Differences in Physiological Responses to Cardiopulmonary Exercise Testing in Adults With and Without Type 1 Diabetes: A Pooled Analysis

Diabetes Care 2021;44:240–247 | https://doi.org/10.2337/dc20-1496

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OBJECTIVE

To investigate physiological responses to cardiopulmonary exercise (CPX) testing in adults with type 1 diabetes compared with age-, sex-, and BMI-matched control participants without type 1 diabetes.

RESEARCH DESIGN AND METHODS

We compared results from CPX tests on a cycle ergometer in individuals with type 1 diabetes and control participants without type 1 diabetes. Parameters were peak and threshold variables of VO_2, heart rate, and power output. Differences between groups were investigated through restricted maximum likelihood modeling and post hoc tests. Differences between groups were explained by stepwise linear regressions ($P < 0.05$).

RESULTS

Among 303 individuals with type 1 diabetes (age 33 [interquartile range 22; 43] years, 93 females, BMI 23.6 [22; 26] kg/m^2, HbA_{1c} 6.9% [6.2; 7.7%] [52 (44; 61) mmol/mol]), VO_{2peak} (32.55 [26.49; 38.72] vs. 42.67 ± 10.44 mL/kg/min), peak heart rate (179 [170; 187] vs. 184 [175; 191] beats/min), and peak power (216 [171; 253] vs. 245 [200; 300] W) were lower compared with 308 control participants without type 1 diabetes (all $P < 0.001$). Individuals with type 1 diabetes displayed an impaired degree and direction of the heart rate-to-performance curve compared with control participants without type 1 diabetes (0.07 [−0.75; 1.09] vs. 0.66 [−0.28; 1.45]; $P < 0.001$). None of the exercise physiological responses were associated with HbA_{1c} in individuals with type 1 diabetes.

CONCLUSIONS

Individuals with type 1 diabetes show altered responses to CPX testing, which cannot be explained by HbA_{1c}. Intriguingly, the participants in our cohort were people with recent-onset type 1 diabetes; heart rate dynamics were altered during CPX testing.

Type 1 diabetes is an autoimmune disease characterized by the destruction of pancreatic β-cells, resulting in hypoinsulinemia with subsequent hyperglycemia and diabetic ketoacidosis (1). Individuals with type 1 diabetes can already present with a cardiac autonomic neuropathy (2) and cardiomyopathy (3) soon after diagnosis.

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However, neither the etiology nor the mechanisms behind the occurrence of these cardiac diseases are fully understood in individuals with type 1 diabetes.

Cardiopulmonary exercise (CPX) testing may offer insights into the origin and complexity of acute cardiovascular and respiratory impairments since it provides information about the course of cardiopulmonary and circulatory responses to physical stress (4). This functional assessment has often been advocated as an initial noninvasive choice in testing for cardiovascular disease because of its high sensitivity, cost-effectiveness, and widespread availability (5). Additionally, CPX testing provides information about the general health status of individuals, as VO_{2peak} expressed relative to body mass (mL/kg/min) is associated with morbidity status and mortality risk in individuals with and without chronic conditions (6). Furthermore, submaximal thresholds derived from CPX testing serve as a tool to accurately prescribe exercise intensity in both healthy individuals and those with type 1 diabetes (7,8).

Because studies have shown that regular physical activity and exercise are associated with a reduced risk of mortality (9), retinopathy, hypertension, and dyslipidemia (10), the question arises of whether subclinical alterations of cardiopulmonary function can already be detected during CPX testing. Individuals with type 1 diabetes showed decreased VO_{2peak} (11) and lower oxygen economy at submaximal metabolic thresholds compared with healthy individuals (12). Also, previous research investigating cardiac responses to CPX testing showed that individuals with type 1 diabetes had linear heart rate (HR) dynamics with increasing exercise intensity, which is contrary to individuals without diabetes (12). This may propose that independent of type 1 diabetes, specific diabetes characteristics, such as elevated HbA_{1c} levels, diabetes duration, low C-peptide levels, and high doses of total daily insulin, might be detrimental to functional capacity.

Consequently, a comprehensive assessment of the impact of type 1 diabetes and its associated specific diabetes characteristics on functional capacity is missing. In particular, in recent-onset ($<$1 year after diagnosis) type 1 diabetes, it is hypothesized that the impact of the condition on alterations to functional and physiological capacity might be low because of lower incidences of micro- and macrovascular complications in this cohort (13). Therefore, the aim of this study was to investigate acute physiological responses to CPX testing in individuals with type 1 diabetes compared with matched control participants without type 1 diabetes. Furthermore, we sought to investigate whether submaximal and peak responses to CPX testing are associated with HbA_{1c} and other diabetes characteristics, such as C-peptide, diabetes duration, and total daily insulin dose.

RESEARCH DESIGN AND METHODS

This study was performed as a retrospective pooled analysis in which data from CPX testing until maximal exhaustion were assessed in individuals with type 1 diabetes and matched control participants without type 1 diabetes. After contacting other researchers, study data from research institutions in Denmark, Germany (German Diabetes Study), Switzerland, the U.K., Austria, and Brazil were included (Supplementary Fig. 1). The analysis protocol was approved by the ethics committee of the Medical University of Graz (32-381 ex 19/20) and registered at the German Clinical Trials Register (drks.de registration no.: DRKS00022106). Furthermore, the study was conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions as well as in accordance with the guidelines provided by the International Conference on Harmonization for Good Clinical Practice (E6 guidelines).

Study Population

All participants received a medical examination before each CPX assessment. The majority of research centers contributing data to our study assessed the diagnosis of type 1 diabetes through the Standards of Medical Care in Diabetes position statement (14).

Eligibility criteria were defined as follows: clinical diagnosis of type 1 diabetes, age 18–65 years (both inclusive) at the time of CPX testing, and availability of age and BMI. Additionally, HbA_{1c}, diabetes duration, and total daily insulin dose were included. C-peptide levels were included if available. Individuals with type 1 diabetes and control participants without type 1 diabetes were matched 1:1 for age, BMI, and sex. No specific health parameters were obtained from the control group except body weight and BMI.

Assessment of CPX Data

Before the start of the analysis, CPX testing data were screened for eligibility. All CPX tests were conducted on cycle ergometers (Ergoselect 100 [Ergoline, Bitz, Germany], Cybex [Cybex International, Medway, MA], PowerCube1-Ergo [Ganshorn Medizin Electronic, Niederlauer, Germany], Ergoline 900 [Ergoline]). Main eligibility criteria were the provision of the CPX testing protocol (wattage increase/time), HR (beats/min [bpm]), absolute VO_2 (L/min), absolute VCO_2 (L/min), ventilation (VE) (L/min), and power output (W) throughout the entire CPX measurement.

Pulmonary gas exchange variables were provided in the form of breath-by-breath measurement, averaged over 5 or 10 s (METAMAX 3B [Cortex Medical, Leipzig, Germany], Quark CPET [COSMED, Albano Laziale, Italy], Cardiovit AT-104 [Schiller, Baar, Switzerland], Masterscreen CPX [Jaeger/VIASYS, Hoechberg, Germany]). HR variables were measured using chest belt telemetry or electrocardiography and were provided as 5- or 10-s averages. Data were excluded if submaximal ventilatory thresholds or peak values were not reached or not detectable because of low data quality, as assessed by a certified exercise physiologist.

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Received 18 June 2020 and accepted 14 October 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.13103585.

D.P. and O.Mo. share senior authorship.

Following the assessment of eligibility and quality, data sets were randomized by a statistician. The preexercise resting period, submaximal ventilatory threshold 1 (VT_1), ventilatory threshold 2 (VT_2), and peak performance were determined by one researcher. Pre-CPX testing resting values were considered as the last 30 s on the cycle ergometer before the start of CPX testing. VT_1 was defined as the first increase in VE accompanied by an increase in VE/VO_2 without an increase in VE/VCO_2. The VT_2 was defined as the second abrupt increase in VE accompanied by an increase in both VE/VO_2 and VE/VCO_2 (15).

All research groups terminated CPX testing if participants reached volitional maximal exhaustion. Contrary to guidelines by the American College of Sports Medicine for the general population, reaching a plateau in VO_2 was not a criterion for peak performance in our analysis since individuals with type 1 diabetes as well as healthy individuals inexperienced in routine exercise often do not achieve a plateau in VO_2 during maximum CPX testing, particularly with cycling exercise (16). Therefore, volitional exhaustion was defined as the point when HR failed to rise with increasing exercise intensity ≥85% age-predicted HR_{peak} and as reaching a respiratory exchange ratio of ≥1.10. Peak values were calculated as the mean over the last 30 s before termination of the CPX test (16). If these criteria were not met, data were excluded from the analysis.

Additionally, the degree and direction of the deflection of the HR (k_{HR}) to the performance curve was calculated by a second-degree polynomial function between VT_1 and the maximum power output (17,18). With this function, two slopes of two tangents were calculated between VT_1 and maximum power output by applying the equation of factor k ($k = [k_1 - k_2] / [1 + k_1 * k_2]$). The k values were classified as linear ($-0.1 \leq k \leq 0.1$), downward deflection ($k > 0.1$) (regular), and upward deflection ($k < -0.1$) (atypical) (19) (Fig. 1). The CPX data were analyzed using the Vienna CPX-Tool (Vienna University, Vienna, Austria), and results were reviewed independently by two investigators for consistency (20). Inclusion and exclusion of data are shown in Supplementary Fig. 1.

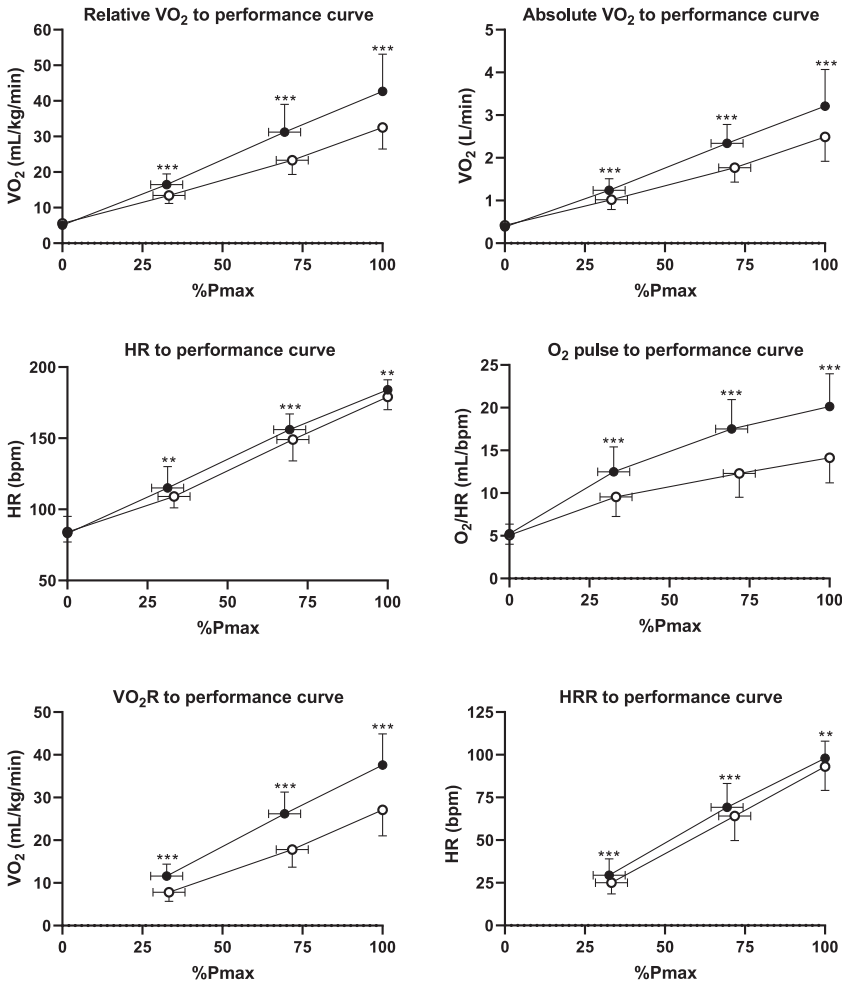

Figure 1—Physiological responses to CPX testing before exercise at VT_1, VT_2, and peak. Black circles represent control participants without type 1 diabetes. Open circles represent individuals with type 1 diabetes. $^{**}P < 0.01$, $^{***}P < 0.001$ between groups.

Statistical Analyses

Data were tested for normal distribution by Kolmogorov-Smirnov test. Data are presented according to their distribution as mean ± SD or median (interquartile range [IQR]) for participants' anthropometric data, specific diabetes characteristics, and performance data (Table 1). Performance data for pre-CPX testing, VT_1, VT_2, and peak values were compared for differences over time and between groups using restricted maximum likelihood model with post hoc testing (Sidak multiple comparisons test). Sex-specific differences were calculated using Fisher exact test for each group.

A stepwise linear regression approach was used to explore relationships when significant differences were found between groups for k_{HR}, VT_1, VT_2, and peak parameters of relative VO_2, HR, and power (P) (dependent variables) against anthropometric (sex, BMI, age) and specific diabetes characteristics (diabetes duration, total daily insulin dose, HbA_{1c}, C-peptide) as independent variables. Stepwise linear regressions were adjusted for anthropometric variables if not included in the regression model.

If data were nonnormally distributed, logarithmic transformations were performed. Analyses were performed using SPSS version 26 (IBM Corporation) and a standard software package, GraphPad Prism 8.0 (GraphPad Software). Statistical significance was accepted at $P < 0.05$ (two-tailed).

RESULTS

A total of 303 individuals with type 1 diabetes and 308 control participants without type 1 diabetes were included in the final analysis. Baseline characteristics before the CPX testing are shown in Table 1. The flow diagram can be found in Supplementary Fig. 1.

Table 1—Baseline characteristics of the study cohort

Characteristic	Group		P value
	Control (n = 308)	Type 1 diabetes (n = 303)	
Age (years)	32 (26; 41)	33 (22; 43)	0.88
BMI (kg/m^2)	24.1 (22; 26)	23.6 (22; 26)	0.21
Males/females, n	220/88	210/93	0.59
Diabetes duration (years)		0.8 (0.4; 12.3)	
Total daily insulin dose (IU)		30 (14; 50)	
HbA_{1c} (%)		6.9 (6.2; 7.7)	
HbA_{1c} (mmol/mol)		52 (44; 61)	
C-peptide (nmol/L)		0.27 (0.14; 0.43)	

Data are median (IQR) unless otherwise indicated.

CPX Testing

Individuals with type 1 diabetes enrolled in studies at different research sites performed the following exercise testing protocols: 62 participants performed stepwise test protocols with 180-s increments with either 30 W (female) or 40 W (male); 191 participants performed a ramp protocol in which the workload increased linearly every minute between 8 and 60 W, depending on the expected performance as determined by experienced exercise physiologists; and 50 participants performed a quasi-ramp protocol in which the workload increased by 15 W (female) or 20 W (male) per minute. Control participants followed similar exercise testing protocols. On average, test protocols increased the workload by 7% (IQR 6; 8%) of the individual P_{peak} per minute in the control group and by 8% (7; 10%) in individuals with type 1 diabetes.

Physiological Response

VO_2

Relative VO_2 was lower in individuals with type 1 diabetes compared with control participants without type 1 diabetes at submaximal thresholds VT_1 (13.41 [IQR 11.18; 15.95] vs. 16.49 [14.00; 19.47] mL/kg/min) and VT_2 (23.33 [19.34; 28.73] vs. 31.20 ± 7.82 mL/kg/min) as well as at VO_{2peak} (32.55 [26.49; 38.72] vs. 42.67 ± 10.44 mL/kg/min; all $P < 0.001$). Absolute VO_2 was lower in individuals with type 1 diabetes compared with control participants at VT_1 (1.00 [0.79; 1.29] vs. 1.23 [0.99; 1.52] L/min), VT_2 (1.69 [1.39; 2.16] vs. 2.32 [1.81; 2.81] L/min), and VO_{2peak} (2.41 [1.87; 3.01] vs. 3.22 [2.43; 3.83] L/min; all $P < 0.001$). Measured VO_2 reserve was lower in individuals with type 1 diabetes compared with control participants at VT_1 (7.80 [5.73; 9.99] vs. 11.61 [8.91; 14.41] mL/kg/min), VT_2 (17.82 [13.68; 22.37] vs. 26.17 ± 7.60 mL/kg/min) and peak VO_2 reserve (27.10 [21.01; 32.94] vs. 37.65 ± 10.33 mL/kg/min; all $P < 0.001$). Oxygen pulse was lower in individuals with type 1 diabetes compared with control participants at VT_1 (9.60 [7.25; 11.40] vs. 12.49 [9.84; 15.41] mL O_2/beat), VT_2 (12.30 [9.50; 15.30] vs. 17.61 ± 5.58 mL O_2/beat), and peak (14.14 [11.19; 17.27] vs. 20.36 ± 6.07 mL O_2/beat; all $P < 0.001$) (Fig. 1).

HR

The HR-to-performance curve increased linearly in individuals with type 1 diabetes, detailing a median k_{HR} of 0.07 [IQR −0.75; 1.09], while in control participants without type 1 diabetes, a k_{HR} of 0.66 [−0.28; 1.45] was present ($P < 0.001$) (Fig. 1). In individuals with type 1 diabetes, HR was significantly lower compared with control participants at VT_1 (109 [101; 118] vs. 115 ± 15 bpm; $P < 0.01$), VT_2 (149 ± 15 vs. 156 [144; 167] bpm; $P < 0.001$), and HR_{peak} (179 [170; 187] vs. 184 [175; 191] bpm; $P < 0.01$). Measured HR reserve was also lower in individuals with type 1 diabetes at VT_1 (25 [19; 30] vs. 29 ± 10 bpm; $P < 0.001$), VT_2 (64 ± 14 vs. 69 ± 14 bpm; $P < 0.001$), and peak (93 ± 14 vs. 98 [88; 108] bpm; $P < 0.01$) (Figs. 1 and 2).

Power Output

Relative power output was lower in individuals with type 1 diabetes compared with control participants without type 1 diabetes at VT_2 (1.95 [IQR 1.64; 2.33]) vs. 2.31 ± 0.60 W/kg) and peak (2.78 [2.35; 3.32] vs. 3.33 ± 0.83 W/kg; $P < 0.001$) but not at VT_1 (0.93 [0.79; 1.07] vs. 1.03 ± 0.30 W/kg; $P = 0.14$). Absolute power output was also lower in individuals with type 1 diabetes at VT_2 (155 [120; 180] vs. 170 [140; 200] W) and P_{peak} (216 [171; 253] vs. 245 [200; 300] W; $P < 0.001$), with no significant difference at VT_1 (72 [56; 89] vs. 80 [65; 100] W; $P = 0.22$) compared with control participants (Fig. 1). Additional parameters of performance for both groups, including a sex-specific subgroup analysis, are presented in Supplementary Tables 2–5.

Association Between Diabetes Characteristics and Functional Capacity

We found statistically significant associations between anthropometric and specific diabetes characteristics with physiological parameters of submaximal and peak performance in individuals with type 1 diabetes and for anthropometric characteristics and physiological parameters for control participants without type 1 diabetes (Table 2).

CONCLUSIONS

This analysis showed that individuals with type 1 diabetes have impaired submaximal and peak responses in VO_2, HR, and power output as well as altered HR kinetics to CPX testing compared with control participants without type 1 diabetes. These alterations in functional capacity coincide with data by Turinese et al. (11) showing lower relative VO_{2peak} in individuals with type 1 diabetes. However, they disagree partly with results by Moser et al. (12), who did not find any differences in HR_{peak} but in k_{HR} between groups, and are contrary to what was shown by Nascimento et al. (21), where no difference in functional capacity between individuals with type 1 diabetes and control participants without type 1 diabetes during exercise testing was evident.

There are several potential explanations for these findings compared with other researchers. First, in contrast to our study, where median diabetes duration was <1 year, diabetes duration was usually longer in previous studies (>10 years) (11,12). Second, age is a major influencing factor when assessing exercise capacity because of its inverse relationship to P_{peak}, HR_{peak}, and VO_{2peak}, and this may prevent comparisons if not adjusted for statistical testing in some studies (19). Furthermore, cohorts that are being investigated in different studies tend to be much smaller in sample size, and the cohort examined often varies in glycemic control, which may further have a deteriorating impact on the

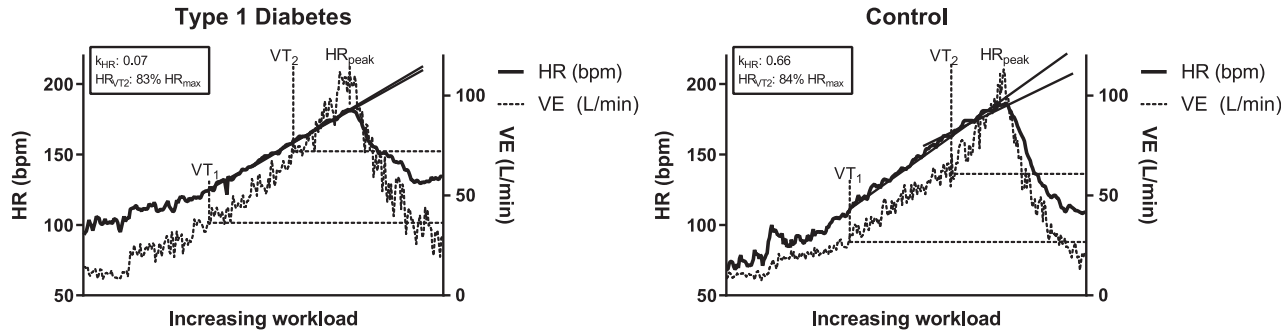

Figure 2—Schematic presentation of the calculation of the degree and direction of the HR-to-performance curve (k_{HR}) for individuals with type 1 diabetes and control participants without type 1 diabetes.

physiological exercise response as shown by Moser et al. (12). We have also found a positive relationship between diabetes duration and HR_{peak}. This can be reflected as a result of a hyperglycemia-induced sympathetic tonus, which may be increased because of a constant catecholamine response (= stress response), indicating a reduced HR_{peak} during CPX testing. This circumstance has previously been discussed since cardiac β-receptors may be desensitized because of a constant stress response (18).

We found that relative VO_2 was ~30% lower in individuals with type 1 diabetes at submaximal thresholds and ~20% lower at peak performance compared with control participants without type 1 diabetes, although body mass was not significantly different between individuals with type 1 diabetes and control participants. Values of VO_{2peak} in our control group are similar to data from the Fitness Registry and the Importance of Exercise: A National Database (22). This similarity implies that our cohort is representative for the general population.

Previously, it has been shown that poor glycemic control detrimentally affects oxygen economy during CPX testing (23). However, this might not apply to our study cohort because the HbA_{1c} averaged 6.9% (52 mmol/mol), which is in line with recommendations by the American Diabetes Association to help to prevent micro- and macrovascular complications (24). It may be speculated that levels of physical activity are reduced in our cohort since early after diagnosis of type 1 diabetes, the attitude toward regular physical activity changes because of several barriers to physical exercise (25). On the basis of our subgroup analysis (Supplementary Tables 5 and 5.1), we show that physical activity had no impact

Table 2—Associations for submaximal and peak parameters in individuals with type 1 diabetes and control participants without type 1 diabetes

	β									
Group	VO_{2VT1}	VO_{2VT2}	VO_{2peak}	HR_{VT1}	HR_{VT2}	HR_{peak}	P_{VT1}	P_{VT2}	P_{peak}	k_{HR}
Type 1 diabetes										
Age		−0.17**		−0.48***	−0.57***	−0.63***		−0.14***		0.24***
BMI	−0.37***	−0.28***	−0.19**				0.22**	0.24***		
Male sex	−0.16*	−0.46***	−0.52***				−0.57***	−0.64***	−0.60****	
Female sex				0.18**						
HbA_{1c}										
TDD		−0.27***	−0.23***					−0.18**		0.20*
DD						0.15**				
C-peptide		−0.29***	−0.32***				−0.21***	−0.26***		
R	0.38	0.65	0.64	0.51	0.57	0.67	0.62	0.68	0.59	0.28
R^2	0.15	0.42	0.41	0.26	0.33	0.45	0.39	0.46	0.36	0.08
Adjusted *R*	0.32	0.65	0.64	0.44	0.46	0.59	0.64	0.68	0.63	0.29
Adjusted R^2	0.10	0.42	0.41	0.19	0.21	0.34	0.41	0.46	0.40	0.09
P value (both)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Control										
Age	−0.28***	−0.36***	−0.42***	−0.36****	−0.42***	−0.53***	−0.44***	−0.39***	−0.39***	−0.18***
BMI	−0.33***	−0.31***	−0.33***		−0.17					−0.33***
Male sex	−0.35***	−0.45***	−0.56***				−0.62***	−0.72***	−0.73***	
Female sex				0.16***						
R	0.53	0.61	0.72	0.43	0.53	0.53	0.68	0.74	0.75	0.45
R^2	0.28	0.38	0.53	0.18	0.28	0.28	0.46	0.55	0.56	0.20
Adjusted *R*				0.43	0.53	0.54	0.68	0.74	0.75	0.45
Adjusted R^2				0.18	0.28	0.29	0.46	0.55	0.56	0.20
P value (both)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

DD, diabetes duration; TDD, total daily dose. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

on the results of the CPX tests. In our analysis, a higher VO_{2peak} was associated with a lower total daily insulin dose, which is not surprising since regular physical activity reflected by a higher VO_{2peak} necessitates reduction in insulin because of improved insulin sensitivity by elevated GLUT4 activity (26).

Interestingly, we found that higher VO_{2peak} was associated with lower C-peptide levels. This is a rather contradictory finding (27) but might be ascribed to the short diabetes duration of <1 year in our cohort. A detectable C-peptide level, and hence, endogenous insulin production, is advantageous for individuals with type 1 diabetes to maintain the inverse relationship between insulin and glucagon secretion (28). It has been shown that individuals with type 1 diabetes and higher C-peptide levels are less prone to exercise-induced hypoglycemia (29). Nonetheless, the clinical importance of our finding with regard to endogenous insulin production is still unclear and suggests further study to explain this finding.

The HR response to CPX testing was lower at submaximal and peak parameters in individuals with type 1 diabetes compared with control participants without type 1 diabetes. An often overlooked complication in diabetes is cardiovascular autonomic neuropathy known to impair exercise tolerance, blunting HR responses, which may also be present at diagnosis of type 1 diabetes (30). Another contributing factor is hyperglycemia, leading to chronically elevated adrenaline and noradrenaline levels that potentially induce β_1-adrenoreceptor insensitivity as shown in adolescent girls with type 1 diabetes (31), subsequently leading to chronotropic incompetence (32). In line with the impaired HR responses to increasing physiological demands, k_{HR} detailed an atypical HR-to-performance curve in the type 1 diabetes group. As shown in healthy individuals (33) and those with a chronic condition (18), only a small proportion of individuals show a linear (6%) or inverted (8%) HR response during incremental exercise testing, which might be a first indication of myocardial function alterations. Interestingly, also in adults with long-standing type 1 diabetes and poorer glycemic control (HbA_{1c} ~7.8% [62 mmol/mol]), the HR-to-performance curve shifts toward a linear or inverted curve and inadequate response of the HR to exercise demands (18). Moser et al. (12) postulated that this chronotropic incompetence reflects dysregulated cardiac muscle contractions during CPX testing. From our point of view, this assumption is questionable and contrary to our findings (Fig. 1) since a linear curve may not lead to a reduction of cardiac performance.

Relative and absolute P_{VT2} and P_{peak} were lower in individuals with type 1 diabetes compared with control participants without type 1 diabetes. These findings coincide with a reduced cardiopulmonary response throughout the CPX test. We did not find a significant difference at P_{VT1} between groups, which indicates a regular aerobic energy supply at low-intensity exercise in individuals with type 1 diabetes. It appears that with increasing exercise intensity, the metabolic demand needed for corresponding muscular performance cannot be covered sufficiently by the cardiopulmonary system as shown by our previous results (12).

No specific diabetes characteristics were associated with P_{peak}, while submaximal P_{VT1} and P_{VT2} both were negatively associated with C-peptide, which is an interesting and unexpected finding. A lower P_{VT2} was associated with a higher total daily insulin dose. It is of interest that submaximal parameters of power output are associated with specific diabetes characteristics, whereas P_{peak} is not. The P_{VT2} is reached earlier during CPX testing in individuals with type 1 diabetes, which is potentially due to higher mismatch in metabolic demand, leading to an overall decreased P_{peak}.

Our analysis is not without limitations since blood glucose values before and during exercise testing in individuals with type 1 diabetes and in the control group are missing, which could have delivered additional value to our analysis (34). Data on HbA_{1c} levels and C-peptide levels are missing in the control participants without type 1 diabetes; hence, a comparison between groups regarding those parameters is not applicable, even though we tried to match the groups as close as possible by sex, age, and BMI. An additional limitation is the lack of data on habitual physical activity behavior, which could be different between individuals without type 1 diabetes and those with type 1 diabetes, potentially influencing our results. However, we have conducted an additional subgroup analysis (Supplementary Tables 5 and 5.1) to show that physical activity had no impact on the results of the CPX tests. Our study is also limited because we did not assess HR variability, which was shown to be linked to functional capacity in adolescents with type 1 diabetes (35). It might be that alterations in cardiac autonomic modulation were present in our study cohort, deteriorating markers of exercise performance in people with type 1 diabetes. Furthermore, a small proportion of individuals with type 1 diabetes were on additional medication, which we do not believe to have a detrimental effect on their physical performance (Supplementary Material 1 and Supplementary Table 1).

The findings of our study may have implications for the future use of CPX testing in individuals with type 1 diabetes. The necessity of testing cardiopulmonary performance shortly after the diagnosis of type 1 diabetes is important since independent of glycemic control, human physiology seems to change early in individuals with type 1 diabetes. However, living with type 1 diabetes is not detrimental to functional capacity because small, specific cohorts, including recreationally active adults and athletes with type 1 diabetes, showed up to a twofold higher VO_{2peak} than that in our cohort (12,36).

Physical activity and exercise management have become an integral component in the therapy of type 1 diabetes within recent decades of fighting this condition (37). CPX testing is a very helpful method to accurately prescribe exercise as a therapy and provides further insight into early physiological alterations. Nevertheless, our analysis has shown that the responses to CPX testing are impaired in individuals with type 1 diabetes independent of HbA_{1c} compared with control participants without type 1 diabetes. In summary, health care professionals should be vigilant when recommending exercise at specific intensities in type 1 diabetes and regularly conduct CPX tests to monitor cardiopulmonary changes and respond accordingly if deemed necessary.

Acknowledgments. The authors are grateful for the support of Farah Abbas and Hakan Yildirim (Medical University of Graz) for data editing.

Funding and Duality of Interest. Data were extracted from clinical trials funded by Novo Nordisk A/S (ClinicalTrials.gov registration no.: NCT01704417; drks.de registration no.: DRKS00013509) and Novo Nordisk Austria (EudraCT registration no.: 2017-000922-37); from the prospective observational German Diabetes Study (ClinicalTrials.gov registration no: NCT01055093) by the German Diabetes Center, which is funded by the Ministry of Culture and Science of the State of North Rhine-Westphalia and the German Federal Ministry of Health and in part by a grant of the Federal Ministry of Education and Research to the German Center for Diabetes Research; and from the Swiss National Science Foundation (ClinicalTrials.gov registration no.: NCT02068638), the Fundo de Incentivo à Pesquisa–Hospital de Clínicas de Porto Alegre (ClinicalTrials.gov registration no.: NCT03451201), and Brazilian National Council for Research and Technological Development (ClinicalTrials.gov registration no.: NCT02939768). M.L.E. has received a KESS2/European Social Fund scholarship and travel grants from Novo Nordisk A/S and a research grant from Sanofi and Novo Nordisk A/S. O.Mc. has received a Zienkiewicz PhD research scholarship and travel grants from Novo Nordisk UK. J.E.Y. has received lecture fees from Dexcom and in-kind research support from Dexcom, LifeScan Canada, and Abbott Nutrition. C.S. reports having received speaker honoraria from Medtronic and Ypsomed and serving on advisory panels for Novo Nordisk, Medtronic, Roche, and Sanofi. M.C.R. has received lecture fees from Medtronic Diabetes, Novo Nordisk, and Insulet; consulting/advisory board fees from Xeris Pharmaceuticals and Zucara Therapeutics; research grants from Sanofi and Novo Nordisk; and material funding from Dexcom. D.P.Z. has received lecture fees from Medtronic Diabetes, Ascensia Diabetes, and Insulet. T.R.P. has received research support from Novo Nordisk and AstraZeneca (paid directly to the Medical University of Graz) and personal fees as a consultant from Adocia, Arecor, AstraZeneca, Eli Lilly, Novo Nordisk, and Sanofi. T.R.P. is also the chief scientific officer of the Center for Biomarker Research in Medicine, a publicly funded biomarker research company. H.H. is an employee and shareholder of Novo Nordisk. E.Z. is an employee and shareholder of Profil. T.H. received speaker honoraria and travel grants from Eli Lilly. M.R. received personal fees from Boehringer Ingelheim, Eli Lilly, Fishawack Group, Novo Nordisk, ProSciento, Sanofi, Servier Laboratories, Target NASH, and Terra Firma and investigator--initiated research support from Boehringer Ingelheim, Danone Nutricia, and Sanofi. H.S. has received honoraria, travel support, or unrestricted research grants by Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, and Sanofi. R.M.B. reports having received honoraria, travel, and educational grant support from Beneo, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi Aventis. O.Mo. has received lecture fees from Medtronic; travel grants from Novo Nordisk A/S, Novo Nordisk AT, Novo Nordisk UK, and Medtronic AT; research grants from Sêr Cymru II COFUND Fellowship/European Union, Sanofi, Dexcom, Novo Nordisk A/S, and Novo Nordisk AT; and material funding from Abbott Diabetes Care and Dexcom. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.L.E., O.Mc., and R.M.B. researched data. M.L.E. and F.A. performed the statistical analysis. M.L.E. and O.Mo. wrote the manuscript. J.B.F., O.Mc., D.J.W., J.E.Y., L.Ba., T.Z., C.S., W.B., A.R.-O., M.C.R., D.P.Z., T.R.P., A.M., P.B., L.Br., H.H., E.Z., T.H., H.S., M.R., P.H., R.M.B., and D.P. reviewed/edited the manuscript and contributed to the discussion. O.Mo. is the coordinator of this initiative. O.Mo. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 56th Annual Meeting of the European Association for the Study of Diabetes, Virtual, 21–25 September 2020.

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