



Original Article

The Effect of Glycemic Control on Left Ventricular Function in Clinical and Experimental Diabetes

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ABSTRACT

Background: Glycemic control in diabetes mellitus (DM) has not improved cardiovascular outcomes with normal left ventricular (LV) function. We assessed the effect on LV dysfunction using a canine model of LV dysfunction and DM, and in patients with DM and LV dysfunction. **Methods:** Chronic LV dysfunction was produced by coronary microsphere embolization in 34 canines (15–25 kg). Following 8 weeks of stabilization, DM was induced in 24 canines and randomized to good or poor glycemic control for 3 months. Ten canines without DM were controls. Hemodynamic and Doppler echocardiographic data were

RÉSUMÉ

Contexte : Chez les personnes atteintes de diabète sucré (DS), la maîtrise glycémique n'a pas amélioré les résultats cardiovasculaires en présence d'une fonction ventriculaire gauche (VG) normale. Nous avons évalué l'effet d'une dysfonction VG au moyen d'un modèle canin de dysfonction VG et de DS, ainsi que chez des patients atteints de ces deux troubles.

Méthodologie : Une dysfonction VG chronique a été produite chez 34 chiens (pesant de 15 à 25 kg) au moyen d'une embolisation coronarienne par microsphères. Après huit semaines de stabilisation, un

Patients with diabetes mellitus (DM) have a greater incidence of morbidity and mortality from cardiovascular disease with a greater incidence of left ventricular (LV) dysfunction and heart failure (HF).^{1–3} The duration of DM correlates with systolic and diastolic LV dysfunction, microvascular damage, and autonomic nervous system dysfunction.^{4,5} An independent LV dysfunction termed “diabetic cardiomyopathy” has been attributed to impaired insulin signaling, glucose toxicity, lipotoxicity, abnormal calcium homeostasis, autonomic nervous system dysfunction, and a proinflammatory state promoting microvascular dysfunction with sarcomere disappearance, cell death, and replacement fibrosis.^{6,7}

Metabolic control of DM with insulin has demonstrated improvement in microvascular dysfunction.⁸ Although cardiovascular complications have been reported to be decreased,^{8–10} results relating to glycemic control and mortality have been variable in clinical trials.^{11,12} The effects of glycemic control on LV systolic and diastolic function, and HF incidence, have been variable.^{13–15} Preservation of global longitudinal strain as a LV systolic performance parameter, but not ejection fraction, has been demonstrated in some

studies with glycemic control.^{16–18} Similarly, diastolic function parameters may improve.^{15,17–19} Finally, improved glycemic control did not affect HF outcomes¹³ in the Veterans Affairs (VA) cooperative study, but it did improve outcomes in the Heart and Soul Study data²⁰ and the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trial.¹⁵

Ample experimental data with induced DM demonstrate abnormal myocardial composition with increased myocardial calcium, and chamber stiffness with increased cytoplasmic calcium.^{21,22} Insulin administration resulted in partial reversibility for both systolic and diastolic dysfunction that correlated with blood glucose levels.²² As experimental data have been based on baseline normal myocardium, no data have been obtained regarding glycemic control and dysfunctional myocardium, nor has any clinical trial stratified the effect of glycemic control based on LV ejection fraction. The purpose of this study was to assess the effect of glycemic control on a canine model of LV dysfunction and DM, and to assess the relevance of these findings to a database of patients with DM and LV dysfunction with varying glycemic control.

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See page 737 for disclosure information.

Material and Methods

Experimental study

The canines used in this study were maintained in accordance with the American Heart Association guidelines

obtained prior to and following pressure loading. We reviewed the Doppler-echocardiography at baseline and follow-up in 207 patients with DM with reduced ejection fraction (EF; median follow-up = 612 days) and 60 age- and sex-matched non-DM patients with normal EF. Laboratory results, medications, and incident adverse events from medical records were obtained.

Results: EF = 43.8% ± 11.2% for all canines at 8 weeks. Canines with poor glycemic control (hemoglobin [Hb]A_{1c} = 8.05% ± 3.02%) demonstrated reduced LV mass and rate-corrected velocity of circumferential fiber shortening, compared to those with LV dysfunction (1.36 ± 0.73 vs 0.88 ± 0.13 circumference per second, $P < 0.01$). Good glycemic control (HbA_{1c} = 3.88% ± 0.89%) demonstrated similar LV parameters, compared to controls (HbA_{1c} = 2.99% ± 0.44%). EF was similar among groups. Patients with vs without DM were followed for up to 3 years. Patients with DM and poor glycemic control had reduced EF, lower rate-corrected velocity of circumferential fiber shortening = 0.93 ± 0.26 vs 1.11 ± 0.26, $P < 0.001$), and greater incidence of heart failure.

Conclusions: Poor glycemic control had an adverse effect on preexisting LV dysfunction experimentally and in patients with type 2 diabetes.

on research animal use and were approved by the Wayne State University Animal Investigation Committee. Canines were chosen for this study for the LV dysfunction model, and their size, which allows for ease in making cardiac chamber and Doppler measurements. Details relating to anaesthesia, instrumentation, LV dysfunction induction, and pressure loading with methoxamine are provided in the [Supplemental Methods](#). Data were obtained from 34 canines (20-25 kg; age = 5.1 ± 0.9 years) who were anaesthetized, intubated, ventilated, and instrumented. Acute ischemic LV dysfunction was induced by sequential coronary microsphere injection into the left main coronary artery and selectively into the left circumflex and left anterior descending artery as previously described²³ (see the Supplemental Methods for a more extensive description). After 8 weeks postembolization, a metabolic profile (hemoglobin [Hb]A_{1c}, renal function, electrolytes) was obtained. Each canine was instrumented as above, and hemodynamic, transthoracic, and transesophageal Doppler echocardiographic data were obtained at baseline and following pressure loading, as previously described.²³

Induction of diabetes

The use of a canine model with induced diabetes that resembles type 1 diabetes was chosen because of previous experience with alloxan tetrahydrate, preexisting induced LV dysfunction, and the ease of ultrasound measuring of cardiac chambers and Doppler. Following equilibration of hemodynamics, all catheters were removed and vessels were

DS a été provoqué chez 24 chiens, qui ont été répartis aléatoirement pour faire l'objet d'une bonne ou d'une mauvaise maîtrise glycémique pendant trois mois. Les 10 chiens sans DS ont servi de témoins. Des données hémodynamiques et échocardiographiques (Doppler) ont été obtenues avant et après la mise en charge. Nous avons aussi étudié l'échocardiogramme Doppler, au départ et lors du suivi, de 207 patients atteints de DS et présentant une fraction d'éjection (FE) réduite (suivi médian de 612 jours) et de 60 patients non atteints de DS qui ont été appariés en fonction de l'âge et du sexe et dont la FE était normale. Enfin, nous avons obtenu leurs dossiers médicaux : résultats des épreuves de laboratoire, listes de médicaments et manifestations indésirables découvertes fortuitement.

Résultats : La FE était de 43,8 % ± 11,2 % pour l'ensemble des chiens après huit semaines. Chez les chiens dont la maîtrise glycémique était mauvaise (hémoglobine [Hb]A_{1c} = 8,05 % ± 3,02 %), la masse VG et la vitesse de raccourcissement circonférentiel des fibres myocardiques corrigée en fonction de la fréquence cardiaque (VCFc) étaient toutes deux réduites comparativement à celles observées chez les chiens présentant une dysfonction VG (1,36 ± 0,73 vs 0,88 ± 0,13 circonférence par seconde [circ/s], $p < 0,01$). Chez les chiens avec une bonne maîtrise glycémique (HbA_{1c} = 3,88 % ± 0,89 %), les paramètres VG étaient semblables à ceux observés chez les témoins (HbA_{1c} = 2,99 % ± 0,44 %). La FE était également similaire dans tous les groupes. Les patients atteints de DS ont été suivis et comparés à des patients non atteints de DS pendant une durée allant jusqu'à trois ans. Les patients qui étaient atteints de DS et dont la glycémie était mal maîtrisée présentaient une FE réduite, une diminution de la VCFc (0,93 ± 0,26 vs 1,11 ± 0,26; $p < 0,001$) et une incidence accrue de cas d'insuffisance cardiaque.

Conclusions : Une mauvaise maîtrise glycémique a eu un effet indésirable sur une dysfonction VG préexistante, tant dans le modèle animal que chez les patients atteints de diabète de type 2.

repaired. The canines were allowed to recover and were observed for 7 days. After 7 days, 24 canines were administered alloxan tetrahydrate (40 mg/kg direct toxic effect on beta cells) every 2 weeks with median doses = 3 and interquartile range = 3-5 doses.²⁴ The noninstrumented canines were observed for at least 4 weeks. Sufficient insulin was administered to keep the fasting blood glucose (FBG) at a level between 250 and 350 mg/dL. Glycemic monitoring was performed to assess the blood glucose every 8 hours for 1 week and then daily. Ketones in the blood were checked to avoid ketoacidosis. If glycemic control was poor (FBG > 350 mg/dL or blood ketones), sufficient insulin was administered, and blood glucose and ketones were obtained more frequently until FBG < 350 mg/dL without ketone detection. This occurred in 3 canines.

Following 4 weeks of observation, the uninstrumented 24 canines were randomized to either good glycemic control (FBG = 100-150 mg/dL) or poor glycemic control (FBG = 250-350 mg/dL) using sufficient dosing of insulin. Optimal glycemic control occurs when HbA_{1c} level < 6.5%. We proposed that a fasting glucose of 100-150 mg% would provide optimal control and avoid hypoglycemia. We defined poor control as unacceptable fasting glucose levels > 250 mg %, which would equate to an HbA_{1c} level > 10.5%. Glycemic monitoring was performed as above to achieve good or poor control. Ketone detection occurred in 1 canine with good glycemic control, and 2 canines with poor glycemic control. The dogs were then observed for 3 months. At 3 months, metabolic parameters were obtained. The canines

were instrumented as above, and following echocardiographic and hemodynamic measurements, each dog was pressure loaded with methoxamine, and hemodynamic and Doppler-echocardiographic parameter measurements were repeated. Ten additional canines were used as controls and were studied similarly at each stage. Following the above procedures, the canines were euthanized.

Measurements: (data were analyzed from the average of 3 consecutive beats)

Hemodynamic. LV, aortic, and mean right atrial pressures with thermodilution cardiac outputs were obtained. Stroke volume was calculated as cardiac output divided by the heart rate and indexed to body size by dividing by weight in kg. Tau was calculated using the logarithmic decay method of Weiss.²⁵

Echocardiographic. LV end diastolic and end systolic volumes were obtained from transesophageal apical 4- and 2-chamber views using biplane Simpson's Rule, and indexed. From the transthoracic parasternal long-axis view at just beyond the level of the mitral valve, the LV dimensions at end diastole (at the R wave) and end systole (smallest cavity size) were obtained. End diastolic and end systolic wall thicknesses of the septum and inferolateral walls were obtained. LV mass was calculated using American Society of Echocardiography (ASE) guidelines,²⁶ and indexed. Maximal left and right atrial areas were obtained from the transesophageal apical 4-chamber view. End diastolic and end systolic right ventricular (RV) areas were also obtained from the transesophageal 4-chamber view. RV area ejection fraction was calculated as the (RV end diastolic area-end systolic area)/end diastolic area.

Doppler. The mitral peak mitral rapid filling velocity (E) and peak mitral valve atrial filling velocity (A) wave velocities were measured, and the mitral E wave deceleration time was calculated from the time from the peak of the E wave to when the rapid filling velocity decelerated to its minimum or the zero baseline. The mitral diastolic velocity integral was obtained by tracing the modal velocity of the transmitral spectrum from the onset of the velocity spectrum to its termination following the A wave. The rapid filling period was determined from onset of the E wave to the end of E wave deceleration. If atrial filling interrupted the rapid filling ending, the rapid filling deceleration curve was extended to 20% of the height of the E wave as rapid filling was ending. The rapid filling fraction was determined as the integral during the rapid filling period/diastolic filling velocity integral. Atrial filling commenced with the onset of the A wave and extended to the termination of the A wave. If rapid filling was interrupted by atrial filling, atrial filling would then commence beginning at 20% of the E wave. The atrial filling fraction was determined as the atrial filling velocity integral/diastolic filling velocity integral.

Pressure loading with methoxamine infusion

For each canine, at each stage, the relationship of end systolic pressure to end systolic dimension during

methoxamine infusion was constructed, and its slope as the end systolic elastance was calculated. From the parasternal long axis at end diastole and end systole, the rate-corrected velocity of circumferential fiber shortening (VCFc) was calculated as the (end diastolic dimension minus the end systolic dimension)/the rate-corrected LV ejection time. The LV ejection time was calculated at the time interval from the upstroke of aortic pressure tracing to the incisura and was rate-corrected by dividing by the R to R interval square root. The end systolic meridional stress (ESSm) was calculated using the method described by Reichek.²⁷ For each canine, and at each stage, VCFc to ESSm was plotted, and the VCFc at a common end systolic stress was calculated for each stage using analysis of covariance.

Clinical study

This retrospective study received expedited approval by the Wayne State University Human Investigation Committee and did not require consent, as all patient information was de-identified. We reviewed the Doppler-echocardiographic recordings from 207 patients followed in the Diabetes Clinic for > 2 years (> 8 years with a DM diagnosis), with adequate Doppler echocardiograms that were > 6 months apart and regular clinical follow-up, at least at 6-month intervals (median follow-up = 612 days; interquartile range = 450-771 days). Inclusion criteria include patients with initial LV ejection fraction < 52% in male patients and < 54% in female patients, absence of greater-than-mild valvular heart disease, and a negative stress test or cardiac catheterization excluding > 50% stenosis in any coronary artery. Patients were excluded (324 patients) for the following reasons: inadequate/only 1 echocardiogram (84 patients); previous myocardial infarction (79 patients); atrial fibrillation or other arrhythmias (48 patients); greater-than-mild valvular heart disease or a prosthetic valve (31 patients); inadequate clinical documentation/follow-up (36 patients); and wall-motion abnormalities (46 patients).

The medical records for the 207 patients were examined, and laboratory results and medications at the time of the echocardiogram were recorded. Patients were deemed to have hypertension if their blood pressure exceeded 140/90 mm Hg, or if they were taking antihypertensive medications. Patients were deemed to have DM if their FBG was > 126 mg%, if they were taking antidiabetic medications, or if they had an HbA1c level > 6.5%. Patients were deemed to have hyperlipidemia if their total cholesterol level was > 200 mg/dL, their fasting triglycerides level was > 150 mg/dL, or they were taking lipid-lowering medications. Patients were deemed to have chronic renal disease if their estimated glomerular filtration rate was < 60 mL/min per 1.73 m². An additional 60 age- and sex-matched patients without DM were followed in the medical clinic with > 3 years follow-up with an adequate Doppler echocardiogram, and with the above exclusions, were chosen as the control population. Patients were followed for a median of 36 months (interquartile range = 20-47 months), utilizing view of clinic and hospitalization notes on the medical chart. The incidence of nonfatal myocardial infarction, HF admission or treatment for HF, and all-cause mortality (ACM) were determined for each patient. Myocardial infarction was defined by the universal

definition.²⁸ HF was defined as being admitted for HF or having had an emergency room visit for therapy. HF verification was assessed using the Framingham HF criteria.²⁹ ACM was determined from medical records (80.2%), 22 conversation with family (11.4%), and the national death index (9.4%).

Doppler-echocardiography. Doppler echocardiography was performed using echocardiographs (Hewlett Packard 2500 and 5500, Andover, MA) with 2.5-3.5 mHz transducers at held end expiration from multiple ultrasonic windows to assess all cardiac chambers and valves. The systolic and diastolic blood pressures were recorded at the time of echocardiography. Transmitral pulsed Doppler was obtained as above. LV outflow tract Doppler was obtained from the LV outflow tract 0.5 cm from the aortic valve using a 1-2 x 1-2 mm sample volume. Doppler spectra were recorded at 50 and 100 mm/s.

Calculated echocardiographic parameters. All measurements were performed in an Intersocietal Commission for the Accreditation of Echocardiography Laboratories (ICAEL)-approved laboratory by the investigators, post-recording of the original study on ½-inch VHS tape-recorded echo-Doppler data, using the Nova Microsonics Data Vue analysis station (Allendale, NJ). Using the average of 3 consecutive cardiac cycles at held end expiration per American Society of Echocardiography recommendations,²⁶ we calculated biplane LV end diastolic and end systolic volumes, LV mass, left atrial volume, and right atrial volume, which were indexed to body surface area. LV dimensions, wall thicknesses, VCFc, and ESSm were obtained as above. Right ventricular (RV) end diastolic area and tricuspid annular systolic plane excursion (TAPSE) were measured per American Society of Echocardiography guidelines.²⁶

From transmitral Doppler, E, A, and deceleration time were calculated as above. Stroke volume index was calculated as the time velocity integral of the LV outflow tract velocity multiplied by the LV outflow tract area obtained from the mid-systolic diameter in the parasternal long-axis view, 3-5 mm from the site of aortic valve insertion, and indexed to body surface area. Tricuspid regurgitation velocity was obtained from a continuous wave transducer using multiple windows, and RV systolic pressure was estimated using the Bernoulli equation with the addition of an estimate of right atrial pressure based on respiratory variations of the inferior caval dimension.³⁰

Statistics

Data were expressed as mean \pm standard deviation for continuous normally distributed data, as determined by the Kolmogorov-Smirnov test. For data not normally distributed, median and interquartile ranges were computed. Differences between baseline and interventions were determined using 1-way analysis of variance for repeated measures. Differences among groups were determined using 1-way analysis of variance or 1-way analysis of variation on ranks if the variable was not normally distributed. The relationship between variables was determined using least-squares linear regression. VCFc and end systolic elastance at baseline, with good and poor control, were determined by analysis of covariance.

For all patients at baseline and with either good control, poor control, or unchanged control, the VCFc was plotted against ESSm. Using analysis of covariance, VCFc was determined for each glycemic condition at a common ESSm as a measure of contractile function.³¹ Time-to-event curves (Kaplan-Meier) were constructed for nonfatal myocardial infarction, HF, and ACM for control patients and for patients with DM and varying glycemic control. Log-rank testing was performed to determine differences between curves. Statistics were performed using SAS, version 9.3 (SAS Institute, Cary, NC) and XL-Stat. (Addinsoft, New York, NY).

Results

Supplemental Table S1 reviews the echocardiographic and hemodynamic variables at baseline, and with chronic LV dysfunction at 8 weeks following the last embolization. With chronic LV dysfunction (ejection fraction = $43.8\% \pm 11.2\%$), increased left atrial size, and LV volume and mass indexes and dimensions were noted. **Supplemental Table S2** summarizes the results of laboratory parameters, with baseline LV dysfunction and following 3 months in control non-DM canines, and in canines with poor glycemic or good glycemic control. HbA1c levels were $2.99\% \pm 0.44\%$ at baseline vs $8.05\% \pm 3.0\%$ with poor glycemic control ($P < 0.001$ vs baseline), and $3.88\% \pm 0.89\%$ with good glycemic control ($P < 0.05$ vs baseline; $P < 0.001$ vs poor glycemic control). Sodium, potassium, and total CO₂ levels were all reduced in both glycemic control groups.

Supplemental Table S3 summarizes the echocardiographic and hemodynamic response to pressure loading with methoxamine at 3 months following randomization to LV dysfunction, poor glycemic control, and good glycemic control. For all stages, pressure loading with methoxamine resulted in an increase in LV volume indexes, a decrease in LV ejection fraction, increases in LV diastolic pressures, and a decrease in stroke volume index. **Table 1** summarizes resting echocardiographic and hemodynamic parameters with LV dysfunction and with good and poor glycemic control after 3 months. Canines with *poor glycemic control* demonstrated reduced LV wall thickness and LV mass index, but unchanged LV ejection fraction, with a lower stroke volume index, compared to those with baseline LV dysfunction. RV size increased with preserved RV systolic function. Canines with *good glycemic control* did not differ significantly from those with baseline LV dysfunction.

Supplemental Table S4 summarizes Doppler-derived variables and response to methoxamine pressure loading for baseline LV dysfunction, poor glycemic control, and good glycemic control. Pressure loading resulted in decreased E/A, a shortened diastolic filling period, and a greater extent of atrial filling. **Table 1** also summarizes Doppler parameters with LV dysfunction, with good and poor glycemic control. As compared to baseline LV dysfunction, a reduction occurred in E/A, with shortening of the diastolic filling period with an increased atrial filling fraction in both the poor and good glycemic control groups.

Myocardial contractile indices (**Table 1**) with LV dysfunction, with poor glycemic control and good glycemic control, demonstrated that with poor glycemic control, the end systolic elastance and VCFc were reduced, whereas end

Table 1. Doppler-echocardiographic and hemodynamic parameters

Parameter	LVD-P (n = 10)	LVD-PC-P (n = 12)	LVD-GC-P (n = 12)
LV end diastolic dimension, mm	40.4 ± 5.2	39.3 ± 5.4	41.8 ± 1.9
LV end systolic dimension, mm	28.9 ± 4.4	27.5 ± 3.7	30.7 ± 4.6
Septal wall thickness, mm	9.4 ± 1.8	8.3 ± 1.1*	9.4 ± 1.2 [§]
Inferolateral wall thickness, mm	9.5 ± 1.4	8.0 ± 1.1 [†]	9.3 ± 1.0
LV end diastolic volume index, mL/kg	1.39 ± 0.39	1.68 ± 0.65	1.61 ± 0.86
LV end systolic volume index, mL/kg	0.85 ± 0.28	0.92 ± 0.38	0.87 ± 0.21
LV ejection fraction, %	42.3 ± 13.5	43.6 ± 9.9	44.5 ± 9.3
LV mass index, g/kg	5.64 ± 1.91	4.40 ± 1.39*	5.85 ± 1.54 [§]
RV end diastolic area, cm ²	4.1 ± 1.1	5.0 ± 1.3*	4.5 ± 0.5 [§]
RV area ejection fraction, %	48.9 ± 11.1	44.8 ± 9.3	47.1 ± 6.4
LV minimal pressure, mm Hg	8.6 ± 3.5	9.0 ± 2.1	8.9 ± 1.8
LV end diastolic pressure, mm Hg	14.3 ± 4.8	15.5 ± 2.4	15.0 ± 2.4
LV systolic pressure, mm Hg	133.8 ± 12.7	113.2 ± 14.0	134.5 ± 27.1
Aortic notch pressure, mm Hg	122.3 ± 14.1	105.6 ± 13.0 [†]	121.8 ± 22.9 [§]
Mean RA pressure, mm Hg	3.1 ± 2.5	4.8 ± 3.2	4.9 ± 3.4
Stroke volume index, mL/kg	2.25 ± 0.46	1.80 ± 0.13 [†]	2.11 ± 0.51
E/A	1.72 ± 0.49	1.50 ± 0.31*	1.48 ± 0.41*
Deceleration time, ms	152.5 ± 45.6	150.9 ± 48.3	157.4 ± 49.4
Diastolic filling period, ms	393.2 ± 93.9	348.1 ± 71.0*	329.3 ± 62.3*
Rapid filling period, ms	177.7 ± 35.7	176.4 ± 32.7	195.5 ± 29.1
Atrial filling period, ms	104.9 ± 37.5	126.5 ± 41.2*	110.9 ± 40.6 [§]
Rapid filling fraction, %	73.3 ± 9.0	62.9 ± 8.4 [†]	63.6 ± 8.9 [†]
Atrial filling fraction, %	24.8 ± 7.8	29.9 ± 7.4*	29.5 ± 9.5*
End systolic elastance, mm Hg/mm	9.776 ± 0.951	7.527 ± 0.665 [‡]	8.343 ± 1.134*
VCFc, 1/s	1.362 ± 0.073	0.876 ± 0.127 [†]	1.254 ± 0.077 [§]
End systolic meridional stress, g/cm ²	135.9 ± 37.8	121.0 ± 42.6	141.0 ± 28.3

A, peak mitral atrial filling velocity; E, peak mitral rapid filling velocity; GC, good glycemic control; LV, left ventricular; LVD, left ventricular dysfunction; P, paced; PC, poor glycemic control; RA, right atrial; RV, right ventricular; VCFc, rate-corrected velocity of circumferential fiber shortening.

* $P < 0.05$.

[†] $P < 0.01$ vs LVD-P.

[‡] $P < 0.001$ vs LVD-P.

[§] $P < 0.05$.

^{||} $P < 0.01$ LVD-PC-P vs LVD-GC-P.

systolic elastance alone was reduced with good control. [Supplemental Figure S1](#) demonstrates for 2 canines (A and B), VCFc-ESSm plots (upper) and end systolic pressure-end systolic dimension plots (lower) with pressure loading. With poor glycemic control, both VCFc and end systolic elastance were reduced (downward displaced). [Figure 1](#) demonstrates VCFc at a common ESSm ([Fig. 1A](#)) and end systolic elastance ([Fig. 1B](#)), plotted against HbA1c for paced LV dysfunction, poor glycemic control, and good glycemic control. VCFc at a common ESSm was lower in the poor glycemic control group, as compared to both good glycemic control and paced LV dysfunction. The end systolic elastance also was reduced in the poor and good glycemic control group, as compared to paced LV dysfunction.

Inter-observer and intra-observer variability

End diastolic dimension, end systolic dimension, peak systolic inferolateral wall thickness, LV end diastolic volume, and LV end systolic volume were measured in 6 canines with baseline LV dysfunction, poor glycemic control, and good glycemic control. Canines were reanalyzed 1 month following the initial analysis, by 2 readers, with random ordering. Intraclass correlation coefficients between observers were 0.92, 0.90, 0.86, 0.86, and 0.87 for end diastolic dimension, end systolic dimension, peak systolic inferolateral wall thickness,

LV end diastolic volume, and LV end systolic volume. The mean differences of absolute values between observations were $4.4\% \pm 0.7\%$, $4.1\% \pm 1.9\%$, $6.5\% \pm 1.9\%$, $5.9\% \pm 1.6\%$, and $5.2\% \pm 2.2\%$. Intraclass correlation coefficients for repeated observations by the same observer were 0.93, 0.91, 0.88, 0.89, and 0.89 for the above parameters. The mean differences for the above parameters for the same observer were $3.9\% \pm 1.2\%$, $3.7\% \pm 1.5\%$, $5.8\% \pm 1.8\%$, $5.6\% \pm 1.6\%$, and $5.0\% \pm 2.1\%$.

Clinical study

[Supplemental Table S5](#) summarizes demographics, Doppler-echocardiographic, and outcome parameters in age- and sex-matched patients with DM (207 patients) and without DM (60 patients). Patients with DM and non-DM patients had similar follow-up. Patients with DM had a greater prevalence of hyperlipidemia and coronary disease, a lower LV ejection fraction, greater LV mass and left atrial volume index, lower E/A, lower VCFc, and a greater HF incidence. [Figure 2A](#) demonstrates a plot of the velocity of VCFc vs ESSm with and without DM. The resting VCFc at a common ESSm was lower in the DM patients. The overall relationship between VCFc and ESSm was moderate in patients with either DM or normal controls ($r = 0.639$, $r^2 = 0.435$, $P < 0.0001$). [Supplemental Table S6](#) demonstrates no

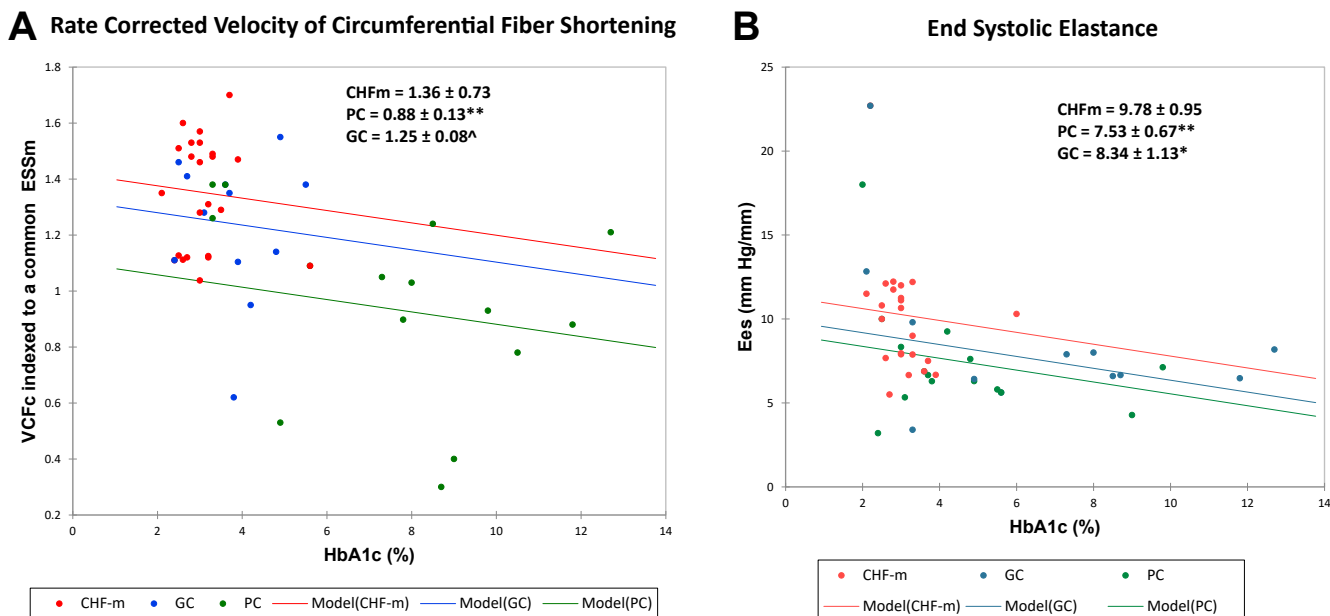


Figure 1. (A) Rate-corrected velocity of circumferential fiber shortening (VCFc) at end systolic meridional stress (ESSm) = 100 dynes/cm² is plotted against hemoglobin (Hb)A1c at baseline, with good glycemic control (GC) and poor glycemic control (PC). Analysis of covariance demonstrated lower values for poor glycemic control as compared to baseline left ventricular (LV) dysfunction and GC. (B) End systolic elastance (Ees) is plotted against HbA1c at baseline LV dysfunction, GC, and PC. Ees was lower for both GC and PC. CHFm, baseline LV dysfunction; DM, diabetes mellitus. **P* < 0.05 vs baseline LV dysfunction; ***P* < 0.01 vs baseline LV dysfunction; [∧]*P* < 0.05 PC vs GC.

differences in any demographic parameter at baseline. Similarly, Table 2 demonstrates no differences in any echocardiographic parameter at baseline in patients with no change in HbA1c, improvement in HbA1c, or increase in HbA1c at follow-up. Furthermore, the use of diabetic therapies did not change in any of the glycemic groups, nor did the incidence of hypertension, hyperlipidemia, coronary disease, or chronic kidney disease change over the course of follow-up in any glycemic control group (Supplemental Table S7). Table 2 and Figure 2, B-D summarize the above parameters in patients with DM with no change in HbA1c, reduced HbA1c, or increased HbA1c during follow-up. The relationship between VCFc and ESSm was moderate for no change in HbA1c ($r = 0.651$, $r^2 = 0.435$, $P < 0.0001$), fair for improvement in HbA1c ($r = 0.531$, $r^2 = 0.282$, $P < 0.001$), and good for increased HbA1c ($r = 0.746$, $r^2 = 0.557$, $P < 0.0001$). Systolic blood pressure declined, heart rate increased, and no change occurred in VCFc at a common ESSm between baseline and follow-up in DM patients with no change in HbA1c. Improvement in glycemic control (HbA1c: $9.4\% \pm 2.6\%$ to $9.0\% \pm 1.8\%$) was associated with reduced diastolic blood pressure, unchanged LV ejection fraction, and no change in VCFc at a common ESSm (Fig. 2C). In patients with reduced glycemic control (HbA1c: $9.8\% \pm 2.3\%$ to $12.8\% \pm 2.7\%$), LV systolic pressure was lower, and LV systolic performance (LV ejection fraction, fractional shortening, and VCFc) declined. Both left atrial and right atrial volume indexes were higher, and the RV area ejection fraction was lower. Figure 2D demonstrates that VCFc at a common ESSm was reduced.

Table 3 summarizes the incidence of myocardial infarction, HF, and all-cause mortality in patients without DM, and in DM patients with unchanged glycemic control, improved

glycemic control, and reduced glycemic control. Myocardial infarction incidence and all-cause mortality were similar in all groups and were low. HF incidence was increased only in DM patients with reduced glycemic control (Fig. 3, A and B).

Inter-observer and intra-observer variability

End diastolic dimension, end systolic dimension, peak systolic inferolateral wall thickness, LV end diastolic volume, and LV end systolic volume of 10 randomly chosen patients were reanalyzed 1 month following the initial analysis, by 2 readers, with random ordering. Intraclass correlation coefficients between observers were 0.91, 0.87, 0.85, 0.86, and 0.88 for end diastolic dimension, end systolic dimension, peak systolic inferolateral wall thickness, LV end diastolic volume, and LV end systolic volume. The mean differences of absolute values between observations were $4.2\% \pm 0.9\%$, $5.1\% \pm 1.7\%$, $5.9\% \pm 1.7\%$, $6.8\% \pm 2.1\%$, and $5.6\% \pm 1.8\%$. Intraclass correlation coefficients for repeated observations by the same observer were 0.92, 0.90, 0.88, 0.90, and 0.89 for the above parameters. The mean differences for the above parameters for the same observer were $3.8\% \pm 1.1\%$, $5.0\% \pm 1.4\%$, $4.8\% \pm 1.2\%$, $5.3\% \pm 1.9\%$, and $5.5\% \pm 1.9\%$.

Discussion

Our experimental data demonstrated a modulating effect of glycemic control on LV structure and function in that poor glycemic control (> 5% absolute increase in HbA1c) resulted in a reduction of LV mass along with reduced stroke volume despite preservation of LV ejection fraction. Evidence of diastolic dysfunction with reduced E/A, shortening of the diastolic filling period, and greater reliance on atrial filling was also noted. With poor glycemic control, compared with good

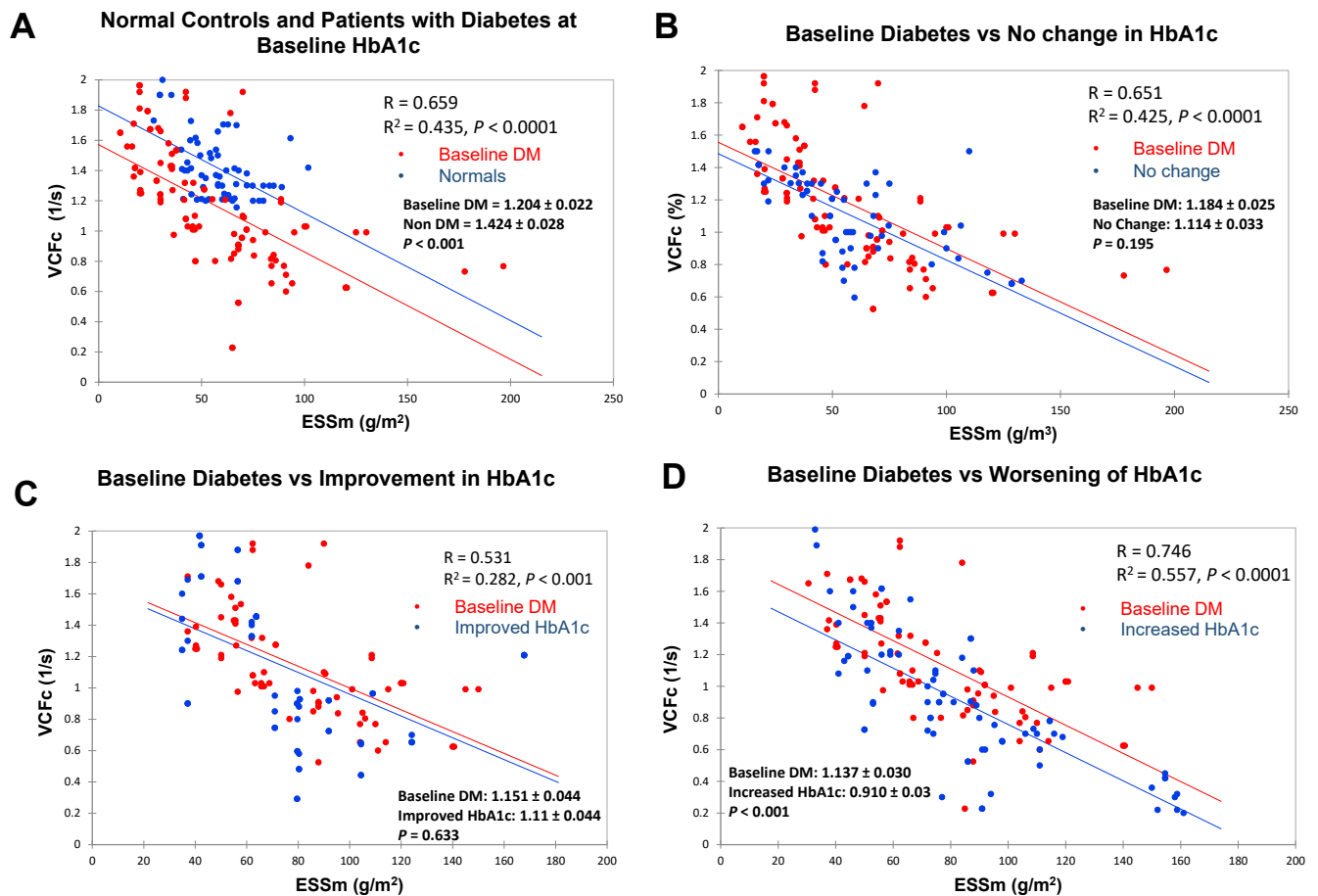


Figure 2. (A) Rate-corrected velocity of circumferential fiber shortening (VCFc) is plotted against end systolic meridional stress (ESSm) for normal control patients (age- and sex-matched) and patients with diabetes mellitus (DM). Using analysis of covariance, patients with DM had a lower VCFc. (B) VCFc-ESSm plot for patients with DM who had no change in their hemoglobin (Hb)A1c over the observation period. (C) VCFc-ESSm plot for patients with DM who had a reduction in their HbA1c over the observation period. (D) VCFc is plotted against ESSm for patients with DM who had an increase in their HbA1c over the observation period, demonstrating a reduction in VCFc.

control (absolute HbA1c difference of 4.17%), LV mass was reduced. Using methoxamine infusion to modulate afterload, end systolic elastance was reduced with both good and poor glycemic control, but the VCFc at a common ESSm was reduced with poor glycemic control but was similar to that with pre-DM and in canines with good glycemic control. These findings were corroborated by a clinical retrospective study of patients with DM followed in a diabetes clinic and age- and sex matched controls from a medicine clinic. A greater incidence of LV dysfunction and an increased incidence of HF events occurred in the group with DM, and specifically with poor glycemic control.

Previous literature

Although microvascular dysfunction has been improved by metabolic control of diabetes, reduction in cardiovascular events has been variable. For example, events were reduced by 41% and 35% in the Diabetes Control and Complications Trial and University Group Diabetes Program (UGDP) study,¹¹ respectively,^{11,12} and mortality was reduced in the Finnish study with insulin.¹³ However, all-cause mortality was noted to be increased with tighter control (HbA1c) in the VA

cooperative study (32% vs 20%).¹⁴ The effect of glycemic control on LV systolic and diastolic function and the incidence of HF has also been variable. Evidence of improved systolic function with better glycemic control was characterized by global longitudinal strain,^{18,19} but not LV ejection fraction at rest or with dobutamine.¹⁵⁻¹⁷ With better glycemic control, improvement in diastolic function parameters occurred in some studies^{19,20} but not in others.^{26,27} Finally, improved glycemic control did not affect HF outcomes¹⁵ in the VA cooperative study but not in others.^{32,33}

Previous studies that assessed the effect of DM on myocardial function did not assess the effect of preexisting LV dysfunction, and interventional trials did not stratify the effect of glycemic control on LV function based on LV ejection fraction. Although larger clinical trials have not provided evidence to support the possibility that glycemic control influences LV systolic or diastolic function, our clinical data indicate that poor glycemic control was associated with greater LV dysfunction, based on reduction of ejection fraction and a VCFc at a common ESSm. The difference in mean HbA1c level (3.3%) exceeded the differences in glycemic control trials reported in the literature.^{11,14,15,32} Furthermore, the average LV ejection fraction in our cohort was significantly lower than

Table 2. Demographic and echocardiographic parameters based on change in hemoglobin A1c (HbA1c)

Parameter	Baseline n = 61	No change HbA1c	Baseline n = 68	Decrease in HbA1c	Baseline n = 78	Increase in HbA1c
HbA1c, %	9.9 ± 2.1	10.1 ± 2.8	9.9 ± 2.6	9.0 ± 1.8 [†]	9.8 ± 2.3	12.8 ± 2.7 [‡]
Body mass index, g/m ²	29.1 ± 4.8	31.8 ± 5.1	28.6 ± 4.2	30.2 ± 3.6	29.8 ± 4.5	31.0 ± 4.8
Systolic BP, mm Hg	152 ± 20	141 ± 21*	147 ± 23	142 ± 21	150 ± 22	142 ± 15
Diastolic BP, mm Hg	82 ± 8	80 ± 10	85 ± 4	79 ± 10*	81 ± 10	81 ± 11
Heart rate, beats/min	71 ± 9	77 ± 13*	74 ± 10	72 ± 11	82 ± 18	801 ± 20
EDD, cm	4.35 ± 0.89	4.59 ± 0.74	4.41 ± 0.94	4.75 ± 1.04	4.48 ± 1.04	4.73 ± 0.95
ESD, cm	3.19 ± 0.71	3.29 ± 0.70	3.27 ± 0.97	3.46 ± 1.11	3.16 ± 0.82	3.46 ± 0.89 [†]
IL-D wall thickness, cm	1.13 ± 0.33	1.15 ± 0.37	1.14 ± 0.28	1.16 ± 0.27	1.13 ± 0.28	1.11 ± 0.33
RWT, %	0.52 ± 0.21	0.50 ± 0.29	0.52 ± 0.16	0.49 ± 0.20	0.50 ± 0.21	0.47 ± 0.23
LV EDVI, mL/m ²	54.7 ± 18.6	51.1 ± 19.9	57.7 ± 16.9	58.7 ± 18.2	56.9 ± 19.6	55.7 ± 22.3
LV ESVI, mL/m ²	28.4 ± 14.1	27.5 ± 12.7	28.1 ± 14.8	30.3 ± 16.9	29.8 ± 14.3	31.8 ± 12.2
LV mass index, g/m ²	82.6 ± 29.4	92.1 ± 27.8	87.9 ± 29.4	98.5 ± 31.2	87.7 ± 29.3	92.1 ± 28.6
LV EF, %	48.0 ± 4.2	45.8 ± 5.1	47.8 ± 5.1	48.3 ± 4.1	47.6 ± 3.9	42.9 ± 6.8*
LAVI, mL/m ²	34.5 ± 11.1	41.5 ± 16.1	37.7 ± 16.3	40.1 ± 18.1	36.9 ± 14.4	46.3 ± 16.4*
RAVI, mL/m ²	37.4 ± 16.1	41.1 ± 16.5	39.1 ± 27.3	43.0 ± 19.9	37.9 ± 16.6	43.3 ± 18.1*
RV area EF, %	40.5 ± 10.6	45.6 ± 17.4	39.7 ± 19.7	38.3 ± 15.7	41.5 ± 15.7	35.6 ± 13.4*
RV base, cm	2.98 ± 0.52	2.89 ± 0.85	2.91 ± 0.49	2.81 ± 1.11	2.87 ± 0.55	3.19 ± 0.91
TAPSE, cm	17.6 ± 4.8	17.2 ± 3.7	16.8 ± 5.4	16.3 ± 2.9	16.9 ± 6.1	16.7 ± 2.6
E, cm/s	88.9 ± 31.6	75.3 ± 31.8	80.5 ± 31.6	92.0 ± 43.2	88.4 ± 22.9	86.8 ± 27.6
E/A	1.14 ± 0.43	1.05 ± 0.50	1.18 ± 0.48	1.41 ± 0.61	1.11 ± 0.40	1.26 ± 0.62
VCFc, 1/s	1.18 ± 0.30	1.11 ± 0.38	1.15 ± 0.31	1.11 ± 0.29	1.11 ± 0.26	0.93 ± 0.22 [‡]
ESSm, dynes/cm ²	78.1 ± 27.2	74.1 ± 24.8	79.3 ± 29.5	79.1 ± 28.1	76.3 ± 29.7	82.9 ± 31.2

A, peak mitral atrial filling velocity; BP, blood pressure; E, peak mitral rapid filling velocity; EDD, end diastolic dimension; EDVI, end diastolic volume index; EF, ejection fraction; ESD, end systolic dimension; ESSm, end systolic meridional stress; ESVI, end systolic volume index; IL-D, inferolateral wall at end diastole; LAVI, left atrial volume index; LV, left ventricular; RAVI, right atrial volume index; RV, right ventricular; RWT, relative wall thickness; TAPSE, tricuspid annular systolic plane excursion; VCFc, rate-corrected circumferential fiber shortening.

* $P < 0.05$ vs baseline.

[†] $P < 0.01$.

[‡] $P < 0.001$ vs baseline.

that in previous glycemic control trials.^{11,14,15,32} Consequently, with the greater differences in glycemic control, the increased levels of HbA1c, and greater preexisting LV dysfunction, changes in LV performance with poorer glycemic control may be more easily demonstrated. With increasing LV dysfunction with poor glycemic control, the incident HF was noted to be increased, though ACM was not and was comparable to the rate seen in a recent comparative glycemic control trial.³⁴

Ample experimental data with induced DM demonstrate that abnormal LV chamber stiffness occurs with increased cytoplasmic calcium and altered myocardial composition occurs with increased triglycerides, cholesterol, and glycoproteins.^{22,23} Insulin therapy resulted in partial reversibility of both systolic and diastolic dysfunction, with near myocardial normalization of myosin calcium ATPase and collagen content that correlated with blood glucose levels.²³ All of the above experimental data are based on the expectation of

normal myocardium. Our canine data demonstrated that with poor glycemic control (HbA1c = 8.05% ± 3.0% vs baseline 2.99% ± 0.44%, $P < 0.001$), stroke volume was smaller with unchanged ejection fraction but with reduced LV wall thickness and mass. Such findings were not noted with good glycemic control. Our experimental data further strengthen the case for impaired systolic and diastolic dysfunction with DM, and specifically, with poor control with regard to systolic performance. Our differences in glycemic control between pre-DM LV dysfunction were > 5% and > 4%, compared to those for good glycemic control, which were far greater than what has been reported in the clinical literature.

Limitations

Experimental. The use of an insulin-deficient model may be more predictive of patients who have type I DM and may be less applicable to those with type 2 DM. The use of mice

Table 3. Clinical outcomes based on glycemic control

Outcome	Patients without DM (n = 60)	No change in HbA1c (n = 61)	Reduction in HbA1c (n = 68)	Increase in HbA1c (n = 78)
Incident myocardial infarction	1.7	8.2	7.3	7.7
Heart failure development	3.3	8.2	8.8	16.7*
All-cause mortality	1.7	3.3	4.4	5.1

Values are %.

DM, diabetes mellitus; HbA1c, hemoglobin A1c.

* $P < 0.05$ vs patients without DM.

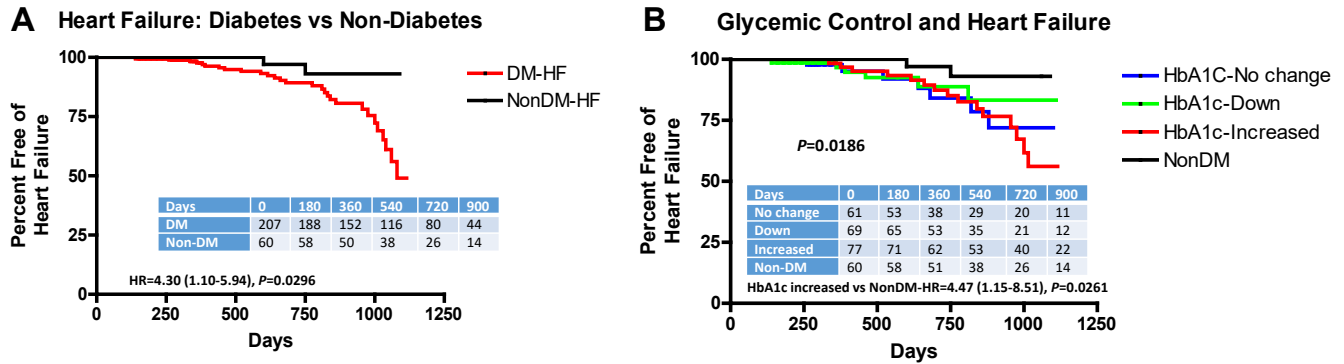


Figure 3. (A) Kaplan-Meier curves for the development of heart failure (HF) in patients with diabetes mellitus (DM) vs without DM (age- and sex-matched). Patients with DM had an increased risk of HF. **(B)** Kaplan-Meier curves for the development of HF in patients with DM based on glycemic control. Patients with increases in hemoglobin (Hb)A1c had an increased risk of HF. HR, hazard ratio.

models reflecting type 2 DM (ob/ob, db/db, NONcNZO10, TALLYHO) or rat models (ZDF Zucker rat or GK rat) would have been more relevant to the clinical study but are also not models of LV dysfunction, which would not have addressed the study question: What is the effect of glycemic control on LV function in the dysfunctional left ventricle? We chose the canine model because of the ability to induce both LV dysfunction and subsequent DM. No available mice models can accomplish both goals. Furthermore, imaging LV performances indices in mice and rodents is more difficult than it is in canines. Second, the finding in poor glycemic control of reduced LV mass in canines and preserved ejection fraction has not been noted in patients with either type 1 or type 2 DM or is a recognized HF phenotype. We suspect that the catabolic effect of poor glycemic control resulted in a reduction of LV mass. Canines did lose weight over the 3-month period (median = 2.1 kg, with interquartile range of 0.5 to 2.7 kg). No data in poorly controlled type 1 DM have revealed reduction in LV mass to date. Third, the length of observation following DM induction was no greater than 6 months, as compared to years following onset of DM in patients. Fourth, the question arises of whether glycemic control or the dose of insulin is responsible for our results. Based on study design, we cannot answer that question. Fifth, we did not alter glycemic control within a given canine, which might provide further information regarding glycemic control and LV function. Sixth, the effect of alloxan hydrochloride on myocardial function could not be separated from the effect of glycemic control. Finally, the baseline LV dysfunction could have been progressive in the groups with DM, and not stable as noted in the control group.

Clinical. This small retrospective cohort study was conducted with patients with varying glycemic control with similar baseline parameters of LV size, structure, and function. Propensity matching was not performed due to the low numbers of patients in each group. No modulation of glycemic control in the individual patient was conducted. Second, changes in LV size and function over time may be unrelated to glycemic control and may be due to adverse events that were not discovered. The reduction in LV ejection fraction with poor glycemic control may be related to other causes not accounted

for in this study. Third, this study was not powered over a > 2-year period to assess clinical outcomes. The finding of increased HF in those with poor glycemic control should be considered exploratory and requires further evaluation. Also, the reliability of follow-up may be questionable, as patients may have left the area or moved to different healthcare systems. We were able to query several of the healthcare systems to identify outcomes in 7 patients. However, other outcomes may have occurred. Fourth, the entire clinical cohort was composed of patients with type 2 diabetes, whereas the experimental study was an insulin-deficient model. Finally, important unaccounted-for differences that were not discernable from the data may be present among groups.

Clinical implications

In this study, we asked the question of whether glycemic control influences LV performance with preexisting LV dysfunction. Using a model of chronic LV dysfunction with subsequently induced DM, we then assessed glycemic control to assess the influence on LV systolic and diastolic function. Clinical relevance was assessed in a retrospective cohort of patients with DM who demonstrated either stable control, improved glycemic control, or reduced glycemic control over a median period of 692 days (415-894 days). Both the experimental (insulin-deficient) and clinical data (type 2 DM) demonstrate that poor glycemic control is associated with worsening LV systolic performance. Clinically, the LV ejection fraction was lower, and the plot of VCFc to ESSm demonstrated a reduced VCFc at a common ESSm. Additionally, poor glycemic control resulted in an increased incidence of HF readmission events. This effect was corroborated further experimentally, using afterload stress induced by methoxamine infusion. One might hypothesize that patients with reduced VCFc at a common ESSm may have limited reserve to afterload stress, which may be related to the increased incidence of HF episodes noted in patients with poor glycemic control over 1-2 years of follow-up. This study might suggest that poor glycemic control affects cardiovascular outcomes, but it was not powered to do so. Most trials assessing glycemic control compared intensive control with HbA1c levels in the 7% range to standard glycemic control in the 8% range.^{12,15,16,19,34} In our study, standard glycemic

control was in the 9%-10% range, and poor glycemic control was much higher, in the 12%-13% range, with differences of 3%-5% as compared to 0.5%-1.5% in clinical trials. Our results might reflect the level and change in HbA1c level, as we did confirm that little change in LV systolic performance and clinical outcomes occurred with improved or no change in HbA1c level, as previously noted.^{12,15,16,19,34}

One might ask how we can reconcile the similar effect of glycemic control on an experimental type I DM and a clinical type II DM. The mechanisms by which glycemic control affects LV performance may differ for type I and II DM. For example, poorly controlled type I DM with weight loss may result in a catabolic effect on the patient or experimental model, resulting in change in LV systolic function predominantly with stress, especially afterload stress. In patients with type II DM, poor glycemic control, hypertension, increased atherosclerotic disease leading to myocardial infarction, and DM cardiomyopathy may result in reduced systolic performance. We suggest that insulin deficiency and type 2 diabetes have similar influences along with glycemic control on LV performance. Furthermore, glycemic control may also affect other risk factors leading to atherosclerotic events or greater inflammation that influences LV systolic function and the response to stress.

Conclusion

In an experimental model of LV dysfunction and insulin-deficient DM, poor glycemic control had an adverse effect on LV systolic function. Similarly, in patients with type 2 diabetes, poor glycemic control was associated with worse LV systolic performance, which was manifested at rest, and with indexing to afterload stress. Furthermore, HF admissions were increased over 2-3 years in patients with poor glycemic control.

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Ethics Statement

The canines used in this study were maintained in accordance with the American Heart Association guidelines on research animal use and were approved by the Wayne State University Animal Investigation Committee.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective case report using de-identified data; therefore the institutional review board did not require consent from the patient. This retrospective study received expedited approval by the Wayne State University Human Investigation Committee and did not require consent as all patient information was de-identified.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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