipose tissue, such as leptin and adiponectin, peripheral endocrine substrates such as insulin and glucagon, as well as central pathways including the leptin-melanocortin system influence metabolism in obese patients. Hypoadiponectinemia, hyperleptinemia, and leptin resistance previously have been identified in both obese people and dogs.[10–15] These metabolic derangements can result in cardiac dysfunction as a consequence of altered cardiac mitochondrial metabolism and result in localized cardiac insulin resistance and intramyocardial lipid accumulation.[16–18]

Recent studies performed in dogs suggest that many of the components of metabolic syndrome including pro-inflammatory states, hypoadiponectinemia, hyperleptinemia, and insulin resistance also exist in obese dogs.[15,19–23] Whereas left ventricular hypertrophy (LVH), in the absence of systemic hypertension, has been documented in obese dogs, few studies have investigated cardiac function in obese dogs.[24–26] The observation warrants further investigation into the cardiac consequences of obesity in dogs.

We hypothesized that obese dogs have cardiac structural changes and dysfunction and have altered insulin sensitivity as assessed by serum fasting insulin:glucose ratio, increased concentrations of inflammatory markers, dyslipidemia, and hypoadiponectinemia consistent with metabolic syndrome when compared with ideal body weight dogs.[27] The aims of our study were, first, to assess the presence of cardiac structural changes and dysfunction in obese dogs compared to dogs with ideal body composition and, second, to compare metabolic variables including insulin:glucose ratio, lipid analysis, adiponectin, and inflammatory markers in obese as compared to ideal weight dogs.

Obesity is becoming more prevalent in dogs.[28,29] As a result, determining the effects of obesity on cardiovascular function and whether obesity can have additive effects on the development of cardiac disease in dogs is imperative.[19,28–30] Cardiac dysfunction related to obesity may be particularly important in small-breed dogs, which are predisposed to valvular heart disease.[31] If ORCD is documented, our study will determine the effects of obesity on cardiac function and may help identify potential biomarkers to identify patients at risk for ORCD.

Materials and Methods

Animals

Healthy dogs weighing <25 pounds with ideal body condition (n = 17) and obese body condition (n = 29) were prospectively recruited over a 3-year period between May 2013 and May 2016 from local primary care veterinary practices. Data collection was carried out during a single visit averaging 3 hours in duration. The study population of small-breed dogs was selected for 2 reasons. First, because dilated cardiomyopathy is rare in small-breed dogs, changes in cardiac function potentially could be related to obesity, assuming that the dog was free of other systemic diseases that could cause secondary myocardial dysfunction. Second, small-breed dogs have a high prevalence of degenerative valvular disease, which could be confounded by the presence of ORCD. Dogs with clinically relevant valvular heart disease were excluded from the study. Dogs with trivial valvular insufficiency were included if they had no evidence of cardiac chamber dilatation on echocardiography. Trivial valvular insufficiency was defined as small-sized regurgitant jets (color encompassing <10% of the right atrial area) with no evidence of tricuspid valve thickening, prolapse, or atrial dilatation, indicating that the regurgitation was physiologic in nature and not hemodynamically relevant. All dogs were fasted overnight and determined to be euthyroid with no evidence of systemic illness on routine laboratory diagnostics including CBC, serum biochemical profile, urinalysis, and serum total T4 concentration. Past infectious diseases, such as ehrlichiosis and Lyme disease, and immune-mediated disease were not evaluated but dogs with a history of infectious or immune-mediated disease were excluded.[32] Body condition was assessed by a validated 9-point scale in which ideal body condition was defined as a body condition score (BCS) of 4 or 5.[33,34] Dogs with normal BCSs of 4 and 5 were allocated to the ideal weight group and dogs with BCSs of 6, 7, 8, and 9 were allocated to the obese group. The study adhered to the Washington State University research ethics policy. The protocol was approved by the Institutional Animal Care and Use Committee at Washington State University (ASAF 4190).

Cardiovascular Evaluation

Systolic Blood Pressure

Noninvasive systolic blood pressure (SBP) measurements were performed with a Doppler blood pressure machine.[a] With patients in right lateral recumbency, the left hind limb circumference was measured and a cuff corresponding to 40% of the circumference of the limb was placed.[35] An average of 5 consecutive SBP measurements was used for statistical analysis. Systemic hypertension was defined as ≥160 mmHg.

Cardiac Structure and Function

Cardiac structure and function were assessed with standard echocardiographic 2-dimensional, M-mode, Doppler, and velocity vector strain imaging.[b] Each measurement used for statistical analysis was the mean of 3 measurements from 3 different cardiac cycles. Measurements were performed by a single clinician with extensive training in the technique (MT). A standard echocardiogram that included 2-dimensional, M-mode, spectral, and color-flow Doppler evaluations was obtained in accordance with the American Society of Echocardiography guidelines.[36,37] By the 2-dimensional, basilar right parasternal view, the B-mode left atrial: aortic ratio was measured.[38] Velocity vector strain echocardiography was performed to assess regional myocardial diastolic motion, as previously described in dogs.[39,40]

Metabolic Evaluation

A canine lipid panel was performed on serum samples including cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL).[c] Glucose concentrations were determined from whole blood with a glucometer immediately after sampling.[d] Serum was collected and frozen at −80°C for later assessment of metabolic variables. Serum insulin concentrations

were analyzed in a single batch to minimize day-to-day laboratory variation by an assay validated by the manufacturer.[e] Serum adiponectin concentrations were measured with a commercially available ELISA mouse-rat assay previously validated for use in dogs.[f,22,41] Samples were run in 1 batch to minimize interassay variability. A canine inflammatory marker ELISA panel was performed by a commercial laboratory by a Luminex-based assay validated by the manufacturer to assess the following markers: granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL) 2, 6, 7, 8, 10, tumor necrosis factor-alpha (TNF-alpha), interferon-gamma (INF-gamma), tumor necrosis factor-gamma (TNF-gamma), C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1), interferon-gamma-induced protein 10 (IP 10), and keratinocyte-derived chemokine (KC)-like inflammatory cytokines.[g,h]

Outcomes

The primary outcomes were the cardiac wall measurements (ratio of interventricular septal width in diastole to left ventricular internal dimension in diastole [IVSd/LVIDd] and ratio of left ventricular posterior wall width in diastole to left ventricular internal dimension in diastole [PWd/LVIDd]) and insulin:glucose ratio. Secondary cardiac outcomes included SBP, systemic hypertension (SBP ≥160 mmHg), left atrial to aortic ratio (LA:Ao), ejection fraction (EF), fractional shortening (FS), ratio of peak early to peak late left ventricular inflow velocities (E:A), ratio of peak early to peak late mitral annular tissue velocities (E′:A′), ratio of peak early left ventricular inflow to mitral annular tissue velocities (E:E′), and systolic and diastolic strain percentage, velocity, and rate measurements. Secondary metabolic outcomes included adiponectin, cholesterol, TG, HDL, LDL, and inflammatory marker concentrations.

Statistical Analysis

Statistical analyses were performed by a computerized statistical software package with the level of significance set at $P < 0.05$ for 2-sided analyses.[i] Mann-Whitney tests were used to compare the groups for all primary and secondary outcomes, except for systemic hypertension, which was analyzed by the chi-square test. For analytic purposes, all measurements for inflammatory markers that were below the limit of detection were replaced with the middle value between zero and the threshold of detection.

Results

Animals

Forty-six of 52 dogs recruited met the selection criteria. Six dogs were excluded for the following reasons: urinary tract infection (1), on concurrent medications (4), unable to tolerate examination without sedation (1). Table 1 displays the descriptive statistics for age, body weight, BCS, breed, and sex of the obese and ideal weight groups. Eleven dog breeds were represented in the obese weight category: 3 Chihuahua, 3 Shih Tzu, 3 Yorkshire Terrier, 2 Miniature Dachshund, 1 Australian Terrier, 1 Australian Shepherd, 1 Cairn Terrier, 1 Cavalier King Charles Spaniel, 1 Maltese Terrier, 1 Miniature Pinscher, and 1 Pug. Twelve dog breeds were represented in the ideal weight category: 2 Miniature Dachshund, 2 Pug, 2 West Highland Terrier, 1 Australian shepherd, 1 Beagle, 1 Border Collie, 1 Chihuahua, 1 Dandie Dinmont Terrier, 1 Jack Russel Terrier, 1 Papillion, 1 Shiba Inu, and 1 Teacup Poodle.

Table 1. Descriptive statistics of the study population. Median (range) and frequency (%) are reported.

	Obese Dogs (n = 29)	Ideal Weight Dogs (n = 17)
Age (years)	7 (1–12)	4 (1–10)
Weight (kg)	8.0 (2.8–11.9)	8.3 (2.3–24.9)
Body condition score (9-point)	8 (6–9)	4 (4–5)
Breed (%)		
Purebred	18 (62)	15 (88)
Mixed	11 (38)	2 (12)
Sex (%)		
Female	19 (66)	8 (47)
Male	10 (34)	9 (53)

Cardiovascular Evaluation

Table 2 displays the results of the cardiovascular evaluation. Echocardiographic structural and functional assessment disclosed differences between the groups of dogs. The primary outcome assessment of left ventricular wall thickness indicated that the IVSd/LVIDd ratio was significantly higher in the obese group indicating ventricular septal hypertrophy in this group ($P = 0.028$; obese dogs, 0.31 [0.20–0.73]; ideal weight dogs, 0.26 [0.16–0.38]). The PWd/LVIDd was not significantly different between the groups ($P = 0.191$; obese dogs, 0.30 [0.22–0.65]; ideal weight dogs, 0.30 [0.15–0.37]). Secondary outcome assessment indicated that obese subjects had significantly higher EF ($P = 0.017$) and FS ($P = 0.009$) percentages compared to ideal weight subjects. Obese subjects had significantly lower mitral E:A ratios ($P = 0.021$) and E′:A′ mitral annular tissue ratios ($P = 0.006$). Median SBP was not significantly different between groups ($P = 0.127$). The number of dogs with systemic hypertension (SBP ≥160 mmHg) was not significantly different between groups ($P = 0.175$).

Metabolic Evaluation

Table 3 displays the results of the metabolic evaluation. Primary outcome analysis indicated that insulin:glucose ratio was significantly higher in the obese group compared to the ideal weight group ($P < 0.001$; obese dogs, 44.39 [11.52–220.57]; ideal weight dogs, 20.02 [8.82–42.23]). Evaluation of secondary outcomes indicated that obese subjects had hypoadiponectinemia ($P = 0.021$) and significantly increased insulin ($P < 0.0001$), cholesterol ($P = 0.005$), TG ($P = 0.003$), and HDL ($P = 0.012$) concentrations compared to ideal weight subjects (Table 3). Interleukin 8 ($P = 0.011$) and KC-like ($P = 0.017$) cytokine concentrations were significantly higher in the obese group (Table 3).

Discussion

Our study investigated both cardiac function and metabolic variables in obese dogs compared to ideal weight dogs. The metabolic evaluation confirmed metabolic derangements including insulin resistance as assessed by fasting insulin:glucose ratio, a

Table 2. Cardiovascular parameters in obese and ideal weight patient groups. Median (range) and frequency (%) are reported.

	Obese Dogs	Ideal Weight Dogs	*P*
IVSd/LVIDd[a]	0.31 (0.20 to 0.73)	0.26 (0.16 to 0.38)	0.028
PWd/LIVDd[a]	0.30 (0.22 to 0.65)	0.30 (0.15 to 0.37)	0.191
LA:Ao	1.39 (1.07 to 1.68)	1.32 (0.97 to 1.54)	0.095
SBP (mmHg)	160 (97 to 250)	145 (90 to 180)	0.127
Systemic hypertension			
Yes	14 (50%)	5 (29%)	0.175
No	14 (50%)	12 (71%)	
EF (%)	71 (45 to 82)	62 (47 to 74)	0.017
FS (%)	47 (29 to 68)	40 (26 to 53)	0.009
E:A	1.03 (0.52 to 1.73)	1.43 (0.69 to 1.81)	0.021
E′:A′	0.80 (0.35 to 1.66)	1.32 (0.62 to 1.62)	0.006
E:E′	−7.78 (−14.12 to −4.17)	−8.46 (−15.49 to −3.97)	0.868
Systolic strain			
Percent (%)	−20.27 (−32.80 to −11.80)	−17.83 (−31.20 to −6.82)	0.133
Velocity (cm/s)	2.10 (−2.75 to 4.40)	2.68 (0.75 to 6.02)	0.222
Rate (1/s)	−2.41 (−4.32 to 1.57)	−2.12 (−.3.91 to −1.44)	0.255
Diastolic strain			
E:A percent	0 (−21.43 to 1.52)	0 (−13.25 to 0.14)	0.540
E:A velocity	1 (−0.39 to 4.27)	1.08 (0 to 8.72)	0.804
E:A rate	1.06 (−1.81 to 4.23)	1.01 (−0.21 to 5.29)	0.851

IVSd/LVIDd: ratio of interventricular septal width in diastole to left ventricular internal dimension in diastole; PWd/LVIDd: ratio of left ventricular posterior wall width in diastole to left ventricular internal dimension in diastole; LA:Ao: left atrial to aortic ratio; EF: ejection fraction; systemic hypertension: systolic blood pressure (SBP) ≥160 mmHg; FS: fractional shortening; E:A: ratio of peak early to peak late left ventricular inflow velocities; E′:A′: ratio of peak early to peak late mitral annular tissue velocities; E:E′: ratio of peak early left ventricular inflow to mitral annular tissue velocities; *P*: *P*-values are derived from Mann-Whitney tests except for hypertension, which is derived from the chi-square test.

[a]Primary outcome.

pro-inflammatory state, hypoadiponectinemia, and dyslipidemias in obese dogs.[42]

The pro-inflammatory state was characterized by increases in IL-8 and KC-like cytokines. Increased serum IL-8 concentration has been documented in obese people with cardiovascular disease and has been demonstrated to have pro-athlerosclerotic, angiogenic properties and is chemotactic for lymphocytes and neutrophils, which perpetuate vascular inflammatory processes.[43–46] Weight loss in obese people results in decreased IL-8 concentrations.[47,48] Interestingly, IL-8 is also upregulated 15-fold in ideal weight, insulin-resistant people.[49] To our knowledge, increases in IL-8 have not been documented in obese dogs. In our study, increased IL-8 concentrations may have been a consequence of obesity, insulin resistance, or a combination of both.

Limited information is available regarding the role of KC-like cytokines, but they appear to play a role in systemic or generalized inflammation. Increased concentrations of KC-like cytokine, a neutrophil chemoattractant, have been found in dogs with pyometra and in experimental Lyme myocarditis models.[50,51] The most commonly found inflammatory biomarkers in human ORCD and metabolic syndrome, CRP, TNF-alpha, and IL-6 were not significantly different between the groups of dogs.[52,53] This difference may represent a difference in the inflammatory profiles of obesity-related inflammation in dogs compared to people. Although the dogs in our study had markers of inflammation, it is not clear whether these cytokines could play a role in the inflammatory mechanisms known to correlate with cardiac dysfunction in humans and is a potential area for future investigation.

Hypoadiponectinemia and dyslipidemia are also supportive of obesity-related metabolic derangements. Hypoadiponectinemia in obese people is a consistent finding that results in loss of protective insulin sensitization, enhanced fatty acid metabolism, and anti-inflammatory actions of adiponectin.[54] Previous studies have shown variable results for adiponectin concentrations in obese dogs ranging from significantly decreased to no significant change. One theory is that the discrepancies may be related to neuter status with obesity correlated to decreased adiponectin concentrations in intact but not in neutered dogs.[41] The dyslipidemia observed in the obese group was different than the pattern of dyslipidemia in people.[8] Typically, people have a dyslipidemia characterized by high cholesterol, TG, and LDL concentrations with decreased HDL concentrations.[55] Although the obese group of dogs had higher cholesterol and TG concentrations, the LDL concentrations were unchanged, and the HDL concentrations were increased. The few studies evaluating lipid profiles in obese dogs have had variable results. One study documented a dyslipidemia profile in insulin-resistant, obese dogs that mirrored that of the profile in humans.[56] However, another study observed increases in the

Table 3. Metabolic variables (median [range]) in obese and ideal weight patient groups.

	Obese Dogs	Ideal Weight Dogs	*P*
Insulin:Glucose[a]	44.4 (11.5–220.6)	20.0 (8.8–42.2)	<0.001
Insulin (μU/mL)	45.9 (11.5–207.3)	18.7 (8.6–34.3)	<0.001
Glucose (mg/dL)	97 (72–135)	93 (74–128)	0.616
Lipid panel			
Adiponectin (μg/mL)	15.9 (1.9–54.7)	25.5 (10.5–50.1)	0.021
Cholesterol (mg/dL)	259 (107–482)	214 (143–292)	0.005
Triglycerides (mg/dL)	108 (41–2171)	55 (32–229)	0.003
HDL (mg/dL)	169 (81–248)	151 (109–195)	0.012
LDL (mg/dL)	49 (0–157)	46 (18–93)	0.679
Inflammatory markers			
IL-8 (pg/mL)	7280 (548–145656)	2468 (6.1–10747)	0.011
KC like (pg/mL)	2226 (327–5430)	873 (211–4430)	0.017
GM-CSF (pg/mL)	6.1 (6.1–3709)	6.1 (6.1–866)	0.615
INF-gamma (pg/mL)	1.22 (1.22–25.91)	1.22 (1.22–2025)	0.199
IL-2 (pg/mL)	6.1 (6.1–5308)	6.1 (6.1–828)	0.389
IL-6 (pg/mL)	12.3 (6.1–3685)	21.6 (6.1–486)	0.576
IL-7 (pg/mL)	6.1 (6.1–6017)	6.1 (6.1–1053)	0.648
IP 10 (pg/mL)	6.1 (6.1–125)	6.1 (6.1–588)	0.206
IL-10 (pg/mL)	6.1 (6.1–18113)	11.1 (6.1–97.2)	0.517
MCP-1 (pg/mL)	259 (6.1–1048)	296 (6.1–524)	1
TNF-alpha (pg/mL)	6.1 (6.1–1356)	6.1 (6.1–221)	0.528

HDL, high-density lipoprotein; LDL, low-density lipoprotein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; TNF-alpha, tumor necrosis factor-alpha; INF, interferon; TNF, tumor necrosis factor; MCP, monocyte chemoattractant protein; IP, interferon gamma-induced protein; KC, keratinocyte-derived chemokine; *P*: *P*-values derived from Mann-Whitney tests.

[a]Primary outcome.

cholesterol, TG, and all lipoprotein fractions in obese dogs.[57] Coronary artery disease is the primary risk factor associated with obesity-related dyslipidemias in people. The lipoprotein composition differs in healthy dogs with a predominance of HDL compared to people in whom there is a predominance of LDL.[58] In the absence of endocrinopathies such as hypothyroidism, hyperaldosteronism, or diabetes mellitus, athlerosclerosis is rare in dogs.[59] The lower incidence of athlerosclerosis is theorized to be due to the predominance of HDL and altered HDL function resulting in decreased cholesterol transfer to peripheral tissues.[60]

Although previous studies have not identified significant differences in the myocardial lipid composition in obese dogs, limited myocardial sampling sites in previous studies may have led to underestimation of the presence of myocardial lipid deposition in dogs.[24] Considering the species differences in lipid profiles, it might be premature to discount the effects of dyslipidemia on cardiac metabolism in obese dogs without additional study.

In people, varied morphologies of obesity-related cardiac structural changes have been described and may include symmetric or asymmetric LVH with or without left ventricular chamber dilatation.[61] Previous studies in dogs indicated that obese, normotensive dogs had isolated LVH of the free wall.[24] This study identified a different pattern of hypertrophy characterized by isolated interventricular septal hypertrophy. Interventricular septal hypertrophy, particularly basal hypertrophy, is commonly associated with pressure overload disease including systemic hypertension in people and cats.[62,63] In our study, the median SBP and the frequency of systemic hypertension were not significantly different between groups. The small sample size and lack of power may have contributed to the lack of significance. The SBP comparison also could have been confounded by increased blood pressure associated with anxiety in the hospital, making it challenging to document a difference between the groups. As such, the potential for LVH secondary to systemic hypertension in the obese group cannot be excluded.

As a shared structure, the interventricular septum also may be hypertrophied in right ventricular pressure overload diseases such as pulmonary hypertension. Obese people and dogs have been shown to have pulmonary dysfunction, pulmonary hypertension, and right ventricular hypertrophy.[64–66] Occult pulmonary hypertension potentially could be a cause for the interventricular septal hypertrophy observed in obese dogs. Because of the absence of clinically relevant tricuspid regurgitation, pulmonary pressures were not assessed in our study but other features of pulmonary hypertension such as right ventricular hypertrophy, right atrial dilatation, and rapid acceleration of the pulmonic flow profile were not identified.[67]

Additional considerations for the observed hypertrophy include histologic structural changes such as myocardial fat accumulation or fibrosis, altered volume or pressure loading conditions, and components of metabolic syndrome including hypoadiponectinemia and insulin resistance.[68,69] Previous studies in dogs have failed to document histologic structural myocardial changes in obese dogs, but the potential for focal

histologic changes could not eliminated and warrants consideration for additional investigation.[24] Insulin resistance in the obese group may provide an explanation for the interventricular septal hypertrophy. A significant positive correlation between insulin resistance and left ventricular mass has been documented in normotensive, obese people. The proposed mechanisms for the correlation between insulin resistance and left ventricular mass are related to the actions of enhanced insulin-like growth factors in the insulin-resistant state.[70]

Diastolic dysfunction is a component of ORCD in humans. Although previous studies have identified evidence of impaired relaxation and myocardial stiffness in dogs, to our knowledge, ours is the first to identify cardiac functional and structural changes as well as changes in metabolic variables associated with obesity in dogs.[24] The decreased E:A and E′:A′ ratios suggest decreased compliance and diastolic dysfunction. The observed LVH in the obese group is considered a likely cause of diastolic dysfunction, but the influence of metabolic derangements resulting in the proinflammatory state, altered serum adipokines, myocardial structural derangements, and altered myocardial metabolism, alone or in combination, contribute to the observed diastolic dysfunction.[69] The functional differences in obese dogs were present at rest, and physical activity potentially could exacerbate these findings. Interestingly, the strain imaging function measurements were not significantly different between groups. It is unclear why the strain image measurements were not significantly different. Function derangements may not have been detected by the endocardial vector strain utilized in our study, but may be detected by more sensitive strain modalities such as speckle-tracking software.

Increased systolic function may be associated with volume loading, increased catecholamine production, or more likely a combination of these factors. Increased vascular volume is present in obese humans and results in an increased stroke volume proportional to the excess body weight.[71] Increased sympathetic nervous system (SNS) stimulation is observed in obese, normotensive human patients with predominantly visceral fat distribution. Proposed mechanisms for SNS stimulation in obesity include baroreflex dysfunction, hypothalamic-pituitary axis dysfunction, insulin resistance, hyperleptinemia, and increased circulating angiotensin II concentrations.[26,72] Given the evidence of insulin resistance in the obese group, this factor as well as increased SNS activity are plausible causes for the observed increase in systolic function.

We acknowledge the limitations of a small sample size and lack of power. The unequal number of dogs in the ideal weight versus obese groups may introduce error despite being relatively matched in age, weight, and sex. We acknowledge that the obese group contained dogs that were overweight and obese based on BCS. Combining all overweight dogs into 1 group may have altered the results if degree of obesity impacts the cardiac and metabolic derangements. Additionally, the fat distribution of obese dogs was not further characterized into visceral or peripheral fat, which also could impact our results because visceral adipose tissue is more metabolically active than peripheral adipose tissue. Given the higher median age in the obese group compared to the ideal weight group and the known association between age and diastolic dysfunction, age cannot be excluded as a confounding factor in the cardiac function results.

In conclusion, obese dogs, compared to ideal weight controls, have alterations in cardiac structure and function as well as altered insulin sensitivity, dyslipidemia, and increased inflammatory markers. These findings are supportive of ORCD and strongly support the need for additional evaluation of the cardiac consequences of obesity in dogs. Obesity is highly prevalent in dogs, and ORCD may have additive effects in dogs with concurrent cardiac disease such as degenerative mitral valve disease. Future studies comparing outcomes in obese versus ideal weight dogs with degenerative valvular disease will help guide prognosis and therapeutic recommendations.

Footnotes

[a] Parks Medical Electronics Inc, Aloha, OR.
[b] Esoate MyLab 70 ultrasound machine with 1–10 MHz phased array transducers, Esoate North America, Indianapolis, IN.
[c] IDEXX Laboratories, Westbrook, ME.
[d] AlphaTrak 2, Abbot Laboratories, Abbott Park, IL.
[e] Michigan State University Diagnostic Center for Population and Animal Health, Lansing, MI.
[f] Mouse/Rat Adiponectin ELISA K1002-1, Otsuka Pharmaceuticals, Tokyo Japan.
[g] University of Texas Health Science Center at San Antonio, San Antonio, TX.
[h] EMD Millipore Corporation, Canine cytokine/chemokine, St. Charles, MO.
[i] IBM SPSS Statistics Data Editor (version 23; IBM Corp.), Chicago, IL.

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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.

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