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Diabetic background retinopathy is associated with impaired coronary vasoreactivity in people with Type 1 diabetes

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Abstract

Aims/hypothesis. We examined whether diabetic background retinopathy is associated with reduced coronary vasoreactivity in people with Type 1 diabetes.
Methods. A total of 21 men with Type 1 diabetes were investigated, including 9 men with background retinopathy and 12 men without retinopathy. In addition, 12 non-diabetic, age-matched subjects were studied. All subjects were non-smokers, otherwise healthy and had no other diabetic complications. Resting myocardial blood flow and hyperaemic dipyridamole-stimulated flow (dipyridamole, 0.56 mg/kg during a 4-min period), a measure of coronary vasoreactivity, were measured during euglycaemic hyperinsulinaemic clamp (1 mU·kg^{-1}·min^{-1}) using positron emission tomography and oxygen-*15*-labelled water.
Results. Resting myocardial blood flow (0.82±0.13 vs 0.96±0.23 vs 0.88±0.25 ml·g^{-1}·min^{-1}, with vs without retinopathy vs non-diabetic subjects) and coronary vascular resistance (111.2±23.4 vs 95.5±15.8 vs 101.9±31.5 mmHg·min·g·ml^{-1} respectively) were not significantly different between the groups. Dipyridamole infusion induced an increase in blood flow and a decrease in coronary vascular resistance in all study subjects (p<0.001). However, dipyridamole-stimulated flow and coronary vascular resistance were blunted in diabetic patients with retinopathy (2.9±0.9 ml·g^{-1}·min^{-1} and 34.1±11.3 mmHg·min·g·ml^{-1}) when compared to diabetic patients without retinopathy (4.0±1.3 ml·g^{-1}·min^{-1}, p=0.04 and 24.6±7.5 mmHg·min·g·ml^{-1}, p=0.03) or non-diabetic subjects (4.5±1.4 ml·g^{-1}·min^{-1}, p=0.008 and 22.2±8.7 mmHg·min·g·ml^{-1}, p=0.01). Myocardial flow reserve was impaired in diabetic patients with retinopathy (3.6±1.0) when compared to non-diabetic subjects (5.3±1.9, p=0.02) but not significantly reduced when compared to diabetic patients without retinopathy (4.2±1.4, p=0.2).
Conclusions/interpretation. Diabetic background retinopathy appears to be associated with impaired coronary vasoreactivity in young people with Type 1 diabetes.

Keywords Myocardial blood flow · Type 1 diabetes · Retinopathy · Dipyridamole · Positron emission tomography

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Abbreviations: PET, positron emission tomography · [^{15}O]H_2O, oxygen-*15*-labelled water

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Introduction

Based on epidemiological studies, diabetic retinopathy is considered to be an early sign of widespread overall vascular damage [1]. Diabetic patients with retinopathy are more likely to have coronary artery disease [2]. Recently, it has been demonstrated that, in patients with Type 2 diabetes, retinopathy is associated with defects in thallium myocardial perfusion imaging [3]. In the study in question, however, the patients also had, as Type 2 patients often do, several other risk factors for coronary artery disease which are known to further reduce coronary vascular reactivity.

There are currently no studies that address whether background retinopathy is associated with impaired coronary vasoreactivity in young people with Type 1 diabetes without hypertension or dyslipidaemia.

Positron emission tomography (PET) imaging is currently the most accurate technique to quantify myocardial blood flow and flow reserve non-invasively. Coronary flow reserve is reduced in the presence of coronary artery disease risk factors [4]. This observation suggests that abnormal coronary vasodilator function is an early indicator of increased risk of future coronary artery disease. Furthermore, it has been shown that reduced coronary vasoreactivity can be improved by medical interventions, e.g. by statins, at least in patients with hypercholesterolaemia [5, 6].

In the present study we tested the hypothesis that background retinopathy is associated with blunted coronary vasoreactivity in patients with Type 1 diabetes. If so, retinal evaluation, which is routinely used in clinical practice, might provide an additional method to estimate coronary health and the need for intensive treatment of coronary artery disease risk factors in patients with Type 1 diabetes. Therefore, resting myocardial blood flow and flow during dipyridamole stimulation, a measure of coronary vasoreactivity, were measured in Type 1 diabetic patients with and without background retinopathy, and in healthy non-diabetic subjects using PET and oxygen-*15*-labelled water ($[^{15}O]H_2O$).

Subjects, materials and methods

Subjects. Characteristics of the study subjects are shown in Table 1. A total of 9 patients with Type 1 diabetes and background retinopathy (mild non-proliferative diabetic retinopathy [7]) and 12 patients with Type 1 diabetes without retinopathy volunteered for the study. The subjects were recruited by advertising or from diabetes outpatient clinics in Turku (Finland) and surrounding areas. Diabetic background retinopathy occurs in approximately half of young Type 1 diabetic patients after 10 years of disease duration. Therefore, to obtain a comparable number of patients with and without retinopathy, only patients having diabetes for over 10 years were selected. Healthy non-diabetic subjects who had been studied earlier with an identical protocol [8] were used as controls. All subjects were non-smokers, otherwise healthy and, if diabetic, were using no medication other than insulin. The subjects showed no clinical signs or symptoms of heart disease, nephropathy (including microalbuminuria) or neuropathy.

All persons studied gave written informed consent. The studies were conducted according to the guidelines of the Declaration of Helsinki, and the study protocols were accepted by the Ethics Committee of the Turku University Central Hospital.

Study design. PET studies were performed after an overnight fast. The subjects were instructed to avoid all food and caffeine-containing drinks in the 12 hours before the PET studies. On the study day, to avoid hypoglycaemia, the normal dose of intermediate-acting insulin was reduced by half and short-acting insulin was withdrawn in diabetic patients. Initially, the euglycaemic hyperinsulinaemic clamp was started for 60 min. Thereafter, myocardial blood flow was measured at rest, and then during hyperaemia induced by dipyridamole (0.56 mg/kg during a 4-min period i.v.). Electrocardiogram and heart rate were monitored continuously during the studies. Blood pressure was monitored using an automatic oscillometric blood pressure monitor (Omron 711, Omron Matsuzaka City, Japan) during the PET studies.

Production of [15O]H2O. We produced ^{15}O using a low-energy deuteron accelerator Cyclone 3 (Ion Beam Application, Louvain-la-Neuve, Belgium). To produce $[^{15}O]H_2O$, we used dialysis techniques in a continuously working water module [9, 10]. In order to verify the purity of the products, we carried out sterility and pyrogenity tests for water, and chromatographic analysis for gases.

Image acquisition, processing and corrections. The subjects were positioned supine in a 15-slice ECAT 931/08-12 tomograph (Siemens/CTI, Knoxville, Tenn., USA). After the transmission scan, myocardial perfusion was measured with an intravenous injection of $[^{15}O]H_2O$ (~1.5 GBq) at rest and 6 min after the beginning of intravenous administration of dipyridamole. Each dynamic scan lasted for 6 minutes (6×5 s, 6×15 s, 8×30 s). All data were corrected for dead time, decay and pho-

Table 1. Characteristics of the study subjects

Characteristic	Diabetic patients		Non-diabetic subjects (n=12)
	With retinopathy (n=9)	Without retinopathy (n=12)	
Age (years)	30 (7)	28 (7)	31 (4)
Duration of diabetes (years)	17 (4)	15 (4)	NA
Dose of insulin (U/kg)	0.85 (0.13)	0.70 (0.20)	NA
BMI (kg/m^2)	26 (3)	25 (2)	24 (2)[a]
Blood pressure (mmHg)	128/69 (15/9)	124/72 (12/9)	123/66 (14/8)
HbA_1c (%)	8.6 (1.0)	7.6 (1.4)	4.8 (0.4)[a]
Cholesterol (mmol/l)	4.3 (0.5)	4.1 (0.6)	4.5 (0.7)
HDL cholesterol (mmol/l)	1.3 (0.3)	1.4 (0.3)	1.2 (0.3)
Triglycerides (mmol/l)	1.0 (0.4)	0.8 (0.3)	0.9 (0.4)
LDL cholesterol (mmol/l)	2.6 (0.2)	2.4 (0.5)	2.9 (0.7)

Data are means (SD); [a]p<0.05 vs diabetic patients; NA, not applicable

ton attenuation, and reconstructed into a 128×128 matrix. Data were reconstructed by filter back-projection, in which the final in-plane resolution in the reconstructed and Hann-filtered (0.3 cycles/s) images was 9.5 mm (full width half maximum), or by the median root prior reconstruction method [11].

Calculation of regional myocardial blood flow, coronary vascular resistance and myocardial flow reserve. Regions of interest were drawn in the lateral, anterior and septal wall of the left ventricle in 4 representative transaxial slices as previously described [12]. The regions of interest were outlined in the baseline images and copied to the images obtained after dipyridamole administration. Values of regional myocardial blood flow (expressed in ml·g tissue^{-1}·min^{-1}) were calculated according to the previously published method using the single compartment model [13]. The arterial input function was obtained from the left ventricular time–activity curve using a previously validated method [14], in which corrections were made for the limited recovery of the left ventricular region of interest and the spillover from the myocardial signals. The average blood flow of the lateral and anterior part of the myocardium showed the lowest coefficient of variation and was used in further analysis. The coronary vascular resistance values were calculated at the baseline and after dipyridamole infusion by dividing the mean arterial blood pressure by the respective flow value. Myocardial flow reserve was defined as the ratio of post-dipyridamole myocardial blood flow to flow at the baseline.

Retinal photography. Retinal photography was performed after mydriatic instillation with a Canon CR4-45NM fundus camera (Canong, Kanagawa, Japan), and one 45°-field photograph, including areas of papilla and macula, was taken from each eye. Polaroid photoprints were analysed by an experienced diabetologist (T. Rönnemaa) with no knowledge of the results of the PET studies. Background retinopathy was defined as the presence of two or more retinal microaneurysms and/or small haemorrhages in at least one eye. Compared with an ophthalmoscopic evaluation by an ophthalmologist, our photography method is more sensitive, but compared with the "gold standard" method, i.e. 7-field photography, the sensitivity of our method to detect any retinopathy is reported to be 0.72 [15].

Euglycaemic hyperinsulinaemic clamp technique and whole body glucose uptake. Insulin and glucose were infused in a catheter inserted in the right antecubital vein. Arterialised venous blood samples were withdrawn from a heated left antecubital vein. Insulin (Actrapid Human; Novo Nordisk, Copenhagen, Denmark) was administered in a primed continuous manner at a rate of 1 mU·kg^{-1}·min^{-1} starting 60 min before the myocardial blood flow measurements and continuing for 120 min. Normoglycaemia was maintained by infusing 20% glucose at a rate determined by plasma glucose concentrations measured every 5 min. Serum insulin was measured every 30 min during clamp. Whole body glucose uptake, a measurement of insulin sensitivity, was calculated from the glucose infusion rate after correcting for changes in the glucose pool size [16].

Autonomic nerve function tests. To detect autonomic neuropathy, a series of standardised cardiovascular reflex tests were performed on the study subjects. Heart rate, heart rate variability and blood pressure were monitored at resting conditions as well as during the Valsalva manoeuvre, during an orthostatic test and during an isometric hand grip test (CAFTS [v.3.3.9], Medikro, Kuopio, Finland). The results were interpreted as pathological if three or more of the measured parameters were outside the range of values of an age- and sex-matched healthy population.

Analytical methods. HbA_1c was measured by fast protein liquid chromatography (Variant II; BioRad, Hercules, Calif., USA). Plasma glucose was determined by the glucose oxidase method [17]. Serum insulin concentrations were measured using a time-resolved immunofluorometric assay (Autodelfia, Wallac, Turku, Finland). Serum total cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride concentrations were measured using standard enzymatic methods (Boehringer Mannheim, Mannheim, Germany) with a fully automated analyser (Hitachi 704; Hitachi, Tokyo, Japan). The low density lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald formula [18]. The first morning urine sample was analysed to define the ratio of urinary albumin (mg/l) to urinary creatine concentration (mmol/l), in order to screen for microalbuminuria [19]. If the screening test gave a positive result (≥2 mg/mmol), we measured the urinary albumin excretion rate (µg/min) during the night. Urinary albumin was determined by immunonephelometry (Behring) using antiserum from Dakopatts (Glostrup, Denmark). Microalbuminuria was defined as an albumin excretion rate of 20 µg/min or more in at least two of three urine samples collected overnight.

Statistical methods. The results are expressed as means ± SD. Student's paired and unpaired *t* tests were used in the group comparisons as appropriate. As HbA_1c is known to be strongly related to retinopathy, we performed analysis of covariance, to adjust for HbA_1c while examining the association between retinopathy and coronary vasoreactivity. We considered *p* values less than 0.05 to be statistically significant. All statistical tests were performed using the SAS statistical analysis system (SAS Institute, Gary, N.C., USA).

Results

Characteristics of the study subjects. No significant differences were detected between the study subjects in the measured parameters seen in Table 1, except that HbA_1c and BMI were lower in non-diabetic subjects than in diabetic patients. However, none of the diabetic patients had a BMI of more than 28.5 kg/m^2. Autonomic nerve function tests were normal in all study subjects and no differences were detected between the groups. None of the diabetic patients had microalbuminuria. All subjects had normal electrocardiograms at rest and during pharmacological stress (dipyridamole). All subjects had normal blood pressure.

Metabolic and hormonal characteristics. Plasma glucose, serum insulin concentrations and insulin-stimulated whole body glucose uptake values were similar in the two groups of diabetic patients during the PET studies (Table 2). Fasting plasma glucose was lower in non-diabetic subjects than in diabetic patients ($p<0.05$). During hyperinsulinaemic clamp, serum insulin concentrations increased significantly in all study subjects ($p<0.01$), but insulin concentrations were lower in non-diabetic subjects than in diabetic patients ($p<0.05$). Plasma glucose concentrations decreased significantly in diabetic patients during clamp ($p<0.01$), and therefore glucose concentrations were

Table 2. Metabolic and hormonal characteristics of the study subjects

Characteristic	Fasting	During clamp
Plasma glucose (mmol/l)		
With retinopathy[a]	13.1 (3.6)	5.4 (1.2)[b]
Without retinopathy[a]	11.5 (4.3)	6.6 (1.5)[b]
Non-diabetic subjects	5.7 (2.2)[c]	5.2 (1.2)
Serum insulin (mU/l)		
With retinopathy[a]	20.9 (15.1)	71.2 (17.8)[b]
Without retinopathy[a]	17.2 (14.7)	73.3 (19.6)[b]
Non-diabetic subjects	17.7 (1.7)	49.7 (8.3)[bc]
WBGU (μmol·kg^{-1}·min)		
With retinopathy[a]	NA	29.2 (8.3)
Without retinopathy[a]	NA	28.7 (7.9)
Non-diabetic subjects	NA	47.8 (15.6)[c]

Data are means (SD); [a] patients with Type 1 diabetes; [b] $p<0.01$ vs fasting; [c] $p<0.05$ vs diabetic patients; NA, not applicable; WBGU, whole body glucose uptake

Table 3. Haemodynamic characteristics during study

Characteristic	Basal	Dipyridamole
Heart rate (beats/min)		
With retinopathy[a]	63 (6)	91 (12)[b]
Without retinopathy[a]	63 (13)	91 (15)[b]
Non-diabetic subjects	62 (12)	84 (14)[b]
Systolic blood pressure (mmHg)		
With retinopathy[a]	128 (15)	132 (16)
Without retinopathy[a]	124 (12)	128 (18)
Non-diabetic subjects	123 (14)	125 (7)
Diastolic blood pressure (mmHg)		
With retinopathy[a]	69 (9)	70 (6)
Without retinopathy[a]	72 (9)	71 (12)
Non-diabetic subjects	66 (8)	70 (9)
Rate–pressure product[c] (mmHg/min)		
With retinopathy[a]	8023 (1392)	12,150 (2460)[b]
Without retinopathy[a]	7859 (2040)	11,833 (3157)[b]
Non-diabetic subjects	7728 (2056)	10,511 (1920)[b]

Data are means (SD); [a] patients with Type 1 diabetes; [b] $p<0.001$ vs basal; [c] systolic blood pressure × heart rate

similar in all three groups. Whole body glucose uptake was reduced in both groups of diabetic patients when compared with non-diabetic subjects ($p<0.05$; Table 2).

Haemodynamic measurements during PET study. In all study subjects, dipyridamole infusion induced a similar significant increase in heart rate and rate–pressure product ($p<0.001$; Table 3). No differences were detected between the study subjects in heart rate, blood pressures or rate–pressure product at the baseline or during dipyridamole infusion (Table 3).

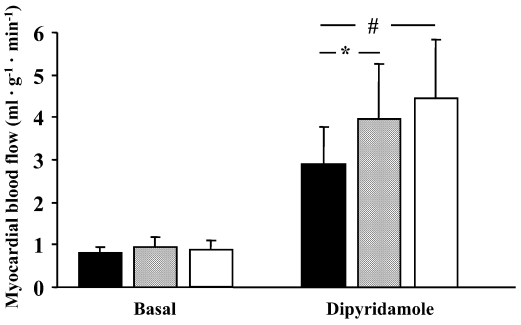

Fig. 1. Myocardial blood flow under basal conditions and during dipyridamole infusion in Type 1 diabetic patients with (*black bar*) or without (*grey bar*) background retinopathy and in healthy non-diabetic subjects (*white bar*). *$p<0.05$, #$p<0.01$

Myocardial blood flow, coronary vascular resistance and myocardial flow reserve. Myocardial blood flow results are presented in Fig. 1. Resting myocardial blood flow values (0.82±0.13 vs 0.96±0.23 vs 0.88±0.25 ml·g^{-1}·min^{-1}, with vs without retinopathy vs non-diabetic subjects; p=0.1, 0.4 and 0.5; with vs without retinopathy, with retinopathy vs non-diabetic subjects and without retinopathy vs non-diabetic subjects respectively) were not significantly different between the study groups (Fig. 1). Resting coronary vascular resistance values (111.2±23.4 vs 95.5±15.8 vs 101.9±31.5 mmHg·min·g·ml^{-1} respectively; p=0.1, 0.5 and 0.5 respectively) were not significantly different between the groups. Dipyridamole infusion induced significant increase in blood flow and decrease in coronary vascular resistance in all study subjects ($p<0.001$). However, dipyridamole-stimulated flow and coronary vascular resistance were blunted in diabetic patients with retinopathy (2.9±0.9 ml·g^{-1}·min^{-1} and 34.1±11.3 mmHg·min·g·ml^{-1}) when compared with diabetic patients without retinopathy (4.0±1.3 ml·g^{-1}·min^{-1}, p=0.04 and 24.6±7.5 mmHg·min·g·ml^{-1}, p=0.03) or non-diabetic subjects (4.5±1.4 ml·g^{-1}·min^{-1}, p=0.008 and 22.2±8.7 mmHg·min·g·ml^{-1}, p=0.01) (Fig. 1). After adjustment for HbA_1c, dipyridamole-stimulated flow tended to be lower in diabetic patients with retinopathy than in diabetic patients without retinopathy (p=0.07). No significant difference was detected in dipyridamole-stimulated flow or coronary vascular reactivity between diabetic patients without retinopathy and non-diabetic subjects (p=0.4 and 0.5; Fig. 1).

Myocardial flow reserve was impaired in diabetic patients with retinopathy (3.6±1.0) when compared with non-diabetic subjects (5.3±1.9, p=0.02), but not significantly reduced when compared with diabetic patients without retinopathy (4.2±1.4, p=0.2). No significant difference was detected in myocardial flow reserve between diabetic patients without retinopathy and non-diabetic subjects (p=0.1). The difference between the dipyridamole-stimulated flow and basal flow in absolute terms was significantly reduced in di-

abetic patients with retinopathy (2.1±0.9 ml·g^{-1}·min^{-1}) when compared with non-diabetic subjects (3.6± 1.4 ml·g^{-1}·min^{-1}, p=0.01), and tended to be lower than in diabetic patients without retinopathy (3.0±1.2 ml·g^{-1}· min^{-1}, p=0.06). No significant difference was detected in the difference between the dipyridamole-stimulated flow and basal flow between diabetic patients without retinopathy and non-diabetic subjects (p=0.3).

Discussion

In the present study we found that diabetic background retinopathy is associated with impaired coronary vasoreactivity in young people with Type 1 diabetes. Patients with Type 1 diabetes and background retinopathy had a lower blood flow response to dipyridamole than diabetic patients without retinopathy, and than healthy non-diabetic subjects.

This study quantitatively measures the effect of background retinopathy on coronary vasoreactivity in young Type 1 diabetic patients who are otherwise healthy. One previous study using single-photon emission computed tomography (SPECT) has demonstrated the association between retinopathy and myocardial perfusion defects in Type 2 diabetic patients who also have other risk factors for coronary artery disease [3]. To investigate the effect of diabetic background retinopathy on coronary vasoreactivity specifically, the Type 1 diabetic patients of the present study had no other diseases such as hypertension or dyslipidaemia.

In the present study, coronary vasoreactivity was measured during dipyridamole infusion. The coronary flow response induced by dipyridamole reflects a combined effect of endothelial-mediated vasodilatory function [20] and vascular smooth muscle relaxation [21]. Dipyridamole acts by increasing interstitial adenosine concentrations in vascular smooth muscle. Recently, it has been found that a significant amount of the adenosine response is endothelium dependent [22]. Therefore, the blood flow response to dipyridamole is an integrating measure of coronary reactivity [23]. Under resting conditions, coronary flow and myocardial work (oxygen consumption) are tightly coupled [24]. In contrast, during dipyridamole stimulation, metabolic control of myocardial blood flow is lost, and flow is directly dependent on endothelial function, neural control and blood pressure. The flow is modulated by mechanical forces in the myocardial wall [24].

Impaired coronary endothelial function seems to predict cardiovascular events in patients with or without clinical coronary artery disease [25, 26]. As discussed above, hyperaemic flow response to dipyridamole is partly related to the endothelium. In addition, vasodilation independent of the endothelium might play a role in the progression of coronary artery disease [26]. Recently, it has been demonstrated using PET that the blunted coronary flow response to dipyridamole is a strong and independent predictor of clinical deterioration and death in patients with hypertrophic cardiomyopathy [27]. In the present study, reduced dipyridamole-stimulated coronary vasoreactivity in diabetic patients with background retinopathy might indicate that these patients are at increased risk of future cardiovascular events and are therefore in particular need of intensive treatment of cardiovascular risk factors. However, further studies are needed to investigate the predictive value of impaired coronary vasoreactivity and the potential benefits of medical interventions in patients with diabetes.

In Type 1 diabetic patients without retinopathy, coronary vasoreactivity was slightly but not significantly reduced when compared with non-diabetic subjects. In previous studies, coronary vasoreactivity has been found to be either normal [28] or more frequently decreased [8, 29, 30, 31, 32] in diabetic patients. However, most of the previous studies have included patients with both Type 1 and Type 2 diabetes or other potentially confounding factors such as diabetic complications, smoking, hypertension, obesity and lipid abnormalities, which are known to further reduce coronary vasoreactivity. Consistent with the results of the present study, the findings of one previous PET study demonstrated that patients with Type 1 diabetes and autonomic neuropathy have decreased adenosine-stimulated coronary vasoreactivity, while the non-neuropathic Type 1 diabetic patients have unaltered myocardial blood flow and coronary flow reserve [28]. Thus, the question of whether coronary reactivity is impaired in non-complicated Type 1 diabetes is still being debated.

It is possible that more specific testing of endothelial function, e.g. using acetylcholine, could have also shown impaired coronary vasoreactivity in diabetic patients without retinopathy. On the other hand, no information about the other factors affecting coronary function would have been obtained. It can be speculated that different kinds of functional changes in the coronary vasculature may be associated with the different degrees of morphological changes, i.e. in the retina. In diabetic patients with retinopathy, the functional impairment of the coronary circulation may involve both endothelial mechanisms and mechanisms independent of the endothelium, while diabetic patients without retinopathy possibly have a mild impairment of endothelial function masked by widely preserved smooth muscle cell function [25, 26].

In the present study, only a limited number of patients were investigated, and thus only the strongest and most important associations could be detected. However, PET enables us to measure myocardial blood flow and coronary vasoreactivity non-invasively, quantitatively and accurately in humans [33], whereby reliable results can be obtained with relative-

ly small numbers of subjects. The variation coefficient of our myocardial blood flow measurements using PET and [^{15}O]H_2O was 14±11% at rest and 16±9% during hyperaemic flow [34].

In summary, we demonstrate that Type 1 diabetic patients with background retinopathy have reduced dipyridamole-stimulated myocardial blood flow when compared with diabetic patients without retinopathy or with non-diabetic subjects. This indicates a novel finding that diabetic background retinopathy is associated with reduced coronary vasoreactivity in young people with Type 1 diabetes. Since patients with Type 1 diabetes had no further risk factors of coronary artery disease, it is possible that the reduced coronary vasoreactivity in diabetic patients with retinopathy is more generally related to the diabetic state.

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