

# Cardiac Denervation in Diabetes

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## Summary

**Evidence for vagal denervation of the heart as a feature of diabetic autonomic neuropathy has been obtained by monitoring beat-to-beat variation in heart rate. Nine diabetics with autonomic neuropathy were assessed; each showed a marked reduction or absence of beat-to-beat variation in comparison with controls. Beat-to-beat variation in normal subjects is abolished by parasympathetic blockade but unaffected by sympathetic blockade. These findings suggest that spontaneous vagal denervation of the heart was present in the cases studied. Measurement of beat-to-beat variation provides a simple test whereby cases of autonomic neuropathy can be screened for cardiac involvement.**

## Introduction

Autonomic neuropathy in diabetics may include abnormalities of cardiovascular reflexes. The effect of the Valsalva manoeuvre is often abnormal in patients with peripheral neuropathy (Sharpey-Schafer and Taylor, 1960; Nathanielsz and Ross, 1967) but interpretation of the results of this test is extremely complex. A resting tachycardia has occasionally been observed (Keen, 1959) and is probably due to diminished vagal tone. Direct evidence for cardiac denervation, however, has hitherto been difficult to obtain.

In recent years more detailed studies of heart rhythm have become possible using instantaneous ratemeters. These instruments record the heart rate on a beat-to-beat basis. Sinus arrhythmia is clearly shown and is described in this paper as beat-to-beat variation of heart rate. This is controlled through the autonomic nervous system. The present study was undertaken to investigate whether beat-to-beat variation was altered in diabetics with autonomic neuropathy.

## Patients and Methods

Nine diabetics with autonomic neuropathy were studied (table 1); five were men and four were women and their ages ranged from 23 to 46 years. All were on insulin and had diabetes of long duration. Only two patients were receiving other medication—one on indomethacin and one on frusemide. All were severely handicapped by peripheral neuropathy and retinopathy. Five had proteinuria. In all cases E.C.G. showed sinus rhythm, and only two patients had minor ischaemic changes. None had ever been in heart failure or suffered angina.

Two control groups were studied—(a) 25 healthy non-diabetic subjects and (b) 15 diabetics requiring insulin but without evidence of peripheral or autonomic neuropathy.

The E.C.G. in each case was obtained from two electrodes placed on the chest and recorded through the Hewlett-Packard 8020A heart rate monitor. This monitor detects each R wave and displays the heart rate in beats per minute for each successive R-R interval. The recordings were made with the subjects lying on a couch in a quiet room. Observations of the heart rate were made for 20 minutes with the patient breathing quietly, and then for one minute during a series of deep inspirations and expirations at a rate of six to eight breaths a minute. Two measurements were made from these records—the mean heart rate during quiet breathing and the differences between the maximum and minimum heart rates with deep breathing (fig. 1).

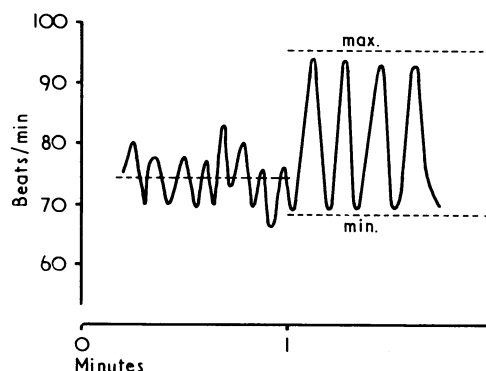


FIG. 1—Recording from instantaneous ratemeter shown diagrammatically. Each "wave" is composed of several heart beats. Beat-to-beat variation, measured as difference between maximum and minimum heart rates, shows normal increase with deep breathing. Mean heart rate during quiet breathing is 74 beats/min. During deep breathing heart rate ranges between maximum of 95 beats and minimum of 68 beats/min and beat-to-beat variation is 27. When beat-to-beat variation was inconstant average readings were taken.

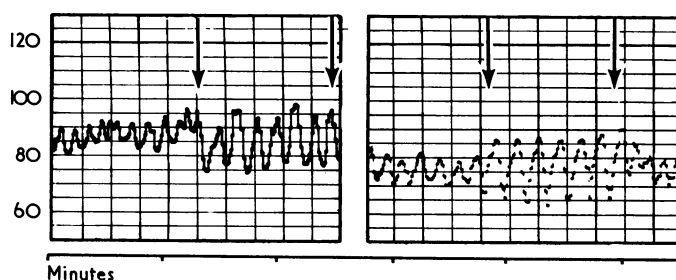


FIG. 2—Recordings from two normal subjects aged 35 and 42 years. Arrows mark points between which deep breaths were taken. Time scale is shown in one-minute divisions. Heart rate in beats/min is shown on each record.

## Results

**Normal Subjects.**—The typical appearance of cardiac beat-to-beat variation with quiet and deep breathing is shown in fig. 2. Beat-to-beat variation was approximately doubled during deep breathing. There was a diminution in beat-to-beat variation with age (see fig. 4).

**Diabetics without Autonomic Neuropathy.**—Patterns of beat-to-beat variation were similar to those observed in the normal subjects.

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TABLE I—Details of Patients Studied

Case No.	Sex	Age	Duration of Diabetes (Years)	Peripheral Neuropathy*	Diabetic Diarrhoea	Impotence	Gustatory Sweating†	Postural Fall of B.P. (mm Hg)	Retinopathy	Proteinuria	Valsalva‡
1	F.	37	33	Severe	+	0	+	20	R.P.	0	Not done
2	M.	41	30	Severe	+	+	++	40	R.P. (blind)	+	Abnormal
3	M.	42	24	Severe	+	+	++	35	R.P.	+	Abnormal
4	M.	37	21	Mild	+	N.K.	++	20	N.V.	0	Normal
5	F.	23	18	Severe	0	0	0	12	R.P.	+	Abnormal
6	F.	26	16	Mild	+	0	0	50	N.K.	+	Abnormal
7	F.	27	16	Mild	0	0	0	10	R.P. (blind)	+	Not done
8	M.	25	12	Severe	+	+	0	40	N.V.	0	Abnormal
9	M.	46	12	Severe	0	+	0	32	H.	0	Abnormal

\*All patients with mild neuropathy had absent ankle jerks. Those with severe neuropathy had all had sepsis of the feet, and five of them had had various operations on their feet; they also had appreciable upper limb neuropathy.  
†Gustatory sweating is a feature of autonomic neuropathy (Watkins, 1973).  
‡Abnormal Valsalva effects were characterized by absence of reflex bradycardia after cessation of blowing; other abnormalities were also present in some cases.  
N.K. = Not known. R.P. = Retinitis proliferans. N.V. = Neovascularization. H. = Haemorrhages.

**Diabetics with Autonomic Neuropathy.**—There was a striking reduction or absence of beat-to-beat variation in these patients with both quiet and deep breathing (figs. 3 and 4).

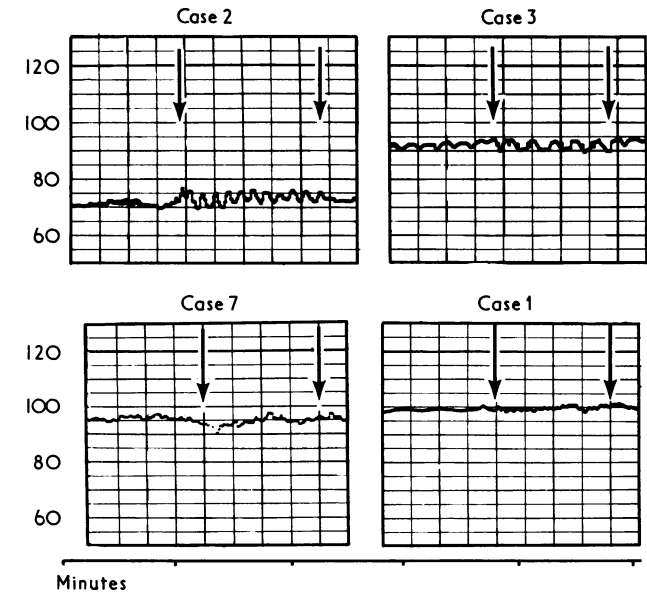


FIG. 3—Recordings from four patients with autonomic neuropathy. (Presentation same as in fig. 2.) Arrows mark points between which deep breaths were taken.

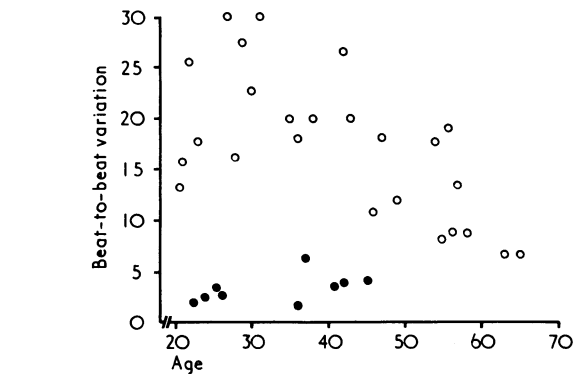


FIG. 4—Degree of beat-to-beat variation during deep breathing in 25 healthy subjects (O) and 9 cases of autonomic neuropathy (●). Beat-to-beat variation is defined in fig. 1.

Discussion

The loss of beat-to-beat variation of heart rate during both quiet and deep breathing in the diabetics with autonomic

neuropathy was probably the result of vagal denervation of the heart, though diminished afferent responses cannot be discounted. There was further evidence of a vagal defect in these patients—namely, the high resting heart rates that were found in some cases (fig. 5), the failure of the heart to accelerate normally after intravenous atropine (table II), and the absence of reflex bradycardia after the Valsalva manoeuvre (table I).

TABLE II—Increase of Heart Rate in response to 1.8 mg of Intravenous Atropine\*

Case No.	1	2	3	4	5	6	8	9
Increase in beats/min	12	12	1	8	8	0	0	17

\*In normal subjects the increase in heart rate is more than 20 beats/min (Chamberlain et al. 1967).

Complex reflexes are responsible for normal beat-to-beat variation. Respiration is the most important stimulus (Clynes, 1960), and changes in the depth and rate of respiration will alter this effect (Angelone and Coulter, 1964). Stretch receptors in the chest probably serve as the principal afferents for this reflex. Changes in vasomotor tone also affect beat-to-beat variation (Sayers, 1971). A reduction in beat-to-beat variation can occur in heart failure and severe depression of the central nervous system (Vallbona et al., 1965).

The efferent pathway regulating beat-to-beat variation is by the vagus nerve. When vagal tone is high, and therefore during bradycardia, beat-to-beat variation is maximal (Friedberg, 1966). As vagal tone decreases with advancing age (Turner, 1969) beat-to-beat variation decreases (fig. 4). Beat-to-beat variation is abolished in man by atropine (fig. 6) and in animals after section of the vagi (Samaan, 1935). It is concluded that intact vagal innervation of the heart is essential to sustain its normal beat-to-beat variation.

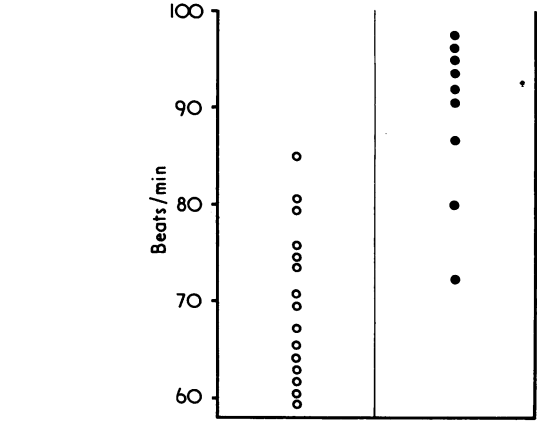


FIG. 5—Mean resting heart rates of the 9 patients with autonomic neuropathy (●) and 15 age-matched healthy subjects (O).

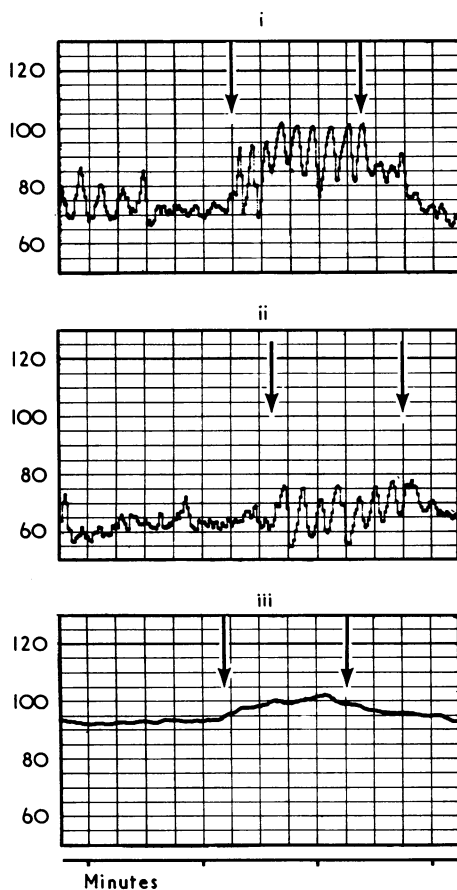


FIG. 6—Effect of intravenous propranolol and atropine on beat-to-beat variation in healthy man aged 30 years (i) before drug administration, (ii) after 10 mg propranolol, (iii) after 1.8 mg atropine. Arrows mark points between which deep breaths were taken.

The dominance of vagal control over beat-to-beat variation (Levy and Zieske, 1969) is indicated by the raised heart rate of

the pharmacologically denervated heart (Turner, 1969) and of the transplanted heart, which is, of course, denervated (Griep et al., 1971). Moreover, sympathetic inhibition by the administration of propranolol to normal subjects has no effect on beat-to-beat variation (fig. 6). These observations lend further support to the theory that loss of vagal tone is responsible for the absence of beat-to-beat variation in diabetics with autonomic neuropathy.

Measurement of cardiac beat-to-beat variation provides objective evidence for the presence of autonomic neuropathy. The test is simple and reproducible and serial observations can easily be made. Certain clinical observations such as the persistent sinus tachycardia found in some patients may be accounted for by vagal denervation of the heart. Two patients (cases 1 and 3) each had two "unexplained" cardiac arrests, and one might speculate that these episodes were in some way the consequence of cardiac denervation.

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## References

- Angelone, A., and Coulter, N. A. (1964). *Journal of Applied Physiology*, **19**, 479.
- Chamberlain, D. A., Turner, P., and Sneddon, J. M. (1967). *Lancet*, **2**, 12.
- Clynes, M. (1960). *Science*, **131**, 300.
- Friedberg, C. K. (1966). In *Diseases of the Heart*, p. 486. Philadelphia, Saunders.
- Griep, R. B., Stinson, E. B., Dong, E., Clark, D. A., and Shumway, N. E. (1971). *Surgery*, **70**, 88.
- Keen, H. (1959). *Postgraduate Medical Journal*, **35**, 272.
- Levy, M. N., and Zieske, H. (1969). *Journal of Applied Physiology*, **27**, 465.
- Nathanielsz, P. W., and Ross, E. J. (1967). *Diabetes*, **16**, 462.
- Samaan, A. (1935). *Journal of Physiology*, **83**, 332.
- Sayers, B. M. (1971). *Proceedings of the Royal Society of Medicine*, **64**, 707.
- Sharpey-Schafer, E. P., and Taylor, P. J. (1960). *Lancet*, **1**, 559.
- Turner, P. (1969). In *Clinical Aspects of Autonomic Pharmacology*, p. 84. London, Heinemann.
- Vallbona, C., Cardus, D., Spencer, W. A., and Hoff, H. E. (1965). *American Journal of Cardiology*, **16**, 379.
- Watkins, P. J. (1973). *British Medical Journal*, **1**, 583.

## From Phiso hex to Hibiscrub

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### Summary

In a field trial of three disinfectant-detergent preparations for the surgical scrub Hibiscrub (a 4% chlorhexidine detergent solution) maintained a significantly greater residual antibacterial action on the skin of the gloved hands of an operating team than was obtained with Disadine (povidone-iodine detergent preparation) ( $P < 0.001$ ). In comparison with Phiso hex (3% hexachlorophane in detergent cream), the established surgical scrub of the operating team for many years, Hibiscrub

maintained marginally more significant residual disinfection ( $P < 0.05$ ). Of the three preparations the members of the team found Hibiscrub to be more acceptable for use than either Disadine or Phiso hex.

### Introduction

Since the first British report on Phiso hex (Smylie et al., 1959), 3% hexachlorophane detergent preparations have dominated the choice of safe and effective agents for the surgical scrub regimen. There is no doubt that both in this field (Lowbury et al., 1960, 1963) and in others, notably infant care (Plueckhahn and Banks, 1963; Baber et al., 1967), the disinfectant hexachlorophane has been shown to contribute significantly to the control of hospital cross-infection. As a narrow spectrum agent acting mainly against skin cocci the continuous use of this compound has been criticized (Forfar et al., 1968) because it gives a selective encouragement to Gram-negative infections. This, together with recent reports on the possibility of its toxic absorption

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