Evaluation of tissue Doppler ultrasonographic and strain imaging for assessment of myocardial dysfunction in dogs with type 1 diabetes mellitus

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OBJECTIVE
To investigate cardiac structural and functional changes by tissue Doppler imaging (TDI) and strain imaging in dogs with spontaneous type 1 diabetes mellitus.

ANIMALS
30 client-owned dogs, of which 10 had normotensive type 1 diabetes mellitus and 20 were healthy.

PROCEDURES
All dogs underwent physical examination, laboratory analyses, standard echocardiography, and TDI.

RESULTS
On TDI and strain imaging, transmitral peak early diastolic velocity (E)-to-tissue Doppler–derived peak early diastolic velocity at basal segment (E′) of septum ratio, E:lateral E′ ratio, and septal tissue Doppler–derived peak late diastolic velocity at basal segment (A′) were significantly higher and the septal E′:A′ ratio and lateral longitudinal strain were significantly lower for diabetic dogs than for control dogs. Furthermore, in diabetic dogs, serum glucose and fructosamine concentrations after a 12-hour period of food withholding were positively correlated with regional systolic functional variables (septal and lateral longitudinal strain) and left ventricular filling pressure indices (E:septal E′ and E:lateral E′ ratios) but were negatively correlated with diastolic functional variables (E:transmitral peak late diastolic velocity and septal and lateral E′:A′ ratios).

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that myocardial function in diabetic dogs may be altered before the development of clinical heart-associated signs and that the change may be more readily detected by TDI and strain imaging than by conventional echocardiography. In addition, findings indicated that hyperglycemia could have detrimental effects on myocardial function, independent of hypertension, other cardiac diseases, and left ventricular hypertrophy, in dogs with type 1 diabetes. (*Am J Vet Res* 2018;79:1035–1043)

ABBREVIATIONS

A	Transmitral peak late diastolic velocity
A′	Tissue Doppler–derived peak late diastolic velocity at basal segment
DM	Diabetes mellitus
E	Transmitral peak early diastolic velocity
E′	Tissue Doppler–derived peak early diastolic velocity at basal segment
E:E′	Transmitral peak early diastolic velocity to tissue Doppler–derived peak early diastolic velocity at basal segment
E:A	Transmitral peak early diastolic velocity to the transmitral peak late diastolic velocity
EF	Ejection fraction
FS	Fractional shortening
IVS	Interventricular septum
IVSd	Interventricular septal thickness in diastole
IVSs	Interventricular septal thickness in systole
LA:Ao	Left atrial diameter to aortic diameter
LV	Left ventricular
LVFW	Left ventricular free wall
LVIDd	Left ventricular internal diameter at end-diastole
LVIDs	Left ventricular internal diameter at end-systole
TDI	Tissue Doppler imaging

In humans, DM is a well-recognized risk factor for development of heart failure, which is largely associated with hypertension and coronary artery disease.[1,2] However, results of studies[3–5] over the past 3 decades have suggested that patients with DM have myocardial dysfunction, which is characterized by ventricular structural or functional abnormalities in the absence of coronary atherosclerosis and hypertension.[6,7] Diastolic dysfunction has been observed in humans with type 1 and type 2 DM during the early stage.[8–10] However, impaired systolic function has been particularly reported in more advanced stages of DM.[11] The exact metabolic perturbations that affect myocardial structure and function are poorly understood, but findings of some human and experimental animal studies[12–14] have indicated that hyperglycemia is the main factor.

Among dogs, DM is fairly common; type 1 DM is predominant and characterized by hypoinsulinemia and hyperglycemia.[15] Although dogs with DM devel-

op a variety of complications, including nephropathy, neuropathy, and vasculopathy, little has been reported about cardiovascular complications.[16]

Conventional echocardiography is the most commonly used technique to evaluate cardiac function in human and veterinary medicine; however, echocardiography can be affected by many factors, including preload, afterload, and blood viscosity.[17,18] Therefore, it is considered to have poor sensitivity for the detection of subtle functional myocardial abnormalities in different heart disease models.[17,19] Tissue Doppler imaging and strain imaging are relatively novel tools that are more sensitive and appropriate for evaluating cardiac function, compared with conventional Doppler, 2-D, or M-mode echocardiography.[17–20]

The purpose of the study reported here was to use TDI and strain imaging and conventional echocardiography to investigate cardiac structural and functional changes in dogs with spontaneous type 1 DM. We hypothesized that dogs with type 1 DM would have functional cardiac abnormalities without ventricular hypertrophy and that the changes would be associated with abnormal serum glucose and fructosamine concentrations.

Materials and Methods

Animals and procedures

The study prospectively evaluated 20 healthy dogs (11 males and 9 females [control group]) and 13 dogs with DM (6 males and 7 females) that were brought to the Chonbuk National University Veterinary Medical Teaching Hospital in October 2013 through May 2014. The control group dogs were admitted to the hospital for cardiac health screening tests and had no evidence of heart disease (as determined from historical, physical examination, and cardiac examination findings). We obtained informed consent from the owners before the dogs entered the study. The study protocol followed the guidelines of the Institutional Animal Care and Use Committee of Chonbuk National University.

All dogs included in the study underwent a physical examination, indirect measurement of systolic arterial blood pressure by the Doppler ultrasonographic method, laboratory measurements (including assessment of serum glucose and fructosamine concentrations after a 12-hour period of food withholding), and an echocardiographic examination. Dogs with hypertension[21] (systolic blood pressure > 160 mm Hg), valvular disease, congenital heart disease, abnormal conduction as determined by ECG, or other severe systemic diseases were excluded. The diagnosis of DM was based on previously reported criteria[15] that included persistent hyperglycemia (> 200 mg/dL) after food withholding for 12 hours.

Other information collected for all dogs included age, sex, weight, body condition score (on a scale of 9), and heart rate. For dogs with DM, the time since diagnosis (DM duration) was recorded.

Conventional echocardiography

Two-dimensional, M-mode, and Doppler echocardiographic examinations were performed on all dogs, which were placed in right and left lateral recumbency. The dogs were not sedated for these examinations. The examinations were performed with concurrent ECG monitoring by use of an ultrasound machine[a] equipped with a 3.0- to 8.5-MHz phased-array transducer. All examinations were conducted by a trained veterinarian (Kim Y-H). M-mode measurements were performed from the right parasternal long-axis and short-axis views in accordance with the recommendations of the American Society of Echocardiography.[22] The M-mode measurements included LVFW and IVS thicknesses at end-diastole and end-systole, LVIDd, and LVIDs. The FS and EF were assessed with an M-mode system.[22,23] The FS was calculated by use the following formula: FS (%) = ([LVIDd – LVIDs]/LVIDd) X 100. The EF was calculated with Teicholz equations.[22] The LA:Ao ratio was assessed on the right parasternal short-axis view in early diastole (ie, the first frame after aortic valve closure).[24,25] The transmitral flow profile was determined by means of pulsed-wave Doppler from the left apical 4-chamber view by placing the sample volume (2 mm in width) between the leaflet tips in the center of the flow stream. Measurements of E and A were obtained, and the E:A ratio was calculated. For each dog, all Doppler echocardiographic measurements were recorded as mean values derived from at least 3 consecutive cardiac cycles.

TDI and strain imaging

Two-dimensional color TDI examinations were conducted by the same trained veterinarian who used the same ultrasound unit as for the conventional echocardiographic examinations. Real-time color Doppler images were superimposed on 2-D images with high frame rates (> 150 frames/s) and stored for off-line analysis. The Doppler receive gain was optimally adjusted, and the Doppler velocity range was set as low as possible to avoid an aliasing artifact. The region of interest, with a width of 0.5 cm and a length extending from the endocardium to the epicardium, was placed between the papillary muscles in the right parasternal short-axis view to evaluate radial motion. The region of interest, with a width of 0.5 cm and a length of 0.6 cm, was placed in the middle of the IVS and LVFW in the left apical 4-chamber view to evaluate longitudinal motion. The off-line data analysis was performed with quantification software[b] by another investigator (CP) who was unaware of the clinical state and conventional echocardiographic findings for each dog. Peak velocities during systole and early and late diastole, peak systolic strain, and strain rate were measured in each segment. For each dog, the peak values of the tissue velocities, strain, and strain rate for each segment were assessed from 3

to 5 cardiac cycles, depending on heart rate, and a mean value was calculated.

Statistical analysis

The statistical analysis was performed with computer software.[c] The distributions of continuous variables were assessed by use of the Shapiro-Wilk test. Values are expressed as mean ± SD. An unpaired *t* test or Mann-Whitney *U* test was used to compare variables between dogs with DM and control dogs. Relationships between the TDI or strain imaging variables and the DM-related factors (DM duration, serum fructosamine concentration, and serum glucose concentration) were determined by Pearson correlation analysis. All data used in the statistical analysis were the mean values obtained for each dog in each group. A value of $P < 0.05$ was considered significant.

Results

In the present study, 10 of the 13 dogs with DM met the inclusion criteria. Three dogs were excluded from the study because of myxomatous mitral valve disease in 2 dogs and myxomatous mitral valve disease concurrent with aortic valve insufficiency in 1 dog. The clinical characteristics and laboratory data for 10 dogs with DM and 20 control dogs were summarized **(Table 1)**. The serum glucose and fructosamine concentrations after a 12-hour period of food withholding were significantly ($P < 0.001$) higher in dogs with DM than in control dogs. The clinical char-

Table 1—Clinical characteristics and laboratory variables of dogs with DM (n = 10) and healthy control dogs (20) included in a study to investigate cardiac structural and functional changes by TDI and strain imaging in dogs with spontaneous type 1 DM.

Variable	Control dogs	Dogs with DM	*P* value
Age (y)	9.4 ± 2.23	10.10 ± 2.42	0.438
Sex (No. of males/No. of females)	11/9	4/6	ND
DM duration (mo)	NA	10.6 ± 7.26	ND
Body weight (kg)	5.61 ± 2.22	7.19 ± 3.48	0.214
Body condition score (9-point scale)	6.08 ± 1.16	5.90 ± 0.95	0.414
Systolic arterial blood pressure (mm Hg)	136.90 ± 12.06	139.0 ± 10.31	0.642
Heart rate (beats/min)	130.75 ± 25.92	124.80 ± 25.80	0.793
Serum glucose concentration after a 12-h period of food withholding (mg/dL)	39.83 ± 14.66	513.80 ± 110.73	< 0.001
Serum fructosamine concentration after a 12-h period of food withholding (mg/dL)	271.08 ± 32.70	501.70 ± 87.87	< 0.001

Data are expressed as mean ± SD. A value of $P < 0.05$ was considered significant.
NA = Not applicable. ND = Not determined.

Table 2—Conventional echocardiographic variables for the dogs with DM (n = 10) and healthy control dogs (20) in Table 1.

Variable	Control dogs	Dogs with DM	*P* value
IVSd (cm)	0.70 ± 0.16	0.66 ± 0.12	0.486
IVSs (cm)	0.97 ± 0.19	1.08 ± 0.35	0.609
LVFWd (cm)	0.66 ± 0.15	0.65 ± 0.19	0.401
LVFWs (cm)	1.00 ± 0.28	0.92 ± 0.18	0.413
LVIDd (cm)	2.16 ± 0.51	2.64 ± 0.62	0.034
LVIDs (cm)	1.13 ± 0.43	1.56 ± 0.51	0.031
FS (%)	48.34 ± 11.59	42.35 ± 9.79	0.172
EF (%)	80.20 ± 11.36	74.46 ± 10.63	0.194
LA:Ao ratio	1.22 ± 0.17	1.31 ± 0.18	0.223
LV mass-cubed (g)	30.06 ± 11.67	37.80 ± 20.88	0.297
E (cm/s)	68.93 ± 7.03	74.49 ± 16.76	0.208
A (cm/s)	63.95 ± 11.24	74.32 ± 18.46	0.066
E:A ratio	1.11 ± 0.19	1.05 ± 0.29	0.486

Data are expressed as mean ± SD. A value of $P < 0.05$ was considered significant.

Two-dimensional, M-mode, and Doppler echocardiographic examinations were performed on all dogs when placed in right and left lateral recumbency. The dogs were not sedated for these examinations. The examinations were performed with an ultrasound machine equipped with a 3.0- to 8.5-MHz phased-array transducer. M-mode measurements were performed from the right parasternal long-axis and short-axis views. The M-mode measurements included LVFW and IVS thicknesses at end-diastole and at end-systole and LVIDd and LVIDs. The FS and EF were assessed with an M-mode system.[22] The FS was calculated by use of a formula as follows: FS (%) = ([LVIDd – LVIDs]/LVIDd) X 100. The EF was calculated on the basis of the Teicholz equations. The LA:Ao ratio was assessed on the right parasternal short-axis view in early diastole (ie, the first frame after aortic valve closure).[24,25] The transmitral flow profile was determined by means of pulsed-wave Doppler examination from the left apical 4-chamber view. All Doppler echocardiographic measurements were recorded as mean values derived from at least 3 consecutive cardiac cycles.

Table 3—Tissue Doppler imaging and strain imaging variables for the dogs with DM (10) and healthy control dogs (20) in Table 1.

Variable	Control dogs	Dogs with DM	*P* value
Radial systolic velocity (cm/s)	3.95 ± 0.99	3.93 ± 1.25	0.967
Radial E′ wave velocity (cm/s)	–2.53 ± 0.96	–2.75 ± 1.14	0.583
Radial A′ wave velocity (cm/s)	–2.80 ± 1.38	–2.24 ± 0.71	0.151
Radial E′:A′ ratio	0.94 ± 0.55	1.31 ± 0.60	0.099
Radial strain (%)	34.47 ± 6.94	32.08 ± 9.14	0.43
Radial strain rate (s^{-1})	3.93 ± 1.22	3.64 ± 0.90	0.507
Septal systolic velocity (cm/s)	3.55 ± 0.83	4.06 ± 0.98	0.15
Septal E′ wave velocity (cm/s)	–3.72 ± 0.45	–3.05 ± 1.23	0.126
Septal A′ wave velocity (cm/s)	–3.23 ± 0.65	–4.06 ± 0.78	0.004
Septal E′:A′ ratio	1.18 ± 0.18	0.75 ± 0.33	< 0.001
Septal longitudinal strain (%)	–26.23 ± 9.49	–20.97 ± 4.95	0.113
Septal longitudinal systolic strain rate (s^{-1})	–2.99 ± 0.97	–2.50 ± 0.70	0.164
E:septal E′ ratio	18.69 ± 2.14	28.27 ± 11.79	0.031
Lateral systolic velocity (cm/s)	3.86 ± 0.68	4.31 ± 0.97	0.143
Lateral E′ wave velocity (cm/s)	–3.91 ± 0.64	–3.37 ± 1.36	0.144
Lateral A′ wave velocity (cm/s)	–3.12 ± 0.80	–3.24 ± 0.86	0.716
Lateral E′:A′ ratio	1.30 ± 0.25	1.16 ± 0.70	0.559
Lateral longitudinal strain (%)	–25.39 ± 7.27	–20.49 ± 4.06	0.026
Lateral longitudinal systolic strain rate (s^{-1})	–3.02 ± 0.97	–2.62 ± 0.80	0.28
E:lateral E′ ratio	17.92 ± 2.51	25.00 ± 9.22	0.039

Data are expressed as mean ± SD. A value of $P < 0.05$ was considered significant.

Two-dimensional color TDI examinations were conducted with the same ultrasonographic unit as that used for the conventional echocardiographic examinations. Real-time color Doppler ultrasonographic images were superimposed on 2D images with high frame rates (> 150 frames/s) and stored for off-line analysis. The region of interest was placed between the papillary muscles in the right parasternal short-axis view to evaluate radial motion and in the middle of the IVS and the LVFW in the left apical 4-chamber view to evaluate longitudinal motion. The off-line data analysis was performed with quantification software. Peak velocities during systole and early and late diastole, peak systolic strain, and strain rate were measured in each segment. The peak values of the tissue velocities, strain, and strain rate for each segment were assessed from 3 to 5 cardiac cycles, depending on heart rate, and a mean value was calculated.

acteristics of the dogs with DM and control dogs did not differ.

Conventional echocardiographic **(Table 2)** and TDI and strain imaging **(Table 3)** findings for the dogs with DM and control dogs were summarized. The dogs with DM had significantly higher LVIDd and LVIDs, compared with those variables in the control group; however, the values of the other conventional echocardiographic variables did not differ between the 2 groups. Septal A′ wave velocities on TDI and strain imaging were higher in dogs with DM than in the control dogs, and the septal E′:A′ ratio in dogs with DM was significantly lower than that ratio in the control dogs **(Figure 1)**. Moreover, LV filling pressure and the E:septal E′ and E:lateral E′ ratios were significantly greater in the dogs with DM, compared with findings in control dogs. For dogs with DM, lateral longitudinal strain was significantly lower than that in the control dogs. Septal longitudinal and radial strain values were lower in the dogs with DM, compared with findings for the control dogs, but these differences were not significant. The radial motion variables did not differ between the 2 groups.

Correlation analysis of DM duration and serum fructosamine and glucose concentrations after a 12-hour period of food withholding with conventional echocardiographic variables **(Table 4)** and TDI and strain imaging variables **(Table 5)** in dogs with DM was performed. The duration of DM was not associated with either the conventional or the TDI and strain echocardiographic variables. Serum glucose and fructosamine concentrations after a 12-hour period of food withholding were significantly and positively correlated with A and consequently negatively correlated with the mitral E:A ratio. Serum fructosamine and glucose concentrations after a 12-hour period of food withholding in dogs with DM were positively related to the regional systolic functional variables (septal and lateral longitudinal strain), LV filling pressure indices (E:septal E′ and E:lateral E′ ratios), and septal and lateral E′ wave velocities but were negatively correlated with the diastolic functional variables (septal A′ velocity and septal and lateral E′:A′ ratios). Furthermore, serum fructosamine concentration after a 12-hour period of food withholding was positively correlated with septal and lateral longitudinal systolic strain rate. Finally, although 11 of the 14 longitudinal motion variables, including the septal and lateral E:E′ ratios, were significantly correlated with serum glucose and fructosamine concentrations after a 12-hour period of food withholding, none of the 6 radial motion variables were associated with those concentrations.

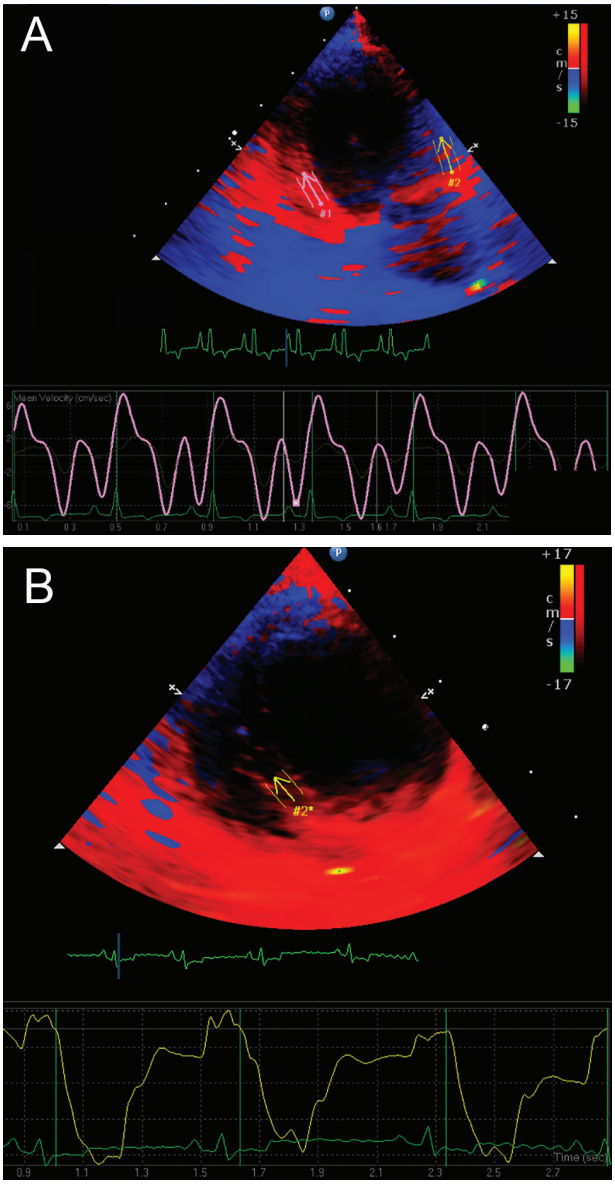

Figure 1—Representative interventricular septal longitudinal tissue Doppler ultrasonographic images obtained in the left apical long-axis view of a control dog without DM (A) and a dog with DM (B) included in a study to investigate cardiac structural and functional changes by TDI and strain imaging in dogs with spontaneous type 1 DM. Each ROI in the middle of the IVS from a control dog and a dog with DM (pink arrow in A and yellow arrow in B) was traced. Diastolic dysfunction is evident in the dog with DM; early diastolic velocity is decreased and the E′:A′ ratio is inversed, compared with findings for the control dog.

Discussion

In the present study, myocardial morphological and functional changes in dogs with type 1 DM were investigated by means of TDI and strain imaging as well as conventional echocardiography. The main findings of the study indicated that dogs with DM had impaired myocardial function and an increased LV filling pressure, which were correlated with variables indicative of glycemic control. Given that the dogs with DM had no accompanying cardiac disease or hypertension, the study results suggested that the physiologic conditions associated with DM directly affected myocardial function. Furthermore, only functional changes without LV hypertrophy and the absence of clinical signs of heart failure supported the concept of subclinical DM-related cardiomyopathy.

In humans, DM-related ventricular dysfunction that is independent of coronary atherosclerosis or hypertension, a condition known as diabetic cardiomyopathy, has been shown to exist. Although studies of humans and experimental animal models have revealed several mechanisms for diabetic cardiomyopathy, elucidation of the exact consequences of the metabolic disturbances associated with DM that predispose to myocardial functional or structural changes has been challenging. It has been suggested that hyperglycemia alone plays a sufficient role in the functional, but not necessarily the structural, abnormalities associated with diabetic myocardial dysfunction.[9] An elevated glucose load has been reported to increase the glycation of interstitial proteins or lipids, leading to decreased elasticity and contractility of the myocardium.[12,26] The present study included dogs with type 1 DM characterized by hyperglycemia and hypoinsulinemia. To our knowledge, this prospective study was the first to have described alterations of ventricular function in a group of dogs with spontaneous type 1 DM and compared the findings with those for a group of control dogs that happened to have a similar mean age.

Abnormalities in diastolic function have been identified in humans with type 1 or type 2 DM.[4,7,8,10,27,28] Moreover, there is little evidence of normal ventricular function in experimental animal models of DM.[29] Diastolic dysfunction has been reported as the main feature of diabetic cardiomyopathy, and it precedes clinical signs and even pathological changes in the myocardium of patients with DM. Therefore, diastolic dysfunction has been considered as an early, preclinical indicator of myocardial function impairment.[27] In accordance with the results of previous studies, the dogs with DM in the present study had signs of impaired relaxation detectable via TDI; the dogs had significantly greater septal A′ and smaller septal E′:A′ ratio than control dogs. In addition, the E:E´ratio, which is a useful indicator of LV filling pressure, was significantly greater in the septum and LVFW of dogs with DM, compared with findings in control dogs. Results of the present study were in keeping with data from a previous study[28] in which decreased annular velocities concurrent with an increased LV filling pressure were detected in humans with DM. These abnormalities may reflect early alteration in myocardial diastolic relaxation and could support the hypothesis for the mechanism of hyperglycemia-induced cardiomyopathy.

Diastolic dysfunction has been suggested to precede systolic dysfunction in patients with DM, whereas systolic dysfunction has been claimed to be a later and progressive consequence of the duration

Table 4—Relationship of conventional echocardiographic variables with DM duration and serum fructosamine and glucose concentrations after a 12-hour period of food withholding in the dogs with DM (n = 10) in Table 1.

	DM duration		Serum fructosamine concentration		Serum glucose concentration	
Variable	**Pearson ρ**	***P* value**	**Pearson ρ**	***P* value**	**Pearson ρ**	***P* value**
IVSd (cm)	–0.133	0.715	–0.093	0.679	–0.123	0.586
IVSs (cm)	–0.127	0.728	0.212	0.342	0.301	0.173
LVFWd (cm)	–0.081	0.824	0.127	0.572	0.032	0.888
LVFWs (cm)	–0.094	0.796	0.032	0.888	–0.07	0.975
LVIDd (cm)	–0.131	0.719	0.359	0.101	0.416	0.054
LVIDs (cm)	–0.073	0.841	0.276	0.213	0.388	0.074
FS (%)	0.07	0.835	–0.013	0.955	–0.123	0.584
EF (%)	0.067	0.854	0.003	0.99	–0.105	0.643
LA:Ao ratio	–0.319	0.369	0.086	0.705	0.123	0.586
LV mass-cubed (g)	–0.246	0.493	0.28	0.207	0.292	0.187
E (m/s)	0.079	0.506	0.097	0.666	0.154	0.495
A (m/s)	–0.126	0.729	0.55	0.008*	0.58	0.005*
E:A ratio	0.19	0.600	–0.552	0.013*	–0.522	0.013*

*A value of $P < 0.05$ was considered significant.

Table 5—Relationship of TDI and strain variables with DM duration and serum fructosamine and glucose concentrations after a 12-hour period of food withholding in the dogs with DM (n = 10) in Table 1.

	DM duration		Serum fructosamine concentration		Serum glucose concentration	
Variable	**Pearson ρ**	***P* value**	**Pearson ρ**	***P* value**	**Pearson ρ**	***P* value**
Radial systolic velocity (cm/s)	0.178	0.623	–0.033	0.884	–0.102	0.652
Radial E′ wave velocity (cm/s)	–0.191	0.597	0.028	0.903	–0.016	0.944
Radial A′ wave velocity (cm/s)	–0.462	0.179	–0.06	0.79	–0.11	0.626
Radial E′:A′ ratio	–0.068	0.851	–0.031	0.892	–0.052	0.817
Radial strain (%)	0.183	0.614	–0.247	0.268	–0.223	0.319
Radial strain rate (s^{-1})	0.616	0.058	–0.337	0.125	–0.32	0.147
Septal systolic velocity (cm/s)	0.388	0.268	0.226	0.311	0.257	0.248
Septal E′ wave velocity (cm/s)	–0.137	0.705	0.449	0.036*	0.491	0.020*
Septal A′ wave velocity (cm/s)	–0.028	0.938	–0.503	0.017*	–0.674	0.001*
Septal E′:A′ ratio	0.124	0.733	–0.714	< 0.001*	–0.834	< 0.001*
Septal longitudinal strain (%)	–0.239	0.506	0.457	0.033*	0.499	0.018*
Septal longitudinal systolic strain rate (s^{-1})	–0.235	0.513	0.425	0.049*	0.386	0.076
E:septal E′ ratio	–0.03	0.934	0.58	0.005*	0.657	0.001*
Lateral systolic velocity (cm/s)	0.494	0.147	–0.055	0.809	0.016	0.943
Lateral E' wave velocity (cm/s)	–0.458	0.183	0.467	0.029*	0.427	0.048*
Lateral A′ wave velocity (cm/s)	–0.307	0.389	–0.179	0.425	–0.331	0.132
Lateral E′:A′ ratio	0.235	0.514	–0.431	0.045*	–0.474	0.026*
Lateral longitudinal strain (%)	0.409	0.24	0.469	0.028*	0.466	0.029*
Lateral longitudinal systolic strain rate (s^{-1})	–0.02	0.957	0.434	0.043*	0.341	0.121
E:lateral E′ ratio	–0.207	0.565	0.618	0.002*	0.657	0.001*

See Table 4 for key.

and magnitude of hyperglycemia.[11,20,27] In the present study, EF and FS did not differ significantly between the dogs with and without DM; this finding is in agreement with the findings of previous studies,[30,31] which indicated that these variables are relatively less sensitive indicators of systolic function. However, in the present study, lateral longitudinal strain was significantly lower in dogs with DM than in control dogs. Impairment of longitudinal contractility has been suggested to be an early effect of LV systolic dysfunction, whereas radial and circumferential myocardial functions are preserved even at the advanced stage of

various cardiovascular diseases.[32,33] Moreover, longitudinal systolic dysfunction has been detected early in humans with DM in a study[34] of myocardial function by use of TDI and strain imaging. Given that FS is an indicator of radial contractility of the myocardium, the data obtained from the dogs of the present study may enhance previous observations of early longitudinal systolic dysfunction in diabetic patients. Furthermore, results of the present study might indicate that DM profoundly impaired the lateral regional systolic function. In addition, the TDI and strain imaging findings that differed between the septal and lateral walls suggested that each wall could be affected differently by metabolic disturbances. Given the small number of dogs investigated and absence of long-term monitoring, it is not possible to confirm these speculations and larger studies are needed. In addition, the dogs with DM were being treated with insulin, so the effects of insulin on systolic function could not be excluded.[35–37] Administration of insulin may conserve global systolic function because it has mitogenic and prosurvival effects on contractile proteins. Experimental animal studies[32,38] have revealed that systolic function is conserved in patients with type 1 DM that are treated with insulin.

With regard to variables indicating LV function, there were significant alterations in TDI and strain imaging variables, but not with conventional echocardiographic variables, identified in the present study, suggesting that TDI and strain imaging can unmask myocardial dysfunction in dogs with DM that have no clinical signs. Therefore, the usefulness of TDI for the detection of subtle alterations during the early stage of myocardial dysfunction remains consistent with that reported in previous studies.[20,28,30] Diastolic dysfunction has been significantly associated with disease duration in humans and experimental animal models.[9] As measured by TDI, LV diastolic dysfunction deteriorates with an increase in the duration of DM in humans, and in 1 study,[37] patients with DM had profoundly impaired diastolic function at 4 years after disease onset. In other studies,[29,39] impaired diastolic function developed within 7 days in experimental animals with type 1 DM, whereas systolic dysfunction developed within 3 weeks and progressed over 1 year. In contrast, DM duration was not associated with TDI or conventional echocardiographic variables in the present study. These findings may be attributed to the influence of insulin, which has a proliferative effect on contractile proteins. Insulin administration partially restores systolic abnormalities in rats with type 1 DM.[32,38] Regional functional indices could reveal more subtle alterations, compared with a global diastolic function index. However, there is sparse information regarding the relationship between glycemic control and regional function indices determined by TDI and strain imaging, so comparisons between findings of the present study and those of previous studies are difficult. Further research is needed to confirm these effects on the correlation findings.

Previous studies[40,41] that evaluated the correlation between glycemic control and diastolic function in type 1 DM by use of echocardiography revealed that glycemic control significantly influences diastolic function. Although several studies[42,43] found no relationship between glycemic control and LV function, most of them evaluated human patients with type 2 DM who may have other metabolic disturbances in addition to hyperglycemia. In the present study, serum glucose and fructosamine concentrations after a 12-hour period of food withholding were positively correlated with septal and lateral E:E′ ratios and septal and lateral E′ velocities and negatively correlated with transmitral E:A, septal and lateral E′:A′ ratios, and the septal A′ wave velocity. Also, these glycemic control indices were positively correlated with regional systolic functional variables (septal and lateral longitudinal strain). These findings indicated that both acute and chronic glycemic control affect LV diastolic and systolic dysfunction in dogs with type 1 DM. Accordingly, we suggest that regardless of the duration, hyperglycemia is an important risk factor for LV dysfunction.

Overall, the present study had several limitations. First, a small population of dogs was evaluated and there were no long-term data obtained. The findings need to be confirmed through larger, long-term studies. Second, although the tools used in the study, particularly TDI and strain imaging, are highly sensitive for evaluating cardiac function, direct measurements of myocardial function and morphology were lacking. In addition, coronary arteries were not evaluated to exclude coronary artery disease. However, coronary artery diseases are rare in dogs, which have abundant anastomoses between the coronary arteries and their branches in the heart.[44] Despite these limitations, results of the present study indicated that myocardial function in dogs with DM is altered before the development of clinical heart-related signs, as observed in diabetic humans. Given the metabolic disturbances associated with type 1 DM and the present study's findings, hyperglycemia could have detrimental effects on myocardial function, independent of hypertension, other cardiac diseases, and LV hypertrophy, in dogs with type 1 DM. Use of TDI and strain imaging may help in the early identification of diabetic myocardial dysfunction. These findings provided a new insight into the treatment of DM in dogs, which has previously focused only on the control of diabetes-induced metabolic alterations. Early detection of subclinical cardiac involvement and a therapeutic approach to decrease the risk of heart failure should be considered when managing DM in dogs. In addition, tight glycemic control could help in preventing development of myocardial dysfunction. Further studies are necessary to clarify the clinical application of TDI and strain imaging in spontaneous diabetic myocardial dysfunction in dogs.

Acknowledgments

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The authors declare that there were no conflicts of interest.

Footnotes

a. HD 15, Philips Healthcare, Bothell, Wash.
b. QLAB quantification software, Philips Healthcare, Bothell, Wash.
c. SPSS, version 18.0, SPSS Inc, Chicago, Ill.

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Correction: Feasibility of near-infrared fluorescence imaging for sentinel lymph node evaluation of the oral cavity in healthy dogs

In the report "Feasibility of near-infrared fluorescence imaging for sentinel lymph node evaluation of the oral cavity in healthy dogs" (*Am J Vet Res* 2018;79:995–1000), the author affiliation should have been listed as "From the Department of Clinical Sciences, Carlson College of Veterinary Medicine, Oregon State University, Corvallis, OR 97331." Also, the individual who performed cytologic evaluations of lymph node aspirates was a board-certified veterinary pathologist, not a veterinary clinical pathologist.