Autonomic and Somatosensory Nerve Function After 2 Years of Continuous Subcutaneous Insulin Infusion in Type I Diabetes

JOHANNES JAKOBSEN, JENS S. CHRISTIANSEN, INGER KRISTOFFERSEN, CRAMER K. CHRISTENSEN, KJELD HERMANSEN, ANITA SCHMITZ, AND CARL ERIK MOGENSEN

Autonomic and somatosensory nerve function was studied in 24 insulin-dependent diabetic subjects (aged 29 ± 7 yrs, diabetes duration 8 ± 4 yr) randomly allocated to either continuous subcutaneous insulin infusion (CSII; *n* = 12) or unchanged conventional insulin therapy (CIT; *n* = 12). Measures of glycemic control and somatosensory and autonomic nerve function were comparable in the two groups at the start. Glycemic control was significantly improved in the CSII group throughout study, whereas it remained unchanged in the CIT group. In the CIT group, vibratory perception threshold (VPT) of the great toe and the medial malleolus deteriorated, as did heart rate variation (HRV) at rest, at deep breathing (.05 < *P* < .06), and at standing. In contrast, CSII patients retained their VPT and HRV. Comparison of nerve function alterations during the 2-yr trial showed better preservation in CSII than in CIT patients of VPT in the great toe (0.8 ± 1.7 vs. −1.4 ± 1.9 V, *P* < .01) and the medial malleolus (1.5 ± 2.9 vs. −1.4 ± 1.8 V, *P* < .05) and of HRV at rest (10 ± 24 vs. −13 ± 22 ms, *P* < .05) and at standing (−0.01 ± 0.13 vs. −0.15 ± 0.16 ms, *P* < .05). We conclude that intensified glycemic control can favorably influence parasympathetic and somatosensory nerve function in insulin-dependent diabetes mellitus. *Diabetes* 37:452–55, 1988

Clinical signs of peripheral neuropathy develop in many patients with insulin-dependent diabetes mellitus (IDDM), but symptoms of neuropathy are less frequent (1,2). Nerve function is more severely impaired in diabetic subjects with symptomatic neuropathy of somatosensory or autonomic nerves than in those without symptoms (3,4). Therefore, alterations of peripheral and autonomic nerve function might predict whether symptomatic neuropathy will develop.

There are several indications that the prevailing glucose levels influence nerve function. Patients with more severe degrees of metabolic derangement have more clinical signs of neuropathy (1,5), and peripheral nerve conduction velocity varies with the degree of metabolic control (6–10).

Two controlled studies show that somatosensory nerve function is better preserved after amelioration of glycemic control for up to 2 yr (11,12). However, it is unknown whether long-lasting improvement of metabolic control delays the deterioration of autonomic nerve function or even improves it.

We studied parasympathetic, sympathetic, and somatosensory function with noninvasive techniques for 2 yr in 12 IDDM patients treated with continuous subcutaneous insulin infusion (CSII) and 12 IDDM patients treated with conventional insulin therapy (CIT).

MATERIALS AND METHODS

Patients. Twelve women and 12 men with IDDM were allocated to either CSII or CIT groups at random. None received any other medication. All patients gave informed consent to the study protocol, which was approved by the ethical committee.

Study design. Patients on CSII treatment used the Nordic Infusor (Nordisk, Gentofte, Denmark). Highly purified crystalline U-100 porcine insulin was infused subcutaneously through a 25-gauge butterfly needle placed subcutaneously in the abdominal wall. This delivered ~50% of the total 24-h dose as basal constant infusion, with the remaining dose given before meals. Patients in the CIT group administered two daily subcutaneous injections of a mixture of crystalline and NPH highly purified porcine insulin. Monitoring of glycemic control was identical in the two groups. All patients were seen monthly in the outpatient clinic, when hemoglobin A_{1c} (HbA_{1c}) was determined. A seven-point blood glucose profile was performed twice monthly with Hemoglucotest 1-

From the Second University Clinic of Internal Medicine and the Department of Neurology, Aarhus Kommunehospital, Aarhus, Denmark.
Address correspondence and reprint requests to J. Jakobsen, MD, Department of Neurology (2081), Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
Received for publication 2 June 1987 and accepted in revised form 25 August 1987.

TABLE 1
Serum glucose and glycosylated hemoglobin in CSII and CIT patients

	Treatment	Time		
		Start	0–12 mo	12–24 mo
Serum glucose (mM)	CSII		6.2 ± 0.9*	6.3 ± 1.3†
	CIT		9.0 ± 2.1	8.8 ± 1.8
HbA_{1c} (%)	CSII	7.3 ± 1.1	6.2 ± 0.7†	7.2 ± 1.3†
	CIT	7.2 ± 1.1	7.7 ± 1.3	8.6 ± 1.3

CSII, continuous subcutaneous insulin infusion; CIT, conventional insulin therapy.
*P = .001 and †P = .01 vs. CIT group.

44 (Boehringer, Mannheim, FRG). Further information about the patients is given elsewhere (13).

Nerve function. The vibratory perception threshold (VPT) was determined with a biothesiometer (Bio-Medical Instrument, Newbury, Ohio) at the pulp of the second finger, the styloid process of the radial bone, the medial malleolus, and the pulp of the great toe. The pressure at the test site was the weight of the head of the biothesiometer maintained in an upright position neither lifted nor pressed. Triple determinations were made at both sides, and false stimuli were applied each time to test the patients' reliability.

Heart rate variation (HRV) was determined at rest after 10 min in a supine position as the standard deviation of the mean consecutive difference of 300 R-R intervals (MCD). Individual values of MCD were corrected for differences in R-R interval length during the trial according to the formula $MCD_{1,2} \times (R\text{-}R)_0/(R\text{-}R)_{1,2}$ (units in ms). HRV during deep breathing at 5 respiratory cycles/min was the difference between maximal and minimal heart rate of 10 cycles, expressed as beats/min. HRV at standing was the maximal-to-minimal ratio during the first 45 s after lying down.

Pupil area in absolute darkness was measured during infrared illumination with an Iriscorder (Hamamatsu TV, Hamamatsu, Japan) continuously for 2 min after 15 min of dark adaption.

Nerve functions were measured at the start and after 1 and 2 yr. One patient in the CSII group was excluded during the 1st yr because of a severe episode of ketoacidosis due to a combination of mechanical pump failure and carelessness. One patient in the CIT group and one in the CSII group did not participate in the study program after 1 and 2 yr, respectively, because of pregnancy.

Statistics. Within each group, differences at various intervals were compared with the paired t test, and differences between the two groups at the same interval were compared with the unpaired t test with a 5% limit of significance. Unless otherwise indicated, values are means ± SD.

RESULTS

Body weight, height, and male-to-female ratio were similar in the two groups. At the start of the study, age was 29 ± 7 yr in the CSII group and 29 ± 6 yr in the CIT group, with diabetes duration 8 ± 4 yr in both groups. Daily insulin dose at the start, number of individuals affected by retinopathy, arterial blood pressure, and urinary albumin excretion rate did not differ between the groups.

Table 1 shows that during the study, patients of the CSII groups had considerable and statistically significant lower values of plasma glucose and HbA_{1c} compared with patients of the CIT group. The metabolic improvement was maintained throughout the 2-yr period; mean glucose level reduction was 30%, and mean HbA_{1c} reduction was 16%.

At the start and end of the study, four of the CSII group and five of the CIT group had weak tendon reflexes of the legs and none had loss of cutaneous sensation. None of the patients had or developed complaints of peripheral neuropathy.

Tables 2 and 3 show that at the start, somatosensory, parasympathetic, and sympathetic function was similar in the two groups. The VPT of the hand increased in both groups and in the foot of patients of the CIT group, whereas the VPT of the great toe and of the medial malleolus decreased insignificantly in the CSII group. Figure 1 shows the mean changes of VPT for both groups. No differences between groups could be demonstrated in the hand. After the 1st yr, the VPT of the medial malleolus and the great toe differed between the groups, but no further changes developed during the 2nd yr.

After the 2nd yr, there was an increase in heart rate and a decrease in HRV at rest and at deep respiration ($.05 < P < .06$) and a decrease in the heart rate response to standing in the CIT group. In contrast, no significant changes occurred in the CSII group (Table 3). Pupil area in darkness remained unchanged in both groups. Figure 2 shows the changes in HRV and pupil area for both groups. After 2 yr, there was significantly better preservation of HRV at rest and of the parasympathetic response to standing in the CSII group than the CIT group.

In CSII patients, there was no relationship between change in somatosensory or autonomic nerve function and glycemia or HbA_{1c}. After 1 yr of CIT treatment, the change in VPT of the medial malleolus was directly related to the glucose level ($r = .60$, $P < .05$), whereas the change in pupil area was inversely related to glycemia ($r = -.70$, $P < .01$). No such relationships were present after 2 yr in CIT patients.

DISCUSSION

In this study, somatosensory function of the lower extremities and parasympathetic activity of cardiovascular reflexes de-

TABLE 2
Vibratory perception threshold in CSII and CIT patients

	Pulp of 2nd finger	Styloid process of radial bone	Pulp of 1st toe	Medial malleolus
CSII				
Start	4.1 ± 0.7	5.4 ± 0.9	7.0 ± 3.3	9.5 ± 3.8
1st yr	4.6 ± 0.6*	5.8 ± 1.2	5.7 ± 2.0	8.0 ± 3.4
2nd yr	4.7 ± 1.1*	5.8 ± 1.2*	6.0 ± 2.8	8.5 ± 3.8
CIT				
Start	4.6 ± 1.2	6.1 ± 1.6	6.2 ± 1.3	8.9 ± 1.9
1st yr	5.1 ± 1.2	6.5 ± 1.9	7.3 ± 2.2*	10.0 ± 2.2*
2nd yr	5.0 ± 1.4	7.2 ± 2.4*	7.8 ± 2.6*	10.3 ± 2.8
Controls	3.4 ± 0.5	4.2 ± 0.7	4.1 ± 0.7	5.3 ± 0.9

Values are in volts. Control values are from 10 age-matched controls. CSII, continuous subcutaneous insulin infusion; CIT, conventional insulin therapy.
*P = .05 vs. start value within same group.

TABLE 3
Heart rate and HRV at rest, deep breathing, and standing, and pupil area in CSII and CIT patients

	Heart rate (beats/min)	HRV at rest (ms)	HRV at deep breathing (beats/min)	HRV at standing (maximal to minimal ratio)	Pupil area (mm^2)
CSII					
Start	67 ± 12	36 ± 19	16.8 ± 5.6	1.41 ± 0.13	35.0 ± 6.9
1st yr	72 ± 12	29 ± 12	15.9 ± 3.7	1.37 ± 0.22	33.8 ± 6.2
2nd yr	69 ± 12	44 ± 35	15.7 ± 5.4	1.37 ± 0.14	34.1 ± 5.9
CIT					
Start	68 ± 9	46 ± 19	21.3 ± 7.5	1.42 ± 0.17	33.2 ± 6.5
1st yr	74 ± 11	35 ± 23†	20.5 ± 8.7	1.41 ± 0.22	31.2 ± 9.1
2nd yr	76 ± 12*	33 ± 25*	17.6 ± 7.1‡	1.26 ± 0.12*	31.2 ± 8.4
Controls		60 ± 44	21.1 ± 8.1	1.46 ± 0.11	38.9 ± 8.7

Control values are from 10 age-matched controls. HRV, heart rate variation; CSII, continuous subcutaneous insulin infusion; CIT, conventional insulin therapy.
*P = .05, †P = .01, and ‡.05 < P < .06 vs. start value within same group.

teriorated after 2 yr of CIT treatment, whereas CSII treatment retained these functions. The intensification of glycemic control led to a better preservation of somatosensory function in CSII patients than in CIT patients during the 1st yr, and this significant difference between the groups was maintained during the 2nd yr. Parasympathetic cardiovascular reflex activity also was preserved better in CSII patients than in CIT patients, a difference that became significant during the 2nd yr only.

Three controlled studies have reported favorable effects of nerve function after long-standing intensification of metabolic control (11,12,14). In the Radcliffe Infirmary study (Oxford, UK), improved glycemic control was obtained by the use of crystalline insulin at mealtimes and by self-monitoring of blood glucose. Intensification of glycemic control was associated with a better preservation of vibration sensation at the lateral malleolus and at the great toe, with only the former being significant (11). The Steno Study Group (Copenhagen) found no change in VPT in a CSII group followed for 2 yr or in an unchanged conventional treatment (UCT) group. The HRV at deep respiration decreased in the UCT group, and no changes occurred in the CSII group (14). In the Mayo Clinic study (Rochester, MN), a CSII group had significantly better vibratory sensation and faster peripheral nerve conduction velocities after 8 mo of treatment than a CIT group (12).

Our study has confirmed the observation of the Radcliffe and the Mayo studies that the VPT improves slightly after intensification of glycemic control. It is a new observation that the improvement occurs during the 1st yr of intensified treatment and not during the 2nd yr. It is possible, therefore, that initial changes in somatosensory nerve function represent metabolic and reversible abnormalities and not the more severe impairments more closely related to nerve fiber loss and symptomatic neuropathy. This suggestion is partly supported by the finding of considerable improvement of vibration sensation within 6 wk of treatment with CSII in patients with symptomatic neuropathy (15). Also, it has been known for years that peripheral nerve conduction velocity of motor nerves varies slightly within days or weeks depending on the degree of metabolic control (5).

Our finding of improvement of VPT of the foot but not of the hand might appear surprising. The usual type of peripheral neuropathy in diabetic patients—the distal symmetrical, mainly sensory, disorder—injures the lower limb earlier and more severely than the upper limb. This makes it possible that the VPT improvement in the lower limb of CSII patients is related to the neuropathy, whereas changes of the hands are age related.

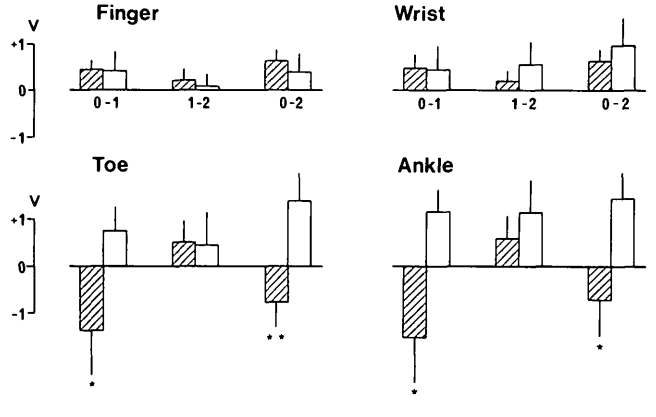

FIG. 1. Changes in vibratory perception threshold at pulp of 2nd finger, styloid process of radial bone, medial malleolus, and pulp of great toe during 1st, 2nd, and both years in continuous subcutaneous insulin infusion (*hatched columns*) and conventional insulin therapy (*open columns*) groups. Values are means ± SE, with units in volts. *P = .05 and **P = .01 vs. CIT value at same time interval.

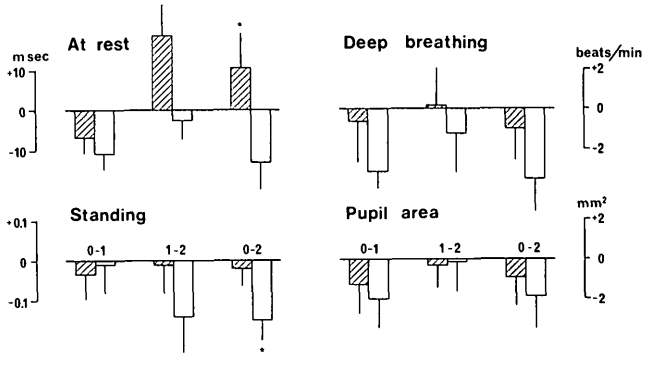

FIG. 2. Changes in heart rate variation at rest, deep breathing, and standing and changes of pupil area during 1st, 2nd, and both years in continuous subcutaneous insulin infusion (*hatched columns*) and conventional insulin therapy (*open columns*) groups. Values are means ± SE. *P = .05 vs. value at same time interval.

The Steno study reported deterioration of HRV during deep breathing after 2 yr in UCT patients but not in CSII patients. This observation was also made in our study. In the Steno study, no effect on parasympathetic activity of improved metabolic control during the 2 yr was found when the CSII and UCT groups were compared. We observed that HRV at rest and at standing was significantly better preserved in CSII patients than in CIT patients. Thus, our study is the first to demonstrate a significant effect of improved glycemic control on the parasympathetic activity compared with CIT.

In addition to dependence on parasympathetic tone, HRV varies with sympathetic tone and heart rate (16). Even though we corrected for differences in heart rate at rest, the interpretation of HRV improvement remains somewhat uncertain because the magnitude of the exact correction is unknown. However, the better preservation of the parasympathetic response to standing in CSII patients than in CIT patients in our study can hardly be due to small differences in heart rate.

Pupil area in darkness is considered an indicator of sympathetic function in diabetes mellitus (17). Pupil area was reduced less in CSII patients than in CIT patients in our study, but the difference remained statistically insignificant.

Our study shows that parasympathetic and somatosensory function can be better preserved in diabetic subjects during intensified glycemic control. However, this observation does not allow a more general neurological recommendation of intensified metabolic control in diabetes mellitus. First, it is unknown whether the improvements obtained are just metabolic and reversible abnormalities unrelated to the neuropathic disease process itself. Second, better preservation of nerve function does not necessarily mean that symptoms of neuropathy can be reduced. Third, intensified glycemic control for several years and under less surveillance than in the clinical study unit may be associated with neuropathy due to hypoglycemic nerve damage.

REFERENCES

1. Pirart J: Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care* 1:168–88, 252–63, 1978
2. Pirart J: Diabetic neuropathy: a metabolic or a vascular disease? *Diabetes* 14:1–9, 1965
3. Young RJ, Zhou YQ, Rodriguez E, Prescott RJ, Ewing DJ, Clarke BF: Variable relationship between peripheral somatic and autonomic neuropathy in patients with different syndromes of diabetic polyneuropathy. *Diabetes* 35:192–97, 1986
4. Ewing DJ, Campbell IW, Clarke BF: The natural history of diabetic autonomic neuropathy. *Q J Med* 49:95–108, 1980
5. Young RJ, Macintyre CCA, Martyn CN, Prescott RJ, Ewing DJ, Smith AF, Viberti G, Clarke BF: Progression of subclinical polyneuropathy in young patients with type 1 (insulin-dependent) diabetes: associations with glycemic control and microangiopathy (microvascular complications). *Diabetologia* 29:156–61, 1986
6. Gregersen G: Variations in motor conduction velocity produced by acute changes of the metabolic state in diabetic patients. *Diabetologia* 4:273–77, 1968
7. Ward JD, Barnes CG, Fisher DJ, Jessop JD, Baker RWR: Improvement in nerve conduction following treatment in newly diagnosed diabetics. *Lancet* 1:428–31, 1971
8. Graf RJ, Halter JB, Halar E, Porte D: Nerve conduction abnormalities in untreated maturity-onset diabetes: relation to levels of fasting plasma glucose and glycosylated hemoglobin. *Ann Intern Med* 90:298–303, 1979
9. Porte D, Graf RJ, Halter JB, Pfeifer MA, Halar E: Diabetic neuropathy and plasma glucose control. *Am J Med* 70:195–200, 1981
10. Service FJ, Daube JR, O'Brien PC, Zimmerman BR, Swanson CJ, Brennan MD, Dyck PJ: Effect of blood glucose control on peripheral nerve function in diabetic patients. *Mayo Clin Proc* 58:282–89, 1983
11. Holman RR, White VM, Orde-Peckar C, Steemson J, Smith B, McPherson K, Rizza C, Knight AH, Dornan TL, Howard-Williams J, Jenkins L, Rolfe R, Barbour D, Poon P, Mann JI, Bron AJ, Turner RC: Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients: a two-year randomized prospective study. *Lancet* 1:204–208, 1983
12. Service FJ, Rizza RA, Daube JR, O'Brien PC, Dyck PJ: Near normoglycemia improved nerve conduction and vibration sensation in diabetic neuropathy. *Diabetologia* 28:722–27, 1985
13. Christensen CK, Christiansen JS, Christensen T, Hermansen K, Mogensen CE: The effect of six months continuous subcutaneous insulin infusion on kidney function and size in insulin-dependent diabetics. *Diabetic Med* 3:29–32, 1986
14. Lauritzen T, Frost-Larsen K, Larsen H-W, Deckert T, Steno Study Group: Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. *Diabetes* 34 (Suppl. 3):74–79, 1985
15. Boulton AJM, Clarke B, Drury J, Ward JD: Comparison of symptomatic relief with biothesiometer measurements in diabetic neuropathy treated with subcutaneous insulin infusion (Abstract). *Diabetologia* 21:505, 1981
16. Pfeifer MA, Cook D, Brodsky J, Tice D, Reenan A, Swedine S, Halter JB, Porte D Jr: Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. *Diabetes* 31:339–45, 1982
17. Hreidarsson AB: Pupil size in insulin-dependent diabetes: relationship to duration, metabolic control, and long-term manifestations. *Diabetes* 31:442–48, 1982