Respiratory influence on heart rate in diabetes mellitus

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Summary and conclusions

To find a simple and accurate test of autonomic nervous dysfunction in diabetes mellitus, 41 insulin-dependent diabetics and 25 controls were investigated. The diabetics, none of whom had symptoms of autonomic dysfunction, were tested for retinopathy and sensory neuropathy. Each subject also performed maximal deep-breathing procedures while undergoing electrocardiographic recording: in normal subjects the intervals are shortened during inspiration and prolonged during expiration, and a difference in the heart rate between inspiration and expiration of 10% or less seems to indicate autonomic dysfunction. This difference was calculated as an E:I ratio of the mean of the longest R-R interval during maximal expiration to the mean of the shortest during maximal inspiration. Ten of the 18 patients found to have sensory neuropathy had abnormal E:I ratios, and among those with absent ankle reflexes the proportion was even higher (9 out of 11). The E:I ratio also seemed to be as accurate as traditional tests for autonomic dysfunction and easier to perform.

Diabetics with autonomic dysfunction have an increased risk of acute cardiorespiratory death during and after surgery, and maximal deep breathing and calculation of the E:I ratio may be a useful test to perform on diabetics at risk.

Introduction

There has recently been increasing interest in the function of the autonomic nervous system in patients with diabetes mellitus. In 1959 Keen observed that patients with diabetes often had tachycardia at rest,[1] which he suspected was caused by decreased vagal tone. Wheeler and Watkins[2] confirmed this observation and showed vagal denervation of the heart in diabetics with autonomic neuropathy. Normal individuals at rest show variation in heart rate induced by respiration; this is most pronounced in children.[3] During maximal deep breathing these changes are accentuated and electrocardiographic (ECG) recording will show the increase in heart rate during inspiration and the decrease during expiration—beat-to-beat variation. This variation is reduced or absent in diabetics with autonomic neuropathy.[2]

Reduced beat-to-beat variation has also been shown in diabetics without other signs of autonomic dysfunction during both normal breathing[4,5] and maximal deep breathing[6] but by complicated analyses. We investigated the possibility of recording abnormalities of the autonomic nervous system by using conventional ECG to work out an index for autonomic dysfunction and studied the relation between autonomic abnormalities and sensory neuropathy and retinopathy.

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Patients and methods

We investigated 41 diabetics (21 men), 23 of whom had retinopathy. All were insulin dependent and without symptoms of autonomic neuropathy. Eleven healthy women and 14 healthy men acted as controls. All 66 subjects were aged under 50, and of those who smoked each smoked more than five cigarettes a day.

All the diabetics underwent ophthalmoscopy, performed by the same ophthalmologist, and examination of the nervous system including analysis of tendon reflexes and vibration sense. Vibration sense thresholds (Bio-Thesiometer), which were also measured in the controls, were determined over the medial malleoli. The results were expressed in volts as the mean of measurements on the left and right ankles. A threshold value above the mean +2 SD value in the controls was considered abnormal.

All subjects underwent ECG recording. After 15 minutes in the supine position their heart rate was checked for at least four minutes, and, once constant, a continuous ECG was recorded for two minutes. During the first minute the subjects breathed normally; in the second they performed six maximal deep-breathing manoeuvres.

ECG analysis—The R-R intervals on the resting ECG during the first minute were measured for every fifth beat. The mean value (in seconds) and its standard deviation were calculated for each subject.

Vital capacity test—During the second minute, while the patients were taking deep breaths, the shortest R-R interval during inspiration and the longest during expiration were measured. The mean values were calculated from the six inspirations and expirations and the E:I ratio calculated as follows:

$$\text{E:I} = \frac{\text{Mean value for longest R-R intervals (s) during each expiration}}{\text{Mean value for shortest R-R intervals (s) during each inspiration}}$$

Student's t test and χ^2 test were used for statistical analysis.

Results

Altogether 18 diabetics had signs of sensory neuropathy: six had isolated absent ankle reflexes, five had absent ankle reflexes combined with an abnormal vibration sense, and seven had normal reflexes but an abnormal vibration sense. As a group, the diabetics had significantly higher vibration thresholds than the controls ($P < 0.005$; table I).

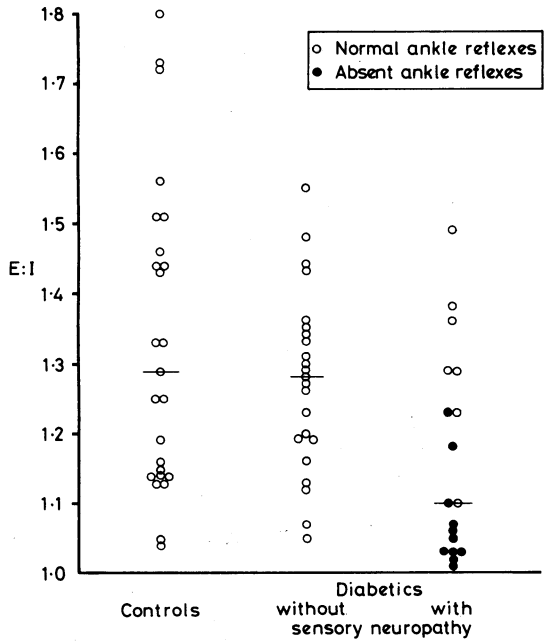
TABLE I—*Details of patients, vibration thresholds, and R-R intervals. Values are means ± SE*

	Controls (n = 25)	All diabetics (n = 41)	Diabetics without sensory neuropathy (n = 23)	Diabetics with sensory neuropathy (n = 18)
Age (years)	39·4 ± 1·7	32·7 ± 1·1	29·7 ± 1·3	36·6 ± 1·7
Duration of diabetes (years)		16·6 ± 1·4	14·0 ± 1·6	19·9 ± 2·2
Daily insulin dose (units/kg)		0·67 ± 0·03	0·74 ± 0·04	0·57 ± 0·04
Vibration threshold (volts)	8·4 ± 0·8	14·5 ± 1·3	9·6 ± 0·4	20·7 ± 2·2
E:I	1·33 ± 0·04	1·23 ± 0·02	1·27 ± 0·03	1·16 ± 0·03
R-R interval (s)	0·916 ± 0·026	0·735 ± 0·015	0·751 ± 0·020	0·714 ± 0·024
R-R interval variation (s)	0·050 ± 0·006	0·028 ± 0·003	0·034 ± 0·003	0·020 ± 0·004

Ten of the 18 with sensory neuropathy had an E:I ratio on or below the median value of 1·10 (see fig), including nine of the 11 with absent ankle reflexes. Among controls and diabetics without sensory neuropathy only two people in each group had such low ratios; and there was no difference in the mean values between these two groups, while the mean value for diabetics with neuropathy was significantly lower ($P < 0.01$ compared with controls; $P < 0.02$ compared with diabetics without neuropathy).

All the diabetics had significantly shorter R-R intervals than controls ($P < 0.001$), and diabetics with an E:I ratio of 1·10 or less

had a significantly shorter R-R interval than those with higher ratios (0·665 ± SE 0·016 s *v* 0·756 ± SE 0·017 s). The controls had greater individual variation in R-R intervals (SD) than either patients with sensory neuropathy ($P < 0.001$) or those without ($P < 0.05$): only one control had a variation below 0·020 s, while only one diabetic with an abnormal E:I ratio had a variation above 0·020 s.



Distribution of E:I ratios in the different groups. Horizontal lines indicate median values.

Twelve of the 18 diabetics with sensory neuropathy and 11 of the 23 without had retinopathy, but retinopathy was significantly commoner among diabetics with low E:I ratios than among those with normal ratios (10/12 *v* 13/29; $P < 0.025$). Diabetics with sensory neuropathy were significantly older than the other patients ($P < 0.005$), had had diabetes for longer, and were taking significantly more insulin ($P < 0.01$). When the diabetics were divided according to their E:I ratios there was no difference in the duration of diabetes. Cigarette smoking was more common among diabetics without sensory neuropathy than among those with neuropathy (16/23 *v* 7/18; $P < 0.05$), but among the latter the difference between those with high and low E:I ratios was much greater (0/8 *v* 7/10; $P < 0.005$). Among non-smokers with sensory neuropathy and E:I ratios of 1·10 or less, two had had diabetes for 31 and 36 years, while an ex-smoker had had it for only 12 years. Table II shows that the E:I ratio was as accurate in distinguishing diabetics with autonomic dysfunction from those without as another method in which a heart rate difference between inspiration and expiration of 10 beats/min or less is considered abnormal.[6] One patient with a normal E:I ratio but a difference in heart rate of under 10 beats/min had no sensory neuropathy and thus probably had no autonomic dysfunction either.

TABLE II—*Diabetics divided according to presence or absence of abnormal E:I ratio and abnormal beat-to-beat variation*

Beat-to-beat variation	E:I ratio			
	≤1·10		>1·10	
	With neuropathy	Without neuropathy	With neuropathy	Without neuropathy
<10	10	2		1
≥10			8	20

Discussion

One of the best ways of showing autonomic dysfunction[2 4–14] in diabetes mellitus is to measure the difference between the heart rate during deep inspiration and expiration with an automatic heart rate meter.[2] It is, however, much simpler to measure the R-R intervals on an ECG. We found that a difference in the heart rate between deep inspiration and expiration of 10% or less (an E:I ratio of 1·10 or less) seemed to indicate autonomic dysfunction. Over half the diabetics with signs of sensory neuropathy had autonomic dysfunction on this test, though none had clinical symptoms. In diabetics with absent ankle reflexes the prevalence was as high as 82%, whereas in those without sensory neuropathy it was seen in only 9%. The heart rate at rest was higher and the R-R interval shorter in the diabetics than in the controls, confirming other observations.[1 2] Diabetics tended to have increased heart rates irrespective of whether or not they had signs of sensory neuropathy, although diabetics with an E:I ratio of 1·10 or less had especially high heart rates. The variation of the R-R intervals was smaller in the diabetics than in the non-diabetics, which also confirms other reports.[4 5] Nervous dysfunction is the most probable explanation, as diabetics with sensory neuropathy had the smallest variation. Analysis of the heart rate at rest might be thought to show autonomic neuropathy better than heart rate changes during maximal deep breathing since the demonstration of defects in R-R variation may be more sensitive to autonomic disturbances. Clinically, however, it is easier to determine the E:I ratio, since statistical calculations are not needed, and the E:I ratio seemed to be as accurate in distinguishing diabetics with autonomic dysfunction as another method of measuring beat-to-beat variation.[6] Maximal deep breathing also seems to be an easier procedure than a recent orthostatic test[13] or examining pupillary signs.[14]

We found an unexpectedly high incidence of cigarette smokers among diabetics without sensory neuropathy, which might indicate that smoking has a beneficial influence. Further analysis, however, showed that among diabetics with sensory neuropathy none of those with normal autonomous nervous functions smoked, while a high proportion of those with autonomic dysfunction did.

Our study clearly shows that diabetics with sensory neuropathy have a high prevalence of autonomic dysfunction, which may be important clinically. Since sudden cardiorespiratory deaths are common in diabetics with autonomic neuropathy during and after surgery,[15] the determination of the E:I ratio might be a suitable preoperative test for those diabetics at risk. Patients with an abnormal ratio should probably be closely monitored in an intensive care unit after operation.

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