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RR interval variations in young male diabetics

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The beat-to-beat (RR interval) variation in resting heart rate was used to detect possible autonomic nerve damage in a group of 42 young asymptomatic male diabetics, employing a sensitive electrocardiographic computer technique.

Compared with 25 age-matched controls, the diabetics showed both a significantly smaller mean RR interval ($P < 0.005$) and less RR interval variation ($P < 0.001$). Whereas only 4 of the diabetic subjects had shorter mean RR intervals, 22 (52%) of the diabetics had RR interval variations that were less than any of the normal subjects.

This reduction in heart rate variation has not been previously reported in diabetics without clinical features of autonomic neuropathy and might provide a sensitive method of assessing early autonomic nerve involvement in diabetes.

Autonomic neuropathy is a well-recognized complication of diabetes and though the onset and insidious progress is such that it may be unrecognized in its earlier stages, symptom-free diabetics can nevertheless be shown to have abnormalities of both peripheral motor nerve conduction (Gregerson, 1967) and autonomic function (Sharpey-Schafer and Taylor, 1960; Ewing *et al.*, 1974). In the later stages of autonomic neuropathy, even though the progress and severity are variable, tests of cardiovascular reflex function correlate well with symptoms and signs of the disorder (Ewing *et al.*, 1973).

The present study was designed to assess a further test of cardiovascular reflex function, the beat-to-beat (RR interval) variation in heart rate, using a sensitive electrocardiographic computer technique, in a group of young diabetic subjects free of symptoms of autonomic neuropathy, as a possible method of detecting autonomic nerve damage in an early and possibly still reversible phase.

Patients and methods

The subjects were 42 male diabetics, aged between 20 and 35 years (mean 29.4 years), with a wide range of duration of diabetes (5 to 27 years, mean 12.9 years), who were all insulin-dependent and free from any of the more obvious clinical features of diabetic autonomic neuropathy, such as postural hypotension, intermittent nocturnal diarrhoea, hypoglycaemic unawareness, or impotence associated with these other features. All were within 10 per cent of their standard body weight and normotensive (systolic blood pressure below 150 mmHg (20.0 kPa), diastolic blood pressure below 90 mmHg (12.0 kPa)) and in sinus rhythm. None had clinical evidence of ischaemic heart disease as detected by a history of angina (Rose and Blackburn, 1968), standard exercise electrocardiography (Master and Rosenfeld, 1961), or coronary artery intimal calcification, as detected by radiological screening (Oliver *et al.*, 1964); all had fasting plasma cholesterol and triglyceride levels within the normal range. Thirteen patients had evidence of diabetic retinopathy (7 background, 6 proliferative), 2 had signs of peripheral neuropathy (absent knee and ankle jerks), and 5 had persistent proteinuria. The diabetics were compared with 25 age-matched male control subjects who were likewise non-obese, normotensive, and had no evidence of ischaemic heart disease.

Electrocardiograms were recorded in each subject under identical resting conditions before they proceeded to an exercise test, the results of which have been published elsewhere (Campbell *et al.*, 1975). The tests were carried out at the same time of day on each subject, approximately one and a half hours after the midday meal. The subjects stood quietly for at least 10 minutes before the resting heart rate was recorded on magnetic tape for approximately 4 minutes. Each subject's electrocardiogram was later fed at high speed (×60) from the previously recorded tape into an arrhythmia computer for accurate timing of the RR intervals. Details of the electrocardiographic recording technique and the arrhythmia computer have been previously described (Neilson and Vellani, 1972). Timing signals supplied by the computer were routed via an interface unit into a multichannel analyser where histograms of the RR intervals of each subject were formed. The data of all histograms were printed onto paper tape for calculation on a digital computer of the mean RR interval and RR

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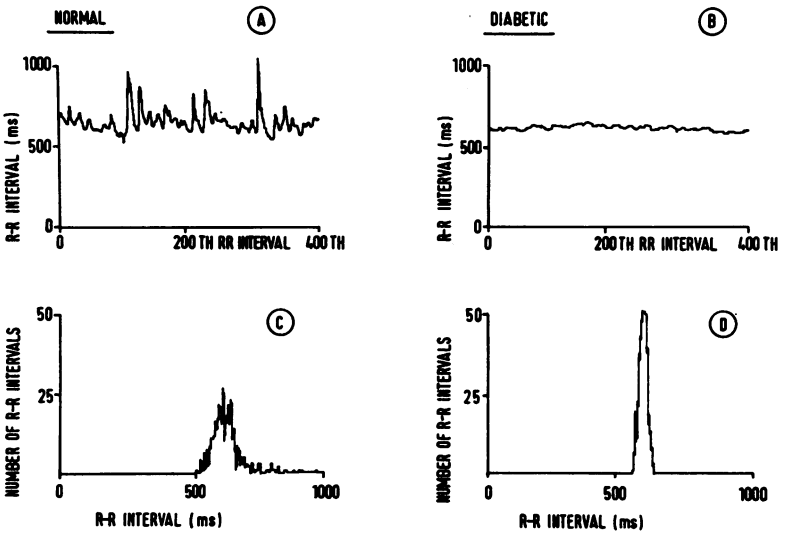

FIG. 1 *Instantaneous RR interval plots and RR interval histograms from a normal and a diabetic subject. A) Normal and B) diabetic: instantaneous RR interval plots. C) Normal and D) diabetic: RR interval histograms.*

interval variation. The latter was defined as the standard deviation of the RR interval distribution for each subject; the standard deviation was used because it gave a recognized measure of the variation about the mean of the complete 4-minute sample. As a check that the 4 minutes of resting electrocardiograms contained no significant trends in the mean RR interval, which would have invalidated the calculation of standard deviation, plots of instantaneous RR intervals were also obtained using the arrhythmia computer and the analyser. The group results are expressed in milliseconds as mean $\pm$SD. Comparisons between the diabetics and normals were made using an unpaired 't' test.

Results

Fig. 1 shows typical results plotted directly from the multichannel analyser for an individual normal subject, and a diabetic subject. It was possible to observe a smaller RR interval variation in about half of the diabetic subjects when compared with the normal controls, and calculation confirmed this impression. Fig. 2 and 3 show the individual data for mean RR interval and RR interval variation for the 25 normal and 42 diabetic subjects. Twenty-two (52%) of the diabetics had an RR interval variation that was less than any of the normal subjects, and 18 (43%) were more than 2 SDs below the mean RR interval variation for the normal group; whereas only 4 (9.5%) of the diabetic subjects were more than 2 SDs below the mean normal value for the RR interval (Fig. 3).

As a group the diabetics had a significantly shorter mean RR interval (diabetics 657 ± 89 ms; normals 736 ± 97 ms; $P < 0.005$), and less R R interval variation (diabetics 41 ± 25 ms; normals 63 ± 14 ms; $P < 0.001$). The duration of diabetes was not significantly correlated with either the mean RR interval ($r = -0.038$, NS) or the RR interval variation ($r = -0.098$, NS).

Fig. 4 summarizes the RR interval variation in the normal subjects, all diabetics, and the diabetics with proliferative retinopathy. The 6 diabetics with proliferative retinopathy had very small RR interval variations (mean 13 ± 7 ms) and their mean RR interval was also reduced (mean 548 ± 67 ms).

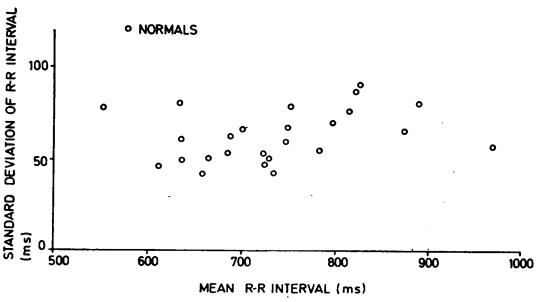

FIG. 2 *Mean resting RR interval and RR interval variation in 25 normal male subjects. RR interval variation was defined as the standard deviation of the RR interval distribution for each subject.*

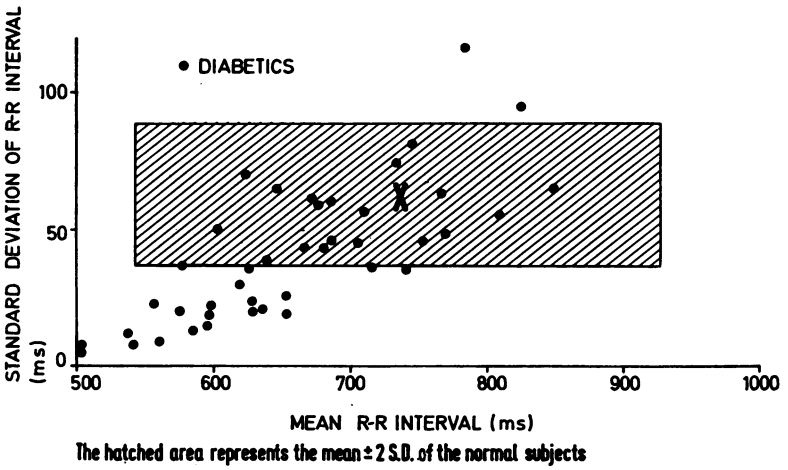

FIG. 3 *Mean resting RR interval and RR interval variation in 42 male diabetic subjects. The cross represents the mean values for the normal group.*

Discussion

These results show that not only was there an increased mean resting heart rate (as measured by RR interval) in these diabetic subjects but also a striking reduction in heart rate variation when compared with age-matched normal controls. An increased resting heart rate is well recognized in diabetics, and has been noted before both by us and others (Campbell *et al.*, 1975; Ewing *et al.*, 1974; Wheeler and Watkins, 1973), but reduction in the heart rate variation has only previously been reported in diabetics with symptomatic autonomic neuropathy (Wheeler and Watkins, 1973). The present study, however, shows that the reduced RR interval variation can be present even without any clinical features of autonomic neuropathy. It is perhaps noteworthy that though all subjects were free from symptoms, those with proliferative retinopathy had the greatest reduction in heart rate variation.

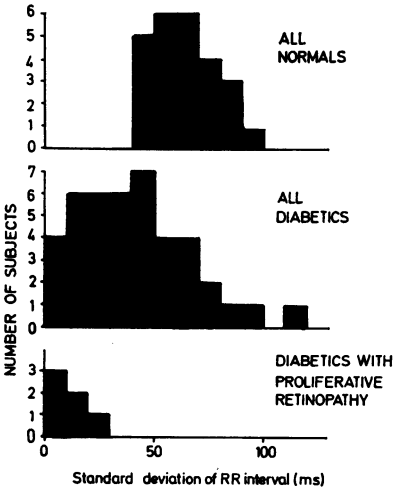

FIG. 4 *Distribution of RR interval variation in normal subjects, all diabetics, and diabetics with proliferative retinopathy.*

In their recent study, Wheeler and Watkins (1973) demonstrated that there was loss of RR interval variation, measured as peak-to-trough instantaneous heart rate, in diabetics with clinical features of autonomic neuropathy and they showed that loss of heart rate variation was caused by vagal denervation of the heart. They were, however, unable to detect any differences between diabetics without autonomic neuropathy and their normal subjects. The results of the present study, using different methods of analysis, have failed to confirm this latter finding, and clearly show that half the diabetics studied had an RR interval variation that was less than any of the normal subjects, thus demonstrating that damage to the autonomic pathways controlling heart rate regulation can occur without any symptoms.

It is not possible from these data alone to draw any conclusions about the relation between the mean RR interval and RR interval variation in the two groups, except to observe that they correlated closely in the 42 diabetics ($r = 0.766$, $P < 0.001$) but not in the 25 normal subjects ($r = 0.315$, NS). Whatever the meaning of this relation, it can be seen from Fig. 3 that only 4 diabetics fell more than 2 SDs away from the mean value for resting RR interval in the normal subjects, in contrast to the 18 who were more than 2 SDs below the mean RR

interval variation for the normal group. Thus it appears that RR interval variation is a better indicator of autonomic nerve damage than RR interval.

Peripheral motor nerve conduction velocities have been found to be abnormal in early and asymptomatic diabetics (Gregerson, 1967), and likewise the responses to other tests of autonomic function, such as the Valsalva manoeuvre (Sharpey-Schafer and Taylor, 1960) and sustained handgrip (Ewing *et al.*, 1974) may be abnormal before symptoms have developed. Thus objective evidence of both peripheral and autonomic nerve damage has been demonstrated in the absence of symptoms; measurement of RR interval variation provides another sensitive method of detecting autonomic nerve involvement. It has not yet been compared by us with other recognized tests of autonomic function, such as the Valsalva manoeuvre and sustained handgrip tests, but studies are currently in progress. One obvious advantage over these two tests is that it does not require patient co-operation beyond keeping still for a few minutes, whereas the other two tests are effort-dependent.

From the results that have been obtained in this study, it appears that autonomic nerve damage is more widespread than was previously thought, and though at present no curative therapy is available for autonomic or peripheral nerve damage, measuring the RR interval variation appears to be a sensitive non-invasive method of detecting autonomic neuropathy in its early stages. This test may enable the natural history and progress of autonomic nerve involvement to be more clearly defined.

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