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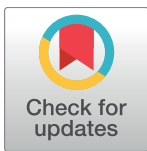
RESEARCH ARTICLE

# Heart rate dynamics during cardio-pulmonary exercise testing are associated with glycemic control in individuals with type 1 diabetes

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## Abstract

### Introduction

This study investigated the degree and direction ( $k_{HR}$ ) of the heart rate to performance curve (HRPC) during cardio-pulmonary exercise (CPX) testing and explored the relationship with diabetes markers, anthropometry and exercise physiological markers in type 1 diabetes (T1DM).

### Material and methods

Sixty-four people with T1DM (13 females; age:  $34 \pm 8$  years;  $HbA_{1c}$ :  $7.8 \pm 1\%$  ( $62 \pm 13$   $mmol \cdot mol^{-1}$ )) performed a CPX test until maximum exhaustion.  $k_{HR}$  was calculated by a second-degree polynomial representation between post-warm up and maximum power output. Adjusted stepwise linear regression analysis was performed to investigate  $k_{HR}$  and its associations. Receiver operating characteristic (ROC) curve was performed based on  $k_{HR}$  for groups  $k_{HR} < 0.20$  vs.  $> 0.20$  in relation to  $HbA_{1c}$ .

### Results

We found significant relationships between  $k_{HR}$  and  $HbA_{1c}$  ( $\beta = -0.70$ ,  $P < 0.0001$ ), age ( $\beta = -0.23$ ,  $P = 0.03$ ) and duration of diabetes ( $\beta = 0.20$ ,  $P = 0.04$ ). Stepwise linear regression resulted in an overall adjusted  $R^2$  of 0.57 ( $R = 0.79$ ,  $P < 0.0001$ ). Our data revealed also significant associations between  $k_{HR}$  and percentage of heart rate at heart rate turn point from maximum heart rate ( $\beta = 0.43$ ,  $P < 0.0001$ ) and maximum power output relativized to body-weight ( $\beta = 0.44$ ,  $P = 0.001$ ) (overall adjusted  $R^2$  of 0.44 ( $R = 0.53$ ,  $P < 0.0001$ )). ROC curve analysis based on  $k_{HR}$  resulted in a  $HbA_{1c}$  threshold of 7.9% ( $62$   $mmol \cdot mol^{-1}$ ).

### Conclusion

Our data demonstrate atypical HRPC during CPX testing that were mainly related to glycemic control in people with T1DM.

## OPEN ACCESS

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**Data Availability Statement:** The authors cannot share the data underlying this study because the data belongs to Profil Institut für Stoffwechselforschung GmbH. Qualified researchers may request data access by contacting Profil Institut für Stoffwechselforschung GmbH ([marketing@profil.com](mailto:marketing@profil.com)). The authors did not have any special access privileges that others would not have. Profil Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, 41460 - Neuss,

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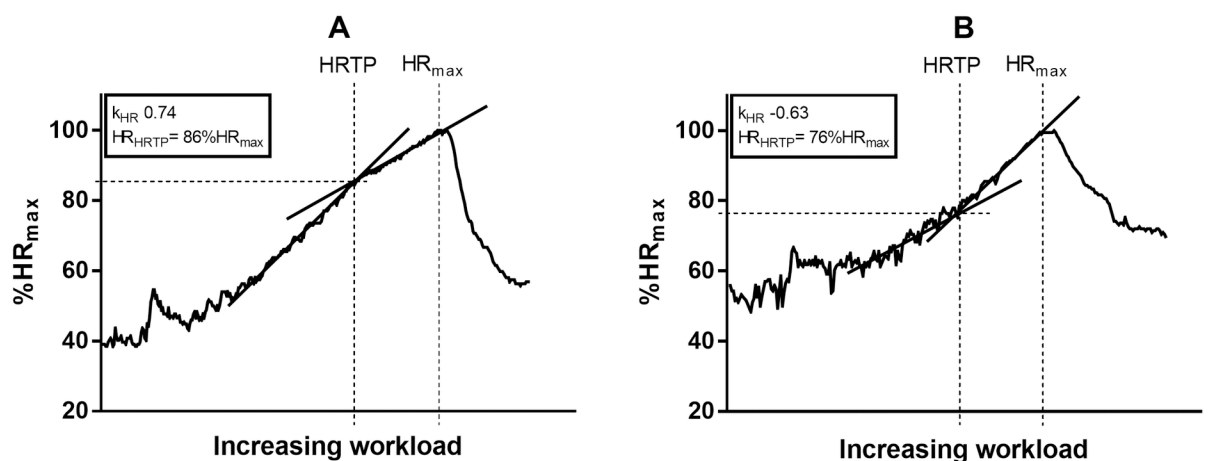
## Introduction

Cardio-pulmonary exercise (CPX) testing provides detailed diagnostic information about cardio-pulmonary, vascular and musculoskeletal adaptations to physical stressors [1]. Aerobic performance markers, like thresholds (e.g. ventilatory thresholds or the heart rate turn point (HRTP)) are recommended to accurately prescribe individualized exercise intensity [2]. These thresholds relativized to maximum oxygen consumption ( $VO_{2max}$ ) serve as sensitive markers to analyze effects of exercise training in both healthy individuals and patients [3]. As an example the HRTP, which is based on findings from Conconi and colleagues, was significantly associated with the second lactate threshold [4–7]. This heart rate (HR) derived threshold is defined as the intersection of two regression lines of the HR to performance curve (HRPC) between early stages of CPX testing (peri-first lactate turn point ( $LTP_1$ )) and maximum power output ( $P_{max}$ ), determined from a second-degree polynomial representation satisfying the condition of least error squares (Fig 1) [8].

From a physiological point of view the main cause for the HRTP can be seen in the  $\beta_1$ -receptor sensitivity to the catecholamine response [9]. Hofmann et al. investigated the response to a single dose of the  $\beta_1$ -selective antagonist bisoprolol in healthy individuals [10]. This study revealed a significant association between the response to the antagonist and different patterns of the HRPC. A regular HRPC translated to inverted HRPC when using the  $\beta_1$ -antagonist. However, an inverted HRPC under placebo did not change its pattern under a  $\beta_1$ -antagonist application. This shows that the inverted HRPC in placebo conditions is caused by a reduced  $\beta_1$ -receptor sensitivity.

Inter-individual differences in HRPC were observed in healthy individuals and in different groups of patients [8]. In the general population, approximately 86% of people show regular deflections of HRPC across a sub-maximal (HRTP) to maximal ( $P_{max}$ ) continuum; however, 8% reveal inverted deflections and 6% display linear increases in HRPC.

Chronotropic incompetence (CI) is the inability of the HR to increase in proportion to raised metabolic demand, and is found mainly in people with coronary artery disease. CI is a strong and independent predictor of overall mortality [11]. Interestingly, this non-physiological cardiac response was also reported in people with type 2 diabetes, where its origin is not



**Fig 1. Schematic of the heart rate to performance curve (HRPC) and detection of the heart rate turn point (HRTP) during CPX testing, illustrating a regular HRPC (A) and an inverted HRPC (B).** The difference in HRPC translates to a lower heart rate at HRTP ( $HR_{HRTP}$ ) when given as percentage of the maximum heart rate ( $\%HR_{max}$ ) (difference 10%).  $k_{HR}$  = degree and direction of the heart rate to performance curve.  $HR_{max}$  = maximum heart rate.

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fully understood. Diabetes *per se* and/or disease-related comorbidities as well as physiological anomalies seem to play a role for CI [12].

Poor glycemic control in people with T1DM may be associated with blunted functional capacity compared to healthy individuals, which is mainly assessed by means of  $VO_{2max}$  [13–15]. Some studies suggested that poor glycemic control may alter cardio-respiratory and metabolic responses to exercise, which translates to a general lower functional capacity in people with T1DM [13,15]. Furthermore, it has been shown that people with T1DM have a reduced maximum HR ( $HR_{max}$ ) in comparison to their healthy counterparts [13]. Intriguingly, the blunted effect of  $HR_{max}$  was shown to be dependent on glycemic control [16].

It is currently not known if the degree and the direction ( $k_{HR}$ ) of the HRPC during CPX testing is related to glycemic control in people with T1DM. Therefore, the aim of this study was to investigate  $k_{HR}$  during CPX testing and explore relationships to diabetes markers, anthropometry and exercise physiological markers in a large group of people with T1DM.

## Material and methods

### Participant characteristics

For this study sixty-four people with T1DM were recruited from October 2012 until March 2013 by advertisement in local newspapers (Table 1, Fig 2):

### Consent procedure

Participants gave their written informed consent before any trial related activities. The trial was performed accordingly to the Declaration of Helsinki (DoH) and Good Clinical Practice (GCP) Guidelines. The primary study protocol was approved by the local ethics committee

**Table 1. Participant characteristics given as mean ± SD and percentage (%).**

Characteristic	Total (n = 64)
Age (years)	34 ± 8
Female (n; %)	13 (20)
Male (n; %)	51 (80)
Body mass index (kg/m <sup>2</sup> )	24 ± 2
Duration of diabetes (years)	17 ± 9
HbA <sub>1c</sub> (% (mmol.mol <sup>-1</sup> ))	7.8 ± 1 (62 ± 13)
Total daily dose of insulin (U)	51 ± 15
Multiple daily injections (n; %)	47 (78)
Insulin pump therapy (n; %)	17 (22)
Arterial hypertension	6
Hypothyroidism	5
Hypercholesterolemia	2
Hashimoto thyroiditis	1
ACE inhibitor	6
Levothyroxine	6
Statin	2
Diuretic medication	1
Calcium channel blocker	1
Physical activity (MET min.wk <sup>-1</sup> )	3086 ± 2736
Maximum oxygen uptake (ml.kg <sup>-1</sup> .min <sup>-1</sup> )	37 ± 5

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CONSORT 2010 Flow Diagram

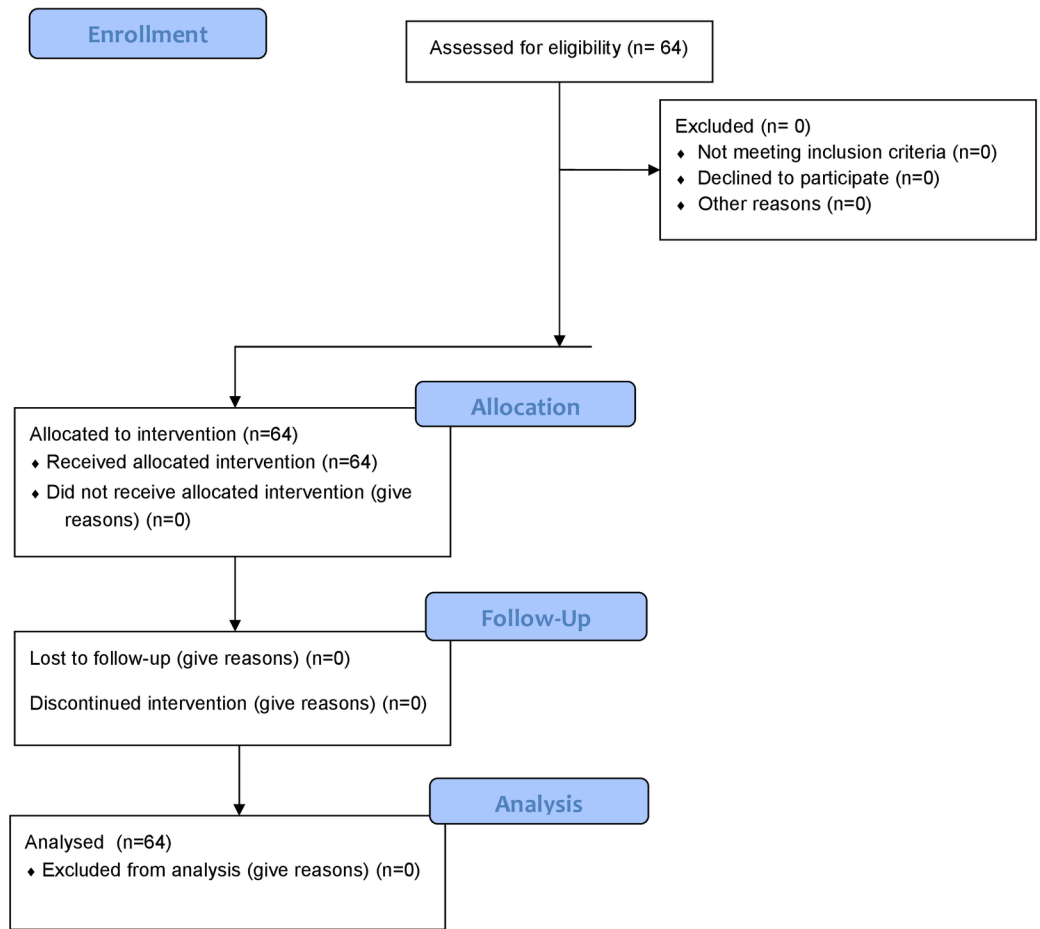


Fig 2. Consort flow diagram.

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and health authority board. The study protocol was registered with the universal clinical trial registry, number NCT01704417 [17].

### Study procedures

Participants filled in the International Physical Activity Questionnaire (IPAQ) to assess physical activity (MET min/week). Medical history, medications and patients' characteristics were documented on the day of the CPX testing. Immediately afterwards, HbA<sub>1c</sub> was measured from a venous blood sample (Automated Glycohemoglobin Analyzer HLC-723G8, Tosoh Europe N.V, Belgium). Venous blood was collected immediately before and after CPX testing

to evaluate blood glucose concentration (Super GL Glucose Analyzer, Dr. Müller Gerätebau GmbH, Germany). Participants performed a CPX test until maximum volitional exhaustion on a cycle ergometer (Ergospirometer PowerCube<sup>®</sup>-Ergo, Ganshorn Medizin Electronic, GER) under medical supervision. Participants sat for 3 min (0 watt (W)) on the cycle ergometer before they started the warm-up period of 3 min cycling at an exercise intensity of 30 W for females and 40 W for males. After the warm-up period, the intensity was increased by 30 W for females and 40 W for males every 3 minutes until maximum volitional exhaustion. Finally, an active recovery period was conducted for 1 min.

## Measurements

Pulmonary gas exchange variables were measured continuously. Data were then averaged over 10 seconds to control for artefacts. Blood pressure and HR were measured continuously via an automatic sphygmomanometer and a 12-lead electrocardiogram (Ergospirometer PowerCube<sup>®</sup>-Ergo, Ganshorn Medizin Electronic, GER). The non-invasive anaerobic threshold was defined by the HRTP. HRTP was demarcated as the intersection of two regression lines of HRPC between post-warm-up and  $P_{\max}$ , determined from a second-degree polynomial representation satisfying the condition of least error squares [8]. All measurements were conducted at Profil, Neuss, Germany.

## Statistical analyses

Data were tested for normal distribution via Shapiro-Wilk test. Descriptive statistics included mean and standard deviation for participant's characteristics.  $k_{\text{HR}}$  was calculated by a second-degree polynomial representation between post-warm up and  $P_{\max}$ . Stepwise linear regression was used to explore relationships between  $k_{\text{HR}}$  and diabetes markers (glycemic control ( $\text{HbA}_{1c}$ ), total daily dose of insulin (both basal- and bolus insulin), duration of diabetes), anthropometry (height, weight, body mass index (BMI)) and physical activity (IPAQ). Stepwise linear regression was also used between  $k_{\text{HR}}$  and exercise physiological markers (CPX derived cardio-respiratory markers at HRTP and at  $P_{\max}$ ). Stepwise linear regressions were adjusted for gender, BMI, physical activity, total daily dose of insulin, duration of diabetes and blood glucose concentration at the start of CPX testing if not included in the regression model. Logarithmic transformation was performed if data were non-normally distributed. Receiver operating characteristic (ROC) curves based on  $k_{\text{HR}}$  for groups  $k_{\text{HR}} < 0.20$  vs.  $> 0.20$  in relation to  $\text{HbA}_{1c}$ . All statistical analyses were carried out using SPSS V.22.0 statistical software (SPSS, Chicago, Illinois, USA). A sample size of 64 individuals with T1DM resulted in a power ( $1 - \beta$  error probability) of 1.0 for the main outcome analyzed via stepwise linear regression, respectively.

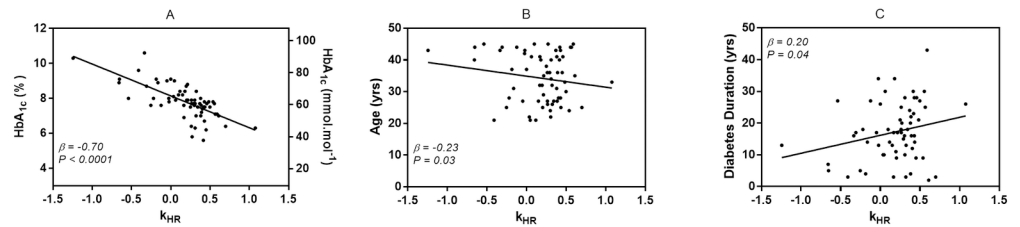
## Results

### Relationships between $k_{\text{HR}}$ and $\text{HbA}_{1c}$ , total daily dose of insulin, duration of diabetes, anthropometry and physical activity

We found significant relationships between  $k_{\text{HR}}$  and  $\text{HbA}_{1c}$  ( $\beta = -0.70, P < 0.0001$ ), age ( $\beta = -0.23, P = 0.03$ ) and duration of diabetes ( $\beta = 0.20, P = 0.04$ ) (Fig 3). Stepwise linear regression resulted in an overall adjusted  $R^2$  of 0.57 ( $R = 0.79, P < 0.0001$ ).

### Relationships between $k_{\text{HR}}$ exercise physiological markers

Our data revealed significant associations between  $k_{\text{HR}}$  and percentage of HR at HRTP from  $\text{HR}_{\max}$  ( $\beta = 0.43, P < 0.0001$ ) and  $P_{\max}$  relativized to bodyweight ( $\beta = 0.44, P = 0.001$ ). Stepwise linear regression resulted in an overall adjusted  $R^2$  of 0.44 ( $R = 0.53, P < 0.0001$ ) (Fig 4).



**Fig 3. Single plots of the association of  $k_{HR}$  and HbA<sub>1c</sub> (A), age (B) and diabetes duration (C).**  $k_{HR}$  = degree and direction of the heart rate to performance curve.

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### ROC curve analysis based on $k_{HR}$

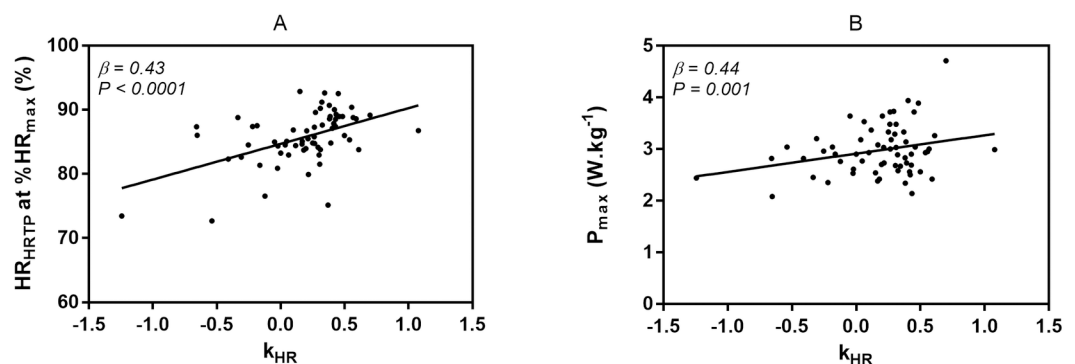
ROC curve analysis based on  $k_{HR}$  for groups  $k_{HR} < 0.20$  vs.  $> 0.20$  resulted in a HbA<sub>1c</sub> threshold of 7.9% (63 mmol.mol<sup>-1</sup>) (81% sensitivity and 82% specificity) (Fig 5).

### Discussion

This study demonstrated the clear association between poor glycemic control and HR dynamics during CPX testing. Intriguingly, higher HbA<sub>1c</sub> and its translation to atypical  $k_{HR}$  resulted in lower HR responses at the HRTP and lower bodyweight-relativized maximum power output. Several physiological mechanisms might explain these novel findings:

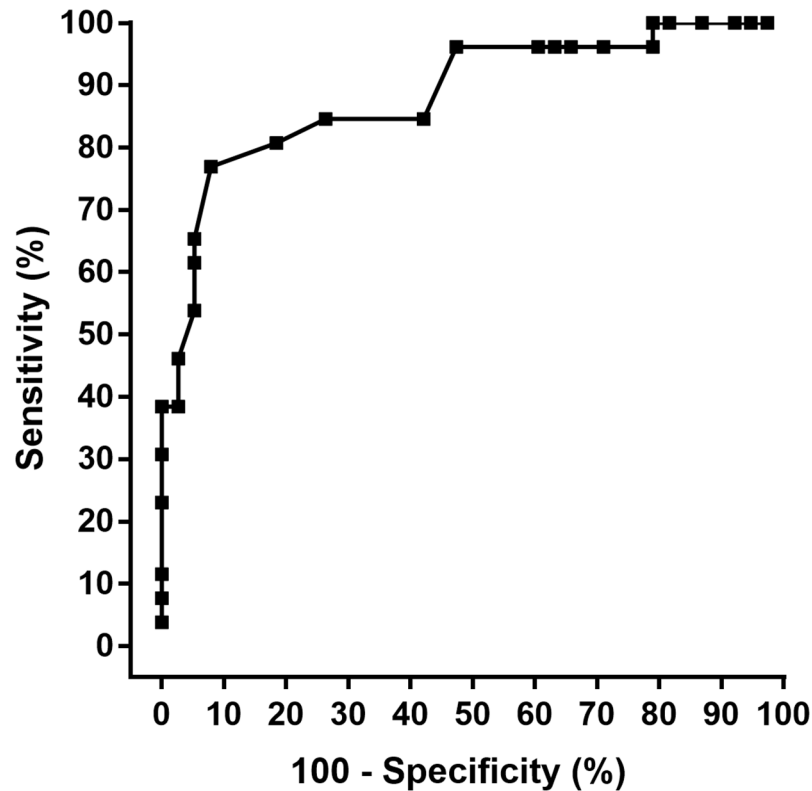
Diabetes specific co-morbidities (e.g. structural myocardial alterations, ventricular and/or arterial stiffness, impaired baroreflex sensitivity and cardiovascular autonomic neuropathy) might minimally contribute to these alterations in  $k_{HR}$ , as the cohort in our trial underwent detailed physical examination [12,18].

Potentially the findings from our study are associated with impairments in  $\beta_1$ -adrenoreceptors. Poor glycaemic control is associated with chronically elevated catecholamine levels [19] and can induce  $\beta_1$ -adrenoreceptor insensitivity. Impairment in  $\beta_1$ -adrenoreceptor sensitivity is known to alter the ability of HR to respond adequately to increasing metabolic demands [20].  $\beta_1$ -adrenoreceptors produces positive inotropy, chronotropy and lusitropy with further positive dromotropic effect and pacemaker activity from the sinoatrial node [21]. We hypothesize if  $\beta_1$ -adrenoreceptor insensitivity is present, a lower rise in free intracellular Ca<sup>2+</sup> concentration dysregulates cardiac muscle contraction [22,23] resulting in CI during CPX testing.



**Fig 4. Single plots of the association of  $k_{HR}$  and HR<sub>HRTP</sub> at %HR<sub>max</sub> (A) and P<sub>max</sub> (B).**  $k_{HR}$  = degree and direction of the heart rate to performance curve, HR<sub>HRTP</sub> at %HR<sub>max</sub> = heart rate at the heart rate turn point given as percentages of the maximum heart rate, P<sub>max</sub> = maximum power output relativized to bodyweight.

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**Fig 5. Receiver operating characteristic (ROC) curve analysis of HbA<sub>1c</sub>.** The sensitivity is plotted against 100–specificity to indicate accuracy. The optimal value for sensitivity was 81%, which corresponded to a specificity of 82%. This represents a cut off level for HbA<sub>1c</sub> of 7.9% (63 mmol.mol<sup>-1</sup>).

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Taking this into account for our study cohort, we postulate that elevated HbA<sub>1c</sub> may modify the typical HR response to stress via β<sub>1</sub>-adrenoreceptor hyposensitivity.

Similar to the findings from our study, previous studies observed reduced cardiac output during sub-maximal exercise intensities in individuals with T1DM [24][13]. Intriguingly, for our data this was not only supported by the decreased ratio of HR at HRTP as percentage of HR<sub>max</sub>, we also found for the non-adjusted stepwise linear regression (data not shown) a significant increased O<sub>2</sub>-Pulse (surrogate parameter for stroke volume) at the HRTP in individuals with poor glycaemic control. We postulate that the decreased ratio of HR at HRTP as percentage of HR<sub>max</sub> is compensated via increased stroke volume at the HRTP to maintain adequate cardiac output in relation to metabolic demands.

Several studies found a decreased exercise performance in comparison of individuals with T1DM and their healthy counterparts [25][26]. However, little research exists on its relation to glycaemic control [13], and to the best of our knowledge, no trials investigated the influence of CI on exercise performance. As found in our study, CI analyzed via k<sub>HR</sub> was associated with lowered P<sub>max</sub> (W.kg<sup>-1</sup>).

ROC curve clearly showed that HbA<sub>1c</sub> above 7.9% (63 mmol.mol<sup>-1</sup>) was associated with k<sub>HR</sub> towards CI in the transition of HRTP to P<sub>max</sub>. A low HbA<sub>1c</sub> accompanied with low risk of hypoglycemic episodes are important aspects of the management of T1DM. However, the percentage of people with T1DM achieving HbA<sub>1c</sub> within 7.0% (53 mmol.mol<sup>-1</sup>) and 7.5% (58 mmol.mol<sup>-1</sup>) is only from 8% to 28% [27–30] and it is unclear if such glycaemic control targets



are attainable for most patients. It might be that more applicable HbA<sub>1c</sub> targets (potentially supported by our threshold of 7.9% (63 mmol.mol<sup>-1</sup>)) accompanied with regular physical activity and exercise could be more beneficial in reduction of risk of all-cause mortality and cardiovascular disease [31] and eventually play a role in restoration of counter-regulatory responses to hypoglycemia [32].

From a clinical point of view the findings from this study could be of immense interest for an exact prescription of exercise intensity. The American Diabetes Association recommends at least 150 min per week of moderate intensity aerobic physical activity, defined as percentages of HR<sub>max</sub> [33]. In consideration of the results from our study regarding HR at H RTP given as percentages of HR<sub>max</sub>, we might dissuade from using percentages of HR<sub>max</sub>. Fixed percentages of HR<sub>max</sub> would lead to an overestimation of exercise intensity in individuals with poor glycaemic control as in these patients the anaerobic threshold (H RTP) was found in a lower percentage to HR<sub>max</sub>.

This study is somewhat limited by possible differences in c-peptide status, which was not measured for the purpose of this study. Further studies are needed to investigate k<sub>HR</sub> and β<sub>1</sub>-adrenoreceptor sensitivity in people with T1DM.

## Conclusions

This is the first study, which found associations between k<sub>HR</sub> and HbA<sub>1c</sub>, age and duration of diabetes in people with T1DM. Individuals with poor glycaemic control showed slower increases in HR during early stages of CPX testing, which translated to (i) a decreased ratio of HR at H RTP as percentage of HR<sub>max</sub> and (ii) a lowered body weight-relativized P<sub>max</sub>. Age and diabetes duration were also found to play a role for these findings. However, both factors contributed minimally to the results (age: β = -0.23; diabetes duration: β = 0.20).

## Supporting information

### S1 Checklist. Trend statement checklist.

(PDF)

### S1 Text. Study protocol.

(PDF)

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## Author Contributions

**Data curation:** Eric Zijlstra, Tim Heise.

**Formal analysis:** Hanne L. Haahr.

**Funding acquisition:** Eric Zijlstra, Tim Heise.

**Investigation:** Othmar Moser, Hanne L. Haahr, Eric Zijlstra, Tim Heise, Richard M. Bracken.

**Methodology:** Othmar Moser, Stephen C. Bain, Hanne L. Haahr, Eric Zijlstra, Tim Heise, Richard M. Bracken.

**Software:** Max L. Eckstein.

**Validation:** Olivia McCarthy.

**Writing – original draft:** Othmar Moser, Richard M. Bracken.

**Writing – review & editing:** Othmar Moser, Max L. Eckstein, Olivia McCarthy, Rachel Deere, Stephen C. Bain, Hanne L. Haahr, Eric Zijlstra, Richard M. Bracken.

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