# Abnormalities of Ambulatory 24-hour Heart Rate in Diabetes Mellitus

D. J. EWING, D. Q. BORSEY, P. TRAVIS, F. BELLAVERE, J. M. M. NEILSON, AND B. F. CLARKE

**SUMMARY**

**Twenty-one normal subjects and 64 diabetics with varying severity of autonomic damage underwent 24-h ambulatory EKG monitoring. No diabetics had the "sick sinus syndrome," and the frequency of arrhythmias was no higher than in the normal subjects. The diabetics had higher mean hourly heart rates, and with increasing autonomic damage there was reduction in diurnal heart rate variation. The mean waking and sleeping heart rates were higher in the diabetics. The maximum heart rates were not significantly different, but the minimum heart rates were significantly higher in the diabetics.**

**These previously unrecognized abnormal 24-h heart rate patterns provide further evidence of damage to the heart rate-controlling mechanisms in diabetes mellitus. DIABETES 32:101–105, February 1983.**

Diabetics have faster resting heart rates and less heart rate variation than normal subjects, and these changes are related to autonomic neuropathy.[1–3] Observations of heart rate in diabetics have usually been made over short time periods, while diurnal heart rate variation has hitherto received scant attention. This study was designed to analyze the changes in heart rate during 24-h ambulatory monitoring in diabetics with different degrees of autonomic nerve damage.

## SUBJECTS

Twenty-one normal, healthy male volunteers, aged 20–65 yr (mean, 39 yr), and 64 diabetics (61 male and 3 female), aged 25–69 yr (mean, 45 yr), were studied. Fifty-five diabetics were on insulin treatment and nine on oral hypoglycemic agents. None of the diabetics was on treatment for hypertension, had cardiac failure or respiratory abnormalities, or was on any drug known to influence the autonomic nervous system. Ten diabetics were excluded from the major part of the analysis (heart rate changes); seven were excluded for technical reasons: one had atrial fibrillation, and two had multiple ventricular ectopic beats.

The remaining 54 diabetics were grouped according to their response to a standardized battery of cardiovascular autonomic function tests, as we have previously described in detail.[1,4,5] Twenty patients (group I) had normal tests ("normal"); 10 patients (group II) had abnormalities indicating cardiac parasympathetic damage ("abnormal PS"); the remaining 24 (group III) had abnormalities both of parasympathetic and sympathetic function ("abnormal PS + S"). The mean ages of group I [42 yr (25–69)], group II [48 yr (25–62)], and group III [44 yr (27–67)] were not significantly different. The mean duration of diabetes was shorter in group I [13 yr (4–31)] than in either group II [21 yr (10–38)] or group III [18 yr (1–39)].

## METHODS

The 24-h ambulatory tape recording of a single lead EKG together with a calibration reference frequency was obtained using a Medilog I recorder (Oxford Medical Systems Ltd., England) while the subject undertook his normal daily activities. Each recording was then scrutinized for ventricular ectopic beats and other arrhythmias by a trained EKG technician using a Pathfinder EKG analyzer (Reynold's Medical Ltd., England),[6] from which a continuous chart record of the heart rate over the 24 h was obtained. Later mean hourly heart rates were measured visually from the chart recording (approximate 95% confidence limits ± 5 beats/min).

Each subject recorded a diary of activities including the times of going to bed and getting up. The "waking" and "sleeping" periods of the 24-h record were further analyzed, and the mean heart rate for each period calculated. There were no significant differences in the lengths of time awake or asleep between the four groups.

From the University Departments of Medicine, Medical Physics and Medical Engineering, and the Diabetic and Dietetic Department, Royal Infirmary, Edinburgh, Scotland.
Address correspondence to Dr. D. J. Ewing, Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW, Scotland.
Received for publication 3 June 1982.

**Statistical analysis.** The hourly heart rate measurements for all individuals were subjected to an analysis of variance to determine whether there were significant differences between the four groups in the patterns of heart rate over the 24-h period.[7] The mean waking and sleeping heart rates were also submitted to statistical analysis, using Student's unpaired *t* test.

## RESULTS

**Rhythm.** All 21 normal subjects and all 64 diabetics except one (atrial fibrillation) were in sinus rhythm throughout the 24-h period. None of the diabetics had changes suggestive of the "sick sinus syndrome."

**Ectopic beats.** One normal subject and four diabetics had ventricular ectopic beats throughout the 24-h period, occurring at a frequency of at least 1/min. Occasional ventricular and supraventricular ectopic beats were seen in another 6 (29%) of the normals and 21 (33%) of the diabetics. The frequency of these occasional ectopic beats was approximately 1–2/h. There were no significant differences in their distribution between any of the four groups. One normal subject and one diabetic each had one run of five ventricular ectopic beats.

**24-h heart rate pattern.** There were no significant differences between the hourly heart rate patterns of the 15 normal subjects under 50 yr and those of the 6 older normal subjects. Figure 1 shows the mean hourly heart rate patterns of the normal and the three diabetic groups. All three diabetic groups had higher mean hourly heart rates; and as autonomic damage increased, there was a reduction in the normal diurnal heart rate variation. An analysis of variance with all four 24-h curves showed that there were significant differences in the overall heart rate patterns within the four groups. A second analysis between the individual groups showed where these differences occurred. The normal subjects were significantly different from group II ("abnormal PS") ($P < 0.01$) and group III ("abnormal PS + S") ($P < 0.01$) but not from the "normal" diabetics (group I).

When the heart rates were arbitrarily analyzed according to "day" (10 a.m.–10 p.m.) and "night" (10 p.m.–10 a.m.) periods, significant differences between the patterns of the four groups were confined to the "night" period, which showed statistically similar changes to the overall 24-h recordings. Although the heart rate patterns through the daytime period were similar in all four groups, the absolute levels of heart rate showed highly significant differences. There were no significant differences in the 24-h patterns when analyzed according to diabetic treatment.

**Mean waking and sleeping heart rates.** Figures 2 and 3 show the individual waking and sleeping heart rates and Table 1 shows the group data. The diabetics had higher mean heart rates than normals during waking and sleeping. Seventeen (31%) had mean waking heart rates and 27 (50%) mean sleeping heart rates at least two standard deviations above the normal mean value.

**Maximum and minimum heart rates.** Table 2 shows the group mean values for the individual maximum and minimum heart rates during the 24 h. The maximum heart rates of the diabetic groups were not significantly different from the normals, but the minimum heart rates were all significantly higher. There was no correlation between age and the maximum, minimum, or variation in heart rate in the normal subjects.

## DISCUSSION

Ambulatory heart rate monitoring has been widely applied to investigate cardiac rhythm. The heart rate pattern over 24 h has, however, received little attention except in normal subjects.[8–12] Bennett reported 11 selected diabetics in whom 24-h ambulatory heart rate was recorded but related the heart rates obtained only to activity, without considering the overall pattern.[13] Our results show an alteration in the heart rate pattern with increasing autonomic damage: reduction of the normal diurnal variation and the normal heart rate fall at night. At the same time, the mean heart rate was higher during the day in the diabetics, but the highest levels of heart rate achieved were similar in normal and diabetic subjects.

The differences in the diabetics were not accounted for by age. The normal subjects showed no differences in heart rate pattern as they got older; therefore, the EKG recordings were analyzed without taking age into account in the diabetics. Nor were the differences accounted for by the type of treatment. In addition, it is unlikely that these findings can be explained by differences of physical activity in the four groups, since all subjects were ambulatory, and the recordings were made during their usual daily activities. Moreover, the differences between the groups were mainly at night

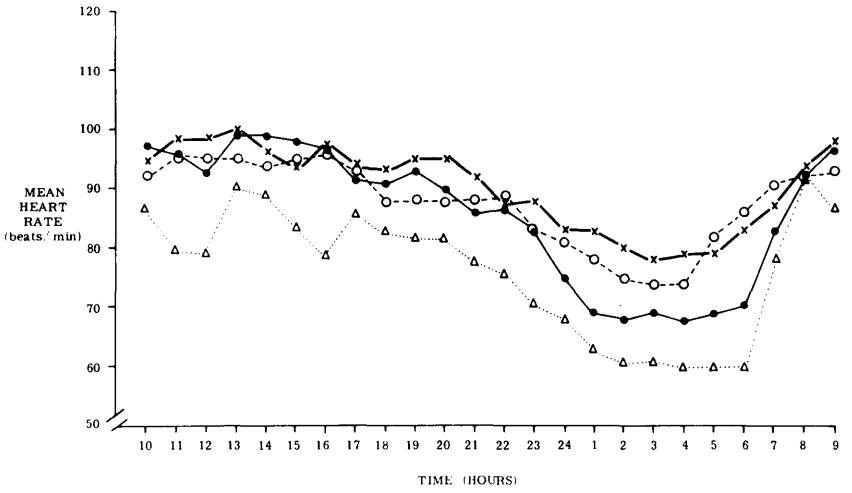


**FIGURE 1. Mean 24-h heart rate pattern in normal subjects (N = 21), △; and in the three diabetic groups: group I ("normal," N = 20), ●; group II ("abnormal PS," N = 10), ○; and group III ("abnormal PS + S," N = 24), X. Group mean hourly heart rate values are given.**

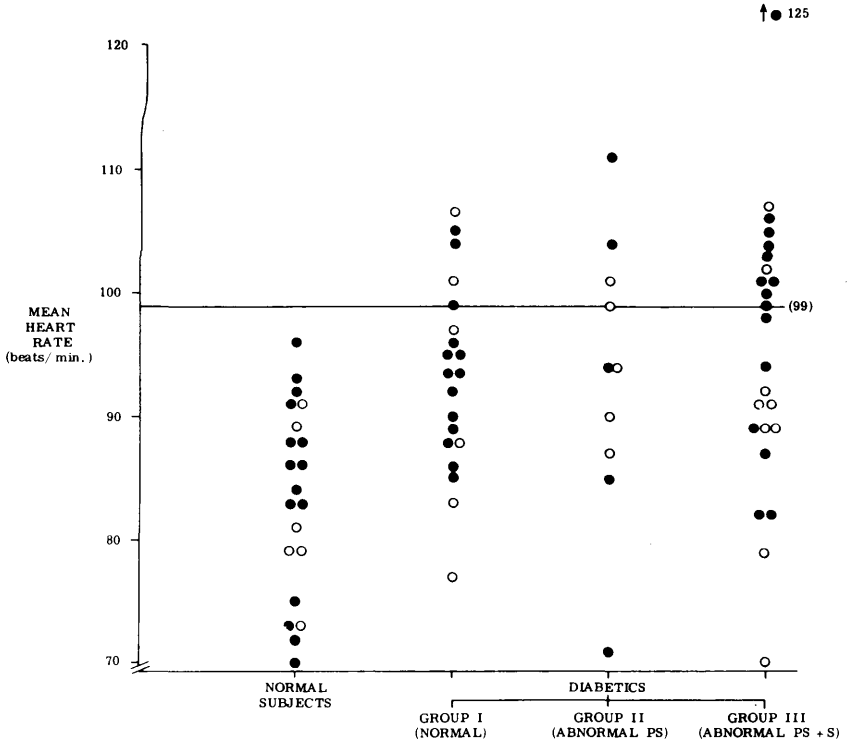


**FIGURE 2. Individual mean waking heart rates for the normal subjects and the three diabetic groups. The solid line at 99 beats/min represents two standard deviations above the mean value for all the normal subjects. ● = under 50 yr old; ○ = 50 yr old or over.**

during sleep. Instead, these findings can probably be explained by the various factors controlling the actual moment-to-moment heart rate. During the day both vagal and sympathetic influences operate, and with the onset of parasympathetic damage the heart rates of diabetics tend to rise.[3] There are other mechanisms of increasing heart rate, such as catecholamine secretion,[14] and this study shows that as the overall highest heart rate levels were similar in all four groups, the loss of autonomic function may be compensated for by other factors. At night, where the vagus is still operative and where there is minimal sympathetic activity, it is not surprising that in diabetics with vagal damage of groups II and III both the mean heart rate during sleep and the minimum recorded heart rates should be so much higher than those of normal subjects.

In diabetics direct damage to the sinus node and intra-

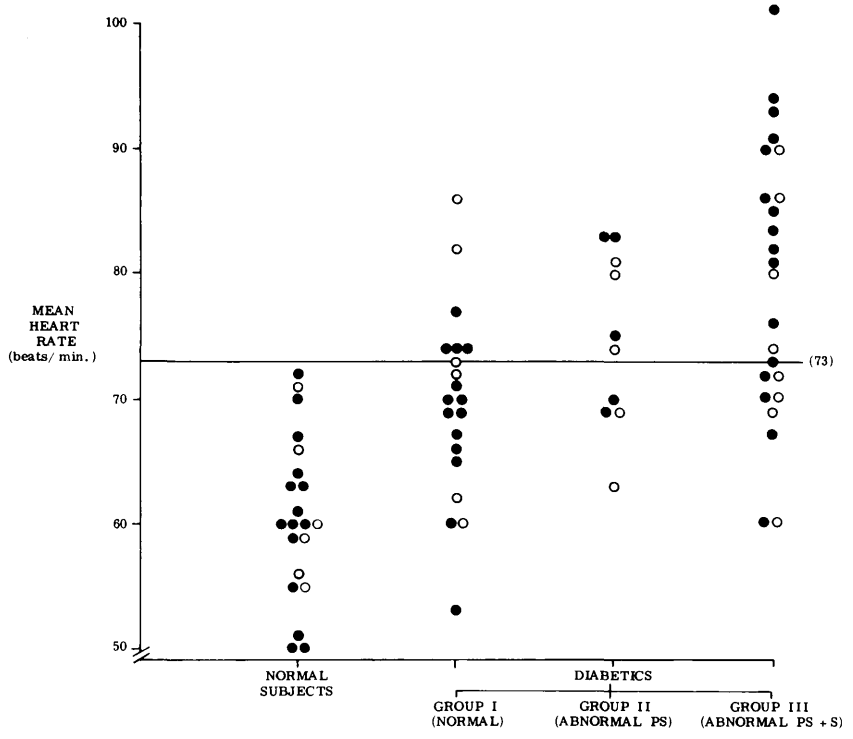


**FIGURE 3. Individual mean sleeping heart rates for the normal subjects and the three diabetic groups. The solid line at 73 beats/min represents two standard deviations above the mean value for all normal subjects. ● = under 50 yr old; ○ = 50 yr old or over.**

TABLE 1
Mean waking and sleeping heart rates (beats/min) in the normal and diabetic groups (mean ± SD)

| | No. | Mean waking heart rate | Mean sleeping heart rate | Difference (waking − sleeping heart rates) |
|---|---|---|---|---|
| Normals | 21 | 83 ± 8 | 61 ± 6 | 23 ± 6 |
| Diabetics | | | | |
| Group I ("normal") | 20 | 93 ± 7* | 70 ± 8* | 23 ± 6 |
| Group II ("abnormal PS") | 10 | 94 ± 11† | 75 ± 7* | 19 ± 8 |
| Group III ("abnormal PS + S") | 24 | 95 ± 11* | 79 ± 11* | 16 ± 7* |

Significantly different from normal group: *$P < 0.001$, †$P < 0.005$.

TABLE 2
Maximum and minimum heart rates (beats/min) in the normal and diabetic groups (mean ± SD)

| | No. | Maximum heart rate | Minimum heart rate | Difference (maximum − minimum heart rates) |
|---|---|---|---|---|
| Normals | 21 | 126 ± 20 | 53 ± 6 | 73 ± 19 |
| Diabetics | | | | |
| Group I ("normal") | 20 | 129 ± 13 | 61 ± 5* | 68 ± 13 |
| Group II ("abnormal PS") | 10 | 114 ± 10 | 66 ± 9* | 48 ± 9* |
| Group III ("abnormal PS + S") | 24 | 118 ± 14 | 71 ± 11* | 47 ± 13* |

Significantly different from normal group: *$P < 0.001$.

cardiac conducting pathways might occur, giving rise to a "sick sinus syndrome," but none of our diabetics had any EKG abnormalities[15] suggesting this condition. Diabetics also have a higher incidence of ischemic heart disease.[16] Only four of our patients had marked ventricular ectopic beats, and three of these were known to have coronary artery disease. Experimental autonomic denervation of the heart prevents arrhythmias,[17] and none of our patients had obvious rhythm disturbances. Less frequent ectopic beats occurred in about one-third of our normal and diabetic subjects, which is similar to the incidence in previously reported normal series.[15] We and others have described sudden, unexpected deaths in diabetics with autonomic neuropathy,[1,2] but the underlying mechanism has not been elucidated. The indirect evidence from this study on cardiac arrhythmias suggests that such arrhythmias are unlikely to be implicated.

"Persistent tachycardia" and "fixed heart rate" have been described in some diabetics with autonomic damage,[2,18] although without much substantive evidence. Among the diabetics in the present study who had a wide spectrum of autonomic damage, the heart rate remained above 90 beats/min throughout the 24 h in only one subject (in group III). Five other subjects, also in group III, had mean sleeping heart rates at or above this level, and it is clear that persistent tachycardia is not a common phenomenon. The completely "fixed heart rate" is equally uncommon. Only one subject (in group III) had a relatively fixed heart rate with a variation of 16 beats/min between the maximum and minimum recorded heart rates, and a further three (all in group III) had variations of less than 35 beats/min during the 24 h. Lloyd-Mostyn and Watkins described one such subject among 13 diabetics with severe autonomic neuropathy.[19]

This study thus demonstrates the progressive loss of the normal 24-h heart rate pattern in diabetics with increasing degrees of autonomic damage, with the loss of the normal day-to-night variation, slightly faster mean waking heart rate, and a much faster than normal mean sleeping heart rate. We conclude that these previously unrecognized abnormalities provide further evidence of damage to the heart rate-controlling mechanisms in diabetics with autonomic neuropathy.

**ACKNOWLEDGMENTS**

We thank Dr. R. Prescott and W. Adams of the Medical Computing and Statistics Unit, University of Edinburgh, for their help in the statistical analysis. Dr. D. J. Ewing holds a Wellcome Trust Senior Lectureship.

This work has been supported by a grant from the Scottish Home and Health Department.

**REFERENCES**

[1] Ewing, D. J., Campbell, I. W., and Clarke, B. F.: Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann. Intern. Med. *92*:308–11, 1980.

[2] Watkins, P. J., and Mackay, J. D.: Cardiac denervation in diabetic neuropathy. Ann. Intern. Med. *92*:304–307, 1980.

[3] Ewing, D. J., Campbell, I. W., and Clarke, B. F.: Heart rate changes in diabetes mellitus. Lancet *1*:183–86, 1981.

[4] Ewing, D. J.: Cardiovascular reflexes and autonomic neuropathy. Clin. Sci. Mol. Med. *55*:321–27, 1978.

[5] Clarke, B. F., Ewing, D. J., and Campbell, I. W.: Diabetic autonomic neuropathy. Diabetologia *17*:195–212, 1979.

[6] Neilson, J. M. M.: High speed analysis of ventricular arrhythmias from 24 hour recordings. *In* Computers in Cardiology, Institute of Electrical and Electronic Engineers Inc., New York, 1974, pp. 55–61.

[7] Snedecor, G. W., and Cochran, W. G.: Statistical Methods, 6th edit. Iowa State University Press, Iowa, 1967, pp. 229–380.

[8] Clarke, J. M., Hamer, J., Shelton, J. R., Taylor, S., and Venning, G. R.: The rhythm of the normal human heart. Lancet *2*:508–12, 1976.

[9] Raftery, E. B., and Cashman, P. M. M.: Long-term recording of the electrocardiogram in a normal population. Postgrad. Med. J. *52* (Suppl. 7):32–37, 1976.

[10] Brodsky, M., Wu, D., Denes, P., Kanakis, C., and Rosen, K. M.: Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. Am. J. Cardiol. *39*:390–95, 1977.

[11] Camm, A. J., Evans, K. E., Ward, D. E., and Martin, A.: The rhythm of the heart in active elderly subjects. Am. Heart J. *99*:598–603, 1980.

[12] Sobotka, P. A., Mayer, J. H., Bavernfeind, R. A., Kanakis, C., and Rosen, K. M.: Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in young women without apparent heart disease. Am. Heart J. *101*:753–59, 1981.

[13] Bennett, T., Riggott, P. A., Hosking, D. J., and Hampton, J. R.: Twenty-four hour monitoring of heart rate and activity in patients with diabetes mellitus: a comparison with clinic investigations. Br. Med. J. *1*:1250–51, 1976.

[14] Christensen, N. J.: Plasma noradrenaline and adrenaline measured by isotope-derivative assay. A review with special reference to diabetes mellitus. Dan. Med. Bull. *26*:17–36, 1979.

[15] Winkle, R. A.: Current status of ambulatory electrocardiography. Am. Heart J. *102*:757–70, 1981.

[16] Kannell, W. B., and McGee, D. L.: Diabetes and cardiovascular disease. The Framingham study. JAMA *241*:2035–2038, 1979.

[17] Ebert, P. A., Vanderbeek, R. B., Allgood, R. J., and Sabiston, D. C.: Effect of chronic cardiac denervation on arrhythmias after coronary artery ligation. Cardiovasc. Res. *4*:141–47, 1970.

[18] Page, M. M., and Watkins, P. J.: The heart in diabetes: autonomic neuropathy and cardiomyopathy. Clin. Endocrinol. Metab. 6:377–88, 1977.

[19] Lloyd-Mostyn, R. H., and Watkins, P. J.: Defective innervation of heart in diabetic autonomic neuropathy. Br. Med. J. *3*:15–17, 1975.