Pain Intensity and Blood Pressure Reactions During a Cold Pressor Test in IDDM Patients

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OBJECTIVE — To determine the contribution of altered pain perception to the impaired blood pressure reactions during a cold pressor test in diabetic patients. Reduced blood pressure increases have been observed in diabetic patients during a cold pressor test and have been attributed to an impaired efferent sympathetic function.

RESEARCH DESIGN AND METHODS — We investigated pain intensities and blood pressure reactions simultaneously during a cold pressor test in 30 IDDM patients (diabetes duration 12 ± 6 years, HbA_{1c} 7.5 ± 1.4%) and in 30 normal control subjects with comparable sex distribution, age, height, BMI, physical fitness, and smoking habits.

RESULTS — Initial pain intensities and respective time courses did not differ between the two groups. The initial blood pressure response was significantly smaller in diabetic patients ($P < 0.002$). Correlations of diastolic blood pressure increases in diabetic patients with initial pain intensity, standard cardiovascular reflex tests, age, clock time, smoking habits, disease duration, and actual blood glucose concentrations did not reach statistical significance. Pain intensity and diastolic blood pressure increases, however, were correlated to HbA_{1c} concentrations in diabetic patients.

CONCLUSIONS — Impaired pain perception is not the cause of the impaired reactions of blood pressure in diabetic patients during the cold pressor test, leaving very early deterioration of either cerebral processing of pain stimuli, cardiac function, efferent sympathetic nerves, or decreased vascular reactivity as possible explanations.

During the last 60 years, the cold pressor test, a standard test to characterize sympathetic function (1), has been used in a variety of different clinical conditions, e.g., to predict later development of arterial hypertension (2), to detect atherosclerosis (3), to identify patients with ischemic heart disease in whom coronary spasms may be important (4), and to identify damage of the sympathetic nervous system in diabetic patients (5–10). Although the cold pressor test elicits a clear response in most subjects, the mechanisms evoking or impairing the reactions are complex.

The diminished reaction of blood pressure in diabetic patients, mostly suffering from advanced late complications including diabetic neuropathy, has been attributed to damage of the efferent sympathetic vasomotor system. Whether or not an impaired pain perception may influence blood pressure reactions has never been investigated. To either prove or rule out this possibility, we performed a cold pressor test in IDDM patients and healthy control subjects, estimated the individual pain intensity, and characterized the metabolic situation during the tests and in the foregoing weeks to find out if either disturbances of afferent sensory pathways or different metabolic conditions may contribute to the impaired responses.

RESEARCH DESIGN AND METHODS

The study protocol was approved by the institutional review board of the University of Tübingen. All participants gave their informed written consent. Patients and control subjects were included in the study only if: *1*) repeated blood pressure measurements were ≤140/90 mmHg and *2*) peripheral sensory or autonomic cardiac neuropathy were not detectable with either a clinical neurological examination or cardiovascular reflex tests. A total of 30 IDDM patients and 30 healthy control subjects were evaluated. Clinical variables did not differ significantly between the groups (Table 1). Besides insulin, medication was excluded. Mean duration of diabetes was 12.1 ± 6.1 years (mean ± SD). The average insulin dose was 48 ± 17 IU/day. All diabetic patients were treated with an intensified insulin therapy. Biochemical variables measured—white and red blood cell counts, creatinine, urea, total serum proteins, cholesterol, triglycerides, liver enzyme activities, and sodium and potassium concentrations—were normal in both groups and did not differ significantly. Albumin excretion in urine exceeded the upper normal limit of 20 mg/g creatinine in 2 of 30 patients (45 and 139 mg/g creatinine, respectively). No retinopathy was detected in 19 patients, minimal background retinopathy in 10 patients, and proliferative retinopathy in 1 patient. Macroangiopathic complications were not detectable in either group. Glucose and HbA_{1c} concentrations (high-performance liquid chromatography), upper normal limit 6.1%, were significantly higher in diabetic patients (Table 1).

Neither medical history nor physical examination nor cardiovascular reflex tests revealed symptoms or signs of either peripheral symmetrical sensory or autonomic neuropathy (Table 2). The vibration perception measured with the graded tuning fork (C 128) on the big toe, albeit being normal in both groups, was significantly lower by 1/8 in diabetic patients ($P < 0.0002$). Cardiovascular reflex tests were performed using the ProSciCard system (ProScience Private Research Institute, Linden, Germany): *1*) coefficient of variation of the resting heart rate over 5 min; *2*) heart rate variation during deep breathing (6 cycles/min) (E:I ratio); *3*) heart rate response to standing (tachycar-

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Table 1—*Clinical and biochemical characteristics of diabetic patients and normal control subjects*

Variable	Diabetic patients	Normal control subjects	*P* value
n	30	30	—
Sex (m/f)	17/13	14/16	0.44
Age (years)	29.5 ± 5.7	30.2 ± 6.4	0.67
Height (cm)	172 ± 9.3	174 ± 8.4	0.42
Weight (kg)	72.4 ± 9.3	71.5 ± 11.7	0.76
BMI (kg/m^2)	24.39 ± 3.09	23.57 ± 2.87	0.29
Physical activity (hours per week)	3 (2–8)	3.5 (1–5.25)	0.50
Smokers	10	11	0.79
Glucose (mg/dl)	166 ± 66	85 ± 6	0.001
HbA_{1c} (%)	7.5 ± 1.4	5.0 ± 0.4	0.001

Data are means ± SD. Physical activity is given as median with interquartile range.

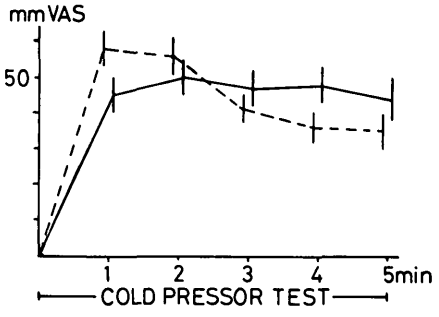

Figure 1—*Time course of pain intensities during a cold pressor test over 5 min in diabetic patients (——) and normal control subjects (- - -). mmVAS: pain intensity in millimeter on the visual analog scale, mean ± SE.*

dia-to-bradycardia ratio or 30:15 ratio depending on what seemed most appropriate to the individual reaction); and 4) Valsalva maneuver (15 s, 40 mmHg, Valsalva ratio). Patients and control subjects were examined between 8:00 and 12:00 A.M. Nicotine and caffeine were not allowed on the day of examination. The cold pressor test was performed by immersion of the dominant hand up to the wrist into iced water (temperature 4–5°C) for 5 min. Probands were seated in an armchair in semi-recumbent position. Individual pain perception was estimated every minute for 5 min using a horizontal visual analogue scale (100 mm) before and during the cold pressor test. Blood pressure was recorded on the contralateral arm simultaneously with the pain recordings using an oscillometric method (Boso Oscillomat, Bosch u. Sohn GmbH & Co., Jungingen, Germany). Heart rate was regular in all patients and control subjects.

Statistical methods

Blood pressure increases were compared with the Welch *F* test allowing for different variances. Comparisons referring to pain intensities, cardiovascular reflex tests, glucose concentrations, and HbA_{1c} concentrations used the (nonparametric) Wilcoxon's rank-sum test. Age, height, weight, and BMI were compared by the Student's *t* test, the proportions of sex and smokers by the χ^2 test, and proportions of physical activities by the Wilcoxon's rank-sum test. Correlations were expressed by the (nonparametric) Spearman's rank-order correlation ρ. Time courses of pain intensities were compared by the multivariate test using Wilks' criterion λ. (The corresponding multivariate rank test yielded almost the same *P* value, 0.08). *P* values <0.05 were considered significant. If multiple comparisons or multiple correlations were performed, *P* values were interpreted after a Bonferroni-Holm correction.

Table 2—*Cardiovascular reflex tests and starting blood pressure values before the cold pressor test in diabetic patients and in normal control subjects*

Test	Diabetic patients	Normal control subjects	*P* value
n	30	30	—
Coefficient of variation, 5 min	5.90 ± 2.19	6.02 ± 2.96	0.78
E:I ratio	1.46 ± 0.21	1.47 ± 0.25	0.80
30:15 ratio	1.42 ± 0.21	1.34 ± 0.22	0.16
Valsalva ratio	1.67 ± 0.21	1.69 ± 0.43	0.90
Systolic blood pressure	114 ± 12	108 ± 13	0.07
Diastolic blood pressure	69 ± 8	68 ± 8	0.67

Data are means ± SD.

RESULTS — Neither initial pain intensities after the 1st min nor the further time course over the following 4 min were significantly different between diabetic patients and normal control subjects ($P = 0.08$) (Fig. 1). In diabetic patients, pain intensities were not related to disease duration, age at diagnosis of diabetes, daily insulin dose, or the actual blood glucose concentrations. There was, however, a significant correlation of the initial pain intensities with the HbA_{1c} concentrations (Table 3). Basal blood pressures did not differ between both groups (Table 2). The systolic, diastolic, and mean blood pressure increases after the first minute of immersion into iced water were significantly smaller in diabetic patients (Table 4). Diastolic blood pressure reactions over 5 min of both groups are shown in Fig. 2. The changes of the systolic and mean

Table 3—*Correlations in diabetic patients of diastolic blood pressure reactions or initial pain intensities to HbA_{1c} concentrations*

	r_1	*P*	r_2	*P*
Diastolic blood pressure pain	0.33	0.073	0.16	0.416
HbA_{1c} pain	−0.45	0.013	−0.36	0.058
HbA_{1c} diastolic blood pressure	−0.46	0.011	−0.37	0.049

r_1: pairwise correlation coefficients; r_2: partial correlations.

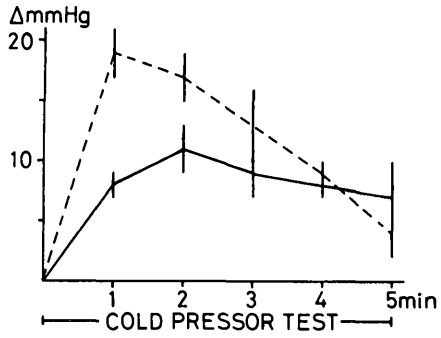

Figure 2—*Time courses of changes of diastolic blood pressure during a cold pressor test over 5 min in diabetic patients (——) and normal control subjects (– –), mean ± SE.*

pressures over time were similar to the diastolic changes. Correlation analyses in diabetic patients of blood pressure reactions were performed using only diastolic changes since most, but not all (6,8), other studies of diabetic patients used either diastolic measurements (7,9) or mean blood pressure increases that correlate significantly with diastolic increases (5,10) or prove to be significantly different from normal controls (9). In diabetic patients, diastolic blood pressure increases tended to correlate with the initial pain intensities, but this did not reach statistical significance (Fig. 3). In neither group were diastolic blood pressure reactions correlated with the results of standard cardiovascular reflex tests, age, clock time, or smoking habits. In diabetic patients, blood pressure reactions were related neither to the duration of diabetes nor to the daily insulin dose or the actual blood glucose concentration (diastolic $\rho = -0.18$, $P = 0.35$). There was, however, a significant inverse correlation of diastolic blood pressure increases to the HbA_{1c} concentrations in diabetic patients (Table 3). Calculations of partial correlations among HbA_{1c}, diastolic blood pressure increases, and pain in diabetic patients reduced the correlation coefficients among all three variables not leaving any correlations statistically significant.

Table 4—*Blood pressure increases after 1 min of cold immersion in diabetic patients and normal control subjects*

Blood pressure (mmHg)	Diabetic patients	Normal control subjects	*P* value
n	30	30	—
Systolic	6.6 ± 8.1	18.4 ± 10.0	<0.0001
Diastolic	7.8 ± 7.8	19.0 ± 11.3	<0.0001
Mean	7.4 ± 6.4	18.8 ± 10.0	<0.0001

Data are means ± SD.

CONCLUSIONS— During a cold pressor test in non-neuropathic normotensive IDDM patients, the systolic, diastolic, and mean blood pressure increases were smaller than in normal control subjects despite similar pain perception. The correlation reported in the literature (11) for normal subjects between blood pressure increases and pain intensity failed to reach statistical significance in our groups of patients and control subjects. Time courses of pain and of blood pressure compare very well with already described observations (12). In our diabetic group, however, the significant correlations between pain and HbA_{1c} (Fig. 4) and between diastolic blood pressure increases and HbA_{1c} (Fig. 5) were no longer demonstrable after partial correlations including all three variables. This may point to a parallel action of blood glucose control (HbA_{1c}) on pain perception and blood pressure increases. Blood pressure reactions did not correlate with age, clock time, or smoking habits in either group.

In previous studies, blood pressure responses during a cold pressor test were impaired only in hypertensive patients with long-standing diabetes and detectable late complications (10) or were found to be of no value in the assessment of diabetic patients with autonomic neuropathy (7). Wide age ranges (13,14) and diabetes duration, heterogeneous distributions of vascular complications, varying degrees of hypertension (14) and arteriosclerosis (3), and different metabolic control and drug treatments may obscure the effect of diabetes per se on the blood pressure responses. Our study design does not allow us to draw any conclusions on relations of impaired blood pressure responses to *1*) autonomic impairment or *2*) microvascular complications because parasympathetic tests were normal, sensitive tests of sympathetic function, e.g., sweat tests were not simultaneously evaluated, the number of patients with microalbuminuria was very small, and also retinopathy was only of minor degree in most patients. Moreover, the study was cross-sectional. In other studies, correlations were found with advanced sympathetic dysfunction, e.g., orthostatic hypotension (9), but not with results of parasympathetic tests (5,7,9).

Whether or not circadian changes of sympathetic activity or breakfast intake or prior insulin injection (15) may influence the test results is unclear. The clock-time of performance did not significantly correlate with the test results (r-diastolic 0.10, $P = 0.58$).

The initial pain intensities and the respective time courses during the cold pressor test were not significantly different in diabetic patients compared with normal control subjects thus not supporting other studies, which have discussed early functional alterations of cerebral

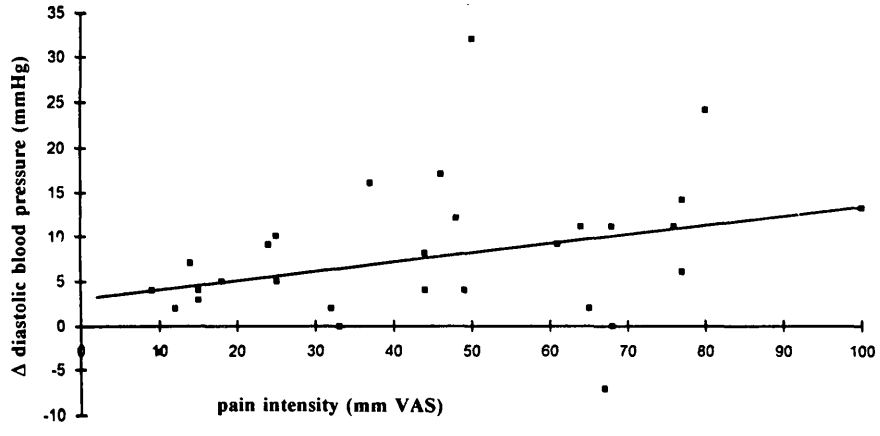

Figure 3—*Correlation of diastolic blood pressure increases with pain intensities after the first minute of immersion in diabetic patients.*

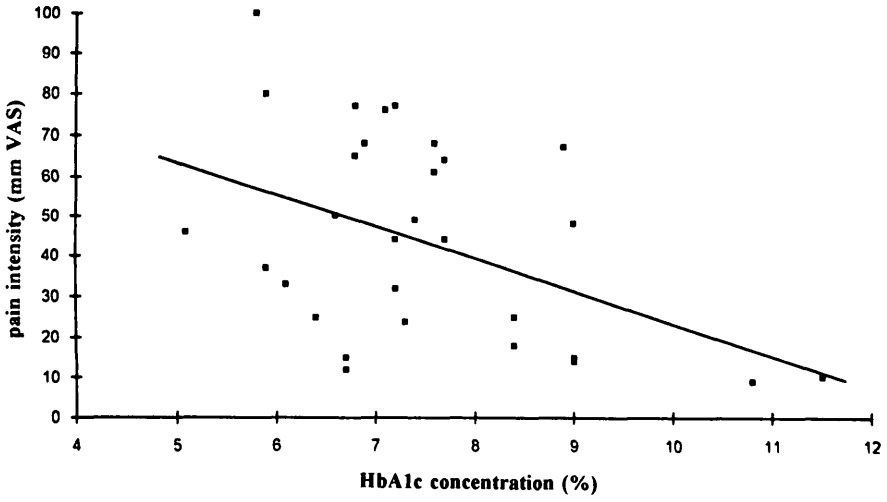

Figure 4—*Correlation of HbA_{1c} concentrations with pain intensities after the first minute of immersion during a cold pressor test in diabetic patients.*

processing of other stimuli in diabetic patients (16–18). Moreover, in accordance with Chan et al. (19) and in contrast to Morley and colleagues (20), no correlation was found between actual blood glucose concentrations and pain intensity. Since pain was inversely correlated to HbA_{1c}, our results are more compatible with a slightly increasing pain threshold induced by long lasting elevated blood glucose levels.

Whether the smaller increase of blood pressure during the cold pressor test was related to a direct effect of blood glucose on cardiac performance was not examined. Abnormal left ventricular function in diabetic patients, inversely related to the HbA_{1c} levels, along with impaired blood pressure reactions have been described (6). Moreover, after a cold challenge, vascular reactivity may be impaired at an early stage of the disease (21). What causes the decreased blood pressure response during a cold pressor test in diabetic patients is unknown: decreased pain sensitivity has been excluded as the main cause in our study.

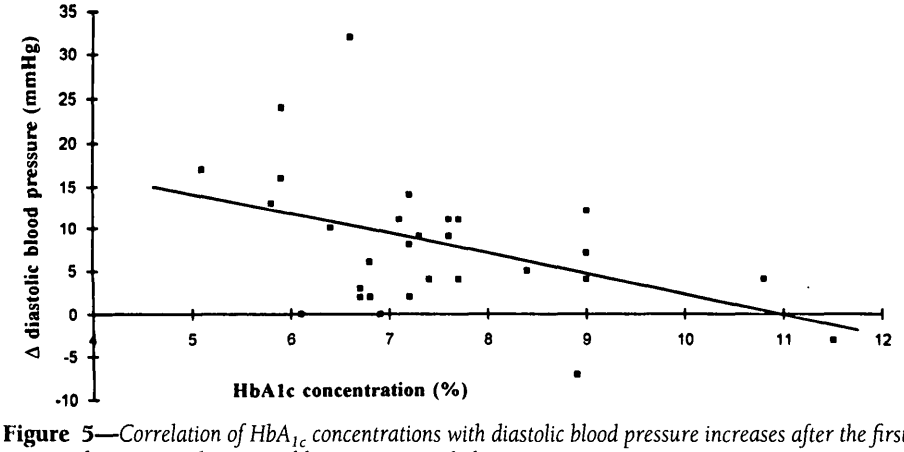

Figure 5—*Correlation of HbA_{1c} concentrations with diastolic blood pressure increases after the first minute of immersion during a cold pressor test in diabetic patients.*

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