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Continuous moderate and intermittent high-intensity exercise in youth with type 1 diabetes: Which protection for dysglycemia?

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ABSTRACT

Aim: From an early age, exercise is key to managing type 1 diabetes (T1D). However, hypoglycemia around aerobic exercise is a major barrier to physical activity in children. We explore whether intermittent high-intensity aerobic exercise (IHE), designed to mimic spontaneous childhood physical activity patterns, offers better protection against glycemic drop than continuous moderate-intensity exercise (CME).
Methods: Five boys and 7 girls with T1D (9.8 ± 1.4y) performed ergo cycle-based randomized CME and IHE of identical duration and total mechanical load [50 $\%PWC_{170}$ *vs.* 15sec(150 $\%PWC_{170}$)/30 sec passive recovery; both during two 10-min sets, 5 min in-between]. Capillary glycemia during exercise and interstitial glucose during recovery were compared between exercises and an inactive condition, controlling for baseline glycemia, carbohydrate and insulin.
Results: The exercise-induced decrease in capillary glycemia was attenuated by 1.47 $mmol{\cdot}L^{-1}$ for IHE *vs.* CME ($P < 0.05$). No symptomatic hypoglycemic episodes occurred during exercises. Post-exercise time in hypoglycemia did not differ between conditions. During early recovery, CME reduced time spent > 16.7 $mmol{\cdot}L^{-1}$ compared with inactive days ($P < 0.05$; CME: 0 %; IHE: 16,7 %; INACTIVE: 41,7 %).
Conclusion: IHE appeared to limit the glycemic drop compared to CME. Performing 20-min CME or IHE was not associated with increased hypoglycemic risk compared to being inactive. CME appeared even transiently protective against serious hyperglycemia.

1. Introduction

Regular physical activity is a key component of type 1 diabetes (T1D) management [1]. In youth with T1D, exercise training is effective in improving aerobic fitness as well as other health outcomes including body composition, lipid profile, quality of life [2] and, albeit less systematically, HbA_{1c} [3,4]. Encouraging active behavior from childhood is important as it sets the foundation for a healthy lifestyle in adult life [5,6]. In addition, some benefits of physical activity acquired during childhood, particularly on body composition, fitness, musculoskeletal and cardiovascular systems, may persist during adulthood [7]. For example, strength of the upper body and abdomen as well as lower back flexibility tracks from adolescence into adulthood [8]. Moreover, the benefits of the practice of sport during childhood on bone size and strength are maintained in adulthood even after stopping a sports activity [9].

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However, many children with T1D do not meet physical activity guidelines and are less active than their non-diabetic peers [10]. Fear of exercise-induced hypoglycemia has been identified as a major barrier to active lifestyle in children with T1D [11]. Continuous moderate-intensity aerobic exercise is the primary type of exercise exposing individuals to a high risk of hypoglycemia [12]. In people without T1D, the insulin secretion during physical activity is rapidly suppressed while counterregulatory hormones (*e.g.*, glucagon, catecholamines, and cortisol) increase. This stimulates hepatic glucose production thus compensating for the increased use of glucose by active skeletal muscles (*e.g.,* leg glucose uptake rising tenfold during a 30-min light-to-moderate aerobic exercise [13]) [14]. In people living with T1D, insulin is exogeneous and even when preventive reduction in insulin dose is applied, a decrease in glycemia may occur during exercise due to several factors including increase in insulin absorption from subcutaneous depot into circulation [15], and possible defective counterregulatory hormone response [16]. Since physical activity enhances insulin sensitivity for more than 24 h [14], and since sleep induces impairments in counterregulatory hormone responses [17], the risk of hypoglycemia is particularly common during the night following exercise [18].

Thus, much of the literature on exercise and T1D focuses on strategies for decreasing hypoglycemic risk during and after aerobic exercise. Besides insulin and diet adaptations [19,20], adapting the ~~form~~ type, duration and intensity of exercise has more recently received attention for its advantage of not needing to be anticipated contrary to insulin modulations, and for it being preferable for weight management by avoiding additional carbohydrate intake [21]. In this respect, intermittent high-intensity exercise might attenuate an exercise-induced drop in glycemia through several mechanisms [22]. For example, this type of exercise is associated with increased epinephrine and growth hormone production, which can respectively increase hepatic glucose production and decrease muscle glucose uptake. These increased counterregulatory hormones also stimulate lipolysis and hence increase circulating levels of free fatty acids. The latter may provide an extra source of ATP to active skeletal muscle, thus sparing blood glucose.

Intermittent high-intensity exercise has been explored in a certain number of trials on children [23–28], without any information on late recovery, even though nocturnal hypoglycemia is the event that is the most feared by children's parents [29]. Diet was not controlled either in the analyses of glycemic results, despite the possibility of the modality/intensity of exercise altering satiety [30]. In addition, these studies were conducted in the morning [23–26,28], while children's spontaneous or club-organized physical activity usually takes place in the afternoon or early evening, a period which could elicit substantially higher exercise-induced glycemia decreases [31]. Lastly, only two studies ($n = 5$ [25] or $n = 8$ [28]), giving divergent results, matched intermittent high-intensity and continuous moderate-intensity exercises on total mechanical load [25] or on total energy expenditure (but without confirming it with oxygen uptake recordings) [28]. Their protocol for intermittent high-intensity aerobic exercise was unrepresentative of bouts of spontaneous physical activity in children (*i.e.,* 95 % of spontaneous high-intensity bouts lasting less than 15 sec) [32].

The aim of this study was therefore to explore whether intermittent high-intensity aerobic exercise (IHE), designed to mimic spontaneous childhood physical activity patterns, offers better protection against glycemic drop than traditional continuous moderate-intensity exercise (CME). In addition to the use of exercise that was representative of spontaneous physical activity, no specific recommendations for preventive insulin or dietary adaptations were given to the children and their parents in order to put the participants under conditions that were similar to their everyday life.

2. Material and methods

Twelve children, attending the Unit of Pediatric Endocrinology at Lille University Hospital (France), volunteered for this study. The sample size was justified by an a priori sample size computation carried out using SigmaStat. It was based on the F-test of a one-way ANOVA for 2 groups (with an alpha of 0.05 and a power of 0.90), for a minimum detectable difference in means of 1.0 mmol·L^{-1} (*i.e.,* the difference, between both exercises, of the delta of blood glucose calculated between post-exercise and pre-exercise glycemia values) and an expected standard deviation of residuals of 0.4 mmol·L^{-1}, as based on results from the previous study of Soon et *al.*) [26]. The actual estimated sample size was 5. We then decided to recruit 12 children to obtain even more transposable results. The participants' characteristics are presented in Table 1 and Supplementary material Table 1. This study was part of a non-interventional educational therapeutic program entitled 'Mieux vivre avec son diabète' (Living better with diabetes) which received the agreement of the 'Agence Régionale de Santé' (Regional Health Authority) and was declared by the Data Protection Officer of the Lille University Hospital to the CNIL (Data Protection and Freedom of Information, declaration 026-03-13 - GC/VB). Written informed consent was obtained from all participants and their parents.

During a first visit, at least 2 days before the two physical exercises described below, aerobic fitness (Physical Working Capacity 170,

Table 1
Participants' characteristics.

	Children ($n = 12$)
Anthropometric and demographic data	
Age (years)	9.8 ± 1.4 (7.6–12.1)
Sex, *n* boys/girls	5/7
Z-score BMI (kg · m^{-2})	0.5 ± 0.97 (–1.9–1.4)
Fat mass (%)	19.1 ± 5.2 (8.1–25.7) ($n = 11$)
Waist to hip ratio	0.9 ± 0.1 (0.8–1.2)
HbA_{1c} at the time of evaluation (%/mmol·mol^{-1})	7.5 ± 0.7 (6.4–8.7)/58 ± 4.3 (46–72)
Mean HbA_{1c} from the last 12 months (%/mmol·mol^{-1})	7.5 ± 0.4 (7.0–8.2)/58 ± 7.5 (46–66)
Diabetes duration (years)	4.9 ± 3.1 (1–10.4)
Insulin delivery (CSII/MDI)	3/9
Daily insulin dose (units · kg^{-1} · day^{-1})	1 ± 0.3 (0.4–1.6)
N with diabetes complications/no complications	0/12
Gold score	3 ± 2 (1–7)
Hypoglycemia unawareness *n* with a Gold score ≥ 4/score < 4‡	
n with a Gold score ≥ 3/score < 3*	7/5
Physical activity level and aerobic fitness data	
Supervised sports activities† (h·week^{-1})	1.5 ± 1.5 (0–5) *Among whom 0 h·week^{-1} for n = 4, between 1 h and 2 h·week^{-1} for n = 5, between 2.5 and 3 h·week^{-1} for n = 2 and 5 h·week^{-1} for n = 1*
PWC_{170} (W.kg^{-1})	1.91 ± 0.4 (1.2–2.4)
Scores for the three main barriers to physical activity$ ***	
Children	
Fear of hypoglycemia	4.1 ± 1.6
Fear of hyperglycemia	3.7 ± 2
Fear of loss of diabetes control	3.3 ± 1.7
Parents	
Fear of hypoglycemia	4.3 ± 2.1
Fear of being tired	3.3 ± 2.1
Weather conditions	3.2 ± 2

Data are means ± SD (minimum–maximum) or number of participants.
Fat mass was assessed from bicipital, tricipital and subscapular skinfolds in children. ‡, based on the Gold Method [34]. *, based on the cut-off suggested for children and adolescents by [42]. †, in addition to physical education at school. $, assessed by BAPAD-1 questionnaire validated in adults with T1D, and adapted for the terminology of 2 items in order to improve children' understanding.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; PWC_{170}, physical working capacity 170.

PWC_{170} [33]) and anthropometric characteristics were assessed. Time spent per usual week practicing supervised sports activities was recorded. Barriers to physical activity were assessed with the BAPAD-1 questionnaire [11] (completed by parents (or careers) and children), and hypoglycemia awareness assessed with the visual analogue scale of Gold et *al.* [34].

During a second visit, a continuous glucose monitoring (CGM) sensor (Enlite iPro2, Medtronic, Inc) was inserted, calibrated with concomitant capillary glycemia at 1 and 3 h after the insertion, and then worn for 7 days. During this 7-day period, children were required to come to the hospital on 2 additional occasions separated by at least 48 h to perform, in randomized order, the 2 types of aerobic exercises. Besides these 2 exercise visits, children were asked to refrain from physical activity (school, clubs, leisure-time) during the whole week they wore the CGM sensor. Compliance with this request was checked by wearing an ActiGraph GT1M accelerometer (activity level thresholds chosen were those from Evenson et *al.* [35]). Inactive days (INACTIVE) were chosen as the days either before the first aerobic exercise day and/or at least 24 h after an exercise day, with at least 70 % of CGM values for each day [36].

2.1. The two aerobic exercises

Both exercises included 2 sets of 10 min of pedaling on a cycle ergometer (Monark 894E Peak Bike, Monark Exercise AB, Vansbro Sweden) at 60–70 rpm, separated by 5 min of passive recovery sitting on the bike. During CME, the pedaling periods were performed at a workload of 50 % PWC_{170}, which corresponds to approximately 40 % of estimated maximal aerobic power for a child aged 10 years [37].

For IHE, each pedaling period of 10 min was composed of 15-sec intervals at a workload of 150 % PWC_{170} (which corresponds to approximately 120 % of estimated maximal aerobic power [37]) interspersed with 30 s of passive recovery [38]. Before each 15-sec high-intensity active interval, we allowed the children to take a fly start by starting to pedal at 60–70 rpm for 5 sec against zero load, while we manually lifted up the load to be then applied to the wheel for the 15-sec high-intensity interval. This process was chosen in order to apply the load instantly while limiting extra energy expenditure related to acceleration against the load. For the 30-sec passive recovery intervals, the only instruction given was to stop pedaling while the load was still applied to the wheel. The latter allowed the wheel to stop rapidly.

The 10-min exercise duration was chosen based on observational studies of healthy children showing that periods of spontaneous physical activity generally do not exceed 10 min [32,39]. The total mechanical work achieved as well as the total duration of the test was therefore similar for the 2 exercises so as to better appreciate the effect of the intensity and the modality of exercise on glycemic variations.

Each child performed the two exercises in the afternoon after a snack or lunch, both meals being identical for both types of exercise. The dose of rapid-acting insulin, or bolus, injected at lunch time and optionally at snack time was chosen according to each child's habits, aiming for a blood glucose level of between 5.6 and 8.3 $mmol{\cdot}L^{-1}$. Exercise was performed only if capillary blood glucose was $\geq$ 4.4 $mmol{\cdot}L^{-1}$ and, in case of hyperglycemia, only if no ketones were found in participants' urine.

2.2. Exercise-induced glycemic excursions

For CME and IHE, capillary blood glucose (Accu-Check Performa Nano, Roche) was measured at rest, at 10, 15, 25 min of exercise, and at 15 min of subsequent passive recovery sitting on a chair. In addition, glycemia was continuously estimated from subcutaneous interstitial glucose values of the professional masked CGM sensor (Enlite iPro2, Medtronic, Inc; with a value every 5 min, placed on the lower abdomen or on the back of the arm), during CME and IHE recovery (1 h, 2 h, 8 h of recovery and subsequent night) and during the same periods for inactive days. The choice of a CGM sensor set to blinded mode for the participant was made because the children were not used to wearing this device on a day-to-day basis. The glycemic excursions from CGM taken into consideration were the percentage of time spent in range (between 3.9 and 10.0 $mmol{\cdot}L^{-1}$), in hypoglycemia (<3.0 $mmol{\cdot}L^{-1}$, <3.9 $mmol{\cdot}L^{-1}$) and in hyperglycemia (>10.0 $mmol{\cdot}L^{-1}$, >13.9 $mmol{\cdot}L^{-1}$, >16.7 $mmol{\cdot}L^{-1}$). Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI) were also calculated. Glycemic variability was assessed through the coefficient of variation (CV), standard deviation (SD) and mean amplitude of glycemic excursions (MAGE) [36].

During the 7-day period, children were asked to fill in a diary for capillary blood glucose (recording time and values), which was measured before each meal and at bedtime when glucose levels are stable, for subsequent CGM sensor calibration. Capillary blood glucose was also taken in case of signs of hypoglycemia or hyperglycemia (in which case, the symptoms were noted).

2.3. Dietary data and insulin treatment

To take into account other factors that may influence blood glucose levels in the analysis of the results, the children were also asked to record information in the diary about insulin treatment (specific doses and times including corrections for hyperglycemia) and diet (including snacks for treating hypoglycemic episodes). Staff explained in detail how this information should be recorded in the diary. Parents received a booklet with pictures and examples for the reporting of the quantities and quality of food (SUIVIMAX book). On removal of the CGM sensor, the children and their parents had an in-person or telephone interview with the staff to complete the dietary details if necessary. In addition, in order to avoid the effects of exercise on blood glucose levels being masked by the diet, the children were asked to stick to fixed times and comparable carbohydrate quantities for lunch, afternoon snack and dinner throughout the exercise and inactive days.

2.4. Rating of perceived exertion and perceived pleasure

Heart rate (Suunto 3 heart rate monitor) and Rating of Perceived Exertion (RPE) [40] were recorded every 2 min during both exercises (for IHE, see Supplementary material Table 2). At the end of each exercise, the children filled in a questionnaire about the pleasure perceived during exercise [41].

2.5. Statistics

Statistical analyses were performed using the IBM SPSS version 27.0 (IBM Corp, Armonk, New York, United States). Results are reported as means ± SD, unless otherwise indicated.

Capillary glycemia (pre-exercise, at 10 min, 15 min, 25 min during exercise, and after 15 min recovery) and glycemia estimated from interstitial glucose (every 5 min from the beginning of recovery until 60 min of recovery) both expressed as relative changes from pre-exercise values, were compared between conditions (see immediately below) using linear mixed models for repeated measurements [random effects for intercept and time (min); fixed effects: 'condition' – *i.e.*, IHE *vs.* CME for capillary glycemia; IHE *vs.* CME *vs.* INACTIVE for glycemia estimated from interstitial glucose, 'time' (min), 'initial pre-exercise glycemia' ($mmol{\cdot}L^{-1}$), and 'time × condition' interaction]. Heart rates and RPE (every 2 min during exercise) were also compared between conditions using linear mixed models (random effects for intercept; fixed effects: condition, *i.e.*, IHE *vs.* CME; time (min); 'time × condition' interaction). Linear mixed models were also used for CV and SD (during 2 h, 8 h of recovery and subsequent night), for MAGE (8 h post-exercise and subsequent night) as well as HBGI (during all recovery periods) [random effects for intercept; fixed effects: condition, *i.e.*, IHE *vs.* CME *vs.* INACTIVE; 'initial pre-exercise glycemia' ($mmol{\cdot}L^{-1}$)]. We performed a second set of analyses of glycemic outcomes during recovery from exercises or similar inactive periods in a subset of children ($n = 10$) who

accurately recorded their diet throughout IHE, CME and inactive days and nights. In these analyses, we added the carbohydrate (g) intake [divided by the insulin dose (U) in the case of concomitant insulin administration] as an additional fixed effect in the above-mentioned mixed models. For all the models, residuals were Gaussian and the results expressed as the mean estimation 'e'.

Non-parametric data (confirmed with Shapiro–Wilk test) as well as data for which linear mixed models showed non-Gaussian residuals were compared between the 3 conditions using either Friedman's ANOVA (*i.e.,* percentage of time spent in range, above 10.0 and 13.9 mmol·L^{-1} during early and late recovery, LBGI during late recovery, CV and SD during 1 h of recovery) or Cochran's Q test (for binary transformed data,

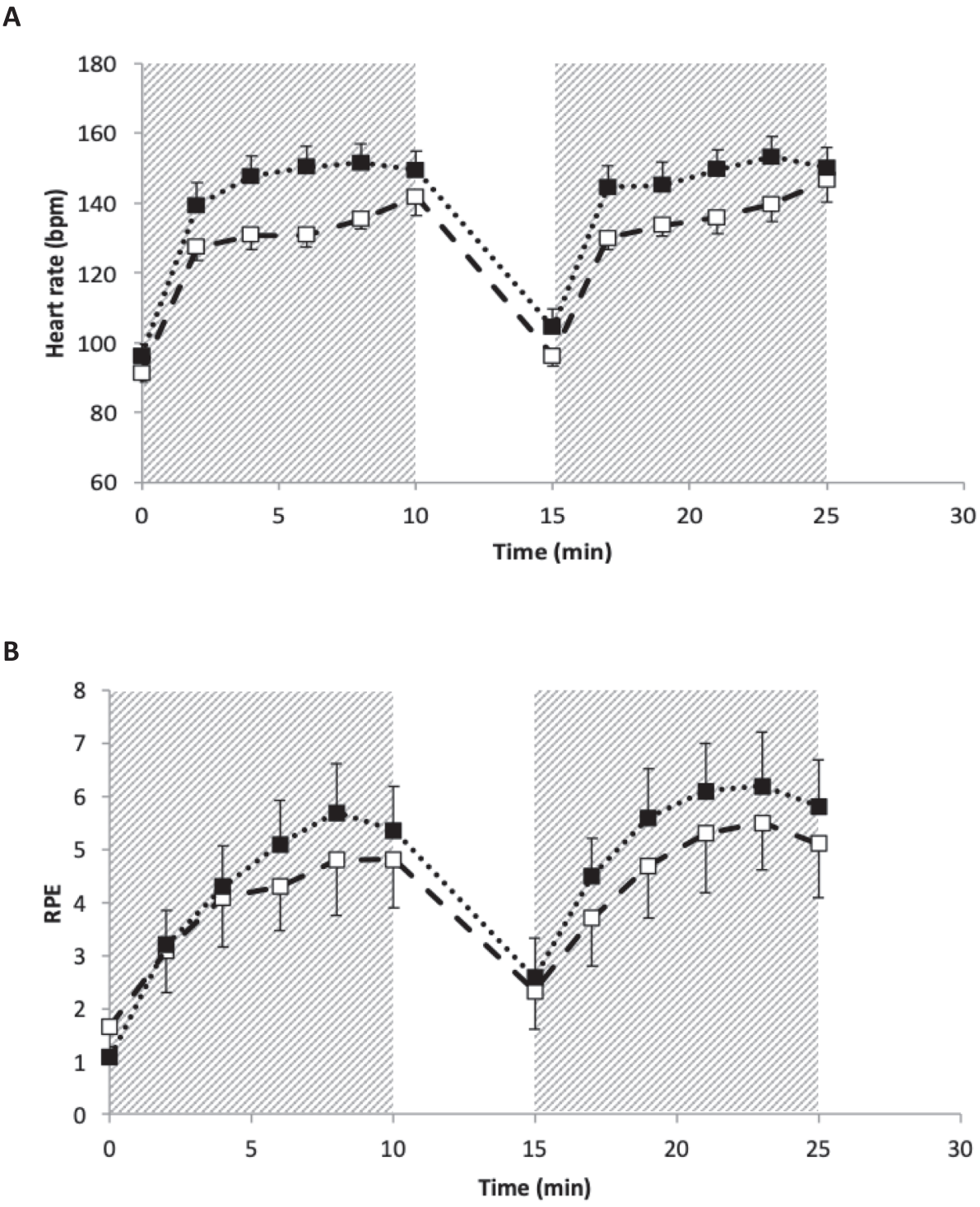

Fig. 1. Heart rates and Rate of Perceived Exertion during continuous moderate-intensity and intermittent high-intensity exercises. Data are means ± SE. IHE, *black squares*; CME, *white squares*. The hatched areas correspond to the exercise periods.**1A**. Heart rates. Main effects for mixed model: Condition, $P < 0.005$, e = +13 bpm during IHE *vs.* CME; Time, $P < 0.001$; Condition × Time, NS. HR, heart rate; Bpm, beat per minute. **1B**. Rate of Perceived Exertion. Main effects for mixed model: Condition, NS; Time, $P < 0.001$; Condition × Time, NS. RPE, rate of perceived exertion.

i.e., percentage of time spent below 3.0, 3.9, and above 16.7 mmol·L^{-1}, during early and late recovery; LBGI during early recovery). Pairwise differences were further examined using the Dunn-Bonferroni post-hoc test.

Spontaneous physical activity levels (accelerometry), macronutrient intake, insulin administration, and carbohydrate intake optionally divided by insulin dose (in cases of insulin administration) were compared between conditions using repeated measures ANOVA (parametric data) or Friedman's ANOVA (non-parametric data). Perceived pleasure was compared between CME *vs.* IHE using Wilcoxon's matched pair test. Time between the last meal with a bolus and the start of exercise as well as the last bolus insulin dose before exercise were compared between CME and IHE using paired *t* test.

$P \leq 0.05$ was considered statistically significant.

3. Results

Participants' characteristics are presented in Table 1.

CME, IHE and INACTIVE periods started in the afternoon at about 16 h57 (±86 min), 17 h07 (±84 min) and 17 h32 (±81 min) respectively, which corresponded to a time before 3 pm for 2 children and after 4 pm for the other 10 children. Time between the last meal with a bolus and the start of exercise did not differ between CME and IHE (CME, 2 h52 ± 2 h17; IHE, 3 h15 ± 2 h02; P = 0.262). The last bolus insulin dose before exercise was also found not to be different between both exercise conditions (CME, 5.28 ± 3.42 U; IHE, 4.66 ± 2.61 U; P = 0.312). The last meal with a bolus was lunch for 7 participants and an afternoon snack for 3 of the participants.

Power output during CME and IHE was respectively 37.9 ± 10.4 Watts (min: 26, max: 55) and 113.7 ± 31.2 Watts (min: 78, max: 165).

CME and IHE were separated by 48 h for 11 participants and 72 h for 1 participant. INACTIVE data were calculated over 1 (n = 3 participants), 2 (n = 8) or 3 (n = 1) days.

The time spent in moderate to vigorous physical activity on inactive days, during the 25-min periods corresponding to the times of IHE and CME protocols, was short, *i.e.*, 1.67 ± 2.0 min.

3.1. Psycho-physiological responses to CME and IHE

Heart rates were significantly higher during periods of IHE *vs.* CME (Fig. 1A). However, no significant effect of 'exercise condition' was detected for RPE (Fig. 1B) and perceived pleasure (5.2 ± 1.5 *vs.* 5.4 ± 1 after IHE *vs.* CME).

3.2. Capillary glycemia during CME and IHE

Pre-exercise glycemia did not differ between CME and IHE conditions (10.7 ± 2.2; min: 7.5 - max: 15.3 *vs.* 9.9 ± 4.3; min: 5.1 - max: 16.4 mmol·L^{-1}, respectively). Among the 12 children, one before CME and three before IHE had a glycemia level above 13.9 mmol·L^{-1}, but without ketosis (tested by urinary sample trips). Capillary glycemia expressed as relative change from initial (pre-exercise) concentrations are presented in Fig. 2. Capillary glycemia drop was attenuated by 1.47 mmol·L^{-1} during IHE *vs.* CME. No symptomatic hypoglycemic episode occurred during CME and IHE.

3.3. Glycemia and glycemic outcomes estimated from continuous interstitial glucose monitoring during early and late recovery from the 3 conditions

No missing CGM data were identified for the recovery periods studied and this for the 12 children across the 3 conditions.

Fig. 3 shows glycemia during the 60-min recovery period immediately following the 25-min experimental period. The higher the pre-exercise glycemia was, the more glycemia decreased during early recovery. While glycemia increased during the INACTIVE condition, it decreased during the IHE condition, and to a greater extent during the CME condition. Incorporating the carbohydrate intake, optionally divided by insulin administration, into the model (Fig. 1 Supplementary material) did not change the above-cited results. There was also a significant main effect for carbohydrates/insulin ratio meaning that children whose glycemia decreased a lot probably subsequently took carbohydrate intake (Fig. 1 Supplementary material). No difference in carbohydrates (optionally divided by insulin) consumed during the hour following exercise was observed between the three 'conditions' (Table 2).

Consistent with these results of changes in glycemia, HBGI and time spent over 16.7 mmol·L^{-1} were different between the 3 conditions during early recovery, with lower values for CME *vs.* INACTIVE condition and to a lesser extent (only for HBGI) with lower values for IHE *vs.*

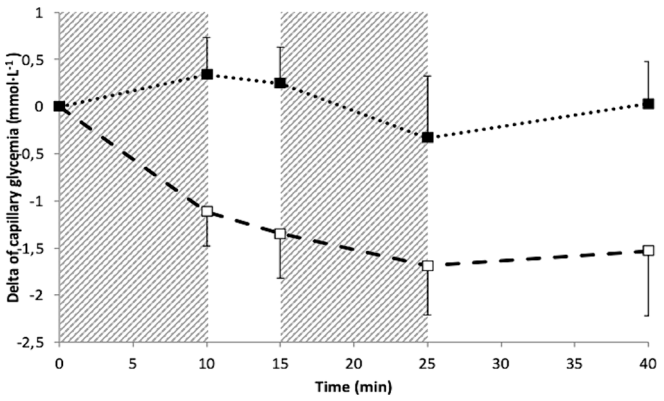

Fig. 2. Changes in capillary glycemia during continuous moderate-intensity and intermittent high-intensity exercises. Data are means ± SE. IHE, *black squares*; CME, *white squares*. The hatched areas correspond to the exercise periods. Main effects for mixed model on relative changes in capillary glycemia from initial values: Pre-exercise glycemia, NS; Condition, P (unilateral) < 0.05, e = +1.47 mmol·L^{-1} during IHE *vs.* CME; Time, NS; Condition × Time, NS. CME, continuous moderate-intensity exercise; IHE, intermittent high-intensity exercise.

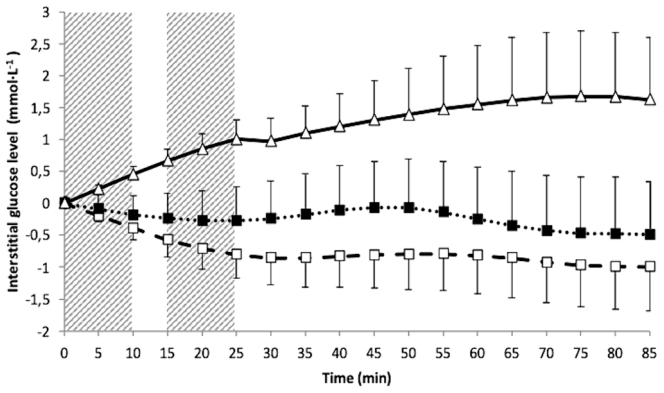

Fig. 3. Interstitial glucose levels as estimated by continuous glucose monitoring during continuous moderate-intensity and intermittent high-intensity exercises and the following 60 min and inactive days. Data are means ± SE. IHE, *black squares*; CME, *white squares*; INACTIVE, *white triangles*. The hatched areas correspond to exercise periods. From 25 to 85 min: 60 min of recovery. INACTIVE: 1 to 3 days, data collapsed across days. Main effects for mixed model performed during the 60 min of recovery: Pre-exercise glycemia, P < 0.001, e = − 0.02 mmol·L^{-1} for every additional 1 mmol·L^{-1} of pre-exercise glycemia; Condition, P < 0.001; Time, NS; Condition × Time, NS. Pairwise differences for 'Condition' effect: CME *vs.* SED: e = –2.8 mmol·L^{-1}, P < 0.001; IHE *vs.* SED: e = –2.1 mmol·L^{-1}, P < 0.001; CME *vs.* IHE: e = –0.6 mmol·L^{-1}, P < 0.001. CME; continuous moderate-intensity exercise; IHE, intermittent high-intensity exercise; INACTIVE, inactive days.

Table 2
Macronutrient intake, insulin administration and spontaneous physical activity before, during early (1 h, 2 h) and late recovery (8 h) following the three conditions ($n = 10$).

	CME	IHE	INACTIVE
Time of last meal before each condition	14 h20 ± 2 h04	14 h58 ± 1 h40	14 h45 ± 1 h52
Dinner time	19 h43 ± 43 min	19 h54 ± 46 min	19 h45 ± 39 min
N with exercise performed before 3 pm/ after 4 pm (n = 12)	2/10	2/10	NA
Rapid acting insulin or insulin bolus injected			
Last meal before each condition (U)	3.6 ± 3.7	3.5 ± 3.1	4 ± 3
During 8 h following each condition (U)	7.2 ± 5.5	7.7 ± 5.6	7.5 ± 5.7
Dinner (U)	7.1 ± 5.6	6.6 ± 5.2	7.2 ± 5.2
Total caloric (TC) intake			
Last meal before each condition (kcal)	327.7 ± 244	251.3 ± 130.2	425.5 ± 236.9
During 8 h following each condition (kcal)	541.9 ± 167.7	615.7 ± 265.6	641.5 ± 270.5
Dinner (kcal)	581.9 ± 289.2	564.4 ± 205.6	546.9 ± 153.4
Carbohydrate			
Last meal before each condition (% of TC)	59.1 ± 21.3	57.2 ± 17	49.4 ± 13.9
During 8 h following each condition (% of TC)	50.5 ± 10.8	44.8 ± 12.8	46.8 ± 11.1
Dinner (% of TC)	47.9 ± 13.9	43.3 ± 13.9	48.3 ± 11.3
Last meal before each condition (g)	38.8 ± 22.5	39.1 ± 20.5	46.3 ± 20.1
During 8 h following each condition (g)	65.6 ± 16.4	67.1 ± 27.5	69.6 ± 20.2
Dinner (g)	63 ± 17.9	59.6 ± 23.7	60.9 ± 10.9
Last meal before each condition: High glycemic-index carbohydrate (% total carbohydrate)	48.1 ± 35.1	49.9 ± 31.5	54.1 ± 28.7
During 8 h following each condition: High glycemic-index carbohydrate (% total carbohydrate)	68.6 ± 12.7	70.9 ± 20.4	67.5 ± 13.4
Dinner: High glycemic-index carbohydrate (% total carbohydrate)	63.9 ± 11.1	66.8 ± 25.2	60.5 ± 14
Last meal before each condition: High glycemic-index carbohydrate (g)	24.3 ± 19.4	19.1 ± 16.9	28.5 ± 17.9
During 8 h following each condition: High glycemic-index carbohydrate (g)	43.7 ± 8.9	45.4 ± 19.8	46.8 ± 15.8
Dinner: High glycemic-index carbohydrate (g)	44.5 ± 13.2	42.8 ± 19.5	42.6 ± 13.3
Last meal before each condition: Low glycemic-index carbohydrate (g)	16.1 ± 8.4	16.4 ± 17.8	17.8 ± 12.8
During 8 h following each condition: Low glycemic-index carbohydrate (g)	21.9 ± 10.1	21.8 ± 19.7	22.8 ± 12.5
Dinner: Low glycemic-index carbohydrate (g)	18.5 ± 7.7	16.8 ± 17.2	18.2 ± 7
Carbohydrates/Insulin ratio			
Last meal before each condition ($g.U^{-1}$)	14.5 ± 9.2	16.9 ± 11.6	17.8 ± 13.7
During 1 h following each condition ($g.U^{-1}$)	1.5 ± 4.4	1.7 ± 5.38	2.7 ± 4.6
During 2 h following each condition ($g.U^{-1}$)	10.6 ± 14.4	4.9 ± 4.9	9.3 ± 10.8
During 8 h following each condition ($g.U^{-1}$)	19.3 ± 20.2	11.3 ± 5.5	21.3 ± 27.8
Dinner	19.3 ± 20.2	15.5 ± 16.6	11.7 ± 6.6
Protein			
Last meal before each condition (% of TC)	12.7 ± 7.9	8 ± 5.3	11.6 ± 7.5
During 8 h following each condition (% of TC)	16.1 ± 7.3	19.9 ± 4.4	18 ± 2.3
Dinner (% of TC)	16.9 ± 6.7	20.8 ± 4.3	19.1 ± 4.5
Last meal before each condition (g)	14.8 ± 14	6.3 ± 6.6	15.5 ± 17.9
During 8 h following each condition (g)	20.5 ± 8.9	30.1 ± 12.2	29.6 ± 14.7
Dinner (g)	24.5 ± 16.2	29.3 ± 11.5	27.3 ± 11.5
Fat			
Last meal before each condition (% of TC)	29.3 ± 15.7	32.5 ± 16.6	37.9 ± 12.1
During 8 h following each condition (% of TC)	33.2 ± 13.3	35 ± 13.9	35.2 ± 10.3
Dinner (% of TC)	34.9 ± 14.9	35.6 ± 14.4	32.7 ± 10.4
Last meal before each condition (g)*	13.1 ± 12.9	12 ± 12.6	21.3 ± 15.4
During 8 h following each condition (g)	21.9 ± 12.8	25.1 ± 16.6	27.2 ± 18.6
Dinner (g)	25.7 ± 21	23.1 ± 13.9	21.5 ± 11.5
Fibre intake			
Last meal before each condition ($g.1000\ kcal^{-1}$)	10.7 ± 18.6	7.7 ± 12.44	4.4 ± 5.6
During 8 h following each condition ($g.1000\ kcal^{-1}$)	13.9 ± 15.5	8.6 ± 7.7	8.7 ± 10.8
Dinner ($g.1000\ kcal^{-1}$)	11.9 ± 9.2	8.9 ± 8.3	9.8 ± 18.1
Percent of time spent in moderate to vigorous physical activity (accelerometry)			
From 6.00am to the start of each condition (%)	5.2 ± 3.3	4.8 ± 2.6	6.1 ± 3.1
During 1 h following each condition (%)	5.8 ± 4.8	5.7 ± 3.7	9.3 ± 8
During 2 h following each condition (%)	5 ± 2.7	5.1 ± 3.2	9.1 ± 5.2
During 8 h following each condition (%)	3.1 ± 1.9	3.2 ± 2.1	4.3 ± 2.7

Data are means ± SD.
The last meal in this table was either lunch or an afternoon snack, with or without an insulin bolus. During the night following each condition, no food was consumed. Friedman ANOVA or repeated measures ANOVA showed no significant differences between the 3 conditions for meal time, rapid acting insulin, total caloric intake and all macronutrients, except for fat (g) content of the last meal: *, significant effect of 'condition' with Friedman ANOVA ($P < 0.05$); no significant pairwise differences.
There was no significant difference between conditions for the time spent in moderate to vigorous physical activity.
CME, continuous moderate-intensity exercise; IHE, intermittent high-intensity exercise; INACTIVE, inactive days.

INACTIVE condition (Table 3). HBGI also tended to be lower after CME *vs.* IHE condition. Higher pre-exercise glycemia was accompanied by a greater risk of high glycemia values (HBGI, Table 3). Time spent in hypoglycemia, LBGI, and glycemic variability did not differ between the 3 conditions during early recovery (Table 3).

The results displayed in the table involve $n = 12$ children. Comparable results were found in $n = 10$ when taking into account carbohydrate intake as a covariate in the mixed models (data not shown), with a significant main effect for 'condition' for HBGI during 1 h of recovery ($P < 0.01$; pairwise differences: CME *vs.* IHE: e = –4.22, $P < 0.05$; CME *vs.* INACTIVE: e = –7.88, $P < 0.001$) and during 2 h of recovery ($P < 0.05$; pairwise differences: CME *vs.* INACTIVE: e = –6.22, $P < 0.01$).

CME, continuous moderate-intensity exercise; IHE, intermittent high-intensity exercise; INACTIVE, inactive days; LBGI, low blood glucose index; HBGI, high blood glucose index; CV, coefficient of

Table 3
Glycemic excursions and variability according to exercise conditions (CME and IHE) and inactive days during early recovery.

	CME	IHE	INACTIVE
Early recovery			
1 h following exercise			
% time < 3.0 mmol·L^{-1}	0 ± 0	5.2 ± 18	0 ± 0
N with a value > 0 %	*n* = 0	*n* = 1	*n* = 0
% time < 3.9 mmol·L^{-1}	0 ± 0	14 ± 33.5	0.7 ± 2.4
N with a value > 0 %	*n* = 0	*n* = 2	*n* = 1
LBGI	0.1 ± 0.2	2.6 ± 5.9	0.4 ± 1.1
% time between 3.9 and 10.0 mmol·L^{-1}*	**55.5 ± 49.9**	**27.6 ± 44.6**	**25.2 ± 34**
***N* with a value > 0 %**	***n* = 7**	***n* = 4**	***n* = 5**
% time > 10.0 mmol·L^{-1}	44.5 ± 49.9	58.3 ± 51.5	74.1 ± 35.5
N with a value > 0 %	*n* = 6	*n* = 7	*n* = 11
% time > 13.9 mmol·L^{-1}	15.8 ± 37	29.6 ± 40.3	42.2 ± 43.8
N with a value > 0 %	*n* = 2	*n* = 5	*n* = 7
% time > 16.7 mmol·L^{-1}**	**0 ± 0**	**9.6 ± 28.8**	**21.7 ± 28**
***N* with a value > 0 %**	***n* = 0**	***n* = 2**	***n* = 5**
HBGI‡&	**8.4 ± 9.7**	**13.5 ± 14**	**21 ± 14.6**
CV (%)	5.8 ± 4	6.4 ± 4.2	6.2 ± 4.1
SD (mmol·L^{-1})	0.5 ± 0.3	0.5 ± 0.3	0.8 ± 0.7
2 h following exercise			
% time < 3.0 mmol·L^{-1}	0 ± 0	2.6 ± 9.1	0 ± 0
N with a value > 0 %	*n* = 0	*n* = 1	*n* = 0
% time < 3.9 mmol·L^{-1}	0.7 ± 2.4	11.1 ± 20.4	0.3 ± 1.2
N with a value > 0 %	*n* = 1	*n* = 3	*n* = 1
LBGI	0.3 ± 0.8	2 ± 3.7	0.3 ± 0.7
% time between 3.9 and 10.0 mmol·L^{-1}	53.7 ± 45.8	33.1 ± 39	26.8 ± 32
N with a value > 0 %	*n* = 8	*n* = 7	*n* = 8
% time > 10.0 mmol·L^{-1}	45.6 ± 46.5	55.8 ± 49.6	72.8 ± 32.7
N with a value > 0 %	*n* = 7	*n* = 7	*n* = 11
% time > 13.9 mmol·L^{-1}	12.4 ± 30.4	23.3 ± 33	35.3 ± 39.8
N with a value > 0 %	*n* = 3	*n* = 5	*n* = 7
% time > 16.7 mmol·L^{-1}	1.2 ± 4.1	6.3 ± 19.6	18.7 ± 25.3
N with a value > 0 %	*n* = 1	*n* = 2	*n* = 5
HBGI‡‡&CV (%)	**8.5 ± 9.4** 13.2 ± 7.1	**12.3 ± 12.1** 11.7 ± 6.8	**19.5 ± 13** 10.3 ± 5.7
SD (mmol·L^{-1})	1.1 ± 0.5	1 ± 0.7	1.3 ± 1

Data are means ± SD and the number of participants with values above 0 %. % time is the percentage of time spent at specific thresholds. HBGI and LBGI were calculated using mg·dL^{-1} as the glycemia unit. Statistics used were Friedman ANOVA, Cochran's Q test, or mixed models.
*significant effect of 'condition' with Friedman ANOVA ($P \leq 0.05$); no significant pairwise differences.
**significant effect of 'condition' with Cochran's Q test ($P \leq 0.05$); pairwise differences: CME *vs*. INACTIVE, $P < 0.05$.
‡, significant main effect for 'condition' ($P < 0.001$) with mixed model; pairwise differences: CME *vs*. INACTIVE: e = –8.7, $P < 0.001$; IHE *vs*. INACTIVE: e = –4.2, $P < 0.05$; trend for CME *vs*. IHE: e = –3.5, $P = 0.084$.
‡‡, significant main effect for 'condition' ($P < 0.01$) with mixed model; pairwise differences CME *vs*. INACTIVE: e = –7.7, $P < 0.001$; IHE *vs*. INACTIVE: e = –4.2, $P < 0.05$. trend for CME *vs*. IHE: e = –3.5, $P = 0.084$.
&, significant main effect for 'pre-exercise glycemia' ($P < 0.001$, e ≤ +0.01 for every additional 1 mmol·L^{-1} of pre-exercise glycemia) with mixed model.

variation; SD, standard deviation; MAGE, mean average of glucose excursions.

During late recovery, no differences in time spent in hyperglycemia or hypoglycemia, nor in HBGI, LBGI and glycemic variability, appeared between conditions (Table 3 Supplementary material; continuous glucose data displayed in Fig. 2 Supplementary material).

3.4. Diet, insulin and spontaneous physical activity

For the 10 subjects with accurate dietary and insulin recordings, meals before each condition (optionally accompanied by insulin administration) and during late recovery were investigated: no significant differences in carbohydrate intake (quantity and quality) and insulin doses were observed (Table 2). There were also no differences in terms of percentage of time spent in moderate to vigorous activity before and after each condition (Table 2).

4. Discussion

This study aimed to compare glycemic excursions and variability during and after intermittent high-intensity and continuous moderate-intensity aerobic exercise, and during inactive days in youth with T1D. The main result was that IHE, and to a greater extent CME, lasting 20 min, caused a drop in blood glucose that persisted during early recovery, without any increase in time spent in hypoglycemia or incidence of symptomatic hypoglycemic episodes. Furthermore, we showed that IHE, and more importantly CME, transiently (*i.e.,* during 1 h after) mitigated the risk of high blood glucose values compared with inactive days.

One of the advantages of the current study is that it closely resembled real-life conditions throughout the experimentation. Participants kept to their habits in terms of insulin and diet, thus performing their exercises under usual conditions. The results underline, for the first time, that including carbohydrate intake as a possible confounding factor in the analyses of glycemia during recovery could be a crucial methodological point, considering that the more the glycemia decreased during early recovery, the more the children consumed carbohydrates.

4.1. Hypoglycemic excursions

In the current study, although glycemia decreased further during exercise and early recovery for the CME condition in comparison to the IHE condition, this format of 20-min moderate-intensity exercise did not lead to a greater hypoglycemic risk compared to the INACTIVE condition. Time spent in hypoglycemia, LBGI, and glycemic variability did not differ between the 3 conditions during early and late recovery, even though 42 % of participants seemed to suffer from impaired awareness of hypoglycemia (Gold score).

However, we cannot rule out the possibility that with longer continuous moderate exercises, a risk of hypoglycemia will emerge. Fear of hypoglycemia remained the primary barrier to physical activity among the participants in the current study and recent research has shown that exercise duration is a predictor of hypoglycemic risk during the 24 h post-exercise period [43]. Indeed, in a previous study of adolescents and adults performing 60-min of continuous moderate-intensity aerobic exercise, we found that the first hypoglycemic episodes occurred after a threshold of 20 min of exercise [19]. Riddell et *al.* [12] also concluded that when no strategies are put in place to limit the drop in glycemia, the incidence of exercise-associated hypoglycemia is ~ 44 % during prolonged (~60 min) continuous moderate-intensity aerobic exercise in adolescents with T1D. Nonetheless, the relatively short-duration CME used in our study, split into 2 bouts of 10 min, is representative of children's spontaneous physical activities during recess at school or in the late afternoon after school when they are relaxing at home: Baquet et *al.* [39] indeed showed that the longest duration of moderate-intensity bouts was 10 min throughout a 7-day real-life recording of 60 non-diabetic children.

From a methodological perspective, our results showing a bigger glycemic drop during early recovery in cases of higher pre-exercise glycemia underline the importance of considering initial glycemia in the statistical analyses of exercise-induced glycemia change. To the best of our knowledge, this methodological point had until now never been considered in previous research exploring the pros and cons of high-

intensity intermittent exercises in type 1 diabetes, except for a very recent study in adults, with however no indications about the duration of intervals composing the 30-min intermittent high-intensity exercise at 80–90 % of age-predicted maximal heart rate [44].

4.2. Hyperglycemic excursions

Our work showed that CME appeared to fully protect against level 2 hyperglycemia (*i.e.,* >16.7 mmol·L^{-1}), which occurred during early recovery from IHE in 17 % of the participants, but which was especially evident over the same period in 42 % of the participants during inactive days.

We also found that the risk of having elevated glycemia (HBGI) tended to be lower in early recovery from CME compared to IHE. This result can be interpreted in light of the results of a previous study which combined an euglycemic clamp with infusion of [6,6-^{2}H]glucose in adults with T1D; this study demonstrated that glucose utilization rapidly declined during early recovery from a 30-min intermittent high-intensity exercise, concomitantly with persistent elevated lactate and growth hormone concentrations, while glucose utilization remained elevated after continuous moderate-intensity exercise [22]. Growth hormone is indeed known to have a rapid direct insulin antagonistic effect on glucose uptake [45], and circulating lactate may serve as an alternative substrate for muscle oxidations, thus sparing circulating glucose [46]. To our knowledge, the current study is the first to demonstrate a transient protective effect of continuous moderate-intensity aerobic exercise against hyperglycemia in youth with T1D. This property of continuous moderate-intensity exercise seems all the more relevant given that the second main barrier to physical activity, among the children participating in the current study, was the fear of hyperglycemia, in line with our previous study [11]. It should be noted, however, that the greater risk for high glucose values following IHE was only transient as no difference was observed between the 3 conditions in late recovery for time spent in hyperglycemia or HBGI. In addition, the INACTIVE condition in our study allowed us to prove that intermittent high-intensity exercise is still better than being inactive for limiting the risk of high glucose values. Ultimately, the CME and IHE protocols used in the current study elicited comparable levels of perceived exertion rates and perceived pleasure, which underlines the possibility of alternating these two forms of aerobic exercise in training programs for children with T1D in order to break monotony.

Thus, doing short-duration physical activity (*e.g.,* short repeated sequences of 10 min) of intermittent type (*e.g.,* games between children during recess or at the end of the day with friends) or continuous type (*e.g.,* physical education at school, bike riding, swimming) could be advised to children to limit hyperglycemia during the day without causing further hypoglycemia.

This study has several strengths, including its close resemblance to real-life conditions and the consideration of possible confounding factors such as carbohydrate intake and objectively measured spontaneous physical activity levels. While exercises were performed during the afternoon, a limitation lies in their specific timing, which varied according to the participants. However, for a same child, both exercises were performed at the same time. To be generalised, our results would have to be confirmed among children who are used to wearing CGM sensors on a day-to-day basis. However, it should be noted that access to novel technologies is restricted to a limited number of children in the world [47]. Another limitation is that we did not directly measure energy expenditure during IHE and CME, although these were matched with total mechanical workload. In addition, more differences in heart rates and RPE between both exercises could have been expected if these outcomes have been recorded continuously. They were indeed collected at isolated times, *i.e.,* at the end of 2-min periods, which corresponded, for 60 %, to passive recovery and, for 40 %, to 15-sec active intervals.

In conclusion, performing 20-min continuous moderate-intensity or intermittent (short bouts) high-intensity exercises in the afternoon is not associated with more hypoglycemic risk compared to being inactive in children with T1D who followed their usual diet and insulin habits. Interestingly, the continuous moderate-intensity form of exercise appeared to be even transiently protective against level 2 hyperglycemia. While the exercises performed in the current study were representative of spontaneous physical activity of children, further studies should also consider the impact of longer-duration exercises, as practiced in sports clubs.

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CRediT authorship contribution statement

Cassandra Parent: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Elodie Lespagnol:** Writing – review & editing, Methodology, Investigation, Data curation. **Serge Berthoin:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Sémah Tagougui:** Writing – review & editing, Funding acquisition. **Chantal Stuckens:** Writing – review & editing, Funding acquisition. **Cajsa Tonoli:** Writing – review & editing, Investigation. **Michelle Dupire:** Writing – review & editing, Formal analysis. **Aline Dewaele:** Writing – review & editing, Formal analysis. **Julie Dereumetz:** Writing – review & editing, Formal analysis. **Chloé Dewast:** Formal analysis. **Iva Gueorgieva:** Funding acquisition. **Rémi Rabasa-Lhoret:** Supervision, Funding acquisition. **Elsa Heyman:** Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111631.

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