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Estimated peak systolic pulmonary artery pressure in young non-complicated patients with type 1 diabetes

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Abstract. – OBJECTIVE: Right ventricle and pulmonary artery pressure have always received less attention in type 1 diabetes than left ventricle. The aim of this study is to compare the right heart performance and the estimated peak systolic pulmonary artery pressure (EPSPAP) in young type 1 diabetes patients with healthy controls.

PATIENTS AND METHODS: Subjects affected by type 1 diabetes without cardiovascular and respiratory diseases (n=93) and healthy controls (n=56) were evaluated with a comprehensive transthoracic echocardiography. The pulmonary peak systolic arterial pressure was calculated with an established formula based on pulmonary artery acceleration time.

RESULTS: The left ventricle's function was found to be normal in all the subjects under study. The estimated peak systolic pulmonary artery pressure was significantly higher in patients with type 1 diabetes compared to the controls (38.5 ± 8.6 *vs.* 35.4 ± 6.7, $p = 0.019$). The highest value of EPSPAP was observed in smoking female patients with type 1 diabetes. Basal and mid cavity diameter of the right ventricle were higher in patients with type 1 diabetes. Factors associated with EPSPAP were sex, body mass index, mid cavity diameter and, with an inverse correlation, HDL-cholesterol.

CONCLUSIONS: The present study suggests that young, uncomplicated patients with type 1 diabetes have a higher estimated peak systolic pulmonary artery pressure. Further studies are needed to define the mechanisms underlying this alteration and its clinical consequences.

Key Words:
Type 1 diabetes, Cardiovascular disease, Pulmonary artery pressure, Echocardiography.

Introduction

Type 1 diabetes (TD1) is a frequent autoimmune disease that afflicts young individuals[1]. The chronic complications of this disease may, virtually, affect any organ[2]. The most studied organs are those related to the cardiovascular system[3], the left ventricle function and major arteries alterations being the main subjects of interest[4,5]. Right ventricular performance and pulmonary artery pressure have always received less attention in type 1 diabetes. Estimates of pulmonary artery pressure through transthoracic echocardiography may be obtained primarily from the maximum velocity of tricuspid regurgitation (TRvmax)[6]. However, TRvmax is quite often absent or trivial[7], especially in young subjects. Alternatively, pulmonary artery acceleration time (PAAT) can be used to provide an accurate EPSPAP[8]. PAAT is easily obtainable in virtually all procedures, thus increasing the number of subjects in whom the EPSPAP can be measured[8]. Therefore, the equation that uses PAAT could be a valid non-invasive approach to measure EPSPAP when tricuspid regurgitation cannot be obtained. An animal model of type 1 diabetes has shown that type 1 diabetes with hypoxia – not diabetes alone – leads to an increase in diastolic and mean pulmonary artery pressure[9]. There are also some case studies reporting an association between primary pulmonary hypertension (PAH) and autoimmune polyendocrine syndrome, raising the hypothesis of an involvement of autoimmunity[10]. Thus, the aim of the present study is to compare the right heart performance and the estimated systolic pulmonary artery pressure (EPSPAP) in young asymptomatic patients with type 1 diabetes with healthy controls.

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Patients and Methods

Consecutive outpatients with type 1 diabetes (n=93) were recruited. Exclusion criteria were known heart diseases (valvular diseases comprising bicuspid aortic valve, ischemic heart disease and uncontrolled hypertension), pregnancy and unwillingness to participate to the study. None of the patients with type 1 diabetes had a history of pulmonary diseases. Healthy, non-smoking volunteers among hospital staff were recruited (n = 56). The study was approved by the Local Ethics Committee, and informed consent was obtained from each participant.

Transthoracic Echocardiography

The participants underwent a complete two-dimensional echocardiography and Doppler study using an Esaote My Lab 70 (Esaote Spa, Genoa, Italy). Conventional echocardiography was used to measure left and right ventricle diastolic diameters, wall thickness and mass according to the standard criteria. The left ventricle (LV) end-diastolic and end-systolic volumes and LV ejection fraction (LVEF) at rest were measured at the apical 4-chamber and 2-chamber views (by modified Simpson rule)[11]. The left atrial volume index (LAVI), measured at the end of LV systole from the apical 4-chamber and 2-chamber views (maximum LA size) using the modified Simpson rule[11], was obtained dividing LA volume by the body surface area. Trans-mitral and trans-tricuspid peak early diastolic velocity (E), peak late diastolic velocity (A) and E-wave deceleration time (DTe) were evaluated by Doppler analysis. Three measurements at the end of expiration were averaged. Tissue Doppler interrogation of the septal and lateral mitral annulus estimated the early peak (e'), late peak (a') and systolic peak (s') and the mean values were included in the analysis. Tissue Doppler imaging of the right free wall in the 4-chamber apical view was performed to obtain the peak velocities of the tricuspid annulus a', e' and s' waves at the end of expiration. Right ventricle global systolic function was assessed with tricuspid annular plane systolic excursion (TAPSE). The pulmonary artery acceleration time (PAAT) was assessed using pulsed-wave Doppler recording of pulmonary flow at the pulmonary valve annulus in parasternal short axes view at the end of expiration. The same view was used to exclude pulmonic stenosis. PAAT was measured as the interval between the onset of systolic pulmonary arterial flow and peak flow velocity. Pulmonary artery systolic pressures were estimated from PAAT using a previously validated equation[7]: $10^{([-0.004*PAAT]+2.1)}$.

Clinical and Laboratory Variables

The clinical variables were collected from the patients. Patients were considered hypertensive when blood pressure was ≥140/90 mmHg or if they were on anti-hypertensive treatments. Venous blood samples were drawn in the morning after an overnight fast. Serum creatinine (measured using a Jaffé rate-blanked and compensated assay) and standard laboratory procedures (DAX 96; Bayer Diagnostics, Milan, Italy) provided other biochemical measurements. Low-density lipoprotein-cholesterol was calculated using the Friedewald's equation. Hemoglobin A1c (HbA1c) was measured using an automated high-performance liquid chromatography analyser (HA-8140; Menarini Diagnostics, Florence, Italy).

The glomerular filtration rate (eGFRCKD-EPI) was estimated by the Chronic Kidney Diseases Epidemiology Collaboration (CKD-EPI) equation[12]. Albuminuria-to-creatinine ratio was obtained on a morning spot urine sample. A dedicated ophthalmologist diagnosed diabetic retinopathy using fundoscopy after pupillary dilation according to a clinical disease severity scale (no retinopathy, non-proliferative, proliferative or laser-treated retinopathy); proliferative retinopathy was assessed with fundus fluorescein angiography. Nephropathy was considered if eGFR <60 ml/min/1.73 m^2 and/or abnormal albuminuria (i.e., an albumin-to-creatinine ratio ≥30 mg/g creatinine).

Statistical Analysis

Results are reported as means ± SD and proportions or absolute frequencies. Tests to compare the subjects under study were: *t*-test, analysis of covariance (age adjusted), one-way ANOVA and non-parametric analyses for continuous variables. Correlations were tested using the Pearson and Spearman coefficients. Multivariate linear and logistic analysis was performed to study the confounding factors for the estimate of the systolic peak pulmonary arterial pressure. In order to categorise the EPSPAP, a cut-off of 36 mmHg, that is the median value, was considered (EPSPAP < 36 = 0 and EPSPAP > = 36 = 1). Covariates for this multivariate model were chosen as potential confounding factors based on their significance or their biological plausibility. *p*-values < 0.05 were considered statistically significant.

Results

A total of 56 healthy controls and 93 patients with type 1 diabetes were compared. Characteristics of patients with type 1 diabetes were reported in a previous study[13]. Parameters of systolic and diastolic function of the left ventricle did not show any significant alteration. Main clinical characteristics of subjects under study are reported in Table I. Patients with type 1 diabetes were older than controls, with higher BMIs, systolic and diastolic blood pressure levels. Pulse pressure and heart rate were also significantly higher in patients with type 1 diabetes compared to controls. Women with TD1 (Table I) showed significantly higher levels of HDL-cholesterol and a higher prevalence of microvascular complications. Table II reports the echocardiographic characteristics of the right ventricle in type 1 diabetic patients and healthy controls. Both basal (34.1 ± 7.2 *vs.* 29.8 ± 4.0 mm, $p < 0.001$) and mid cavity (28.8 ± 4.9 *vs.* 25.4 ± 5.3 mm, $p<0.001$) diameters were significantly higher in TD1 patients compared to controls. The Tricuspid Deceleration time was shorter in patients with type 1 diabetes than in controls (198.6 ± 47.1 *vs.* 239.4 ± 69.3 ms, $p = 0.005$). Tissue Doppler interrogation of the lateral tricuspid annulus showed higher a' and s' waves velocity in patients with type 1 diabetes compared to healthy controls (Table II). Moreover, the e'/a' ratio was significantly lower in TD1 patients compared to controls (1.2 ± 0.4 *vs.* 1.6 ± 0.6, $p < 0.001$). PAAT was lower in TD1 patients, while EPSPAP was significantly higher in patients with type 1 diabetes with respect to the controls (38.5 ± 8.6 *vs.* 35.4 ± 6.7, $p = 0.019$). Slightly higher difference in the EPSPAP was observed in women as shown in Figure 1. Even though the number was quite small, women with type 1 diabetes who smoked (n = 6) showed a mean ESPPAP of 44.9 ± 6.9 mmHg. However, when the current smokers were eliminated from the analysis, the results did not change; women with diabetes showed significantly higher values of ESPPAP compared to healthy controls (38.6 ± 8.7 *vs.* 34.3 ± 5.3 mmHg, $p = 0.031$).

To understand factors associated with the EPSPAP in TD1 patients, we analysed two multivariate models, one linear and one logistic, as shown in Table III. As expected, women with type 1 diabetes had a risk twice as much as men who present an altered EPSPAP. The BMI and the mid cavity diameter of the right ventricle were significantly associat-

Table I. Descriptive statistics for the clinical characteristics of subjects with type 1 diabetes mellitus compared to controls.

	Control females (n = 28)	T1D females (n = 41)	*p*-value	Control Male (n = 28)	T1D Male (n = 52)	*p*-value
Age, years	29.2 ± 7.2	33.2 ± 11.0	0.096	27.1 ± 4.4	33.0 ± 8.8	0.003
BMI, kg/m^2	20.5 ± 1.7	23.6 ± 4.1	< 0.001	22.1 ± 2.4	24.3 ± 3.3	0.002
Systolic pressure, mmHg	111.4 ± 8.0	121.2 ± 12.2	< 0.001	119.1 ± 9.4	128.8 ± 11.6	< 0.001
Diastolic pressure, mmHg	70.7 ± 7.2	74.9 ± 6.8	0.018	74.6 ± 6.2	76.6 ± 7.9	0.258
Pulse pressure, mmHg	40.7 ± 6.6	46.4 ± 11.4	0.011	44.4 ± 9.5	52.2 ± 11.3	0.003
Heart rate, bpm	68.0 ± 12.1	76.5 ± 11.5	0.005	70.4 ± 10.6	72.9 ± 13.5	0.389
Ventricular septal thickness, mm	7.6 ± 0.9	8.2 ± 1.1	0.015	8.9 ± 1.3	9.1 ± 1.3	0.535
Diabetes duration, years		18.9 ± 10.4			18.0 ± 10.2	0.690$^+$
HbA1c, %		7.9 ± 1.3			7.7 ± 0.9	0.388$^+$
Total Cholesterol, mol/l		4.7 ± 0.9			4.4 ± 0.7	0.195$^+$
HDL cholesterol, mol/l		1.7 ± 0.5			1.3 ± 0.3	< 0.001$^+$
Triglycerides, mol/l		1.0 ± 0.7			1.1 ± 0.6	0.208$^+$
eGFRCKD-EPI, ml/min/1.73 m^2		108.6 ± 17.8			109.0 ± 11.5	0.903$^+$
Current smokers, %		14.6			23.1	0.504$^+$
Microvascular complications, %		31.7			5.8	0.001$^+$
Hypertension, %		1.4			6.3	0.143$^+$

Values are means ± SD, percentages or percentage. BMI: body mass index. T1D: type 1 diabetes. HbA1c: glycosylated haemoglobin; eGFRCKD-EPI: estimated glomerular filtration rate LDL: low-density lipoprotein; HDL: high-density lipoprotein. Microvascular complications: retinopathy or neuropathy or nephropathy. ^+p-values refer to the differences between females and males with type 1 diabetes.

Table II. Right side echocardiographic characteristics of type 1 diabetic patients with preserved LVEF compared to healthy controls.

	Controls (n = 56)	Type 1 diabetes (n = 93)	*p*
TAPSE, mm	23.4 ± 3.0	23.2 ± 2.8	0.613
Basal diameter, mm	29.8 ± 4.0	34.1 ± 7.2	<0.001
Mid cavity diameter, mm	25.4 ± 5.3	28.8 ± 4.9	<0.001
Longitudinal dimension, mm	70.1 ± 7.2	70.5 ± 8.5	0.780
Peak E velocity, m/s	0.62 ± 0.14	0.57 ± 0.11	0.018
Peak A velocity, m/s	0.36 ± 0.09	0.36 ± 0.08	0.996
E/A ratio	1.79 ± 0.53	1.65 ± 0.46	0.101
DTe, ms	239.4 ± 69.3	198.6 ± 47.1	0.005
e' velocity, cm/s	15.4 ± 3.0	15.7 ± 3.1	0.530
a' velocity, cm/s	10.5 ± 3.2	14.0 ± 3.7	<0.001
s' velocity, cm/s	14.2 ± 2.5	15.4 ± 2.9	0.014
E/e' ratio	4.23±1.20	3.71±0.82	0.01
e'/a' ratio	1.6 ± 0.6	1.2 ± 0.4	<0.001
PAAT, ms	139.6 ± 20.7	131.4 ± 24.7	0.043
EPSPAP, mmHG	35.4 ± 6.7	38.5 ± 8.6	0.019

Values are means ± SD or percentages. DTe: deceleration time. TAPSE: Tricuspid annular plane systolic excursion; PAAT: pulmonary artery acceleration time. EPSPAP: estimate of the systolic peak pulmonary arterial pressure.

ed with increased EPSPAP, while HDL-cholesterol was inversely associated with EPSPAP.

Finally, as controls and subjects differed from each other in terms of many demographic and echocardiographic variables other than age, we performed a multivariate logistic model with the EPSPAP as the dependent variable in order to statistically make up for these differences. The presence of TD1 was included as a dummy variable. The selected independent variables were namely age, BMI, pulse pressure, presence of TD1, ventricular septum thickness and mid cavity diameter. In females, the presence of TD1 showed a clear trend (OR 2.06, CI 95% 0.44-9.64; $p = 0.363$), while in males, both BMI and TD1 showed a trend (OR 1.30, CI 95% 0.99-1.71; $p = 0.063$ and OR 1.44, CI 95% 0.33-6.29; $p = 0.625$, respectively).

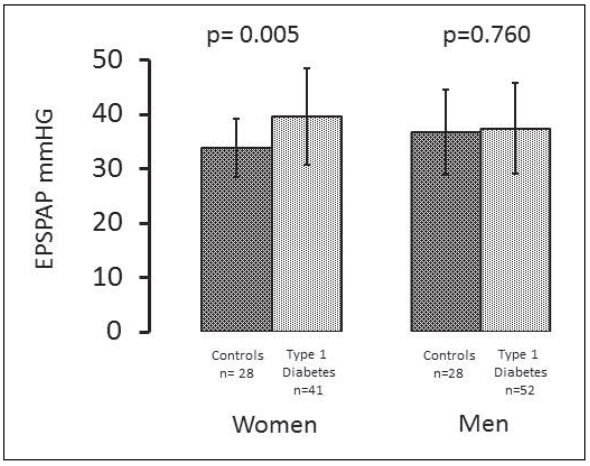

Figure 1. EPSPAP stratified by sex in patients with type 1 diabetes compared to healthy controls. The comparison was adjusted for age.

Discussion

The main finding of the present study is the increased EPSPAP in type 1 diabetes patients compared to healthy controls, especially in women. However, no difference was observed between women and men with type 1 diabetes. As tricuspid regurgitation velocity was present in about 20% of the diabetic cohort, we estimated the systolic pulmonary pressure by using PAAT with an established formula[8]. It should also be mentioned that pulmonary hypertension, as previously reported, was present in almost half of the patients without a measurable tricuspid regurgitation velocity[14]. However, the interpretation of right ventricular diastolic function should be very cautiously done, as all the measures were within the normal range variations[15]. Considering that the e' and a' tricuspid waves are less load dependent[15], the observed reduction in e'/a' ratio in TD1 patients may suggest a dysfunction of the right ventricle.

Table III. Multivariate linear and logistic regression analysis with estimated peak systolic pulmonary artery pressure as the dependent variable in type 1 Diabetes patients.

	Standardized beta coefficient	*p*	OR (95% CI)	*p*
Age, years	-0.003	0.983	1.00 (0.93-1.08)	0.977
Sex	- 0.529	< 0.001	0.05 (0.01-0.35)	0.002
BMI, kg/m^2	0.311	0.005	1.21 (1.03-1.44)	0.024
HDL cholesterol, mol/l	- 0.386	0.002	0.95 (0.90-0.99)	0.011
Diabetes duration, years	- 0.080	0.499	0.96 (0.89-1.03)	0.217
Glycated haemoglobin, mmol/mol	- 0.026	0.811	0.99 (0.56-1.75)	0.966
Basal diameter, mm	- 0.111	0.350	0.96 (0.89-1.05)	0.396
Mid cavity diameter, mm	0.348	0.010	1.33 (1.10-1.61)	0.003

BMI: body mass index; HDL: high density lipoprotein.

Thus, alterations in the right ventricular function and pulmonary pressure seem to precede left ventricular alterations in type 1 diabetes.

To the best of our knowledge, the present data are the first to show an increase in pulmonary systolic arterial pressure in young non complicated TD1 patients.

Pulmonary arterial hypertension is a progressive disease characterised by increased pulmonary resistance and pulmonary artery remodelling. Since our results seem to indicate that the EPSPAP is higher in type 1 diabetes, they may have important clinical implications.

The increased EPSPAP was more evident in women with type 1 diabetes, in line with recent figures that show a female-to-male ratio of 4:1 of pulmonary arterial hypertension[16].

In the present study, factors associated to EPSPAP were sex, BMI, HDL-cholesterol and mid cavity diameter of right ventricle.

The increased mid cavity diameter of the right ventricle may be a consequence of the increased EPSPAP that yields an increase in right ventricular afterload, thus determining a remodelling of the right ventricle. Overweight has been shown to be a comorbidity in PAH[17]. Obesity may be related to PAH through different mechanisms such as hypoventilation, hypoxia and inflammation[17]. Recently, it has been shown that obesity can induce pulmonary hypertension through changes in oestrogen metabolism[18].

Also, the inverse relation with HDL-cholesterol is noteworthy. Lower level of HDL-cholesterol increased the risk of death in patients with PAH[19]. The mechanism underlying this relation could stem from the important role that HDL-cholesterol plays in endothelial function[20]. HDL-cholesterol promotes the nitric oxide synthase and, therefore, the synthesis of the vasodilator nitric oxide[21]. Moreover, it stimulates the release and increases the half-life of prostacyclin[22]. Reduced levels of HDL-cholesterol may interfere with the endothelial pulmonary function.

At least three mechanisms could explain the relationship between type 1 diabetes and arterial systolic pulmonary pressure: microvascular disease, inflammation and autoimmunity.

Microvascular pulmonary disease can be implicated as the pulmonary circulation has the largest capillary network in the body[23]. Moreover, in this system, even a small increase in resistance may have measurable deleterious consequences[24]. Roberts et al[25] using a non-invasive technique measured the microvascular pulmonary function. Unlike our study, this study enrolled both type 1 and type 2 diabetes patients, mostly men (73%). They found an alteration of pulmonary microvascular function in subjects with diabetes compared to matched controls. Also, the systolic pulmonary pressure was higher in diabetes. The prevalence of the altered microvascular function was higher even in uncomplicated subjects with diabetes[25].

Inflammation may be another possible mechanism leading to the alteration of the pulmonary artery function. Several alterations caused by inflammation have been described in pulmonary artery hypertension, such as increased levels of neutrophil elastase[26], remodelling of the extracellular matrix of the pulmonary arteries[27] and increased pro-inflammatory cytokines and other biomarkers of inflammation[28-30]. In our study, the role of inflammation may be suggested by the inverse correlation with HDL-cholesterol that has been shown to have anti-inflammatory properties. Recently, Jonas et al[31] reported a reduction in triglyceride-HDL-cholesterol ratio and systemic inflammation in subjects with pulmonary artery hypertension[31].

Finally, an interesting mechanism may be autoimmunity. Autoimmunity could also explain our results in women, as all forms of pulmonary artery hypertension have been reported to be more frequent in females compared to males. Pulmonary artery hypertension has been found even in other autoimmune diseases, such as Hashimoto thyroiditis[32], polyglandular autoimmune disease and rheumatologic diseases[33-35].

We would also like to emphasise that, even though the number of current smokers was low, the values of EPSPAP found in smoking female patients with type 1 diabetes were high. Recent evidence has showed a deleterious effect of smoking on cross-sectional area of small pulmonary vessels[36]. This result shows the need to quit smoking.

Limitations

Our study has some limitations: 1) It is a cross-sectional study and no causal relation may be inferred, 2) The measure of pulmonary pressure was indirect. Even though we performed an adjusted statistical model, the controls differed in terms of variables from the patients with TD1 and 3) It was a single centre study. In spite of these limitations, our study has several strengths. Our patients with type 1 diabetes were a homogeneous sample having a good glycaemic control, with a slight prevalence of mild chronic complications. The echocardiographic indices of the left ventricle systolic and diastolic function were substantially normal. The use of PAAT may be clinically relevant, as the tricuspid velocity is measurable in a small number of subjects, that is, less than 20% of the subjects in our cohort.

Conclusions

The present study suggests that in type 1 diabetes the EPSPAP is increased, mainly in female patients. Quitting smoking may be an important measure to preserve a normal pulmonary pressure. Further studies are recommended to confirm our results and to better define the connections between type 1 diabetes and pulmonary arterial pressure.

Acknowledgments

Authors Contributions: C.B. performed the echocardiographic study. G.Z. wrote the manuscript and analysed the data. G.T., M.T., E.B. reviewed/edited the manuscript. A.M., E.R. contributed to the preparation of the data and the discussion. G.Z. is the guarantor.

Conflict of Interests

The authors declare that they have no conflict of interests.

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