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

Othmar Moser1,2*, Max L. Eckstein1,2, Olivia McCarthy1,2, Rachel Deere1,2, Stephen C. Bain1, Hanne L. Haahr3, Eric Zijlstra4, Tim Heise4, Richard M. Bracken1,2

1 Diabetes Research Group, Medical School, Swansea University, Swansea, United Kingdom, 2 Applied Sport, Technology, Exercise and Medicine Research Centre (A-STEM), College of Engineering, Swansea University, Swansea, United Kingdom, 3 Novo Nordisk A/S, Søborg, Denmark, 4 Profil, Neuss, Germany

* othmar.moser@swansea.ac.uk

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 ± 8 years; HbA1c: 7.8 ± 1% (62 ± 13 mmol.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 HbA1c.

Results

We found significant relationships between k_{HR} and HbA1c (β = -0.70, P < 0.0001), age (β = -0.23, P = 0.03) and duration of diabetes (β = 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 (β = 0.43, P < 0.0001) and maximum power output relativized to body-weight (β = 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 HbA1c threshold of 7.9% (62 mmol.mol^{-1}).

Conclusion

Our data demonstrate atypical HRPC during CPX testing that were mainly related to glycemic control in people with T1DM.
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 (VO₂max) 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 (LTP₁)) and maximum power output (Pmax), 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 β₁-receptor sensitivity to the catecholamine response [9]. Hofmann et al. investigated the response to a single dose of the β₁-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 β₁-antagonist. However, an inverted HRPC under placebo did not change its pattern under a β₁-antagonist application. This shows that the inverted HRPC in placebo conditions is caused by a reduced β₁-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 (Pmax) 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 (HRHRTP) when given as percentage of the maximum heart rate (%HRmax) (difference 10%). k转型 = degree and direction of the heart rate to performance curve. HRmax = maximum heart rate.](https://doi.org/10.1371/journal.pone.0194750.g001)
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\textsubscript{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\textsubscript{max}) in comparison to their healthy counterparts [13]. Intriguingly, the blunted effect of HR\textsubscript{max} was shown to be dependent on glycemic control [16].

It is currently not known if the degree and the direction (k\textsubscript{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\textsubscript{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.

| Characteristic             | Total (n = 64) |
|---------------------------|---------------|
| Age (years)               | 34 ± 8        |
| Female (n; %)             | 13 (20)       |
| Male (n; %)               | 51 (80)       |
| Body mass index (kg/m\textsuperscript{2}) | 24 ± 2       |
| Duration of diabetes (years) | 17 ± 9   |
| HbA\textsubscript{1c} (% (mmol.mol\textsuperscript{-1})) | 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\textsuperscript{-1}) | 3086 ± 2736 |
| Maximum oxygen uptake (ml.kg\textsuperscript{-1}.min\textsuperscript{-1}) | 37 ± 5 |

https://doi.org/10.1371/journal.pone.0194750.t001
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$_1c$ 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 PowerCube² 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 PowerCube² 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. kHR was calculated by a second-degree polynomial representation between post-warm up and P_{max}. Stepwise linear regression was used to explore relationships between kHR and diabetes markers (glycemic control (HbA₁c), 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 kHR 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 kHR for groups kHR < 0.20 vs. > 0.20 in relation to HbA₁c. 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 – β error probability) of 1.0 for the main outcome analyzed via stepwise linear regression, respectively.

**Results**

**Relationships between kHR and HbA₁c, total daily dose of insulin, duration of diabetes, anthropometry and physical activity**

We found significant relationships between kHR and HbA₁c (β = -0.70, P < 0.0001), age (β = -0.23, P = 0.03) and duration of diabetes (β = 0.20, P = 0.04) (Fig 3). Stepwise linear regression resulted in an overall adjusted R² of 0.57 (R = 0.79, P < 0.0001).

**Relationships between kHR exercise physiological markers**

Our data revealed significant associations between kHR and percentage of HR at HRTP from HR_{max} (β = 0.43, P < 0.0001) and P_{max} relativized to bodyweight (β = 0.44, P = 0.001). Stepwise linear regression resulted in an overall adjusted R² of 0.44 (R = 0.53, P < 0.0001) (Fig 4).
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$_1c$ threshold of 7.9% (63 mmol.mol$^{-1}$) (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$_1c$ 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$^{2+}$ 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$_{HRTP}$ at %HR$_{max}$ (A) and $P_{max}$ (B). $k_{HR}$ = degree and direction of the heart rate to performance curve. $HR_{HRTP}$ at %HR$_{max}$ = heart rate at the heart rate turn point given as percentages of the maximum heart rate, $P_{max}$ = maximum power output relativized to bodyweight.

https://doi.org/10.1371/journal.pone.0194750.g004
Taking this into account for our study cohort, we postulate that elevated HbA$_1c$ may modify the typical HR response to stress via $\beta_1$-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$_{\text{max}}$ we also found for the non-adjusted stepwise linear regression (data not shown) a significant increased O$_2$-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$_{\text{max}}$ 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 $k_{HR}$ was associated with lowered P$_{\text{max}}$ (W.kg$^{-1}$).

ROC curve clearly showed that HbA$_1c$ above 7.9% (63 mmol.mol$^{-1}$) was associated with $k_{HR}$ towards CI in the transition of HRTP to P$_{\text{max}}$. A low HbA$_1c$ accompanied with low risk of hypoglycemic episodes are important aspects of the management of T1DM. However, the percentage of people with T1DM achieving HbA$_1c$ within 7.0% (53 mmol.mol$^{-1}$) and 7.5% (58 mmol.mol$^{-1}$) is only from 8% to 28% [27–30] and it is unclear if such glycemic control targets...
are attainable for most patients. It might be that more applicable HbA1c targets (potentially supported by our threshold of 7.9% (63 mmol.mol\(^{-1}\)) 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\(_{\text{max}}\) [33]. In consideration of the results from our study regarding HR at HRTP given as percentages of HR\(_{\text{max}}\), we might dissuade from using percentages of HR\(_{\text{max}}\). Fixed percentages of HR\(_{\text{max}}\) would lead to an overestimation of exercise intensity in individuals with poor glycaemic control as in these patients the anaerobic threshold (HRTP) was found in a lower percentage to HR\(_{\text{max}}\).

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 \(k_{\text{HR}}\) and \(\beta_1\)-adrenoreceptor sensitivity in people with T1DM.

Conclusions

This is the first study, which found associations between \(k_{\text{HR}}\) and HbA1c, 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 HRTP as percentage of HR\(_{\text{max}}\) and (ii) a lowered body weight-relativized P\(_{\text{max}}\). Age and diabetes duration were also found to play a role for these findings. However, both factors contributed minimally to the results (age: \(\beta = -0.23\); diabetes duration: \(\beta = 0.20\)).

Supporting information

S1 Checklist. Trend statement checklist.
(PDF)

S1 Text. Study protocol.
(PDF)

Acknowledgments

O. Moser has received lecture fees from Medtronic, a travel grant from Novo Nordisk A/S and research grants from Sêr Cymru II COFUND fellowship/European Union and Novo Nordisk A/S. M. L. Eckstein has received a KESS2/European Social Fund scholarship. S. C. Bain reports having received honoraria, teaching and research grants from the Abbott, Astra Zeneca, Boehringer Ingelheim, BMS, Diartis, Eli Lily and Company, GlaxoSmithKline, Johnson & Johnson, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, Servier and Takeda. T. Heise reports having received research funds from Adocia, Astra Zeneca, BD, Biocon, Boehringer Ingelheim, Dance Pharmaceuticals, Grüenthal, Eli Lily and Company, Medtronic, Novo Nordisk, Novartis, Sanofi and Senseonics and having received speaker honoraria and travel grants from Eli Lily and Company, Mylan and Novo Nordisk. R. M. Bracken reports having received honoraria, travel and educational grant support from, Boehringer-Ingelheim, Eli Lily and Company, Novo Nordisk, Sanofi-Aventis. E. Zijlstra, R. Deere and O. McCarthy have no disclosures to report. H. L. Haahr is employee and shareholder in Novo Nordisk A/S. This does not alter our adherence to PLOS ONE policies on sharing data and materials.
This study was funded by Novo Nordisk A/S. Data were extracted from a clinical trial (NCT01704417). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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.

References
1. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician’s Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. Circulation. 2010; 122: 191–225. https://doi.org/10.1161/CIR.0b013e3181e59e69 PMID: 20585013
2. Hofmann P, Tschakert G. Special Needs to Prescribe Exercise Intensity for Scientific Studies. Cardiol Res Pract. 2011; 2011: 1–10. https://doi.org/10.4061/2011/209302 PMID: 21974779
3. Moser O, Tschakert G, Mueller A, Groeschl W, Hofmann P, Pieber T, et al. Short-acting insulin reduction strategies for continuous cycle ergometer exercises in patients with type 1 diabetes mellitus. Asian J Sports Med. 2017; 8. https://doi.org/10.5812/asjsm.42160
4. Conconi F, Ferrari M, Ziglio PG, Droghetti P, Codecà L. Determination of the anaerobic threshold by a noninvasive field test in runners. J Appl Physiol. 1982; 52: 869–73. https://doi.org/10.1152/jappl.1982.52.4.869 PMID: 7085420
5. Ribeiro JP, Fielding RA, Hughes V, Black A, Bochese MA, Knuttgen HG. Heart rate break point may coincide with the anaerobic and not the aerobic threshold. Int J Sports Med. 1985; 6: 220–4. https://doi.org/10.1055/s-2008-1025844 PMID: 4044107
6. Hofmann P, Bunc V, Leitner H, Pokan R, Gaisl G. Heart rate threshold related to lactate turn point and steady-state exercise on a cycle ergometer. Eur J Appl Physiol Occup Physiol. 1994; 69: 132–9. PMID: 7805667
7. Bunc V, Hofmann P, Leitner H, Gaisl G. Verification of the heart rate threshold. Eur J Appl Physiol Occup Physiol. 1995; 70: 263–9. PMID: 7607203
8. Hofmann P, Pokan R, Duvillard S, Seibert F, Zweiker R, Schmid P. Heart rate performance curve during incremental cycle ergometer exercise in healthy young male subjects. Medicine & Science in Sports & Exercise. 1997: pp. 762–768.
9. Hofmann P, Pokan R. Value of the application of the heart rate performance curve in sports. Int J Sports Physiol Perform. 2010; 5: 437–447. PMID: 21266729
10. Hofmann P, Wonisch M, Pokan R, Schwaaberger G, Smekal G, Von Duvillard SP. β1-adrenoceptor mediated origin of the heart rate performance curve deflection. Med Sci Sports Exerc. 2005; 37: 1704–1709. https://doi.org/10.1249/01.mss.0000176308.70316.cc PMID: 16260969
11. Dresing TJ, Blackstone EH, Pashkow FJ, Snader CE, Marwick TH, Lauer MS. Usefulness of impaired chronotropic response to exercise as a predictor of mortality, independent of the severity of coronary artery disease. Am J Cardiol. 2000; 86: 602–609. https://doi.org/10.1016/S0002-9149(00)01036-5 PMID: 10980208
12. Keytcsman C, Dendale P, Hansen D. Chronotropic incompetence during exercise in type 2 diabetes: aetiology, assessment methodology, prognostic impact and therapy. Sport Med. 2015; 45: 985–995. https://doi.org/10.1007/s40279-015-0328-5 PMID: 25834997

13. Baldi JC, Cassuto NA, Foxx-Lupo WT, Wheatley CM, Snyder EM. Glycemic status affects cardiopulmonary exercise response in athletes with type I diabetes. Med Sci Sports Exerc. 2010; 42: 1454–1459. https://doi.org/10.1249/MSS.0b013e3181f1fbd3 PMID: 2039786

14. Nadeau KJ, Regensteiner JG, Bauer TA, Brown MS, Dorosz JL, Hull A, et al. Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. J Clin Endocrinol Metab. 2010; 95: 513–21. https://doi.org/10.1210/jc.2009-1756 PMID: 19915016

15. Baldi JC, Hofman PL. Does careful glycemic control improve aerobic capacity in subjects with type 1 diabetes? Exerc Sport Sci Rev. 2010; 38: 161–7. https://doi.org/10.1097/JES.0b013e3181f4501e PMID: 20871232

16. Niranjan V, McBrayer DG, Ramirez LC, Raskin P, Hsia CC. Glycemic control and cardiopulmonary function in patients with insulin-dependent diabetes mellitus. Am J Med. 1997; 103: 504–13. PMID: 9428834

17. Heise T, Bain SC, Bracken RM, Zijlstra E, Nosek L, Stender-Petersen K, et al. Similar risk of exercise-related hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes: a randomized cross-over trial. Diabetes Obes Metab. 2016; 18: 196–199. https://doi.org/10.1111/dom.12588 PMID: 26450456

18. Béra LG, Pepin ME, Wende AR. My sweet heart is broken: role of glucose in diabetic cardiomyopathy. Diabetes Metab J. 2017; 33: 344–9. https://doi.org/10.4093/dmj.2017.33.4.344 PMID: 29007807

19. Heyman E, Delamarche P, Berthon P, Meeusen R, Briard D, Vincent S, et al. Alteration in sympathoadrenergic activity at rest and during intense exercise despite normal aerobic fitness in late pubertal adolescent girls with type 1 diabetes. Diabetes Metab. 2007; 33: 422–429. https://doi.org/10.1016/j.diabet.2007.10.003 PMID: 18035572

20. Wonisch M, Hofmann P, Fruhwald FM, Kraxner W, Hodl R, Pokan R, et al. Influence of beta-blocker use on percentage of target heart rate exercise prescription. Eur J Cardiovasc Prev Rehabil. 2003; 10: 296–301. https://doi.org/10.1002/hje.12019 PMID: 14555866

21. Colucci WS, Wright RF, Braunwald E. New positive inotropes in the treatment of congestive heart failure. N Engl J Med. 1986; 314: 349–358. https://doi.org/10.1056/NEJM198602063140605 PMID: 2418353

22. Bers DM. Calcium cycling and signaling in cardiac myocytes. Annu Rev Physiol. 2008; 70: 23–49. https://doi.org/10.1146/annurev.physiol.70.113006.100455 PMID: 17988210

23. Lymperopoulos A, Rengo G, Koch WJ. The adrenergic nervous system in heart failure: pathophysiology and therapy. Circ Res. 2008; 6: 2166–2171.

24. Gusso S, Hofman P, Lalande S, Cutfield W, Robinson E, Baldi JC. Impaired stroke volume and aerobic capacity in female adolescents with type 1 and type 2 diabetes mellitus. Diabetologia. 2008; 51: 1317–1320. https://doi.org/10.1007/s00125-008-1012-1 PMID: 18446317

25. Wilson LC, Peebles KC, Hoye NA, Manning P, Sheat C, Williams MJA, et al. Resting heart rate variability and exercise capacity in Type 1 diabetes. Physiol Rep. 2017; 5: e13248. https://doi.org/10.14814/phy2.13248 PMID: 28420762

26. Peltonen JE, Koponen AS, Pullinen K, Häggglund H, Aho JM, Kyröläinen H, et al. Alveolar gas exchange and tissue deoxygenation during exercise in type 1 diabetes patients and healthy controls. Respir Physiol Neurobiol. Elsevier B.V.; 2012; 181: 267–276. https://doi.org/10.1016/j.resp.2012.04.002 PMID: 22538274

27. Wallymahmed M, Pinkney J, Saunders S, MacFarlane I. Vascular risk factors in patients with type 1 diabetes. Pract Diabetes Int. 2005; 22: 81–85. https://doi.org/10.1002/pdi.761

28. Sastré J, Pinés PJ, Moreno J, Aguirre M, Blanco B, Calderón D, et al. Metabolic control and treatment patterns in patients with type 1 diabetes in Castilla-La Mancha: the DIAbetes tipo 1 en Castilla La Mancha study. Endocrinol y Nutr. 2012; 59: 539–46. https://doi.org/10.1016/j.endonut.2012.07.003 PMID: 23039989

29. Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J, et al. Risk of Cardiovascular Disease and Total Mortality in Adults with Type 1 Diabetes: Scottish Registry Linkage Study. PLoS Med. 2012; 9: e1001321. https://doi.org/10.1371/journal.pmed.1001321 PMID: 23055834

30. McKnight JA, Wild SH, Lamb MJ, Cooper MN, Jones TW, Davis EA, et al. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabet Med. 2015; 32: 1036–1050. https://doi.org/10.1111/dme.12676 PMID: 25510978
31. Kodama S, Tanaka S, Heianza Y, Fujihara K, Horikawa C, Shimano H, et al. Association between physical activity and risk of all-cause mortality and cardiovascular disease in patients with diabetes: A meta-analysis. Diabetes Care. 2013; 36: 471–479. https://doi.org/10.2337/dc12-0783 PMID: 23349151

32. McNeilly AD, Gallagher JR, Huang JT-J, Ashford MLJ, McCrimmon RJ. High-intensity exercise as a dishabituating stimulus restores counterregulatory responses in recurrently hypoglycemic rodents. Diabetes. 2017; 66: 1696–1702. https://doi.org/10.2337/db16-1533 PMID: 28270522

33. Chiang JL, Kirkman MS, Laffel LMB, Peters AL. Type 1 diabetes through the life span: A position statement of the American Diabetes Association. Diabetes Care. 2014; 37: 2034–2054. https://doi.org/10.2337/dc14-1140 PMID: 24935775