Reduced Forearm Blood Flow in Children and Adolescents With Type 1 Diabetes (Measured by Near-Infrared Spectroscopy)

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OBJECTIVE — The aim of this study was to measure forearm blood flow (FBF) to detect any possible changes that might indicate vascular disorders in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — FBF was measured by near-infrared spectroscopy (NIRS), venous occlusion at rest, and after handgrip exercise. A total of 40 children and adolescents with type 1 diabetes and 40 healthy children and adolescents (6–18 years) were matched for age and sex for comparison.

RESULTS — In the diabetic group (age 12.79 ± 2.9 years, duration of diabetes 5.15 ± 36 months), FBF at rest was significantly lower (1.39 ± 0.76 ml·100 g muscle−1·min−1) than in control subjects (age 12.66 ± 2.9 years, FBF at rest 1.90 ± 1.19 ml·100 g muscle−1·min−1). After exercise, FBF increased significantly less in the diabetic group (0.70 ± 0.82 ml·100 g muscle−1·min−1) compared with the control subjects (1.15 ± 0.55 ml·100 g muscle−1·min−1). FBF at rest decreased with increasing age in both groups. The change in FBF after exercise was independent of age in the diabetic group and increased with increasing age in control subjects. FBF is reduced with impaired hyperemic response after exercise in children and adolescents with type 1 diabetes.

CONCLUSIONS — These data suggest that vascular disorders in childhood are detectable noninvasively by NIRS.

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Diabetes is one major risk factor for development of vascular disorders. Vascular disorders described in childhood are microvascular complications of the eye, kidney disorders (low creatinine clearance, fluctuating microproteinuria), or echocardiographic changes (1–4). With near-infrared spectroscopy (NIRS), a relatively new technique, an assessment of skeletal muscle blood flow, especially of the small vessels, is possible and has been validated in several studies (5–9). By means of NIRS, impaired peripheral muscle blood flow and oxygenation has been detected in adult patients with diabetes, peripheral vascular disease, and heart failure (10–12).

No data on muscle blood flow in children and adolescents with type 1 diabetes have been published until now. In the present study, skeletal muscle forearm blood flow (FBF) was measured by means of NIRS in children and adolescents with type 1 diabetes without otherwise clinically detectable microangiopathy and in healthy control subjects. The aim of the present study was to investigate whether muscle blood flow measured by NIRS is already impaired in children and adolescents with type 1 diabetes in the absence of any other clinical signs of vasculopathy.

RESEARCH DESIGN AND METHODS — Children and adolescents with type 1 diabetes aged 6–18 years were studied. Patients with microalbuminuria and eye diseases were excluded from the study. Furthermore, patients had to have no evidence of neuropathy, cardiac failure, or intermittent claudication. Both patients with type 1 diabetes and control subjects who were obese or had taken any medication (except insulin) within the last 7 days were excluded. The patients with type 1 diabetes were matched for age (±6 months) and sex to healthy control subjects. Each subject was a volunteer, and informed consent was obtained from all parents and adolescents before initiation of measurement. The study was approved by the local ethical committee.

NIRS measurements were performed using the NIRO 500 (Hamamatsu Photonics, Shizuoka, Japan), which includes four laser diodes for measurement with wavelengths of 775, 825, 850, and 904 nm. The optodes were placed over the brachial muscle of the left forearm 4 cm distal to the elbow, the interoptode distance was 3.5, and the sampling rate was 2/s. A differential path length factor of 4.16 was used (13). NIRS enables noninvasive continuous measurement of changes in the concentration of oxygenated hemoglobin (cHbO2) and deoxygenated hemoglobin.
Changes in the concentration of total hemoglobin (cHbtot) were calculated from the sum of changes in cHbO2 and cHb. NIRS parameters were measured in micromolar units.

Venous occlusion causes an increase of forearm blood volume by an undisturbed forearm arterial (in)flow and interrupted venous (out)flow. Therefore, the increase of forearm blood volume per minute corresponds to arterial FBF per minute. FBF can therefore be calculated during venous occlusion from the linear increase of cHbtot measured by NIRS taking into account the hemoglobin value of each subject. Furthermore, the molecular weight (64.458 g/mol) and the molecular ratio between hemoglobin and oxygen (1:4) were taken into account. FBF was expressed in milliliters per 100 g muscle per minute.

For venous occlusion, a pneumatic cuff was placed around the arm above the elbow with the subjects seated comfortably in a chair. The left hand was placed ~10 cm above heart level. Heart rate and peripheral arterial oxygen saturation were measured by pulse oximetry, for which the sensor was placed on the third finger of the left hand.

After positioning of the optodes and pneumatic cuff and oximetry, a 10-min rest period followed. Measurement of blood pressure was then performed. After a rest period of 1 min, the pneumatic cuff was inflated within 0.5–1 s to a pressure less than the diastolic arterial pressure and greater than the venous pressure. The cuff was maintained in the inflated state for 20 s. This procedure was repeated three times with a rest period of 40 s between inflations.

After the first three measurements, the children and adolescents performed a rhythmic handgrip exercise at a frequency of 60/min for 1 min. Six groups of different forces of handgrip exercise were undertaken according to age of the participants. Children and adolescents with type 1 diabetes and their matched control subjects had the same force in the handgrip exercise. After the handgrip exercise, there was another rest period of 1 min to obtain a baseline measurement. Four successive venous occlusions were then performed as described above.

To define FBF at rest, the mean of the three measurements before handgrip exercise was calculated. To define the increase in FBF after exercise, the difference in FBF at rest and the first venous occlusion after exercise was calculated.

The diabetic and healthy groups were compared using the unpaired Student’s t test. For comparison of the three measurements of FBF at rest and for comparison of FBF at rest and FBF after exercise, the paired Student’s t test was used. In both groups, a comparison of male and female subjects was performed by a Mann-Whitney U test. In both groups, FBF at rest and the increase in FBF after exercise were correlated with age, BMI, hemoglobin concentration, blood pressure, and heart rate by linear and polynomial regression analysis. In the diabetic group, FBF at rest and the increase in FBF after exercise were correlated to age, duration of diabetes, blood glucose levels, and HbA1c by multiple regression analy-

Table 1—Data from 40 children and adolescents with type 1 diabetes compared with 40 healthy children and adolescents

<table>
<thead>
<tr>
<th></th>
<th>Diabetic subjects</th>
<th>Healthy subjects</th>
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<tr>
<td>n</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.8 ± 2.9</td>
<td>12.7 ± 2.9*</td>
</tr>
<tr>
<td>Male/female</td>
<td>20/20</td>
<td>20/20*</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>19.8 ± 3.7</td>
<td>19.1 ± 2.6*</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.1 ± 1.0</td>
<td>13.3 ± 1.5*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>102.8 ± 13.1</td>
<td>98.0 ± 10.7*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>59.9 ± 8.7</td>
<td>56.9 ± 8.7*</td>
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<tr>
<td>Oxygen saturation (%)</td>
<td>98 ± 0.7</td>
<td>98 ± 0.4*</td>
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<tr>
<td>Duration of diabetes (months)</td>
<td>51.5 ± 36.0</td>
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</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.2 ± 1.8</td>
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<tr>
<td>Blood glucose level (mg/dl)</td>
<td>226.9 ± 83.4</td>
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</table>

Data are means ± SD. *No significant difference.

Figure 1—FBF at rest and after 1-min rhythmic handgrip exercise in children and adolescents with type 1 diabetes and in healthy children and adolescents (mean ± SD). *Significant difference in FBF at rest between both groups (P = 0.026); **significant difference in FBF 1 min after exercise between both groups (P = 0.003); #significant increase in FBF after exercise (P < 0.001).
Forearm blood flow in patients with diabetes

Figure 2—FBF at rest in children and adolescents with type 1 diabetes and healthy children and adolescents (mean, 25th and 75th quartiles). *Significant difference (P = 0.026).

Figure 3—Increase in FBF after rhythmic handgrip exercise in children and adolescents with type 1 diabetes and in healthy children and adolescents (mean, 25th and 75th quartiles). *Significant difference (P = 0.039).

RESULTS—A total of 40 children and adolescents with type 1 diabetes were matched to 40 healthy children and adolescents (Table 1).

The three measurements of FBF at rest showed high reproducibility in the diabetic group (1.35 ± 0.81, 1.37 ± 0.73, and 1.45 ± 0.89 ml·100 g muscle⁻¹·min⁻¹; P > 0.05) as well as in the control group (1.79 ± 1.19, 1.95 ± 1.21, 1.96 ± 1.25 ml·100 g muscle⁻¹·min⁻¹; P > 0.05).

Both FBF at rest (P = 0.026) and FBF 1 min after exercise (P = 0.003) were significantly lower in the diabetic group (Fig. 1). FBF 1 min after exercise was significantly higher than FBF at rest in both groups (P < 0.001). A comparison of FBF at rest is shown in Fig. 2. Figure 3 shows a comparison of the changes in FBF after handgrip exercise, and it can be seen that the increase in FBF after exercise was significantly lower in the diabetic group (P = 0.039). No change of SaO₂ and heart rate was observed during and after handgrip exercise and venous occlusion (P > 0.05). In both groups, no differences were observed between female and male subjects (P > 0.05). In both groups, FBF at rest decreased with increasing age (diabetic group: r = 0.45, P = 0.003; healthy group: r = 0.57, P < 0.001) (Fig. 4). In the diabetic group, the changes in FBF after exercise were independent of age (P > 0.05), whereas in control subjects, the changes in FBF after exercise increased with increasing age (r = 0.37, P = 0.016) (Fig. 5). In both groups, FBF at rest and the changes in FBF after exercise were independent of BMI, hemoglobin concentration of the blood, blood pressure, and heart rate (P > 0.05). With increasing duration of diabetes, FBF at rest, and the changes in FBF after exercise tended to become less; however, regression analysis did not reach significance (P > 0.05). FBF at rest and the changes in FBF after exercise were independent of blood glucose levels and HbA₁c (P > 0.05).

CONCLUSIONS—The present study is the first to perform measurements of skeletal muscle FBF in children and adolescents with type 1 diabetes and healthy children and adolescents. Both FBF at rest and changes in FBF after exercise were lower in the diabetic group. This reduction in FBF was observed despite the absence of any otherwise clinically detectable vascular disorders.

Principally, differences in muscle perfusion may be due to metabolic, vascular, or neurogenic disorders. First, metabolic disorders influence local vasoactive biochemical compounds, of which acetylcholine, nitric oxide, and adenosine play an important role (14) and can, therefore, be responsible for changes in muscle perfusion. Second, vascular disorders can influence muscle perfusion. In contrast to adults, clinically detectable diabetic vascular disorders are rare in children and adolescents (1–3). Nevertheless, Malone et al. (2) demonstrated retinal vascular abnormalities with fluorescein angiography in 75% of children with type 1 diabetes. Karahanyan et al. (1) described microscopic alterations of the capillary loops of the nail bed in children with type 1 diabetes. Third, neurogenic disorders can influence muscle perfusion. Impaired autonomic nerve function in children with type 1 diabetes has been demonstrated in several studies (4,15,16). Muscle contractions cause an elevation of the muscle sympathetic nerve activity, which is related to exercise intensity, and thus influence muscle perfusion. However, no alteration of sympathetic nervous system activity is expected in small muscle group exercise (14). In the present study, rhythmic handgrip exercise induced no change in heart rate and SaO₂, and arterial blood pressure was not measured during and after exercise because measurement maneuvers...
would have interfered with measurement of FBF.

With the data from the present study, it is not possible to distinguish whether the reduced FBF in children and adolescents with type 1 diabetes is due to metabolic, vascular, or neurogenic disorders. Most probably, the reduced FBF is due to a combination of all three factors.

In adult patients with type 1 diabetes, basal and exercise-induced skeletal muscle blood flow is augmented (17). In contrast, in the present study, the children and adolescents with type 1 diabetes showed decreased blood flow estimated by NIRS. One reason for the observed age dependency of blood flow and different findings in adult patients with type 1 diabetes might be the ongoing development of the muscle during childhood. The development of fiber-type distribution of type 1 and type 2 fibers during childhood has been the subject of controversy (18–20). Nevertheless, a comparison of local muscular fatigue in boys and men suggest that more fatigable type 2 fibers are involved in men, resulting in greater lactic acid and ion accumulation during fatigue (21). The metabolic behavior of muscle has been observed to be different between children and adults. Children rely less on glycolysis than adults during high-intensity exercise, leading to a lower production of lactate during intense cycling efforts (22). However, no data are available regarding muscle development in children with type 1 diabetes and consequent possible impairment.

The development of maximal isometric handgrip force is not only dependent on chronologic age but is also largely determined by body size, and height should especially be taken into account (23). In the present study, no difference in body size was observed between the two groups.

Correlation of severity of vascular complications with duration of diabetes has been reported in several studies (1,2,24). In the present study, FBF tended to decrease with increasing duration of diabetes but without significance. No correlation of FBF to blood glucose levels and HbA1c was observed; this is in agreement with former studies (2,24). Nevertheless, longitudinal studies will be necessary to rule out the influence of the blood glucose control on reduction of FBF in childhood.

In NIRS measurements of skeletal muscle blood flow, the skin blood flow is believed to be negligible (<5%) when the interoptode distance is >20 mm, as it was in the present study, with an interoptode distance of 35 mm (5,9). Abnormalities of skin blood flow have been described in
children and adolescents with type 1 diabetes using infrared thermography and laser Doppler fluximetry (24–26). In one of these studies, raised systolic and diastolic blood pressure in children with type 1 diabetes with impaired skin blood flow has been demonstrated (24). In the present study, no differences in blood pressure at rest between the two groups were observed. Another confounding factor of measurement of muscle blood flow with NIRS might be the adipose tissue thickness. Van Beekvelt et al. (27) found a weak correlation of FBF with adipose tissue thickness, which showed that FBF became higher as adipose tissue thickness increased. Because of this, we excluded subjects with obesity from the present study.

The present findings of changes in FBF after exercise in children and adolescents are difficult to compare with data found in adults because of different protocols, different time points of measurement, and different forces of handgrip exercise (5, 6, 8). In the present study, measurements were performed after exercise with a resting period of 1 min to exclude any movement artifacts. Therefore, in a few subjects, 1 min after exercise, FBF had decreased again even to levels lower than before exercise. Mean overall change still showed an increase in FBF, which was lower in children with type 1 diabetes.

We demonstrated that children and adolescents with type 1 diabetes have a reduced FBF compared with healthy control subjects; however, the influence of vascular and neurogenic disorders requires further investigations. This reduction of the FBF can be detected by means of NIRS early in childhood. NIRS measurement in combination with venous occlusion of skeletal muscle blood flow is a relatively new method but has been used increasingly in adults in recent years (5, 6, 8, 9). In children and adolescents with type 1 diabetes who have no other clinical signs, this method is promising, well tolerated, and noninvasive when assessing disorders of muscular perfusion.

References