Regional Cerebral Hemodynamic Response to Incremental Exercise Is Blunted in Poorly Controlled Patients With Uncomplicated Type 1 Diabetes

Semah Tagougui,[1] Pierre Fontaine,[2] Erwan Leclair,[3] Julien Aucouturier,[1] Régis Matran,[4] Kahina Oussaidene,[1] Aurélien Descatoire,[5] Fabrice Prieur,[6] Patrick Mucci,[1] Anne Vambergue,[2] Georges Baquet,[1] and Elsa Heyman[1]

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OBJECTIVE

Cerebral vasoreactivity to pharmacologically induced hypercapnia is impaired in poorly controlled patients with type 1 diabetes but otherwise free from microangiopathy. However, whether this response is also compromised during exercise, a daily-life physiological condition challenging regional cerebral hemodynamics, is unknown. We aimed to investigate prefrontal cortex hemodynamics during incremental maximal exercise in patients with uncomplicated type 1 diabetes, taking into account long-term glycemic control as well as exercise- and diabetes-influenced vasoactive stimuli.

RESEARCH DESIGN AND METHODS

Two groups of patients (type 1 diabetes with adequate glycemic control [T1D-A], n = 8, HbA_{1c} 6.8 ± 0.7% [51 ± 7.7 mmol/mol]; type 1 diabetes with inadequate glycemic control [T1D-I], n = 10, HbA_{1c} 9.0 ± 0.7% [75 ± 7.7 mmol/mol]) were compared with 18 healthy control subjects (CON-A and CON-I) matched for physical activity and body composition. Throughout exercise, near-infrared spectroscopy allowed investigation of changes in oxyhemoglobin (O_2Hb), deoxyhemoglobin (HHb), and total hemoglobin (THb) in the prefrontal cortex. Venous and arterialized capillary blood was sampled during exercise to assess for factors that may alter prefrontal cortex hemodynamics and oxygenation.

RESULTS

No differences were observed between T1D-A and CON-A, but VO_{2max} was impaired ($P < 0.05$) and cerebral blood volume (THb) increase blunted ($P < 0.05$) in T1D-I compared with CON-I. Nonetheless, O_2Hb appeared unaltered in T1D-I probably partly due to blunting of simultaneous neuronal oxygen extraction (i.e., a lower HHb increase; $P < 0.05$). There were no intergroup differences in arterial oxygen content, P_{ACO_2}, pH, $[K^+]$, and free insulin levels.

CONCLUSIONS

Maximal exercise highlights subtle disorders of both hemodynamics and neuronal oxygenation in the prefrontal cortex of poorly controlled patients with type 1 diabetes. These findings may warn clinicians of brain endothelial dysfunction occurring even before overt microangiopathy during exercise.

[1]University of Lille, URePSSS, "Physical Activity, Muscle, Health" Research Team, Lille, France
[2]Department of Diabetology, Lille University Hospital, EA 4489, Lille, France
[3]School of Kinesiology and Health Science, Faculty of Health, York University, Toronto, ON, Canada
[4]Department of Physiology, EA 2689 and IFR 22, Lille, France
[5]Regional Hospital Centre of Roubaix, Roubaix, France
[6]University Paris Sud-University of Orléans, EA 4532 CIAMS, Orléans, France

Corresponding author: Elsa Heyman, elsa.heyman@univ-lille2.fr.

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P.F. and E.L. contributed equally to this article.

Type 1 diabetes can have an impact on brain structure and function, especially in cases of poor glycemic control (i.e., high level of glycated hemoglobin [HbA_{1c}]) over the long term (1,2). Thus, compared with healthy control subjects, young to middle-aged adults with type 1 diabetes show a modest but significant cognitive decline (2), and this can affect their quality of life. Neurophysiological or hemodynamic abnormalities in the central nervous system may occur before the clinical appearance of other diabetes complications (3,4) and before development of neurological dysfunction (5).

Evidence of impaired cerebral vasoreactivity (6) (i.e., change in cerebral blood flow in response to a vasodilatory stimulus) in patients with diabetes has arisen from studies using pharmacologically induced hypercapnia. In these studies, the increase in regional (5) or middle cerebral artery (7) blood flow following acetazolamide injection (5), carbon dioxide inhalation (4), or propofol anesthesia hypoventilation (7) was blunted. This sometimes occurred even in patients with no clinical evidence of vascular complications (4).

The impairment in cerebral vasoreactivity appears all the more marked in cases of high HbA_{1c} levels (7), which is not surprising considering the deleterious effect of chronic hyperglycemia on endothelial function (8). In addition, high HbA_{1c} levels usually reflect inadequate current insulin supply or action, which might impair cerebral vasodilation (9) and metabolism (10,11), although these effects remain controversial (12–15). Remarkably, compared with baseline cerebral perfusion measurement, regional cerebrovascular reactivity to vasodilatory stimuli like hypercapnia has been shown to be more sensitive for detection of subclinical ischemic-induced irregularities (5). In this respect, short bouts of exercise represent an everyday life physiological stimulus during which regional blood flow also undergoes specific adaptations in response to neural activity (16) and exercise-linked dilatory stimuli (e.g., hypercapnia) (17). In particular, the prefrontal cortex, which is greatly involved in the planning of voluntary movement (18), is an important area of exercise-induced increase in blood flow (18).

Cerebral hemodynamic and oxygenation responses to an exercise stimulus remain unstudied in clinically uncomplicated patients with type 1 diabetes and according to their degree of long-term glycemic control. This response all the more merits further attention considering that regular exercise is strongly encouraged in type 1 diabetes care, particularly for its beneficial effects on long-term glycemic control. Therefore, the purpose of this study was to examine prefrontal cortex hemodynamics and oxygenation during maximal incremental exercise in either adequately or poorly controlled patients with type 1 diabetes but free from overt microangiopathy compared with matched healthy control subjects.

RESEARCH DESIGN AND METHODS

Written informed consent was obtained from all participants before their inclusion in the study, which was approved by the North-Western IV Regional Ethics Committee (N°EudraCT:2009-A00746-51). Eighteen patients aged 18–40 years with type 1 diabetes for at least 1 year and free from vascular complications volunteered to participate in this study (Table 1). The absence of microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (hypertension, coronary disease, peripheral arteriopathy) complications was carefully checked by the clinician during the initial examination. The patients were then divided into two groups according to their HbA_{1c} levels measured at inclusion: a group with adequate glycemic control (T1D-A) (n = 8; HbA_{1c} <7.0% [53 mmol/mol] [i.e., 6.8 ± 0.7% (51 ± 7.7 mmol/mol) the day of the test]) and a group with inadequate glycemic control (T1D-I) (n = 10; HbA_{1c} >8% [64 mmol/mol] [i.e., 9.0 ± 0.7% (75 ± 7.7 mmol/mol) the day of the test]). Two control groups, CON-A and CON-I, comprising healthy subjects aged 18–40 years were recruited to strictly match the T1D-A and T1D-I groups, respectively.

Selection Process of the Healthy Control Subjects

Healthy subjects were selected from a list (n = 250) drawn up from patients' friends and contacts. Each healthy control subject was chosen to strictly

Table 1—Participant characteristics

	CON-A (n = 8)	T1D-A (n = 8)	CON-I (n = 10)	T1D-I (n = 10)
Anthropometric and demographic data				
Male/female sex	7/1	7/1	6/4	6/4
Age (years)	29.6 ± 4.5	30.1 ± 6.8	25.8 ± 5.9	26.1 ± 7.8
BMI ($kg \cdot m^{-2}$)	23.5 ± 2.4	22.7 ± 3.4	23.8 ± 1.9	23.2 ± 1.9
Fat mass (%)	16.8 ± 3.7	18.2 ± 5.9	19.6 ± 5.4	19.9 ± 7.5
Smoking status				
Smoker	1	1	2	2
Nonsmoker	7	7	8	8
HbA_{1c} (%)	5.3 ± 0.2	6.8 ± 0.7‡‡‡**	5.3 ± 0.3	9.0 ± 0.7***
HbA_{1c} (mmol/mol)	34 ± 2.2	51 ± 7.7‡‡‡**	34 ± 3.3	75 ± 7.7***
Diabetes duration (years)	—	4.3 ± 3.5‡‡‡	—	10.7 ± 3.7
Age at disease diagnosis	—	24.8 ± 8.1‡	—	15.4 ± 9.4
Insulin delivery (MDI/CSII)	—	4/4	—	4/6
Insulin dose ($units \cdot kg^{-1} \cdot day^{-1}$)	—	0.48 ± 0.14‡‡‡	—	0.78 ± 0.12
Accelerometry ($min \cdot day^{-1}$)				
Light + moderate + vigorous	87.1 ± 26.5	72.9 ± 23.1	70.1 ± 18.9	76.5 ± 19.6

Data are mean ± SD or n. Fat mass was measured by DXA; HbA_{1c} recorded just before exercise. CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections. Significantly different from their respective CON group (Wilcoxon test): **$P < 0.01$, ***$P < 0.001$. Significantly different from T1D-I: ‡$P < 0.05$, ‡‡‡$P < 0.001$.

match a patient with type 1 diabetes according to the following pre-established ranges or values: sex same as the patient; age ± 7 years; BMI ± 4 kg · m^{-2}; moderate to vigorous physical activity levels ±1 h when the patients' physical activity category was 0 h/week, ±2 h for category 2–6 h/week, ±4 h for category >6 h/week, and patient/control subject pairs being in the same category; and tobacco status grouped according to no smoking, <10 cigarettes/day, and >10 cigarettes/day. The healthy controls chosen were then recruited after a 75-g oral glucose tolerance test. Individuals were excluded if they had a fasting blood glucose level >6.05 mmol · L^{-1} or an abnormal glucose tolerance test based on World Health Organization criteria. After inclusion, the similarity of body composition and physical activity levels between groups was accurately checked using DXA (Hologic Inc.) and accelerometry (GT1M; ActiGraph) over 7 consecutive days, respectively (Table 1).

Laboratory Testing

Subjects were requested to refrain from vigorous activity for 48 h before the test and from using tobacco the morning of the test. Patients with type 1 diabetes took their usual morning insulin bolus, and all subjects ate their usual breakfast (9.1 ± 3.8% protein, 41.3 ± 16.1% lipids, 49.6 ± 16.1% carbohydrates) as previously agreed on by the dietitian. The exercise test began 3.4 ± 0.5 h after breakfast. After a 2-min resting period while sitting on the cycle ergometer (Excalibur; Lode), the test started at 30 W and continued with 20-W increments every 2 min until exhaustion. During all experiments, the room temperature was maintained at 18–20°C using an air conditioning system, and subjects wore shorts and a T-shirt.

Cardiopulmonary Response

Electrocardiography (Ergo Card; Medisoft) was performed at rest and continually monitored throughout the exercise test by a cardiologist. Pulmonary gas exchanges were measured continuously throughout exercise (Ergo Card breath-by-breath system). VO_{2max} was determined as the highest 15-s average value during the exercise. Validation of VO_{2max} was obtained at the termination of the test when three of the following five criteria were attained: *1*) an O_2 uptake increase <100 mL · min^{-1} with the 20-W increase in power output, *2*) a heart rate >90% of the theoretical maximal heart rate (210−0.65 × age), *3*) a rate of perceived exertion score ≥19, *4*) blood lactate level >8 mmol · L^{-1}, and *5*) a respiratory exchange ratio >1.1. According to these criteria, all subjects achieved their VO_{2max} (Table 2). End-tidal pressure of carbon dioxide (P_{ETCO_2}) values, continuously recorded throughout exercise, were used as an index of P_{ACO_2}.

Prefrontal Cortex Hemodynamics and Oxygenation

Prefrontal cortex hemodynamics and oxygenation were monitored noninvasively by near-infrared spectroscopy (NIRS) (Oxymon Mk III; Artinis) in real time throughout exercise (19). Subjects were equipped with NIRS optodes housed in an optically dense plastic holder and attached with elastic bandage on the left-side prefrontal cortex between Fp1 and F3 according to the modified international electroencephalography 10-20 system (18). The interoptode distance was 50 mm to reduce the interference of scalp blood flow on cerebral hemodynamic variables quantified by NIRS (18,20). Data were collected with a sampling frequency of 10 Hz.

The Beer-Lambert law was used to calculate the changes in tissue oxygenation (oxyhemoglobin [O_2Hb] and deoxyhemoglobin [HHb]) (18) across time using received optical densities from two continuous wavelengths of NIR light (780 and 850 nm). Total hemoglobin (THb) was the sum of O_2Hb and HHb and used as an index of change in regional blood volume within the illuminated area (18). NIRS measurements were normalized to reflect changes from a 1-min baseline period immediately before the beginning of the exercise protocol (arbitrarily defined as 0 μmol · L^{-1}) to express the magnitude of changes throughout exercise. The use and limitations of NIRS for monitoring cerebral regional hemodynamics and oxygenation have been extensively reviewed (18,21).

Blood Analyses

We carefully took into account several blood variables able to modulate cerebral vasodilatory and/or metabolic responses and that can be influenced by diabetes and/or exercise [glucose, insulin, arterial oxygen content (C_{AO_2}), P_{ACO_2}, arterial pH, and arterial potassium ($[K^+]$)]. Venous blood samples were collected from a forearm catheter at rest and during maximal exercise. HbA_{1c} was measured at rest on EDTA anticoagulated blood (VARIANT II TURBO System; Bio-Rad) (Table 1). At rest and during maximal exercise, fluorinated and free-additive containers were used to analyze, in duplicate, plasma glucose (hexokinase enzymatic assay by modular automatic analyzer) and serum free insulin (noncompetitive radioimmunoassay using the BI INS IRMA kit; Cisbio), respectively.

At rest and immediately at exhaustion, a microcapillary arterialized earlobe blood sample (vasodilator pomade applied 5 min before sampling) was collected to analyze lactate by amperometry (ABL800 FLEX; Radiometer) as well as factors that may alter prefrontal cortex hemodynamics and oxygenation. These factors were P_{ACO_2}, pH, $[K^+]$ by potentiometry (ABL800 FLEX), and components of C_{AO_2} (i.e., arterial O_2 saturation [S_{AO_2}] by spectrophotometry, P_{AO_2} by amperometry, and hemoglobin concentration by spectrophotometry (ABL800 FLEX). C_{AO_2} was calculated as the sum of bound (1.39[hemoglobin] × S_{AO_2}) and dissolved O_2 (0.003 P_{AO_2}).

Statistical Analyses

Results are reported as mean ± SD except where otherwise indicated. Normality was tested using Shapiro-Wilks test. Demographic, anthropometric, and aerobic fitness data were compared between patients with type 1 diabetes and healthy control subjects with the Wilcoxon matched pairs test. NIRS data, arterialized oxygen transport, and blood factors able to alter prefrontal cortex hemodynamics were compared between patients with type 1 diabetes and their respective control subjects using a two-way ANOVA (group × exercise) with repeated measures on both factors. The group effects corresponded to T1D-A versus CON-A and T1D-I versus CON-I. For NIRS and P_{ETCO_2} data, the exercise effect corresponded to relative intensity levels −10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100% of VO_{2max}, and for other data, they corresponded to rest and maximal exercise. If significant main effects and/or interactions were observed with ANOVA, Bonferroni post hoc pairwise comparisons were applied. $P < 0.05$ was

Table 2—Cardiopulmonary and metabolic data of participants during incremental maximal exercise

	CON-A	T1D-A	Main effect by ANOVA	CON-I	T1D-I	Main effect by ANOVA
Aerobic fitness						
VO_{2max} (mL · min^{-1} · kg^{-1})	41.7 ± 6.9	39.6 ± 8.5	—	40.3 ± 7.3	34.6 ± 7.1*	—
MAP (W)	222 ± 28	197 ± 30	—	224 ± 54	186 ± 46	—
HR_{max} (bpm)	189.4 ± 8.6	190.6 ± 11.5	—	189.2 ± 10.2	186.7 ± 11.9	—
RER_{max}	1.1 ± 0.1	1.1 ± 0.1	—	1.1 ± 0.1	1.2 ± 0.1	—
Blood lactate max (mmol · L^{-1})	11.9 ± 5.1	12.7 ± 2.6	—	12.9 ± 4.5	13.9 ± 2.3	—
RPE at max	19.0 ± 0.6	18.7 ± 0.8	—	18.8 ± 0.5	19.1 ± 0.7	—
Factors possibly influencing prefrontal cortex hemodynamics and oxygenation						
O_2 arterial content						
P_{AO_2} (mmHg)						
Rest	97.8 ± 10.5	92.1 ± 4.3	Exercise: $P < 0.01$ Group: NS	98.4 ± 5.4	90.2 ± 8.3	Exercise: $P < 0.01$ Group: NS
Max	110.8 ± 15.4†	97.7 ± 4.9	Interaction: NS	105.6 ± 5.8†	104.2 ± 15.6†††	Interaction: NS
S_{AO_2} (%)						
Rest	98.1 ± 0.4	98.2 ± 1.0	Exercise: $P < 0.05$ Group: NS	98.3 ± 0.8	98.3 ± 0.7	Exercise: $P < 0.01$ Group: NS
Max	97.3 ± 2.1	96.7 ± 1.3†	Interaction: NS	97.2 ± 1.1†	97.3 ± 0.7	Interaction: NS
Hb (g · dL^{-1})						
Rest	15.0 ± 0.8	15.7 ± 1.1	Exercise: $P < 0.001$ Group: $P < 0.05$	14.7 ± 1.6	14.8 ± 1.1	Exercise: $P < 0.01$ Group: NS
Max	15.7 ± 1.1	17.7 ± 2.0	Interaction: NS	15.7 ± 1.9	15.9 ± 0.9†	Interaction: NS
C_{AO_2} (mL · 100 mL^{-1})						
Rest	20.4 ± 1.1	21.5 ± 1.4	Exercise: $P = 0.07$ Group: $P < 0.05$	20.1 ± 2.1	20.3 ± 1.5	Exercise: $P < 0.01$ Group: NS
Max	21.5 ± 1.4	23.8 ± 2.6†	Interaction: NS	21.2 ± 2.5	21.6 ± 1.8†	Interaction: NS
Exercise-influenced metabolic vasoactive stimuli						
P_{ACO_2} (mmHg)						
Rest	39.0 ± 2.2	38.8 ± 2.4	Exercise: $P < 0.001$ Group: NS	37.3 ± 3.9	39.4 ± 2.8	Exercise: $P < 0.001$ Group: NS
Max	28.3 ± 3.2†††	29.6 ± 2.4†††	Interaction: NS	30.7 ± 4.6†††	31.9 ± 3.7†††	Interaction: NS
Arterial pH						
Rest	7.41 ± 0.02	7.39 ± 0.05	Exercise: $P < 0.001$ Group: NS	7.43 ± 0.02	7.43 ± 0.01	Exercise: $P < 0.001$ Group: NS
Max	7.27 ± 0.07	7.25 ± 0.04	Interaction: NS	7.26 ± 0.08	7.27 ± 0.05	Interaction: NS
[K^+] (mmol · L^{-1})						
Rest	4.84 ± 0.36	5.15 ± 0.38	Exercise: $P < 0.01$ Group: NS	4.80 ± 0.57	5.10 ± 0.91	Exercise: $P < 0.05$ Group: NS
Max	5.62 ± 0.61	6.61 ± 0.90	Interaction: NS	5.52 ± 1.11	5.49 ± 0.69	Interaction: NS
Diabetes-influenced metabolic variables						
Plasma glucose (mmol · L^{-1})						
Rest	5.4 ± 0.4	6.2 ± 1.8	Exercise: $P < 0.001$ Group: NS	4.3 ± 1.4	7.5 ± 3.4	Exercise: $P < 0.001$ Group: $P < 0.05$

Continued on p. 862

Table 2—Continued

	CON-A	T1D-A	Main effect by ANOVA	CON-I	T1D-I	Main effect by ANOVA
Max	6.3 ± 0.8†	6.8 ± 1.7	Interaction: NS	6.8 ± 1.4	9.1 ± 2.4††*	Interaction: NS
Serum free insulin (mIU · L^{-1})						
Rest	10.8 ± 5.6	34.3 ± 49.2	Exercise: NS Group: NS	12.5 ± 9.8	31.7 ± 33.9	Exercise: NS Group: NS
Max	10.3 ± 4.3	35.5 ± 43.8	Interaction: NS	9.6 ± 6.8	43.4 ± 49.0	Interaction: NS

Data are mean ± SD unless otherwise indicated. Hb, hemoglobin; HR, heart rate; MAP, maximal aerobic power; Max, at exhaustion from the incremental exercise; NS, not significant; RER, respiratory exchange ratio; Rest, at rest just before the exercise; RPE, rating of perceived exertion. Wilcoxon test (variables only indicated at max) significantly different from their respective CON group: *$P < 0.05$. Main effects from ANOVA: exercise, exercise effect; group, group effect; interaction, exercise × group interaction. ANOVA post hoc analyses significantly different from their respective CON group: *$P < 0.05$. Significantly different from rest: †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$.

considered statistically significant. Statistics were calculated using Statistica 8.0 software.

RESULTS

Subject Characteristics

Demographic and physical activity data from patients with type 1 diabetes and their matched healthy control subjects are summarized in Table 1. Because of the possible effect of physical activity level on cerebral perfusion, we took care to closely match each patient with a healthy control subject, taking into account the usual demographic data as well as the exact levels of physical activity (determined by accelerometry).

T1D-I had a lower VO_{2max} than CON-I (Table 2) despite comparable levels of habitual physical activity as well as comparable heart rates achieved at exhaustion. No significant difference in VO_{2max} was observed between T1D-A and CON-A.

Prefrontal Cortex Hemodynamics and Oxygenation

THb increased significantly in patients and control subjects throughout the exercise test (Fig. 1). However, the levels of THb as well as the slope of THb increase were lower in T1D-I than CON-I, particularly at exercise intensities >60% of VO_{2max}. In contrast, no differences were found in THb between T1D-A and CON-A.

O_2Hb increased significantly with exercise intensity in all the groups, and no intergroup differences appeared between patients with type 1 diabetes and their respective control subjects. HHb increased significantly in patients and control subjects throughout the exercise test. However, the slope of HHb increase was lower in T1D-I than CON-I, whereas no differences appeared between T1D-A and CON-A. The use of absolute workload instead of relative intensity for the exercise effect in the ANOVAs did not change the NIRS results.

Factors That May Alter Prefrontal Cortex Hemodynamics and Oxygenation

Arterial O_2 Content

C_{AO_2} and its components ([hemoglobin], S_{AO_2}, P_{AO_2}) did not differ between T1D-I and CON-I during exercise (Table 2). T1D-A had higher C_{AO_2} than CON-A, which could be explained by higher hemoglobin concentrations.

Exercise-Influenced Metabolic Vasoactive Stimuli

In all the groups, P_{ETCO_2} increased during light and moderate exercise intensities and thereafter decreased until exhaustion to achieve lower levels than at baseline (Fig. 2). Likewise, P_{ACO_2} was lower at maximum exercise compared with rest. There were no intergroup differences in P_{ACO_2} and P_{ETCO_2} throughout exercise. pH decreased and [K^+] increased significantly with exercise intensity in all the groups, without intergroup differences.

Diabetes-Influenced Metabolic Variables

Plasma glucose concentrations increased during exercise in all the groups, with higher levels at exhaustion in T1D-I. The latter was not accompanied by higher hematocrit levels, thus excluding the possibility of a concomitant higher dehydration (22). None of the patients with type 1 diabetes became hypoglycemic during exercise.

There were no intergroup differences in free insulin levels and changes during exercise. However, intraindividual variability was larger in patients with type 1 diabetes than in healthy control subjects.

CONCLUSIONS

There is increasing evidence that the brain may be susceptible to the effects of hyperglycemia. Altered cerebral function (2), structure (1), and metabolism (11) and hemodynamics (6,7) have been demonstrated in patients with type 1 diabetes, especially in those with high HbA_{1c} levels (1,2,7). In line with the latter studies, we observed that an increase in regional cerebral blood volume (i.e., THb) was blunted at moderate to high intensities of exercise in patients with inadequate glycemic control despite the absence of any clinically detectable vascular complications. Considering recommendations of physical activity as a crucial component in diabetes care, the current results are of concern for poorly controlled, albeit still uncomplicated patients at risk for long-term cognitive decline.

Prefrontal Cortex Blood Volume During Exercise

We observed a significant increase in prefrontal cortex blood volume in patients with adequate glycemic control and both groups of healthy subjects

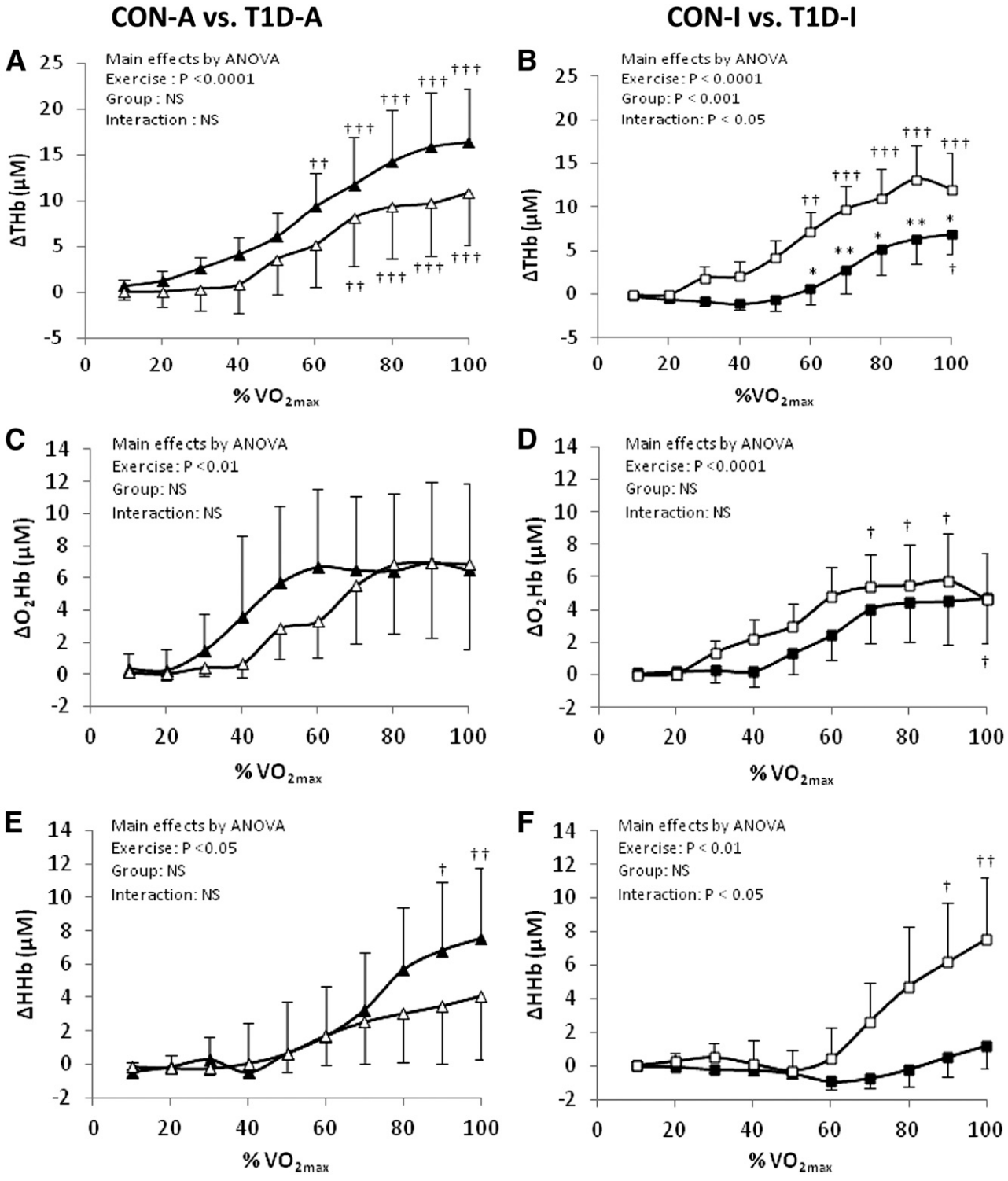

Figure 1—NIRS recordings made of the left-side prefrontal cortex. *A* and *B*: Change in THb. *C* and *D*: Change in O_2Hb. *E* and *F*: Change in HHb. The 0 indicates the baseline value before incremental exercise. ▲, T1D-A; △, CON-A; ■, T1D-I; □, CON-I. Post hoc analyses for group effect significantly different from healthy controls: $^*P < 0.05$, $^{**}P < 0.01$. Post hoc analyses for time effect significantly different from rest: $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, $^{\dagger\dagger\dagger}P < 0.001$.

as a function of mild- to moderate-intensity exercise. A reasonable explanation for this is that elevation of P_{ACO_2} (as reflected by P_{ETCO_2}) during light and moderate exercise intensities resulted in cerebral vasodilation and, hence, increased regional blood volume (17,19). The fact that the decrease in P_{ACO_2} and P_{ETCO_2} at maximal exercise did not elicit a reduction in THb appears common in healthy, aerobically trained individuals, although the underlying mechanisms remain hypothetical (21).

Of particular note, we found that the increase in blood volume was

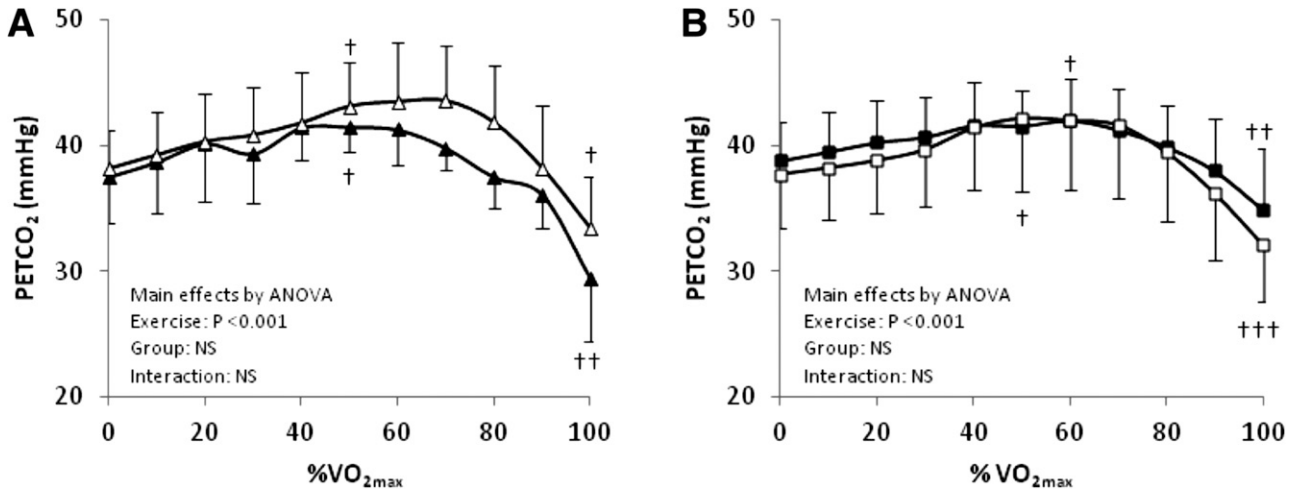

Figure 2—*A* and *B*: Breath-by-breath recordings of P_{ETCO_2} during incremental exercise. The 0 indicates the baseline value before incremental exercise. ▲, T1D-A; △, CON-A; ■, T1D-I; □, CON-I. Post hoc analyses for time effect significantly different from rest: †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$. NS, not significant.

significantly blunted in T1D-I despite these patients being free from clinical microvascular complications. The current results supplement those of Albert et al. (23) in poorly controlled patients with type 1 or type 2 diabetes, among whom some suffered from a background of diabetic retinopathy and/or from autonomic neuropathy. Albert et al. did not find differences in middle cerebral artery and ophthalmic artery velocities between patients and healthy control subjects in response to incremental submaximal exercise. The current study, in a homogeneous and well-characterized sample of uncomplicated patients with type 1 diabetes, suggests that the physiological condition of maximal exercise was sufficient to induce an alteration in regional cerebral perfusion in cases of poor glycemic control.

However, the integrity of cerebrovascular reactivity of this brain region appears clinically important. The prefrontal cortex plays a major role in executive functions and, in conjunction with the hippocampus, in memory formation and retrieval. The adequate increase in its perfusion is considered a guarantee of normal short-term improvement in cognitive performance (9). Although the patient's inability to adequately increase cortical blood flow in response to short bouts of exercise would probably not be reflected in clinical symptoms in the short term, this limitation might become problematic in the long term while undertaking strenuous exercise programs for many years. Incidentally, executive functions, which highly depend on prefrontal cortex functioning, are significantly impaired by the so-called "diabetes-associated cognitive decline," and this is especially common in patients with HbA_{1c} >8% (2). In line with this, the prefrontal cortex appears to be one of the brain areas showing microstructural abnormalities in elderly people with diabetes (24). Moreover, a decreased cerebral blood flow in this region correlated with neuropsychological deficits (25), microangiopathy dementia (26), and retinopathy (12).

Thus, from a clinical perspective, it appears worthwhile to take into consideration and try to understand this relative exercise-induced prefrontal cortex hypoperfusion observed in the current poorly controlled, albeit uncomplicated, patients. During a bout of exercise, several factors may explain a reduction in cerebral THb increase. First, the increase in P_{ACO_2} during low to moderate exercise intensities is one of the major stimulators of exercise-induced brain regional vasodilation (17). We found comparable levels in P_{ETCO_2} and P_{ACO_2} in patients with type 1 diabetes and their matched healthy control subjects throughout exercise. However, the reactivity of cerebral vessels to CO_2 has been shown to be noticeably altered in patients with type 1 diabetes (5,7). Further studies coupling CO_2 inhalation and exercise would help to verify the putative involvement of a decrease in P_{ACO_2} sensitivity in the observed dysregulation of exercise-induced cerebrovascular adaptation. Second, the altered hemodynamic response under the condition of exercise in the current poorly controlled patients with long-standing type 1 diabetes may underline the presence of endothelial dysfunction and functional alterations of the microcirculation (8). In a study by Fülesdi et al. (12), patients with a longer duration of type 1 diabetes had a lower cerebrovascular reactivity to acetazolamide but experienced more microvascular complications. The current study confirms that cerebral endothelial dysfunction response to vasodilatory stimuli might occur even before overt microangiopathy in cases of chronic hyperglycemia and long diabetes duration. Ultimately, the possible influence of actual circulating glucose and free insulin levels on cerebral hemodynamics merits consideration (14). Although the role of circulating insulin on endothelium-dependent vasodilation is well-established in the periphery (27), its central effect appears more controversial (12–14). In the current study, although free insulin levels were not significantly different between groups, their ranges were much larger in patients than control subjects. This illustrates the important fluctuation of peripheral insulin in response to insulin therapy depending, among other reasons, on degree of insulin resistance. The maximum free insulin level among patients in the current study (156.1 $mU \cdot L^{-1}$) remains, nonetheless, lower than that obtained by Cranston et al. (14) in patients with type 1 diabetes at rest during euglycemic-hyperinsulinemic

clamp, which altered neither total nor regional (including prefrontal cortex) brain perfusion. These results suggest that brain vessels are not sensitive to high insulin concentrations in the physiological range, at least when euglycemia is maintained. However, this is no longer valid when hyperinsulinemia triggers hypoglycemia (28), an adverse event that did not occur in the current study. Acute short-term hyperglycemia was, nevertheless, observed at the end of exercise in 3 of the 10 poorly controlled patients (10.7, 12.7, and 13.0 mmol · L^{-1}). Controversies exist about the effect of acute hyperglycemia, as mimicked by 2–3 h of 15 mmol · L^{-1} hyperglycemic clamp, on cerebral blood flow in healthy humans. This hyperglycemia either decreased resting cerebrovascular reactivity to CO_2 (29) or increased resting middle cerebral artery blood flow (30), whereas it did not alter middle cerebral artery blood flow during 10-min rhythmic handgrip exercise (31). Considering the latter results, the acute hyperglycemia, present only in a small proportion of the current patients, was probably not involved in the observed relative hypoperfusion in response to maximal exercise.

Prefrontal Cortex Oxygenation During Exercise

Exercise-induced regional O_2Hb changes have been accepted to depend on changes in regional cerebral blood flow (32), C_{AO_2} (33), and neuronal oxygen extraction (21). Thus, in cardiac patients, smaller or even negative changes in O_2Hb were explained by prefrontal cortex hypoperfusion during incremental exercise (34). However, in the current study, we observed comparable O_2Hb, despite the blunted THb increase in T1D-I compared with CON-I. This absence of an intergroup difference in O_2Hb despite the lower THb response could not be explained by an enhanced arterial O_2 transport (33), given that C_{AO_2} levels were comparable between T1D-I and CON-I.

Therefore, we can raise the hypothesis that the maintenance of normal O_2Hb despite the blunted THb is attributable to a lower exercise-induced increase in neuronal oxygen extraction, as actually reflected by the blunted HHb increase in the T1D-I group. In contrast, in accordance with literature in healthy subjects (21), CON-I, CON-A, and T1D-A showed a great HHb increase during hard to very hard exercise intensities, probably partly attributable to arterial acidosis (Table 2) facilitating hemoglobin oxygen release. The blunted HHb increase in T1D-I might be favored by two factors. The first is a disturbed O_2Hb dissociation rate in patients with high HbA_{1c} levels. It has indeed been shown in vitro that glycation of hemoglobin, at percentages that might be found in patients with diabetes (i.e., 8% HbA_{1c}), reduces the kinetics of hemoglobin oxygen release by 10% compared with a 4% HbA_{1c} level (35). The second factor is a reduced glucose metabolism and, hence, O_2 use in neurons. Although hyperinsulinemia within the normal physiologic range does not seem to affect glucose metabolism in several brain regions in healthy humans (36) and in patients with type 1 diabetes (14), this is no more the case when insulin decreases under basal levels. Thus, in healthy subjects with somatostatin-induced suppression of endogenous insulin, decreasing insulin from 27.1 $\pm$ 1.3 to 3.5 $\pm$ 0.4 mU · L^{-1} significantly impairs glucose metabolism in cortical areas (10). In the current study, although free insulin levels were not lower in T1D-I patients compared with healthy control subjects, their higher plasma glucose levels despite comparable insulin levels at the end of exercise presumably illustrate a state of peripheral insulin resistance. Because the existence of central insulin resistance has been proposed (13), we could assume that insulin resistance in T1D-I patients might have impaired their prefrontal cortex glucose metabolism and O_2 consumption during exercise, hence partly blunting HHb increase. van Golen et al. (11) indeed observed a 21% reduced cerebral glucose metabolism in patients with type 1 diabetes compared with healthy control subjects at rest in a fasting state, and this despite higher ambient insulin and glucose levels. Ultimately, whether the likely compromised O_2 release and/or use in prefrontal cortex neurons observed in the current patients may impair the ability of the central nervous system to sustain motor output (37) remains to be elucidated. This is a particularly relevant question because an impaired physical fitness level represents a great barrier to physical activity observance in poorly controlled patients with type 1 diabetes (38).

Methodological Limitations

A persisting concern with NIRS is the extent to which light is contaminated by the extracranial tissues and particularly by scalp blood flow (39). Further studies investigating both scalp and cortical blood flow would allow confirmation that the subtle hemodynamic and oxygenation disorders highlighted in the current study were mainly due to neurovascular factors in the prefrontal cortex. Of note, we took care to standardize several factors known to influence skin blood flow during exercise, such as the training state (subjects strictly matched on physical activity level), the thermoneutral environment, and the subjects' clothing.

Besides, we acknowledge the fact that prefrontal cortex hemodynamic recordings not only reflect local exercise-induced vasodilatory response but also may be influenced by other variables such as blood pressure (6). Unfortunately, the latter was not measured in the current study. Further studies interrogating a cortical region not involved in motor planning or function (e.g., the occipital region) in addition to the prefrontal region would help to distinguish between local and general influences.

Ultimately, for a real partition of the respective impact of chronic and acute metabolic control on exercise cerebral hemodynamics, further studies using clamp methodology, varying glycemia and insulinemia levels in a standardized way, would be required. Compared with the clamp methodology, which imposes an isometabolic state, the current study nonetheless presents the advantage of investigating patients in a real-life situation under normal daily conditions of ambient glucose and insulin levels. Patients with type 1 diabetes are indeed prone to higher and, more importantly, fluctuating glucose and insulin levels.

In summary, the physiological stimulus of maximal exercise highlights subclinical disorders of both hemodynamic and neuronal oxygenation in the prefrontal cortex of poorly controlled patients with type 1 diabetes who were otherwise free from clinical microangiopathy. These disorders might be the consequences of hyperglycemia-induced endothelial dysfunction and of an increased O_2 affinity accompanying hemoglobin glycation and/or an impaired cerebral

glucose metabolism. Of note, maximal exercise coupled with local cerebral hemodynamic measurements may represent a promising noninvasive method, which would presumably be better received than a pharmacological one, for detecting and following subtle cerebrovascular reactivity impairments in type 1 diabetes.

The challenge in diabetes care is to optimize metabolic control to slow the progression of vascular disease. This may be achieved, at least in part, by regular physical activity. One way of motivating patients to be active is by prescribing exercises of various intensities. However, the current study aroused the possibility of exposure to cerebral hypoperfusion during intense exercise in patients with type 1 diabetes, and this even in the early stages of disease development (i.e., before the clinical recognition of microvascular complications). Although the positive long-term effects of exercise on the brain are becoming widely acknowledged in nondiabetic populations, further prospective studies are needed in poorly controlled patients with type 1 diabetes to check whether long-term intensive exercise training would not portend an increased risk for cognitive decline.

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