Vibratory perception during ischaemia in uraemic patients and in subjects with mild carbohydrate intolerance

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Diabetic patients retain their vibratory perception during ischaemia longer than non-diabetics. This abnormality is found even in patients with newly diagnosed diabetes and it can be normalized after several days of intensive treatment with insulin (Steiness, 1959, 1961a; Gregersen, 1968a). Further studies in diabetics have demonstrated that the retained ability of nerve conduction during ischaemia also applies to other sensory modalities as well as to efferent nerve conduction (Castaigne, Cathala, Dry, and Mastropaolo, 1966; Gregersen, 1968a; Seneviratne and Peiris, 1968).

It seems of considerable interest to try to clarify the basis for this acute reversible disorder in diabetics as well as its possible significance for the later irreversible diabetic neuropathy. The abnormality may be due to either biochemical or morphological alterations in the nerves. Steiness (1961b) was not able to induce a similar phenomenon in non-diabetics in biochemical experiments such as glucose loading, cortisone treatment, or prolonged fasting. Neither has the abnormality so far been demonstrated in any other disorder than diabetes mellitus. The finding of a similar abnormality in other metabolic and neurological diseases might well supply new information on the pathophysiological basis of this phenomenon.

We have studied vibratory perception during ischaemia in patients with uraemia and, for purposes of comparison, in two groups of subjects with normal kidney function: one with mild carbohydrate intolerance and one with normal glucose tolerance.

METHODS AND PROCEDURES

The vibratory perception threshold was measured in the big toe by a standardized technique (Steiness, 1963) with a Biothesiometer (Bio-Medical Instrument Co., Chagrin Falls Ohio). It is expressed in volts; 50 V on the Biothesiometer correspond to maximal amplitude of oscillations. The ischaemia was induced by inflating

a pressure cuff placed above the knee so that the systolic blood pressure was exceeded by 80 mm Hg. The vibratory perception threshold was measured before and at five minute intervals during arterial occlusion for 30 minutes.

Glucose tolerance was evaluated after a 12 hour fast using an oral glucose load of 70 g as well as by an intravenous load of 25 g glucose. Venous blood was collected at 0, 30, 60, 90, 120, 150, and 180, and 0, 10, 20, 30, 40, 50, 60, 90, 120, 150, and 180 minutes respectively in the two tests. Blood glucose was determined with a glucose oxidase method (Christensen, 1967).

Other laboratory determinations included haemoglobin, serum sodium, potassium, total CO₂, calcium, creatinine, urea, and plasma proteins. Daily urinary protein excretion and creatinine clearance was also determined.

PATIENTS Only patients with an initial vibratory perception threshold below 20 V were included in the study. We have come across some uraemic subjects with an abnormally high initial value, but these patients were not admitted into the material.

The following groups of subjects between the age of 12 and 49 years were studied:

1. Nineteen subjects with chronic renal failure of a varying degree (see Table I). Thirteen patients were in a fairly stable phase of azotaemia. Six patients were in treatment with intermittent dialysis. In these six patients the tests for vibratory perception and for glucose tolerance were not performed earlier than three days after dialysis.

A few patients were reinvestigated after their successful renal transplantation. One patient was reinvestigated at intervals of a few days for several months while her renal acidosis was altered by successively instituting and withdrawing treatment with sodium bicarbonate.

2. Six young subjects without kidney disease who had shown slightly abnormal carbohydrate tolerance—that is, they had normal fasting blood sugars but definitely abnormal glucose tolerance tests verified at repeated examinations.

3. Six young subjects with normal glucose tolerance tests and five young subjects with classical untreated juvenile diabetes, all having normal kidney function, were included for illustration of the normal and the

TABLE I

No.	Age	Sex	Ideal weight (%)	Creatinine clearance (ml./min)	Serum creatinine (mg%)	Serum urea (mg%)	K value	Blood glucose				Vibratory perception							
								0 (mg%)	2 hr (mg%)	2½ hr (mg%)	3 hr (mg%)	0	5	10	15	20	25	30	
Uraemic patients																			
1	46	F	101	11.6	5.2	170		84	223	195		8	9	8	9	10	14	25	
2	16	F	85	2.5	21.5	290						9	7	8	12	23	30	35	
3*	29	F	95	2.8	18.5	240						9	10	15	13	21	†	†	
4	37	M	118	13.0	6.3	100		86	143	109	100	10	10	10	18	30	40	44	
5	44	M	103	1.7	17.5	350		75	141	132	132	3	4	7	11	18	28	28	
6	19	M	75	10.0	6.7	135		88	145	108	68	10	13	13	23	30	31	35	
7*	19	F	79	1.4	18.0	190		75	151	155	100	11	8	11	12	26	30	35	
8	41	F	82	1.7	23.0	360						18	16	18	20	22	28	30	
9*	28	M	82	2.4	25.5	310	1.39	94	126	111	124	13	10	16	16	18	25	40	
10*	22	M	94	0.7	26.0	280	0.69	77	160	145	126	13	13	13	13	12	15	24	
11	35	F	83	12.0	5.7	147		85	151	140	121	13	13	15	15	34	†	†	
12	47	F	101	28.0	3.3	85	0.77	71	120	122	123	14	14	16	14	14	14	14	
13	24	F	79	7.0	10.0	140	1.31	73	101	86	70	8	7	8	8	12	16	22	
14	14	F	96	0.9	28.0	330	0.92					12	12	12	14	20	20	24	
15*	28	M	79	0.4	9.9	98	1.10	74	134	103	81	12	11	13	20	25	23	28	
16	22	F	70	2.0	18.5	370	1.19	82	176	200	142	8	8	12	10	10	14	14	
17*	18	M	87	2.0	23.0	230	0.82	96	123	125	140	10	8	13	18	14	18	28	
18	49	M	90	28.0	3.8	88	1.10	85	139	86	63	12	12	14	35	†	†	†	
19	32	F	70	13.0	4.9	126	3.85	92	69	74		13	14	14	16	19	19	24	
Mean	30		88	7.4	14.5	213	1.31	82	140	126	107								
S.D.			12	8.6	8.7	101		8	34	37	28								
Patients with mild diabetes																			
1	15	F	144		0.9		1.03	86	165	122	122	8	11	11	18	32	†	†	
2	32	F	75		0.6		1.16	91	193	196	160	10	10	13	18	38	†	†	
3	12	M	87		0.8		1.14	73	216	168	150	10	10	18	40	†	†	†	
4	25	M	139		0.8		0.82	82	173	157	118	12	14	20	28	†	†	†	
5	21	M	80		1.1		0.58	75	238	235	204	10	10	17	22	†	†	†	
6	40	F	102		0.8		1.02	100	156	135	120	12	30	24	38	†	†	†	
Mean	24		105		0.8		0.96	85	190	169	146								
S.D.			30		0.2		0.22	10	32	42	34								
Control subjects																			
1	42	M	101		0.7			81	96	95	76	10	10	15	35	50	†	†	
2	42	M	87		1.0			90	144	104	86	12	20	30	34	†	†	†	
3	45	F	86		0.7			75	84	76	59	13	16	18	36	50	†	†	
4	44	F	86		0.7			76	112	100	82	11	14	17	42	†	†	†	
5	27	F	129		0.9			77	115	113		14	20	29	45	†	†	†	
6	47	F	87		0.9			80	82	48	55	12	14	18	23	†	†	†	
Mean	41		96		0.8			80	106	89	72								
S.D.			17		0.1			6	23	24	14								

*Patients in intermittent dialysis.

†Time when vibration could no more be perceived at maximal stimulation.

diabetic vibratory perception threshold pattern during ischaemia. The results obtained in these two groups were identical with those obtained by Steiness (1959) in this laboratory in much larger groups of subjects.

4. Three normal young subjects were studied before as well as after inducement of metabolic acidosis with ammonium chloride and with the carbonic acid anhydrase inhibitor acetazolamide (Diamox).

Further clinical data appear in Table I.

RESULTS

Figure 1 (upper left part) shows the time course of the vibratory perception threshold during ischaemia in the six normal subjects. After approximately 15 minutes the threshold increases rapidly.

After 25 minutes none of the normal subjects are able to perceive vibration.

The lower left part of Fig. 1 shows the pattern of vibratory perception threshold during ischaemia in the five patients with classical juvenile diabetes. Their fasting blood sugar ranged between 272 mg% and 412 mg% and averaged 342 mg%. In these patients the vibratory perception threshold remained low throughout the ischaemic period.

The results obtained in the uraemic patients are shown in the lower right part of Fig. 1. In 16 out of 19 patients a clearly abnormal pattern was observed, similar to that found in diabetic patients. The abnormality of the vibratory perception threshold as judged from the 30 minutes value had no

FIG. 1. Vibratory perception threshold pattern during ischaemia in four groups of subjects. Upper left: normal subjects; lower left: classic juvenile diabetics; upper right: subjects with mild carbohydrate intolerance; lower right: uraemic subjects.

association with either the serum creatinine, serum urea, or with the renal clearance (Table I).

Uraemic patients often have impaired carbohydrate tolerance, although their fasting blood sugar is normal. This was also the case in the present study (Table I). It appears that 12 patients out of 15 studied had a two hour value higher than 120 mg% and eight patients had a two and a half hour value higher than 120 mg%. In another study in this laboratory (Ørskov and Christensen, 1969), on the hormonal response to glucose, we found that only two out of 16 normal subjects matched for age, sex, and weight had a two hour value above 120 mg%. None of these normal subjects had two and a half hour values higher than 120%. Ten of the patients with uraemia were also studied using intravenous glucose tolerance tests. All K values except one were very low (Table I). There was no association between the abnormality of the vibratory perception threshold in the uraemic patients and their oral glucose tolerance expressed as the two, two and a half, or three hour value, nor was there any association with the K value from the intravenous test.

The significance of the abnormality of the glucose

tolerance for altered vibratory perception was further studied in investigations on the six subjects with mild carbohydrate intolerance. As seen in Table I, their glucose tolerance was somewhat more reduced than that of the uraemic patients. The upper right part of Fig. 1 shows the vibratory perception threshold in these patients. A normal pattern was found in all the subjects.

The total plasma CO_2 varied widely in the uraemic patients (Table II). No association could be established between the total CO_2 and the vibratory perception threshold expressed as the 30 minutes value. However, in one patient (case 1) a definite abnormality in vibratory perception threshold during ischaemia, which was observed on several occasions, disappeared during treatment with oral sodium bicarbonate at a time when the total plasma CO_2 had increased from the original 11 m-equiv/l. to normal values. In this patient, the vibratory perception remained normal during the continued bicarbonate treatment at five consecutive examinations. After withdrawal of treatment the abnormality reappeared. At later attempts to normalize the blood acid-base balance a normal vibratory response was never reattained. It should be noticed, however, that during the first period of bicarbonate administration the azotaemia and the general condition of the patient had simultaneously improved considerably.

The significance of blood acid-base abnormalities was further investigated in experiments on three normal subjects by inducing metabolic acidosis with acetazolamide (Diamox). Diamox 500 mg was given three times daily for a week. In two to three days the total plasma CO_2 decreased from 25, 23, and 21 m-equiv/l. to 16, 15, and 11 m-equiv/l. in the three subjects respectively and stayed at these low values during the continued drug administration. No change was observed in the vibratory perception pattern during ischaemia in any of these subjects. In similar experiments with the same subjects given ammonium chloride (2 g every fourth hour for a week) to induce acidosis, negative results were likewise obtained.

Finally, no association could be established between the abnormality of vibratory perception during ischaemia in the uraemic patients and their serum sodium, serum potassium, serum calcium, serum protein concentration, daily urinary protein excretion, or with the degree of anaemia.

Two patients were reinvestigated after successful renal transplantation (cases 2 and 7). Both patients had normal serum creatinine values after the operation. They were studied three and six months respectively after their transplantation. The abnormal patterns found before transplantation remained

TABLE II

No.	Total plasma CO ₂ (m-equiv/l.)	Serum sodium (m-equiv/l.)	Serum potassium (m-equiv/l.)	Serum calcium (mg %)	Haemo- globin (g %)	Serum protein (g %)	U-inary protein (g/die)
1	11	143	3.2	9.0	10.2	7.6	0.0
2	12	139	4.6	9.1	6.8	6.2	3.4
3*	20	137	6.0	9.5	7.0	5.8	3.6
4	12	142	4.2	8.1	12.0	6.5	2.4
5	15	144	5.8	9.6	7.6	6.4	1.9
6	21	139	5.2	7.7	8.4	5.0	10.1
7*	19	135	5.7	10.4	7.7	7.9	2.9
8	11	136	3.8	8.6	7.2	5.9	1.6
9*	13	132	4.5	9.0	6.8	7.0	2.3
10*	16	137	5.1	8.0	7.3	5.8	1.5
11	12	144	5.7	8.9	11.5	6.7	0.9
12	21	136	4.0	8.6	13.0	3.8	19.0
13	17	141	4.1	9.4	9.6	6.9	3.1
14	17	144	4.2	8.5	8.2	7.4	2.5
15*	22	127	3.8	9.8	5.9	5.0	0.1
16	4	130	4.9	9.8	13.6	8.3	0.7
17*	17	133	3.7	9.8	5.9	5.5	0.5
18	22	142	4.5	9.4	10.3	6.7	1.2
19	13	141	4.1	7.8	7.7	7.2	1.9
Mean	15.5	138	4.6	9.0	8.8	6.4	3.1
S.D.	4.8	5	0.8	0.8	2.4	1.1	4.4

*Patients on intermittent dialysis.

entirely unchanged. This intriguing result does not justify any definite conclusion. It requires further studies to elucidate the course of the vibratory perception pattern during ischaemia after normalization of kidney function.

DISCUSSION

The present study has demonstrated that the abnormality of the vibratory perception during ischaemia—that is, the retained ability for sensory transmission—is not confined to diabetic patients. The same phenomenon is present in the majority of uraemic patients.

The immediate explanation for the presence of this phenomenon in uraemic patients would of course be impaired glucose tolerance, which occurs with high incidence in patients with uraemia. We believe that this possibility can be ruled out with certainty for two reasons. Firstly, no association was observed between the abnormality of the vibratory perception threshold during ischaemia and the degree of carbohydrate tolerance. The lack of correlation was observed whether the values from the oral tests or the K value from the intravenous tests were used. The second reason is that the patients with mild carbohydrate intolerance and with normal kidney function did not reveal any abnormality of their vibratory perception threshold. These patients demonstrated an impairment of carbohydrate tolerance which was similar to if not worse than that of the uraemic patients.

This lack of connection between vibratory perception threshold during ischaemia and glucose intolerance in uraemic patients indicates apparently that the presence of the same dysfunction of the peripheral nerves in diabetics and uraemics is due to two different mechanisms. It must be kept in mind, however, that the existence of this abnormality in diabetic patients is not a direct consequence of high blood sugar; because the abnormality will not disappear just by normalizing the blood sugar. Normalization will only occur after several days of intensive insulin treatment.

The improbability of glucose being the direct factor responsible for the altered nerve function during ischaemia made pertinent the search for other mechanisms. With the peculiarities of the two metabolic diseases, diabetes and uraemia, in mind, it was reasonable to examine the significance of blood acid-base balance as well as the role of other plasma electrolytes. Alterations of the concentrations of these factors might well exert an influence on nerve membrane potential during ischaemia.

The possible role of ketone bodies for the development of this nervous abnormality in diabetic patients was already studied by Steiness (1961b). Firstly, he was not able to induce the phenomenon in normal subjects during prolonged fasting. Secondly, he showed (Steiness, 1959) that the occurrence of the phenomenon in diabetics was not dependent on demonstrable changes in the blood acid-base balance. Concerning the uraemic patients,

our results do not support any direct connection with the presence or degree of renal acidosis. Neither could any change in the vibratory perception threshold during ischaemia be provoked during prolonged experimental acidosis in normal subjects.

The role of the blood electrolyte composition was also studied in our uraemic patients, who demonstrated large inter-individual variations in the levels of serum sodium, serum potassium and serum calcium. These patients should accordingly be ideal for a search for any association. However, in our material the results were totally negative.

In our experiments no biochemical explanation has been forthcoming for the presence of the vibratory abnormality during ischaemia. Undoubtedly, intracellular concentrations of sodium, potassium, etc. are more relevant to the problem and these cannot be deduced from the present study. At the moment it seems reasonable, however, to look for another type of explanation for the altered nerve function in diabetes and uraemia.

Steiness (1963) suggested that the ability to maintain prolonged sensory transmission during ischaemia in diabetic patients was associated with an ability to maintain membrane polarization for longer periods than non-diabetics. Gregersen (1968a) discussed various possible explanations for the occurrence of the ischaemic phenomenon. The well-known resistance against anoxia of the so-called non-myelinated nerve fibres suggested to him the possibility that a functional or morphological defect of the myelin sheaths might somehow explain the ischaemic abnormality. He therefore investigated sensory modalities presumed to be transmitted by non-myelinated fibres. As virtually no changes occur in the threshold values of heat and pain during the 30 minutes period of ischaemia in diabetics or non-diabetics, he was unable to draw any conclusions whether non-myelinated fibres in diabetic patients are also more resistant to ischaemia.

It is well documented that segmental demyelination is present in the nerves of diabetic patients (Thomas and Lascelles, 1966). Myelin degeneration can also be demonstrated in the nerves of patients with recently diagnosed diabetes (Reske-Nielsen, personal communication). Demyelination is a prominent morphological feature also in the nerves of uraemic patients (Asbury, Victor, and Adams, 1962, 1963). It has been proposed that segmental demyelination is the pathophysiological factor responsible for the reduced motor conduction velocity found in diabetic patients (Cragg and Thomas, 1964).

Is it possible that demyelination not only explains the reduced motor conduction velocity but also

the retained ability of nervous conduction during ischaemia found in both diabetic and uraemic patients? We believe it can, and propose the following simple mechanism: a widespread, although not necessarily intensive, demyelination will produce new points of depolarization between the nodes of Ranvier leading to reduced saltatory distances. In the experimental situation employed in the present study ischaemia leads to a reduction of resting membrane potential and action potential in the peripheral nerves distal to the occlusion cuff. This reduction prevents conduction in a normal nerve with undamaged myelin sheath at a certain point of time. On the other hand, the presence of reduced saltatory distances created by demyelination may permit nerve conduction at a lower membrane and action potential—that is, for a longer period of ischaemia.

The interpretation is in accordance with the fact that patients with newly diagnosed diabetes demonstrate both a reduced motor conduction velocity (Gregersen, 1968b) and an abnormal threshold pattern during ischaemia. It is also compatible with the observation that patients with newly diagnosed diabetes (Terkildsen and Christensen, 1969) have required intensive insulin treatment for at least one week before the ischaemic abnormality disappeared.

There are several implications of the hypothesis. It makes it unnecessary to assume that the resting nerve membrane potential decreases at a lower rate in diabetics than it does in non-diabetics. Further, to explain the normalization of vibratory perception threshold occurring during intensive insulin treatment, it is sufficient to presume that a small part of the nerve only has been entirely remyelinated because this small remyelinated part will stop nerve conduction at the same point of time as it will be stopped in normal myelinated nerves.

This last-mentioned implication should be open to experimental verification. If it is true that remyelination of a small part of a nerve only is sufficient to restore a normal threshold pattern during ischaemia, then it would be expected that experiments including a considerable length of nerve would reveal normal conditions at an earlier stage of insulin treatment than a short segment, because the long segment will have a greater chance of containing an entirely remyelinated part. With this in mind, we have started a series of experiments in this laboratory (Terkildsen and Christensen, 1969), where we have investigated patients with newly diagnosed diabetes at the stage of intensive insulin treatment when the vibratory perception threshold was just normalized using our usual

technique—that is, with the arterial occlusion cuff placed above the knee. In these experiments, however, the threshold was also studied with the cuff placed just above the ankle. Although the results must be regarded as preliminary, they have invariably shown that when the cuff is placed at the ankle the threshold values have not returned to the values obtained in normal subjects.

There is clearly one more implication of this hypothesis. The same abnormal ischaemic phenomenon must occur not only in diabetics and in uraemics, but also in all patients demonstrating a widespread demyelination. This question is currently under investigation.

Finally, if the ischaemic abnormality is caused by morphological changes in the nerves rather than biochemical defects, it becomes more likely that this reversible neurological dysfunction is a very early stage on the way leading to the irreversible neuropathy present in long-term diabetes.

SUMMARY

It is well documented that diabetic patients retain their vibratory perception for a longer period of ischaemia than non-diabetics. This neurological abnormality is particularly interesting because it is present already at the clinical appearance of diabetes and because it can be normalized after some days of intensive insulin treatment.

In the present study it is shown that uraemic patients demonstrate exactly the same abnormality, as 16 out of 19 patients exhibited an abnormal vibratory perception threshold pattern during ischaemia.

No association could be demonstrated in the uraemic patients between the degree of abnormal low threshold values obtained during ischaemia and the degree of glucose intolerance. The same negative results were obtained when the ischaemic abnormality was associated with the degree of renal acidosis and electrolyte abnormalities. The role of carbohydrate intolerance for the presence of the

phenomenon was further investigated by measuring the vibratory perception threshold during ischaemia in six young subjects with normal kidney function and very mild carbohydrate intolerance. A normal response was found in all these subjects.

It is proposed that the ability of retained sensory transmission during ischaemia in diabetic as well as in uraemic patients is caused by demyelination of the nerves. Demyelination will reduce saltatory distances between points of depolarization on the nerve fibres and therefore permit nerve conduction at a time when the reduced resting membrane potential caused by ischaemia has prohibited nerve conduction in normal myelinated nerves.

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