Assessment of vagal control of the heart in diabetes

Measures of R-R interval variation under different conditions

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R-R intervals and R-R interval variation were measured in 2 selected groups of diabetic subjects; 1 group was selected because vagal control of the heart appeared normal, the other group was selected because they lacked vagal control of the heart. The means of the R-R intervals for the 2 groups were not significantly different under various conditions (sleeping, lying, during deep breathing, sitting, standing, and during upright activity). The standard deviations of the R-R intervals for the 2 groups were only significantly different during deep breathing and upright activity. It is suggested that cardiac vagal function is not reliably assessed by measurement of R-R interval variation during quiet standing, but useful information may be obtained during deep breathing.

The integrity of the autonomic nervous system can be investigated by a variety of tests, but the simplest, non-invasive method is the measurement of maximal beat-to-beat variation in heart rate, which depends on the parasympathetic innervation of the heart being intact (Wheeler and Watkins, 1973; Freyschuss and Melcher, 1975).

Although measurement of heart rate variability has been used to assess autonomic dysfunction in patients with diabetes mellitus (Wheeler and Watkins, 1973; Bennett *et al.*, 1975; Murray *et al.*, 1975), there is disagreement about the best way of quantifying this variation. In particular, Murray *et al.* (1975) have suggested that calculation of the standard deviation of R-R intervals during a period of quiet standing serves to distinguish diabetic patients with subclinical autonomic neuropathy from normal subjects. Their technique has the advantage of being easily performed using computer analysis. However, under the conditions employed by Murray *et al.* (1975), R-R interval variability might be affected by factors other than activity of the autonomic nervous system. For this reason we have, hitherto, assessed cardiac vagal activity from the mean difference between peak and trough heart rates during deep breathing (Wheeler and Watkins, 1973; Bennett *et al.*, 1975). Elsewhere

(Hosking *et al.*, 1976), we have shown that this measure correlates closely with baroreflex sensitivity, the latter being generally accepted as a measure of cardiac vagal competence (Bennett *et al.*, 1976a).

We have re-examined our data to measure the standard deviation of R-R intervals under different conditions and to determine whether this provides an indication of the integrity of the cardiac vagus.

Patients and methods

The data were collected from selected patients in the series previously described (Bennett *et al.*, 1975, 1976a, b). Detailed investigations of autonomic nervous function had already been carried out, and on the basis of those findings patients were separated into two groups: in group 1 were 5 subjects (1 to 5) who had normal baroreflex sensitivities (Bennett *et al.*, 1976a), and who showed a bradycardia after the Valsalva manoeuvre (Bennett *et al.*, 1976a) and on immersing the face in water (Bennett *et al.*, 1976b). These responses indicate that the vagal efferent control of the heart was intact. The 8 subjects (6 to 13) in group 2 showed none of the above responses, and were judged to have lost vagal control of the heart. There were no significant differences between the mean age or systemic blood pressure of the two groups, but the

mean time since diagnosis of diabetes was 5.2 years for group 1 and 11.3 years for group 2.

SHORT-TERM MONITORING OF HEART RATE

During the previous investigations, continuous electrocardiograms had been recorded onto magnetic tape. The recordings were made while the subject rested supine for 5 minutes, while standing quietly for 5 minutes, and then during a period in which the subject breathed as deeply as possible in time to fixed instructions from one of the experimenters. The tapes were replayed, in real time, through a Devices 275 instantaneous ratemeter, modified to give a voltage output proportional to the R-R interval. In order to ensure reliable triggering of the meter, the signal was first fed through a band pass filter (Barr and Stroud EF 40), adjusted as required by inspection of the filtered and unfiltered signals. The R-R intervals measured were recorded on punched paper tape using a low-frequency data logging system (Fitton *et al.*, 1972); and the tape was fed into a PDP8/L computer programmed to calculate the mean and standard deviation of the R-R interval and to construct a histogram of the latter. Though the subjects were in sinus rhythm during the recordings, occasional ectopic beats and excessive signal noise were excluded from the analysis by visual inspection of the R-R interval data and subsequent adjustment of the acceptable limits for normal R-R intervals.

LONG-TERM MONITORING OF HEART RATE

Some 10 to 12 months after the clinic investigations continuous electrocardiograms were recorded from 6 subjects (2 to 4 in Group 1, and 8, 10, and 11 in Group 2) during unrestricted activity over 24 hours, using body-borne tape recorders (Oxford Instruments Medilog recorder Type 4-24). The subjects also wore a pedometer device on one foot; this device distinguishes between sustained activity, intermittent activity, and standing (Barber *et al.*, 1973). The voltage output from the pedometer was fed onto another channel of the tape recorder. Subjects were also asked to fill in diary cards giving specific details of activities and times.

The tapes were replayed at 25 times real time using an Oxford replay unit (Oxford Instruments Type MAP E). The electrocardiographic output from this unit was filtered and passed through a pulse interval timer. Continuous R-R interval and the pedometer output were recorded using an ultraviolet monitor (S.E. Labs). Visual inspection of this recording, together with reference to the diary cards, made it possible to identify periods during which specific activities were being undertaken. The R-R intervals during these periods were re-

coded onto digital magnetic tape through a PDP8/L computer and analogue to digital converter. Subsequent analysis provided an R-R interval histogram and the mean and standard deviation for the R-R intervals during specified activities.

Results

During deep breathing, subjects in group 1 and group 2 showed changes in R-R interval that were clearly distinguishable by eye (Fig. 1). For the two subjects in Fig. 1, the difference between the R-R interval traces and the corresponding R-R interval histograms are particularly clear. The subject from group 1 (on the left) had a mean R-R interval of 706 ms, with a standard deviation of 41.8 ms; the corresponding values for the subject in group 2 (on the right) were 752 ms and 15.9 ms, respectively. The histograms clearly show these differences, but examination of the R-R interval trace for the subject in group 2 indicates that some of the R-R interval variation in this case was caused by a period of rapid heart action unrelated to respiration (see below).

There was no overlap between R-R interval variation for groups 1 and 2 during deep breathing (Fig. 2; Table), in spite of the fact that the 3 subjects in group 2 who showed the highest R-R interval variation did so because tachycardia occurred during the manoeuvre (Fig. 2). Also, despite this, the differences between groups 1 and 2 were significant (Table).

Fig. 1 Continuous recordings of R-R intervals and R-R interval histograms for a subject from group 1 and a subject from group 2 during deep breathing. Examination of the trace indicates that some of the variability in the latter case is caused by a change unrelated to respiration.

Table Summary of analysis of R-R intervals (ms) recorded either in diabetic clinic (short-term observations) or under unrestricted conditions (long-term observations)

	Short-term observations					
	Deep breathing R-R interval (mean $\pm$ 1SD)	SD of R-R interval (mean $\pm$ 1SD)	Lying R-R interval (mean $\pm$ 1SD)	SD of R-R interval (mean $\pm$ 1SD)	Standing R-R interval (mean $\pm$ 1SD)	SD of R-R interval (mean $\pm$ 1SD)
Group 1 (subjects 1 to 5)	664 $\pm$ 72	39.3 $\pm$ 6.1	666 $\pm$ 66	28.8 $\pm$ 8.1	602 $\pm$ 43	24.6 $\pm$ 6.5
Group 2 (subjects 6 to 13)	702 $\pm$ 72	12.6 $\pm$ 4.8***	693 $\pm$ 76	15.0 $\pm$ 10.2*	578 $\pm$ 70	16.5 $\pm$ 8.8
	Long-term observations					
	Sleeping		Sitting		Active	
Group 1 (subjects 2 to 4)	799 $\pm$ 56	36.2 $\pm$ 26.7	774 $\pm$ 77	28.2 $\pm$ 15.5	646 $\pm$ 108	47.5 $\pm$ 11.7
Group 2 (subjects 8, 10, 11)	758 $\pm$ 108	17.7 $\pm$ 0.6	714 $\pm$ 100	13.7 $\pm$ 2.6	622 $\pm$ 154	9.9 $\pm$ 3.8**

*0.05 > P > 0.025; **0.01 > P > 0.005; ***0.001 > P for the differences between corresponding values for groups 1 and 2 by Student's unpaired t test.

Fig. 2 Mean R-R intervals and standard deviations of R-R intervals for the 5 subjects in group 1 (○) with functional cardiac vagi, and the 8 subjects in group 2 (■) with no vagal control of the heart. Note the clear separation of the standard deviations of R-R intervals for subjects in the 2 groups during deep breathing, and the increasingly greater overlap between subjects in the two groups while lying and standing.

The differences in R-R interval variation for groups 1 and 2 were less obvious when the subjects were resting lying down (Fig. 2; Table), and were insignificant when the subjects were standing (Fig. 2; Table).

Analysis of the long-term recordings indicated a significant difference in R-R interval variability for groups 1 and 2 during sustained activity (Table), but different subjects undertook different activities. The problems associated with interpretation of R-R interval variability during long-term recordings are exemplified by the finding that during sleep, subjects with absence of cardiac vagal control could show small or large standard deviations (Fig. 3).

Fig. 3 R-R interval recordings and histograms for a single subject in group 2; the observations were made 1 hour apart during a single night's sleep. The data on the left have a mean R-R interval of 779 ms and a standard deviation of 17.2 ms; the corresponding values for the data on the right are 792 ms and 50.2 ms. Note that the variability in the latter case arises from a series of bouts of rapid heart action. The histogram classes are 20 ms.

In some subjects baroreflex sensitivity had previously been assessed from the slope of the linear regression of R-R interval on systolic blood pressure during a rise in the latter by intravenous injection of phenylephrine (Bennett *et al.*, 1976a). In those subjects for whom baroreflex sensitivities were available it was found that the relation between baroreflex sensitivity and the standard deviation of the R-R interval during quiet standing (cf Murray *et al.*, 1975) was less close than the relation between

Fig. 4 The relations between baroreflex sensitivities and standard deviations of R-R intervals during quiet standing (cf. Murray *et al.*, 1975) and between baroreflex sensitivity and the mean difference between peak and trough heart rates during deep breathing. The prediction of baroreflex sensitivity is more reliably made in the latter case; group 1 subjects ($\circ$), group 2 subjects ($\blacksquare$).

baroreflex sensitivity and heart rate variability (see methods) during deep breathing (Fig. 4).

Discussion

Murray *et al.* (1975) concluded that reduction of R-R interval variation during quiet standing showed 'damage to the autonomic pathways controlling heart rate regulation' in subjects with diabetes mellitus. In the present study, however, there were several instances in which it was not possible to distinguish between subjects with different degrees of vagal impairment using the method suggested by Murray *et al.* (1975). This is in clear distinction to the pronounced differences in R-R interval variation shown by such subjects during deep breathing. It seems probable that cardiac vagal function is impaired in many diabetics (Wheeler and Watkins, 1973; Bennett *et al.*, 1975, 1976a, b; Lloyd-Mostyn and Watkins, 1975). Thus it seems to be logical to quantify this impairment on the basis of manoeuvres that elicit vagal efferent activity. The close relation between baroreflex sensitivity and heart rate variability during deep breathing (Hosking *et al.*, 1976), and the poor relation between baroreflex sensitivity and the standard deviation of R-R interval during quiet standing (Fig. 4) indicates that our previous procedure may be the most reliable way of assessing vagal control of the heart.

The present observation that diabetics with little cardiac vagal function could show obvious R-R interval variation, indicates that other factors can influence the heart in such a way as to obscure vagal dysfunction. In order to discern such a loss in the absence of a specific manoeuvre likely to show it up,

calculation of the standard deviation of the R-R interval (Murray *et al.*, 1975) may be misleading, and a more reasonable approach would be a Fourier analysis with identification of the components in R-R interval variability caused by specified inputs (Sayers, 1971, 1973).

Although it appeared that it was possible to distinguish between subjects with and without vagal function from the continuous R-R interval recordings during unrestricted activity, we suggest that, in general, the problem can be investigated most reliably in the short-term by measuring variability in heart rate during deep breathing.

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