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Analysis of heart rate variations in patients with multiple sclerosis

A simple measure of autonomic nervous disturbances using an ordinary ECG

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SUMMARY A simple method requiring only an ordinary ECG apparatus and a ruler has shown a hitherto unknown abnormality of the autonomic nervous system in patients with multiple sclerosis. The main findings were that both long-term and short-term variations in heart rate were reduced in patients with multiple sclerosis. The reduction was comparable with that observed in other patients with autonomic abnormalities—for example, long-term diabetics—but in addition patients with multiple sclerosis presented unexpected large shifts in pulse rate levels, lasting from a few to 10 or 20 beats.

Multiple sclerosis is characterised by the dissemination of the central nervous system disturbances, which may also involve the autonomic nervous system—for example, the severe bladder dysfunction seen in some patients.

A few years ago Wheeler and Watkins (1973) showed that exaggerated excursions in heart rate provoked by deep respiration are reduced in diabetics with severe neuropathy. Recently, Gundersen and Neubauer (1977) have described simple methods for studying the variations in heart rate under basal and reproducible conditions.

The aim of the present investigation was to study whether the presence of functional abnormalities of the autonomic nervous system in patients with multiple sclerosis can be detected by the use of an ordinary ECG apparatus and a ruler.

Patients and Methods

Thirteen patients with multiple sclerosis and 11 controls (staff personnel) were studied, all aged between 30 and 40 years. There was no reasonable doubt in any patient as to the diagnosis of multiple sclerosis, based on the start of symptoms, their recurrences, the presence of physical disability as well as abnormalities of cerebrospinal fluid with increased γ-globulin fraction. All except one were hospitalised for examination and for treatment of complications of their disease. For comparison, 12 patients with diabetes mellitus of more than 20 years duration were included in the study. Males and females were equally represented in all groups. None had diastolic blood pressure above 110 mmHg, arrhythmia, clinical signs of cardiac disease, or ECG abnormalities, other than those described in this study.

On each subject an ECG was obtained in a period of 3 to 5 minutes using an ordinary ECG apparatus and a paper speed of 50 mm per second. During this procedure the subjects, who had been at rest for half an hour, were recumbent and completely undisturbed. They were unaware when the ECG was obtained, and since nothing was said about breathing patterns their respiration was spontaneous. The lengths in millimetres of at least 150 consecutive RR intervals were measured on each ECG using a ruler. The accuracy was 0.5 mm.

Two types of pulse rate variations can be distinguished in the series of RR intervals from a normal subject, an example of which is shown in Fig. 1. The interval from beat to beat shows a certain variability. Furthermore, gradual shifts or long-term fluctuations occur, including the normal degree of respiratory arrhythmia. The two

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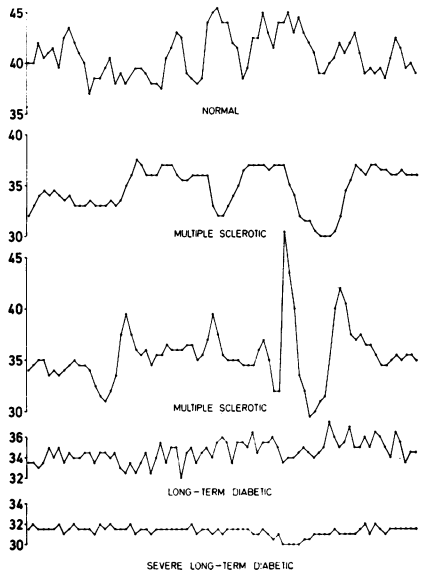

Fig. 1 *The length of 75 consecutive RR intervals in mm are given on the ordinate for an average normal subject (upper curve), two patients with multiple sclerosis (curves 2 and 3 from above), and two patients with long-term diabetes mellitus (lower curves).*

types of variation in pulse rate were estimated in each ECG by different statistical methods: (1) the mean square successive difference (MSSD)—that is, the standard deviation of the differences between any RR interval and the next (Diem and Lentner, 1970). This figure is exclusively a measure of the short-term variation from one beat to the next. (2) the usual standard deviation (SD) of the RR intervals. This parameter is more sensitive to long-term than to short-term fluctuations. If trends or long-term fluctuations are present in a series of RR intervals the SD is enhanced whereas the MSSD is almost unaffected.

The general pattern of the ECGs from patients with multiple sclerosis seemed to consist of an abnormally great regularity, broken now and then by peculiar bursts of changes in heart rate. It was reasonable, therefore, to determine the kurtosis of the distribution of beat-to-beat differences in each individual. Kurtosis is defined as $\frac{\Sigma(x-\bar{x})^y}{(\Sigma(x-\bar{x})^2)^2}$ and is a measure of the shape of a distribution (Sokal and Rohlf, 1969). The normal (Gaussian) distribution has a kurtosis of 3. A larger kurtosis means that a relatively large number of observations are distributed either close to the mean or far away from it, and the shape is, therefore, that of a narrow distribution with long tails.

The values of the SD and the MSSD of RR intervals are approximately log normally distributed within groups of subjects. Accordingly, the significance of differences between groups are tested by means of Student's *t* test carried out on the logarithmic transformed values. The mean and the standard deviation of these values are directly related (through the logarithmic function) to the geometric mean and its tolerance factor of the untransformed values. The geometric mean values and their tolerance factors are given in the text.

Results

The individual values of the MSSD of RR intervals are shown in Fig. 2 A. The geometric mean was 1.95 x/÷ 1.35 mm in normal subjects, and 0.93 x/÷ 1.73 mm in patients with multiple sclerosis. This difference is highly significant, 2 P=0.00061. Figure 2 B presents the SD of the RR intervals, the parameter especially sensitive to prolonged variations and trends in pulse rate level. A statistically significant difference was also found between the geometric mean SD of normal subjects (2.00 x/÷ 1.24 mm) and patients with multiple sclerosis (1.27 x/÷ 1.77 mm), 2 P= 0.019. No differences obtained between men and women within any group of subjects.

Most of the patients with multiple sclerosis showed some periods of 5 to 10 seconds duration

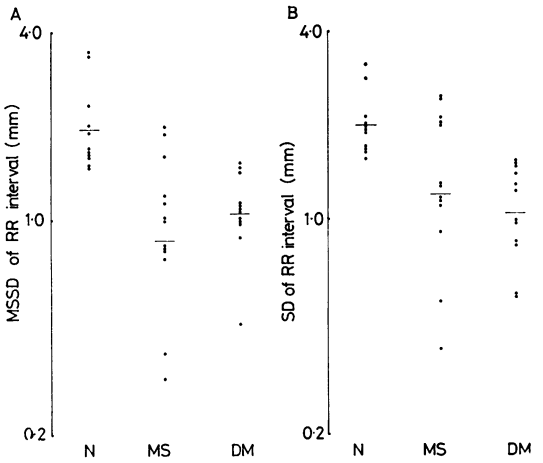

Fig. 2 *The individual mean square successive difference (MSSD), A, and standard deviation (SD), B, of RR intervals in normal subjects (N), patients with multiple sclerosis (MS), and with long-term diabetes mellitus (DM). The ordinate is logarithmic.*

in which a change in pulse rate occurred, either suddenly or gradually (see Fig. 1). Except for these periods, the beat-to-beat variation was much smaller than normal. In some patients this combination of a few, relatively deviating beat-to-beat intervals and many almost without variation at all results in the non-normal distribution of the beat-to-beat differences with a large kurtosis (Fig. 3 A). This phenomenon also results in the decreased ratio between MSSD and SD in patients with multiple sclerosis (Fig. 3 B).

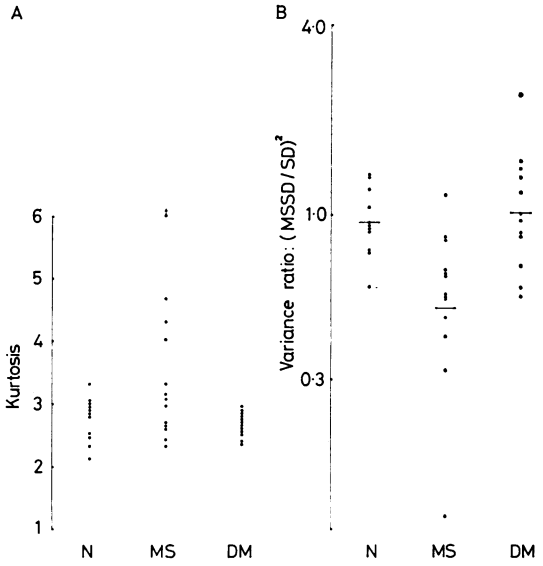

Fig. 3 *A: kurtosis of the distribution of beat-to-beat differences. B: individual variance ratio* $(MSSD/SD)^2$ *on a log scale. N denotes normal subjects, MS and DM indicate patients with multiple sclerosis and long-term diabetes mellitus, respectively.*

Discussion

The technique employed in this study is very simple and reproducible, and requires only an ordinary ECG apparatus and a ruler.

The two statistical procedures used for estimating variation have shown that beat-to-beat variation and long-term shifts in pulse rate are reduced in multiple sclerosis. The decreased ratio MSSD/SD means that the long-term variation is more preserved than the beat-to-beat variation, and inspection of the curves showed this long-term variation to be of a particular type characterised by a great regularity broken abruptly by shifts in the level of heart rate lasting a few to more than 10–20 beats. Accordingly the kurtosis of the distributions of beat-to-beat intervals was large. The bursts in heart rate may be analogues of the well-known paroxysmal phenomena in multiple sclerosis—for example, the uninhibited neurogenic bladder.

From experiments of Wheeler and Watkins (1973) with pharmacological and surgical denervation of the heart, it is known that the regulation of variation in heart rate is mediated through the vagus nerve. In the present study the ECG was taken with the patients breathing spontaneously, thereby avoiding the problem of variations or abnormalities of the afferent pathway inherent in the test when deep breathing is required. It seems reasonable to conclude, therefore, that the reduced variations observed in heart rate of patients with multiple sclerosis are due to vagal abnormalities.

As regards the estimates of variation the MSSD is the parameter most insensitive to systematically induced variation in pulse rate, and its interpretation, therefore, carries with it a minimum of assumptions concerning reproducibility of a stimuli, co-operation of subjects, and long-term stability of the timing mechanisms in the recording equipment. The MSSD is thus preferable for detection of autonomic nervous system abnormalities. In an earlier study of diabetic patients the MSSD has been found to be the most sensitive of the two parameters for the early detection of cardiac denervation (Gundersen and Neubauer, 1977). Since the MSSD was the parameter most consistently reduced in patients with multiple sclerosis, it is probably also to be preferred for detecting small and early abnormalities.

Clinical studies in multiple sclerosis concerning correlations of these pulse rate abnormalities with the different phases and symptoms of the disease are currently in progress.

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