Evaluation of cardiac involvement in asymptomatic patients with type 1 diabetes mellitus

Máté Hajdu MD

Supervisor: Prof. Réka Faludi MD, PhD, DSc

Clinical medical sciences doctoral school, The clinical and molecular research of the new mechanisms, diagnostics and therapy of cardiovascular diseases

Head of the Doctoral Program: Prof. István Szokodi MD, PhD, DSc

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1. Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic disorders affecting young adults. It is associated with serious microvascular and macrovascular complications resulting in at least tenfold increase in cardiovascular diseases as compared with the age matched healthy population. Besides, heart failure develops 10-15 years earlier in T1DM patients than in the general population.

Although in young asymptomatic T1DM patients the standard echocardiographic parameters reflect normal cardiac size and function, tissue Doppler imaging (TDI) and speckle tracking echocardiography seem to be useful techniques for assessing subclinical myocardial involvement in this population. Left ventricular (LV) systolic dysfunction was proved by speckle tracking-derived global longitudinal strain (GLS) data, both in T1DM children and adults, whereas TDI measurements suggested impaired LV diastolic function. Nevertheless, conflicting results were also reported. Less is known about right ventricular (RV) function, or atrial performance in this disease.

Duration of diabetes and quality of the glycemic control have been reported as critical factors contributing toward development of cardiovascular complications. Data about their effect on myocardial mechanics, however, are scarce and controversial.

Cardiac autonomic neuropathy (CAN) is a consequence of the diabetes and is defined as the impairment of the cardiovascular autonomic control. It is one of the most neglected long-term complications of diabetes, remaining subclinical until late stages of the disease. Diabetic patients with CAN have a 3.4 times higher risk of mortality than patients without CAN. It has been proved that, in T1DM, major risk factors for CAN are age, duration of diabetes, glycemic control, systemic hypertension, dyslipidemia, obesity, smoking habits, and the existence of diabetic microvascular complications (nephropathy or microalbuminuria and retinopathy).

Evaluation of heart rate variability (HRV) detects the early subclinical alterations of the autonomic nervous system. Thus, impaired HRV is the earliest subclinical marker of CAN in asymptomatic patients with T1DM. Reduced HRV has already been reported in T1DM patients. In addition, it has been proved that major risk factors for CAN are significant determinants of the reduced HRV in this disease. These data, however, are limited and controversial.

2. Objectives

Our work aimed to provide a comprehensive analysis of the myocardial size and function using standard and novel echocardiographic techniques and to investigate the potential associations between disease duration, glycemic control, and the echocardiographic markers of the myocardial mechanics in asymptomatic T1DM patients. Potential correlations between HRV indices and the established risk factors for CAN and cardiovascular diseases were also investigated.

3. Materials and methods

3.1. Study population

70 T1DM patients (38±12 years, 46 female) and 30 healthy volunteers were investigated. The exclusion criteria were as follows: atrial fibrillation, known diseases of the coronary (Coronary artery disease [CAD]) or peripheral arteries, clinical diabetic nephropathy [macroalbuminuria (≥300 mg/day) and/or eGFR (estimated glomerular filtration rate) <60 ml/min/1.73 m2] or retinopathy, impaired left ventricular systolic function (ejection fraction <55%), significant valvular heart disease, echocardiographic suspicion of primary cardiomyopathies, abnormal treadmill stress test result indicative of CAD.

3.2. Echocardiography

Besides the conventional and tissue Doppler measurements, left ventricular global longitudinal (GLS) and circumferential (GCS) strain as well as left and right atrial strain parameters were measured with 2D speckle tracking technique. LV hypertrophy, elevated relative wall thickness and enlarged LV chamber size were considered as signs of the hypertensive heart disease.

3.3. Assessment of HRV

Following a 15-min orthostatic adaptation period, beat-to-beat heart rate was recorded for 30 min. The less noisy 5-min segment of the recording was analyzed by Bittium Cardiac Navigator HRV analysis software. Time domain (SDNN – standard deviation of the normal-normal intervals, rMSSD – root mean square differences of successive normal-normal intervals), frequency domain [very low-frequency component or VLF (<0.04 Hz), low-frequency component or LF (0.04 Hz-0.15 Hz), and high-frequency component or HF (0.15 Hz-0.4 Hz)], and nonlinear indices were calculated. In addition, the Total Power of the spectrum and the ratio of low to high frequency component (LF/HF) were calculated.

3.4. Statistical analysis

The frequencies of categorical variables were compared using chi-square test or Fisher's exact test. The normality of distribution of continuous variables was tested by Shapiro-Wilk test. Means of two continuous normally distributed variables were compared by independent samples Student's t-test. Mann-Whitney U test was used to compare means of two variables not normally distributed. Echocardiographic variables that correlate with current HbA_{1c} or disease duration were determined using bivariate Pearson correlation. In a second step, multiple linear regression analysis (enter method) was used and adjusting for age and hypertension.

Patients were subgrouped according to the median HbA_{1c} level and the presence/absence of the hypertensive heart disease. Four groups were created according to the number of cardiovascular risk factors: normal volunteers (NORM); patients below the median HbA_{1c} and without hypertensive heart disease (T1DM-LOW); patients above the median HbA_{1c} but without hypertensive heart disease (T1DM-MED); patients above the median HbA_{1c} and with hypertensive heart disease (T1DM-HIGH). Comparisons of normally distributed data among multiple groups were performed using one-way ANOVA with LSD post hoc test. Kruskal-Wallis test with Dunn's multiple comparison test was used to compare means of multiple groups of variables not normally distributed.

Since HRV parameters did not display normal distribution, logarithmic transformation (ln) was implemented. Univariate predictors of the HRV parameters were determined by linear regression analysis. In a second step, multiple stepwise linear regression analysis was used. Variables with $p<0.1$ on univariate analysis were incorporated into the multiple models.

4. Results

Median HbA_{1c} level was 7.4 (1.8)%. Echocardiographic signs of hypertensive heart disease was found in 27 patients. Detailed clinical data of the T1DM patients and the healthy volunteers are reported in Table 1, echocardiogaphic parameters are reported in Table 2. Averaged mitral annular S and e′ values were significantly lower, whereas LV E/e′ ratio was significantly higher in T1DM patients, but typically within the normal range. In the right heart, tricuspid S was significantly reduced in the T1DM population. HRV parameters of the T1DM patients and their comparison with those in healthy persons are displayed in Figure 1. Regarding LF/HF ratio, no differences were found between the two populations. Further time domain, frequency-domain, and nonlinear parameters of the HRV, however, were significantly lower in T1DM patients.

Table 1. *Clinical data of the T1DM population and comparison with healthy subjects. Statistically significant p-values (p<0.05) are formatted in bold. *Median (IQR).*

Clinical characteristics	Healthy volunteers (n = 30)	T1DM patients (n = 70)	p
Age (years)	34 (14.25)*	38 (20)*	0.709
Female gender n (%)	17 (57)	46 (66)	0.39
Body surface area (m^2)	1.88 ± 0.2	1.84 ± 0.2	0.408
Body mass index (kg/m^2)	24.8 ± 4.2	23.5 ± 3.6	0.152
Resting heart rate (beat/min)	68.9±7.5	73.7 ± 12.0	**0.019**
Office systolic blood pressure (mmHg)	134.0 ± 14.7	135.8 ± 18.1	0.63
Office diastolic blood pressure (mmHg)	78.7 ± 8.8	79.8 ± 9.8	0.538
Disease duration (years)		21.0 ± 10.3	
Daily dose of insulin (U/kg)		0.64 ± 0.22	
On insulin pump therapy n (%)		47 (67)	
Polyneuropathy n (%)		21 (30)	
Smoking			
Never n (%)	22 (73.3)	43 (61.4)	0.505
Previously n (%)	3 (10)	13 (18.6)	
Currently n (%)	5 (16.7)	14 (20)	

Table 1. – *continue*

Laboratory data	Healthy volunteers (n = 30)	T1DM patients (n = 70)	p
Current HbA_{1c} (%)		7.6 ± 1.3	
Fasting glucose (mmol/l)		8.4 ± 4.6	
Fructosamine (µmol/l)		387.7 ± 65.3	
Creatinine (µmol/l)		73.6 ± 11.7	
eGFR (ml/min/1.73 m^2)		95.9 ± 19.5	
Hemoglobin (g/l)		138.7 ± 15.2	
Total cholesterol (mmol/l)		4.7 ± 1.2	
Triglyceride (mmol/l)		1.0 ± 0.6	
Erythrocyte sedimentation rate (mm/h)		7.9 ± 7.4	
C-reactive protein (mg/l)		3.1 ± 4.1	
Medication			
ACE inhibitors/ARBs n (%)		17 (24)	
Calcium channel blocker n (%)		4 (6)	
Beta receptor antagonists n (%)		12 (17)	

Table 2. *Echocardiographic data of the T1DM population and comparison with healthy subjects. Statistically significant p-values ($p<0.05$) are formatted in bold.*

Echocardiographic characteristics (LV and LA)	Healthy volunteers (n = 30)	T1DM patients (n = 70)	p
LV EF (%)	61.1 ± 4.0	62.8 ± 3.2	**0.033**
LV GLS (%)	-19.9 ± 2.4	-19.0 ± 1.9	0.054
LV GCS (%)	-25.9 ± 3.6	-28.1 ± 4.7	**0.023**
LVM index (g/m^2)	80.2 ± 14.4	78.4 ± 16.4	0.611
Relative wall thickness	0.37 (0.04)	0.40 (0.06)	**0.003**
Enddiastolic diameter/height (cm/m)	2.7 (0.3)	2.7 (0.3)	0.117
Mitral E (cm/s)	81.0 ± 11.3	82.5 ± 14.5	0.617
Mitral A (cm/s)	53.8 (13.2)	64.0 (23.4)	**0.008**
Mitral E/A	1.5 ± 0.3	1.4 ± 0.5	0.123

Table 2. – *continue*

Echocardiographic characteristics (LV and LA)	Healthy volunteers (n = 30)	T1DM patients (n = 70)	p
Averaged mitral annular S (cm/s)	10.8 ± 1.4	10.0 ± 1.6	**0.015**
Averaged mitral annular e′ (cm/s)	12.9 ± 1.4	11.1 ± 2.4	**< 0.001**
Averaged mitral annular a′ (cm/s)	9.2 ± 1.9	9.5 ± 1.7	0.525
Mitrali E/e′	6.3 ± 0.9	7.8 ± 2.0	**< 0.001**
LA Vmax index (ml/m^2)	24.6 ± 6.2	25.9 ± 7.8	0.421
LA Vmin index (ml/m^2)	8.4 (3.3)	8.2 (4.3)	0.513
LA Vp index (ml/m^2)	13.6 (6.1)	15.0 (6.5)	0.204
LA reservoir strain (%)	35.0 ± 9.5	32.9 ± 7.9	0.272
LA contractile strain (%)	13.8 ± 4.0	13.8 ± 3.9	0.985
LA conduit strain (%)	21.1 ± 7.5	19.1 ± 7.0	0.2
Echocardiographic characteristics (RV and RA)			
RVFAC (%)	48.2 ± 8.5	51.2 ± 7.7	0.107
TAPSE (mm)	22.7 ± 2.9	21.7 ± 2.7	0.114
RV wall thickness (mm)	4.5 (1.0)	4.0 (0.5)	0.915
RV basal diameter index (mm/m^2)	15.0 ± 3.1	15.2 ± 1.6	0.586
PASP (mmHg)	22.9 ± 3.9	23.8 ± 3.8	0.582
Tricuspid E (cm/s)	61.3 ± 10.3	60.8 ± 11.0	0.847
Tricuspid A (cm/s)	40.4 ± 7.1	40.8 ± 9.3	0.836
Tricuspid E/A	1.5 ± 0.3	1.6 ± 0.4	0.138
Tricuspid annular S (cm/s)	13.7 ± 1.7	12.8 ± 2.0	**0.035**
Tricuspid annular e′ (cm/s)	12.6 ± 2.7	11.7 ± 2.8	0.199
Trikuszpidális annular a′ (cm/s)	11.2 ± 2.7	11.4 ± 3.7	0.747
Tricuspid E/e′	5.1 (1.2)	5.2 (1.6)	0.061
RA Vmax index (ml/m^2)	21.1 ± 7.4	19.5 ± 5.8	0.298
RA Vmin index (ml/m^2)	7.8 ± 3.8	7.6 ± 3.2	0.718
RA Vp index (ml/m^2)	12.8 ± 5.0	12.7 ± 4.5	0.918
RA reservoir strain (%)	50.4 ± 13.9	47.8 ± 12.0	0.356
RA contractile strain (%)	20.5 ± 7.0	20.6 ± 5.7	0.893
RA conduit strain (%)	29.9 ± 11.4	27.2 ± 10.3	0.243

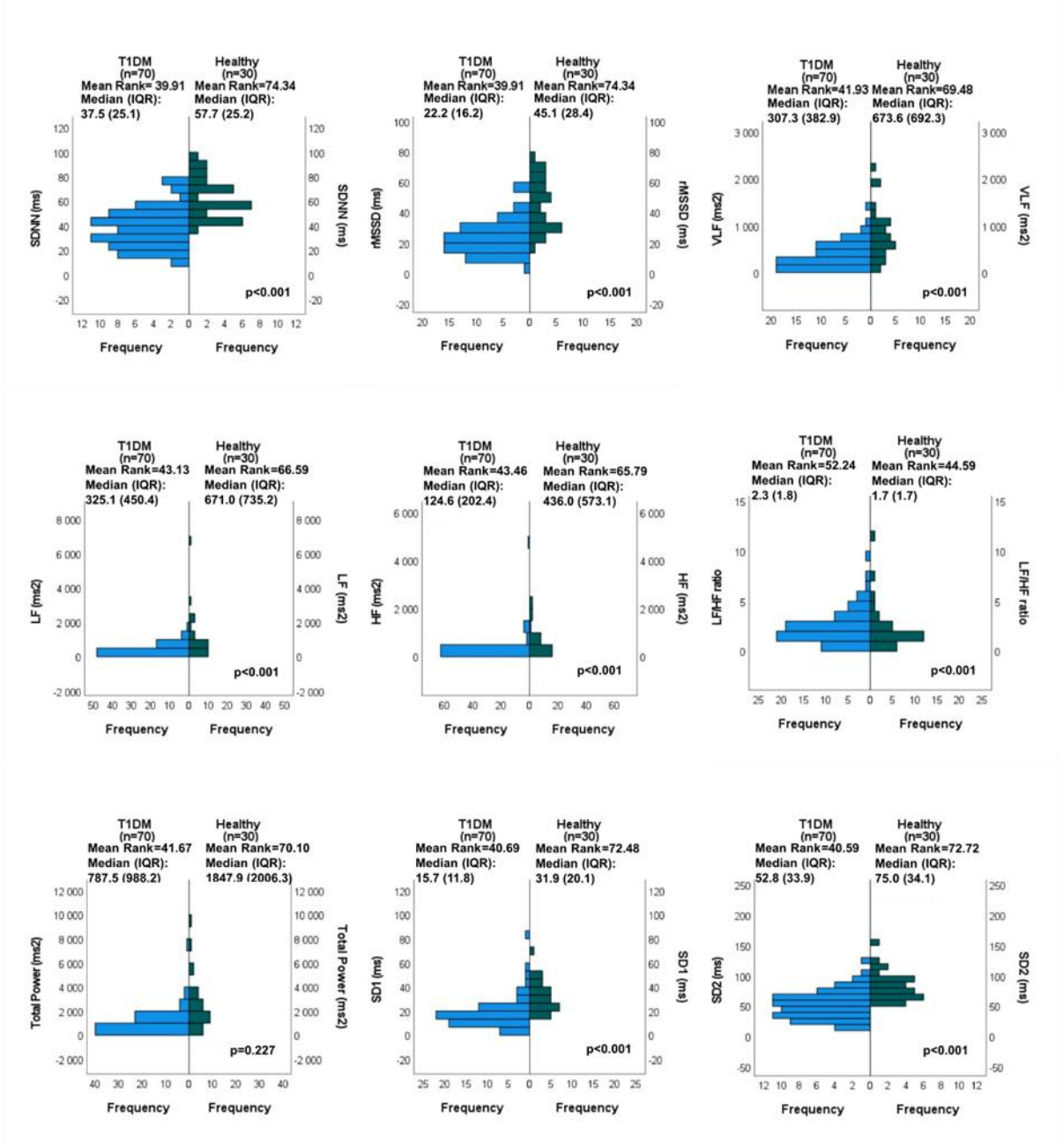

Figure 1. *HRV parameters in the T1DM population and comparison with healthy subjects: Independent samples Mann-Whitney U test results.*

Both HbA_{1c} and disease duration showed significant correlations with various echocardiographic parameters (Table 3). Even when added age and hypertension to the model, current HbA_{1c} level remained independent predictor of LV GLS, LV GCS, mitral and tricuspid e′ and LA and RA conduit strain in multiple linear regression models (Table 4) whereas disease duration lost its significance in similar multiple regression analyses. Partial regression plots demonstrate that HbA_{1c} level correlates significantly with various echocardiographic variables even in age and hypertension adjusted analyses (Figure 2).

In patients with a combination of $HbA_{1c} \leq 7.4\%$ and no hypertension, echocardiographic findings did not differ from those in healthy volunteers. Patients with $HbA_{1c} > 7.4\%$ and no hypertension and especially patients with coexisting hypertension and $HbA_{1c} > 7.4\%$, exhibited significantly impaired myocardial mechanics (Figure 3). Comparison of echocardiographic variables among the study subgroups are reported in Table 5.

Table 3. *Significant univariate predictors of the echocardiographic variables in the T1DM population: correlations of current HbA1c and disease duration. Statistically significant p-values (p<0.05) are formatted in bold.*

	Correlations of current HbA_{1c} (%)		Correlations of disease duration (years)	
	r	p	r	p
Age (years)	0.186	0.144	0.469	**<0.001**
LV GLS (%)	0.385	**0.002**	0.076	0.552
LV GCS (%)	-0.531	**<0.001**	-0.127	0.300
Mitral A (cm/s)	0.288	**0.024**	0.087	0.486
Averaged mitral annular S (cm/s)	-0.221	0.082	-0.304	**0.012**
Averaged mitral annular e' (cm/s)	-0.390	**0.002**	-0.293	**0.016**
Mitral E/e'	0.329	**0.010**	0.304	**0.014**
LA reservoir strain (%)	-0.256	**0.045**	-0.264	**0.031**
LA conduit strain (%)	-0.353	**0.005**	-0.312	**0.010**
Tricuspid annular e' (cm/s)	-0.330	**0.008**	-0.227	0.066
RA conduit strain (%)	-0.326	**0.010**	-0.212	0.089

Table 4. *Predictors of the echocardiographic variables in T1DM population: multivariate regression analyses. Unstandardized (B) and standardized (β) regression coefficients. Statistically significant p-values (p<0.05) are formatted in bold.*

Variables	B	β	p	F	adj. R^2	p
LV GLS (%)				3.654	0.119	**0.018**
Age (years)	-0.002	-0.014	0.910			
Hypertension (0/1)	-0.486	-0.124	0.318			
HbA_{1c} (%)	0.568	0.399	**0.002**			
LV GCS (%)				22.502	0.268	**<0.001**
Age (years)	0.025	0.064	0.568			
Hypertension (0/1)	-1.260	-0.138	0.216			
HbA_{1c} (%)	-1.740	-0.523	**<0.001**			
Averaged mitral annular e' (cm/s)				22.502	0.514	**<0.001**
Age (years)	-0.130	-0.639	**<0.001**			
Hypertension (0/1)	-0.148	-0.032	0.729			
HbA_{1c} (%)	-0.403	-0.227	**0.018**			
LA conduit strain (%)				23.224	0.522	**<0.001**
Age (years)	-0.392	-0.664	**<0.001**			
Hypertension (0/1)	0.308	0.022	0.805			
HbA_{1c} (%)	-1.115	221	**0.018**			
Tricuspid annular e' (cm/s)				9.035	0.280	**<0.001**
Age (years)	-0.112	-0.448	**<0.001**			
Hypertension (0/1)	-0.504	-0.086	0.431			
HbA_{1c} (%)	-0.496	-0.234	**0.039**			
RA conduit strain (%)				9.003	0.286	**<0.001**
Age (years)	-0.404	-0.444	**<0.001**			
Hypertension (0/1)	-2.869	-0.132	0.233			
HbA_{1c} (%)	-1.765	-0.226	**0.047**			

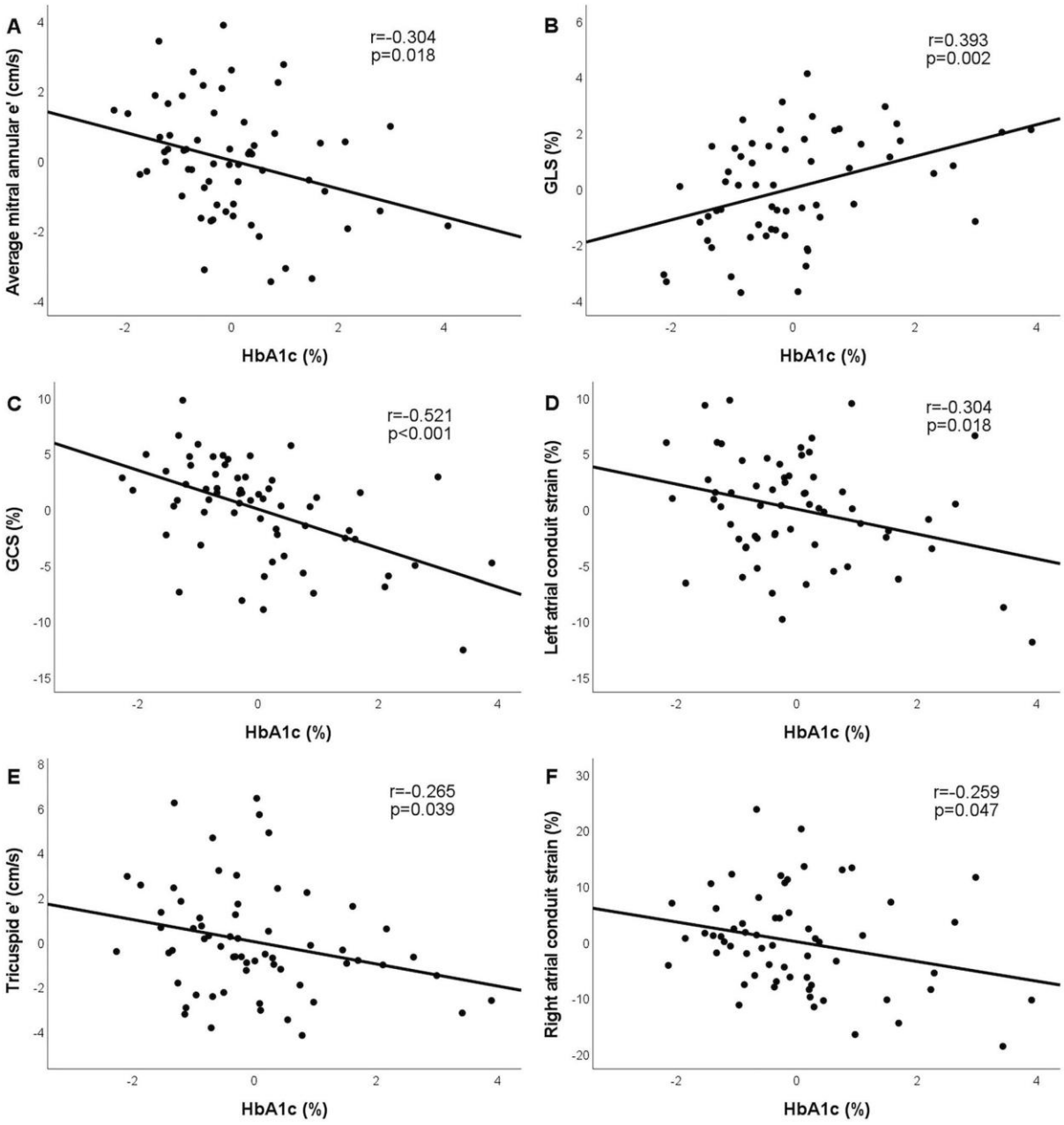

Figure 2. *Partial regression plots demonstrate that in age and hypertension adjusted analyses HbA_{1c} (%) correlates with average mitral annular e' (A); LV GLS (B); LV GCS (C); LA conduit strain (D); tricuspid annular e' (E) and with RA conduit strain (F). Partial correlation coefficients are reported.*

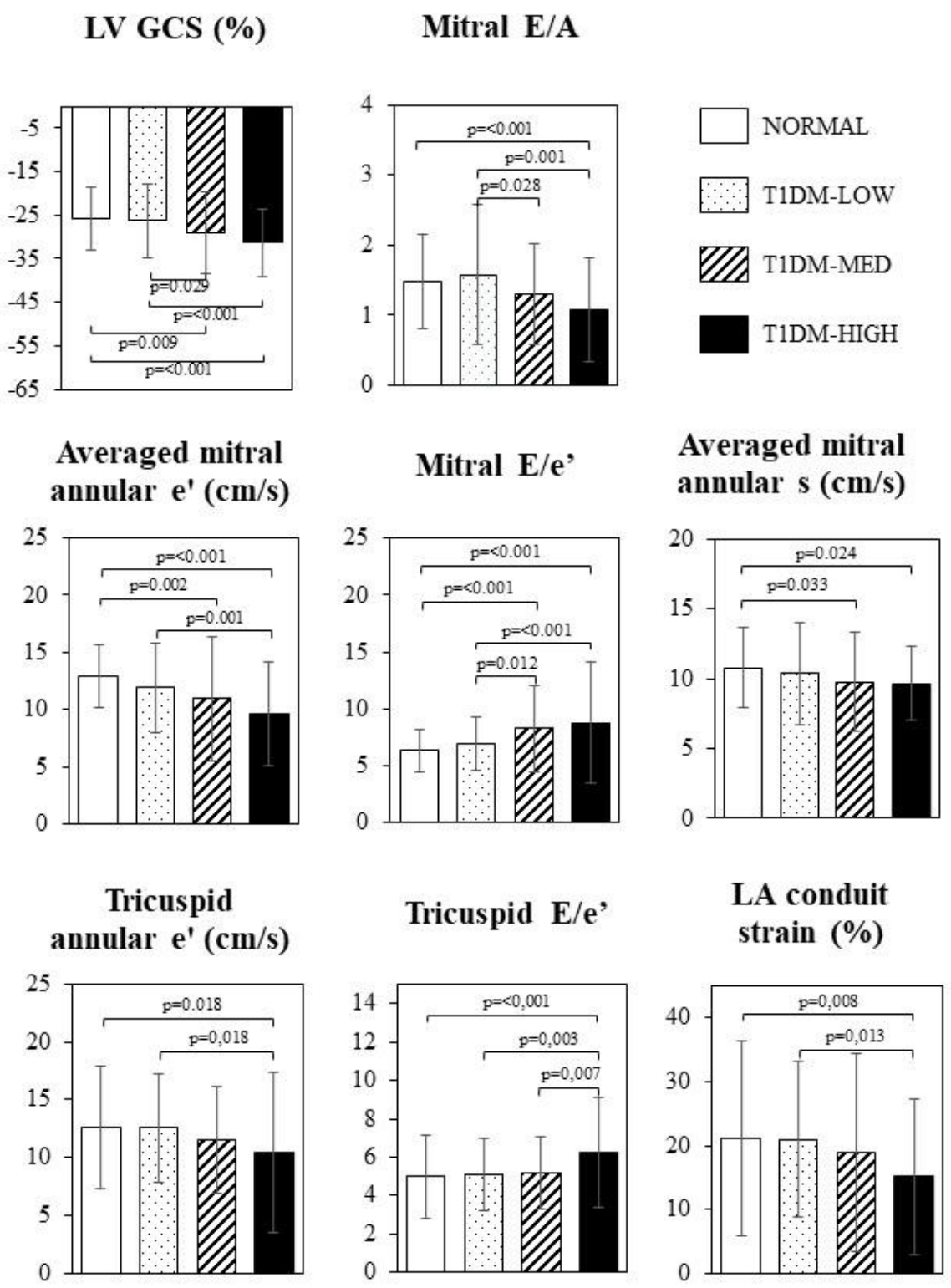

Figure 3. *Comparison of echocardiographic variables among healthy subjects and T1DM subgroups.*

Table 5. *Comparison of echocardiographic variables among healthy subjects and T1DM subgroups. Statistically significant p-values (p < 0.05) are formatted in bold. *p < 0.05 vs. NORM; #p < 0.01 vs. NORM; †p < 0.05 vs. T1DM-LOW; §p < 0.01 vs. T1DM-LOW; ‖p < 0.05 vs. T1DM-MED; $p < 0.01 vs. T1DM-MED*

	Healthy volunteers (NORM) (n=30)	**T1DM-LOW** *HbA_{1c} ≤7.4% and NO hypertension* **(n=24)**	**T1DM-MED** *HbA_{1c} >7.4% and NO hypertension* **(n=19)**	**T1DM-HIGH** *HbA_{1c} >7.4% AND hypertension* **(n=16)**	**p**
Age (years)	34 (14.25)	32.5 (17.25)	43 (24)	40.5 (13.75)*†	0.097
Female gender n (%)	17 (57)	16 (67)	12 (63)	11 (69)	0.830
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.668
Body mass index (kg/m^2)	23.5 ± 3.6	24.7 ± 3.0	23.9 ± 3.9	27.2 ± 6.1#‖	**0.029**
Systolic blood pressure (mmHg)	134.6 ± 14.6	132.5 ± 17.9	129.6 ± 13.4	142.1 ± 15.2‖	0.114
Diastolic blood pressure (mmHg)	79.1 ± 8.6	79.3 ± 8.1	77.2 ± 9.8	81.5 ± 10.7	0.582
HbA_{1c} (%)		6.6 ± 0.6$	8.7 ± 1.2§	8.6 ± 0.8§	**<0.001**
On insulin pump therapy n (%)		19(79)	12 (63)	9 (56)	0.275
LV EF (%)	61.1 ± 4.0	62.5 ± 3.2	61.7 ± 3.4	63.9 ± 2.8*	0.088
LV GLS (%)	-19.9 ± 2.5	-19.0 ± 1.7	-18.7 ± 2.0	-18.4 ± 2.0*	0.126
LV GCS (%)	-25.9 ± 3.6$	-26.3 ± 4.2‖	-29.1 ± 4.7#†	-31.3 ± 3.9#§	**<0.001**
LVM index (g/m^2)	80.2 ± 14.4†	71.2 ± 10.3*	75.8 ± 13.0	87.5 ± 20.1§‖	**0.005**
Relative wall thickness	0.38 (0.4)	0.38 (0.4)	0.39 (0.4)	0.45 (0.7)#§$	**<0.001**
Enddiastolic diameter/ height (cm/m)	2.7 (0.3)	2.7 (0.2)	2.7 (0.3)	2.6 (0.4)	0.157
Mitral E (cm/s)	81.0 ± 11.3	82.1 ± 14.4	87.1 ± 17.1	79.0 ± 11.9	0.332
Mitral A (cm/s)	53.8 (13.2)$	53.0 (26.1)$	66.9 (19.0)#§	74.4 (22.8)#§	**<0.001**
Mitral E/A	1.5 ± 0.3	1.6 ± 0.5$	1.3 ± 0.4†	1.1 ± 0.4#§	**<0.001**
Averaged mitral annular S (cm/s)	10.8 ± 1.4‖	10.4 ± 1.8	9.8 ± 1.8*	9.7 ± 1.3*	0.067
Averaged mitral annular e' (cm/s)	12.9 ± 1.4$	11.9 ± 2.0	11.0 ± 2.7#	9.7 ± 2.3#§	**<0.001**
Averaged mitral annular a' (cm/s)	9.2 ± 1.9	9.1 ± 1.9	9.4 ± 1.2	10.1 ± 1.6	0.378
Mitral E/e'	6.3 ± 0.9$	7.0 ± 1.2‖	8.3 ± 1.9#†	8.8 ± 2.7#§	**<0.001**
LA Vmax index (ml/m^2)	24.6 ± 6.2	25.8 ± 8.2	27.5 ± 8.2	25.8 ± 8.0	0.644

Table 5. – *continue*

	Healthy volunteers (NORM) (n=30)	T1DM-LOW *HbA1c ≤7.4% and NO hypertension* (n=24)	T1DM-MED *HbA1c >7.4% and NO hypertension* (n=19)	T1DM-HIGH *HbA1c >7.4% AND hypertension* (n=16)	p
LA Vmin index (ml/m²)	8.4 (3.3)	8.1 (4.7)	8.8 (4.8)	8.0 (3.0)	0.560
LA Vp index (ml/m²)	13.6 (6.1)	15.0 (6.1)	16.7 (7.4)	15.0 (7.2)	0.453
LA reservoir strain (%)	35.0 ± 9.5	33.9 ± 7.5	32.6 ± 9.5	30.9 ± 5.5	0.468
LA contractile strain (%)	13.8 ± 4.0	12.9 ± 4.0	13.7 ± 3.8	15.8 ± 3.6†	0.156
LA conduit strain (%)	21.1 ± 7.5	21.0 ± 6.1	18.9 ± 7.8	15.1 ± 6.1#†	**0.039**
RVFAC (%)	48.2 ± 8.5	50.6 ± 9.8	51.8 ± 6.9	51.7 ± 6.6	0.449
TAPSE (mm)	22.7 ± 2.9†	21.0 ± 2.0*	22.6 ± 3.0	21.4 ± 2.6	0.075
RV wall thickness (mm)	4.5 (0.8)	4.5 (0.5)	4.0 (0.8)	4.8 (2.0)	**0.242**
RV basal diameter index (mm/m²)	15.0 ± 3.1	15.1 ± 1.5	15.8 ± 1.3	14.4 ± 1.4	0.284
PASP (mmHg)	22.9 ± 3.9	24.2 ± 4.3	25.7 ± 4.6	21.5 ± 2.4	0.360
Tricuspid E (cm/s)	61.3 ± 10.3	62.6 ± 9.4	59.5 ± 13.7	59.3 ± 11.0	0.742
Tricuspid A (cm/s)	40.4 ± 7.1	37.8 ± 7.8	42.0 ± 9.4	45.3 ± 10.1§	0.060
Tricuspid E/A	1.5 ± 0.3	1.7 ± 0.4‖	1.5 ± 0.4†	1.4 ± 0.4§	0.050
Tricuspid annular S (cm/s)	13.7 ± 1.7	12.9 ± 1.8	13.3 ± 2.2	12.6 ± 2.2	0.255
Tricuspid annular e' (cm/s)	12.6 ± 2.7	12.6 ± 2.3	11.5 ± 2.3	10.4 ± 3.5*†	0.057
Tricuspid annular a' (cm/s)	11.2 ± 2.7	10.2 ± 3.3$	13.1 ± 4.8§	12.1 ± 2.5	0.057
Tricuspid E/e'	5.0 (1.2)	5.1 (1.4)	5.1 (1.4)	6.2 (1.8)#§$	**0.005**
RA Vmax index (ml/m²)	21.1 ± 7.4	20.0 ± 5.8	19.9 ± 6.9	18.0 ± 5.1	0.563
RA Vmin index (ml/m²)	7.8 ± 3.8	7.3 ± 2.6	8.2 ± 4.4	7.2 ± 2.8	0.807
RA Vp index (ml/m²)	12.8 ± 5.0	12.2 ± 4.1	13.5 ± 5.6	12.6 ± 4.0	0.856
RA reservoir strain (%)	50.4 ± 13.9	49.5 ± 8.9	46.9 ± 15.4	45.4 ± 14.4	0.629
RA contractile strain (%)	20.5 ± 7.0	17.9 ± 4.7‖	21.6 ± 4.7†	23.0 ± 5.2†	0.051
RA conduit strain (%)	29.9 ± 11.4	31.6 ± 8.3	25.3 ± 12.8	22.4 ± 10.3*†	**0.048**

4.1. Correlations between HRV parameters and the major risk factors for CAN

In univariate analyses, age, BMI, disease duration, systolic blood pressure, smoking, current HbA_{1c}, eGFR, use of ACE inhibitors/ARBs, and use of beta receptor antagonists showed significant correlations with various HRV parameters (Table 6).

In multiple linear model, disease duration remained the only independent predictor of LF/HF ratio (Figure 4). HbA_{1c}, on the other hand, was proved to be the significant independent predictor of all the further time domain, frequency domain, and nonlinear indices, alone, or in combination with other factors, such as age or BMI (Table 7). Partial regression plots indicate that HbA_{1c} level correlates significantly with various HRV parameters in multiple models (Figure 5).

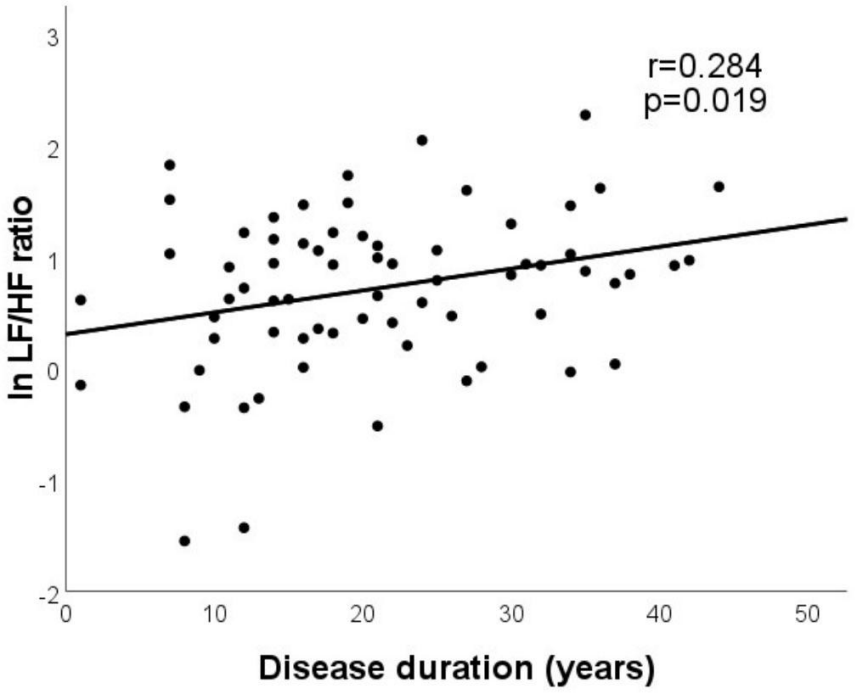

Figure 4. *Disease duration was found to be the only independent predictor of LF/HF ratio in multiple model. Partial correlation coefficients are reported.*

Table 6. *Univariate predictors of the HRV parameters in the T1DM population. Statistically significant p-values (p<0.05) are formatted in bold, 0.05≤p<0.1 values are formatted in italics.*

		Age (years)	Gender (male/ female)	BMI (kg/m^2)	Disease duration (years)	Office blood pressure, systolic (mmHg)	Office blood pressure, diastolic (mmHg)	Smoking (never/ previously/ currently)	Current HbA_{1c} (%)	eGFR (ml/min/ 1.73 m^2)	Total cholesterol (mmol/l)	Triglyce-ride (mmol/l)	Use of ACE inhibitors/ ARBs (yes/no)	Use of beta receptor antagonists (yes/no)	Use of calcium channel blockers (yes/no)
ln SDNN	r	-0.365	-0.145	-0.356	-0.205	-0.240	-0.069	-0.260	-0.448	0.335	-0.088	-0.048	-0.230	-0.222	0.039
	p	**0.002**	0.231	**0.002**	*0.094*	**0.045**	0.572	**0.030**	**<0.001**	**0.007**	0.526	0.729	*0.056*	*0.065*	0.746
ln rMSSD	r	-0.321	-0.101	-0.319	-0.218	-0.210	-0.135	-0.173	-0.409	0.345	-0.097	-0.015	-0.241	-0.185	0.002
	p	**0.007**	0.407	**0.007**	*0.074*	*0.081*	0.265	0.152	**<0.001**	**0.005**	0.486	0.914	**0.044**	0.126	0.986
ln VLF	r	-0.318	-0.175	-0.250	-0.124	-0.229	-0.101	-0.198	-0.425	0.229	-0.063	-0.103	-0.220	-0.176	0.021
	p	**0.012**	0.175	*0.050*	0.338	*0.074*	0.407	0.123	**<0.001**	*0.073*	0.650	0.460	*0.067*	0.144	0.866
ln LF	r	-0.438	-0.224	-0.380	-0.225	-0.272	-0.135	-0.222	-0.396	0.279	-0.129	-0.111	-0.333	-0.308	-0.103
	p	**<0.001**	*0.062*	**0.001**	*0.065*	**0.023**	0.264	*0.065*	**<0.001**	**0.025**	0.353	0.424	**0.005**	**0.009**	0.396
ln HF	r	-0.411	-0.086	-0.260	-0.330	-0.208	-0.094	-0.199	-0.387	0.301	-0.130	0.012	-0.234	-0.160	-0.047
	p	**<0.001**	0.478	**0.030**	**0.006**	*0.083*	0.440	*0.098*	**0.001**	**0.015**	0.349	0.933	*0.051*	0.185	0.702
ln LF/HF ratio	r	0.088	-0.201	-0.114	0.284	-0.039	-0.039	0.027	0.109	-0.141	0.048	-0.199	-0.047	-0.193	-0.079
	p	0.469	*0.096*	0.347	**0.019**	0.751	0.751	0.823	0.371	0.268	0.730	0.149	0.702	0.109	0.518
ln Total Power	r	-0.405	-0.159	-0.300	-0.217	-0.275	-0.120	-0.249	-0.388	0.274	-0.122	-0.084	-0.263	-0.212	-0.041
	p	**<0.001**	0.189	**0.012**	*0.076*	**0.021**	0.321	**0.038**	**<0.001**	**0.028**	0.379	0.544	**0.028**	*0.078*	0.734
ln SD1	r	-0.352	-0.074	-0.307	-0.217	-0.216	-0.150	-0.172	-0.385	0.334	-0.123	-0.020	-0.250	-0.193	-0.013
	p	**0.003**	0.544	**0.010**	*0.075*	*0.072*	0.214	0.154	**0.001**	**0.007**	0.375	0.886	**0.037**	0.110	0.916
ln SD2	r	-0.385	-0.164	-0.369	-0.207	-0.234	-0.071	-0.288	-0.393	0.331	-0.106	-0.055	-0.240	-0.233	0.037
	p	**0.001**	0.175	**0.002**	*0.091*	*0.051*	0.560	**0.016**	**<0.001**	**0.007**	0.447	0.693	**0.045**	*0.052*	0.761

Table 7. *Significant independent predictors of the HRV parameters in T1DM population: multivariate regression analyses. Unstandardized (B) and standardized (β) regression coefficients. Statistically significant p-values (p<0.05) are formatted in bold.*

	B	β	p	F	adj. R^2	p
ln SDNN				12.719	0.366	**<0.001**
HbA_{1c} (%)	-0.142	0.395	**<0.001**			
BMI (kg/m²)	-0.027	-0.259	**0.016**			
Age (years)	-0.011	-0.257	**0.019**			
Disease duration (years)		-0.17	0.889			
Office blood pressure, systolic (mmHg)		-0.19	0.862			
Smoking (n/p/c)		-0.180	0.083			
eGFR (ml/min/1.73 m²)		0.119	0.308			
Use of ACE inhibitors/ARBs (y/n)		0.113	0.365			
Use of beta receptor antagonists (y/n)		0.085	0.472			
ln rMSSD				11.436	0.255	**<0.001**
HbA_{1c} (%)	-0.167	-0.405	**<0.001**			
eGFR (ml/min/1.73 m²)	0.008	0.280	**0.015**			
Age (years)		-0.154	0.222			
BMI (kg/m²)		-0.215	0.060			
Disease duration (years)		-0.097	0.409			
Office blood pressure, systolic (mmHg)		-0.065	0.563			
Use of ACE inhibitors/ARBs (y/n)		-0.081	0.498			
ln VLF				14.108	0.172	**<0.001**
HbA_{1c} (%)	-0.321	-0.431	**<0.001**			
Age (years)		-0.231	0.051			
BMI (kg/m²)		-0.185	0.112			
Office blood pressure, systolic (mmHg)		-0.216	0.061			
eGFR (ml/min/1.73 m²)		0.170	0.145			
Use of ACE inhibitors/ARBs (y/n)		-0.106	0.385			

Table 7. – *continue*

	B	β	p	F	adj. R^2	p
ln LF				13.207	0.375	**<0.001**
HbA_{1c} (%)	-0.311	-0.336	**0.002**			
Age (years)	-0.034	-0.325	**0.003**			
BMI (kg/m^2)	-0.072	-0.270	**0.012**			
Gender (male/female)		-0.185	0.071			
Disease duration (years)		-0.033	0.781			
Office blood pressure, systolic (mmHg)		-0.057	0.592			
Smoking (n/p/c)		-0.113	0.278			
eGFR ($ml/min/1.73\ m^2$)		0.012	0.917			
Use of ACE inhibitors/ARBs (y/n)		0.010	0.938			
Use of beta receptor antagonists (y/n)		0.011	0.927			
ln HF				11.975	0.265	**<0.001**
Age (years)	-0.045	-0.353	**0.003**			
HbA_{1c} (%)	-0.363	-0.326	**0.006**			
BMI (kg/m^2)		-0.173	0.125			
Disease duration (years)		-0.111	0.388			
Office blood pressure, systolic (mmHg)		-0.088	0.434			
Smoking (n/p/c)		-0.102	0.364			
eGFR ($ml/min/1.73\ m^2$)		0.118	0.337			
Use of ACE inhibitors/ARBs (y/n)		-0.036	0.765			
ln LF/HF ratio				5.787	0.067	**0.019**
Disease duration (years)	0.020	0.284	**0.019**			
Gender (male/female)		-0.213	0.072			

Table 7. – *continue*

	B	β	p	F	adj. R^2	p
ln Total Power				12.346	0.271	**<0.001**
HbA_{1c} (%)	-0.295	-0.357	**0.002**			
Age (years)	-0.031	-0.329	**0.005**			
BMI (kg/m^2)		-0.196	0.079			
Disease duration (years)		0.004	0.978			
Office blood pressure, systolic (mmHg)		-0.133	0.232			
Smoking (n/p/c)		-0.122	0.271			
eGFR (ml/min/1.73 m^2)		0.081	0.507			
Use of ACE inhibitors/ARBs (y/n)		-0.046	0.703			
Use of beta receptor antagonists (y/n)		0.023	0.852			
ln SD1				8.413	0.267	**<0.001**
HbA_{1c} (%)	-0.148	-0.323	**0.006**			
Age (years)	-0.013	-0.246	**0.035**			
BMI (kg/m^2)	-0.031	-0.233	**0.042**			
Disease duration (years)		-0.036	0.781			
Office blood pressure, systolic (mmHg)		-0.022	0.851			
eGFR (ml/min/1.73 m^2)		0.150	0.231			
Use of ACE inhibitors/ARBs (y/n)		0.042	0.752			
ln SD2				10.016	0.372	**<0.001**
HbA_{1c} (%)	-0.111	-0.296	**0.007**			
Age (years)	-0.011	-0.269	**0.014**			
BMI (kg/m^2)	-0.033	-0.302	**0.005**			
Smoking (n/p/c)	-0.128	-0.219	**0.038**			
Disease duration (years)		0.008	0.949			
Office blood pressure, systolic (mmHg)		0.016	0.885			
eGFR (ml/min/1.73 m^2)		0.100	0.388			
Use of ACE inhibitors/ARBs (y/n)		0.062	0.618			
Use of beta receptor antagonists (y/n)		0.054	0.650			

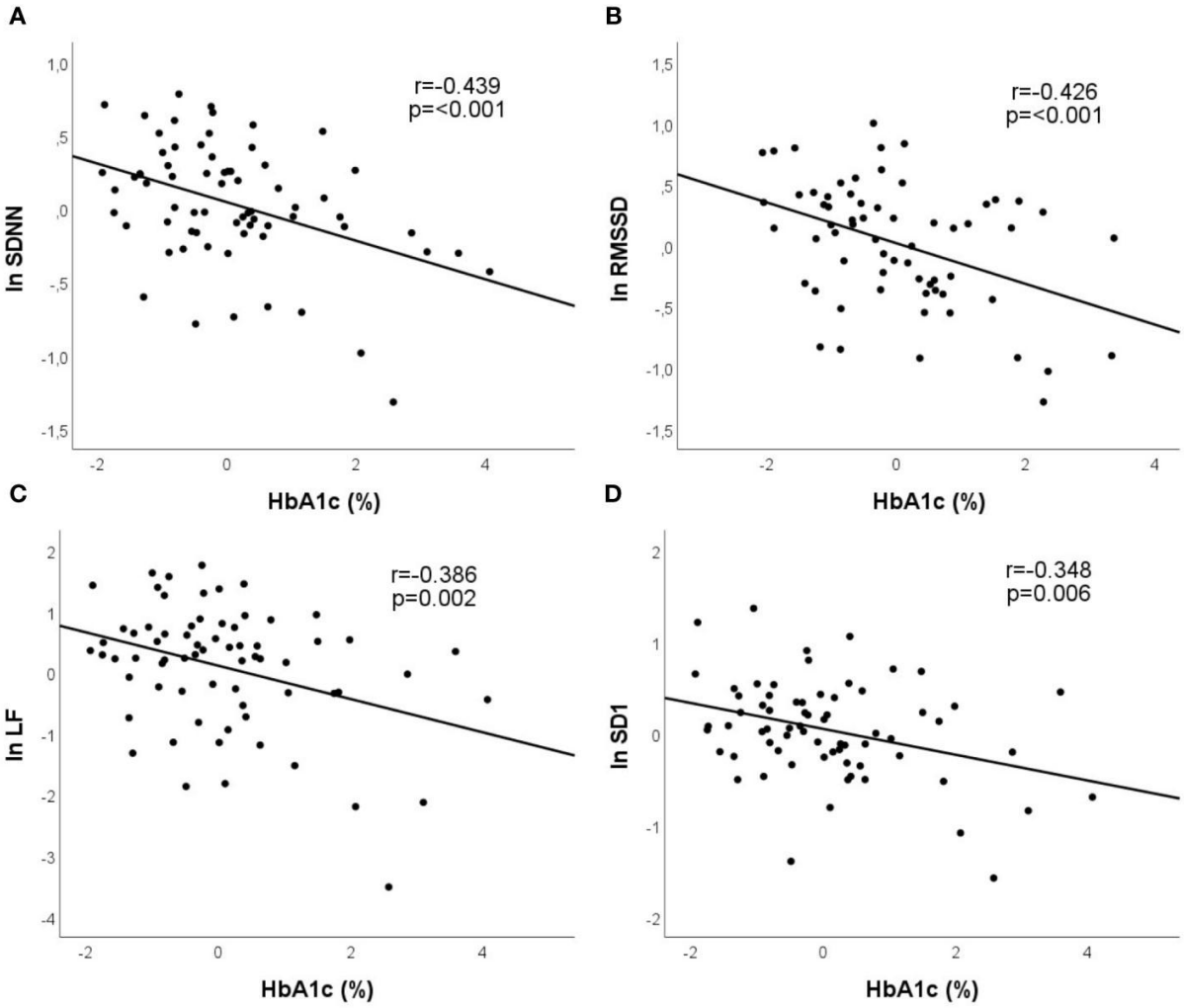

Figure 5. *Partial regression plots demonstrate that in multiple models HbA_{1c} (%) shows significant correlation with SDNN (A), rMSSD (B), LF (C) and with SD1 (D). Partial correlation coefficients are reported.*

5. Conclusions

Our data suggest that quality of the glycemic control has a significant impact on the subclinical myocardial involvement in T1DM patients. Regarding disease duration, we could not prove this relationship.

Asymptomatic T1DM patients have significantly reduced overall HRV as compared with healthy subjects, indicating early, subclinical CAN. Quality of the glycemic control is an important determinant of HRV among T1DM patients. This relationship is independent of other risk factors for CAN or traditional cardiovascular risk factors.

Thus, tight glycemic control must be a high-priority therapeutic aim for diabetic patients to minimize the risk of myocardial damage and consequential heart failure or development of CAN.

6. Novel findings

- A more comprehensive analysis of myocardial mechanics was performed than previously reported, encompassing all four chambers in asymptomatic patients with T1DM.
- HbA_{1c} was confirmed as a significant determinant of myocardial mechanics in all four chambers, even after adjustment for age and the presence of hypertension.
- Disease duration was not identified as an independent determinant of myocardial mechanics.
- A more comprehensive analysis of HRV was conducted in asymptomatic T1DM patients than previously reported, evaluating time domain, frequency domain and nonlinear parameters.
- HbA_{1c} emerged as a significant determinant of multiple HRV parameters in T1DM patients. This correlation is independent of other CAN risk factors and traditional cardiovascular risk factors.
- Disease duration proved to be an independent predictor of the LF/HF ratio.

7. Publications

7.1. Publications related to the subject of the thesis

Hajdu M. Garmpis K. Vértes V. Varga N. Molnár GA. Hejjel L. Wittmann I. Faludi R: Determinants of the heart rate variability in type 1 diabetes mellitus. Frontiers in Endocrinology. 2023;14:1247054 **(IF: 3.9; Q1)**

Hajdu M. Knutsen MO. Vértes V. Varga N. Molnár G. Wittmann I. Faludi R: Quality of glycemic control has significant impact on myocardial mechanics in type 1 diabetes mellitus. Scientific Reports 2022;12:20180 **(IF: 4.6; Q1)**

Hajdu M. Knutsen MO. Faludi R**:** Echocardiographic assessment of the myocardial dysfunction in diabetes. Cardiologia Hungarica 2021;51:33-38.

7.2. Other publications

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Vértes V. Porpáczy A. Nógrádi Á. Tőkés-Füzesi M. **Hajdu M**. Czirják L. Komócsi A. Faludi R: Galectin-3 and sST2: associations to the echocardiographic markers of the myocardial mechanics in systemic sclerosis – a pilot study. Cardiovascular Ultrasound. 2022;20:1. **(IF: 1.9; Q2)**

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7.3. Citable abstracts related to the subject of the thesis

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Hajdu M. Garmpis K. Vértes V. Varga N. Hejjel L. Molnár G. Wittmann I. Faludi R: Heart rate variability shows significant correlation with the echocardiographic markers of the myocardial involvement in type 1 diabetes mellitus. Cardiologia Hungarica 2024;54(Suppl C):C414.

Hajdu M. Knutsen MO. Vértes V. Varga N. Molnár G. Wittmann I. Faludi R: Quality of glycemic control has significant impact on myocardial mechanicsin type 1 diabetes mellitus. European Journal Of Heart Failure 2023;25(Suppl S2):398.

Hajdu M. Garmpis K. Vértes V. Varga N. Hejjel L. Molnár G. Wittmann I. Faludi R: Quality of glycaemic control has significant impact on heart rate variability in type 1 diabetes mellitus. Cardiologia Hungarica 2022;52(Suppl C):335.

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7.4. Other citable abstracts

Hajdu M. Porpáczy A. Kis E. Tornóczky T. Komócsi A. Simor T. Szabados S. Cziráki A. Faludi R: Post-irradiation constrictive pericarditis or something else? European Heart Journal-Cardiovascular Imaging 2019;20(Suppl 1):P1271

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Hajdu M. Vértes V. Varga N. Illés MB. Sárosi V. Alexy Gy. Faludi R: Determinants of the elevated natriuretic peptide level in COPD. Cardiologia Hungarica 2015;45(Suppl D):D95

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