Use of Runs Test to Assess Cardiovascular Autonomic Function in Diabetic Subjects

NGUYEN PHONG CHAU, PHD
DENIS MESTIVIER
XAVIER CHANUDET, MD
BERNARD BAUDUCEAU, MD
DANIEL GAUTIER, MD
PIERRE LARROQUE, MD

OBJECTIVE — We suggest a simple, noninvasive method to assess the autonomic function in diabetic subjects. The method requires only a monitoring of heart rate (HR) with subjects in the sitting position.

RESEARCH DESIGN AND METHODS — Sixty diabetic subjects, 44 men and 16 women, between 20–80 years of age, were recruited, chronologically, for this study. Subjects treated for high blood pressure were not included. Their autonomic function was assessed by the total score of five classical cardiovascular function tests. In the same subjects and in 44 healthy subjects, blood pressure and HR were determined from beat to beat by the Finapres system with subjects in the sitting position. We examined the randomness of the HR changes by calculating the z statistic of the runs test on 1,000 successive HR readings (the z value is low if the HR changes are random). When the HR changes are random, we consider that the autonomic control of HR is impaired.

RESULTS — The z values of HR changes were significantly lower in diabetic subjects compared with normal subjects (2.98 ± 0.97 vs. 3.54 ± 0.97, $P < 0.004$). In diabetic subjects, the z value was closely correlated to the total score of disautonomy ($r = -0.66$, $P < 0.0001$, after correction for age effect) and to the office systolic blood pressure ($r = -0.43$, $P < 0.001$).

CONCLUSIONS — The z value of HR changes might be a marker of the autonomic function in diabetic subjects.

Autonomic neuropathy, frequently observed in diabetic subjects, can be assessed by several cardiovascular function tests (1). In this study, we suggested that autonomic neuropathy can be disclosed by an appropriate analysis of heart-rate (HR) changes when the subject is resting.

From the URBB, INSERM U263, University Paris 7 (N.P.C., D.M.), Paris; the Cardiovascular Pathology Unit (X.C., P.L.) and the Diabetologia and Hypertension Unit (B.B., D.B.), Begin Hospital, Saint Mandé, France.

Address correspondence and reprint requests to Nguyen P. Chau, PhD, URBB, Université Paris 7, 2 place Jussieu, tour 53, 1er étage, 75251 Paris Cedex.

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HR, heart rate; BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure.

RESEARCH DESIGN AND METHODS

— Forty-four subjects in good health (34 men and 10 women, group N) and 60 diabetic subjects (44 men and 16 women, group D) were recruited, chronologically, for this study. Informed consent was given by each subject. The protocol was approved by the Begin Hospital Ethics Committee (St. Mandé, France).

Office blood pressure (BP) was measured with the patients supine after 10 min at rest. BP and HR were measured from beat to beat by the Finapres system, with subjects sitting in a quiet, temperature-controlled room. The Finapres system has been validated in humans (2) by comparison with simultaneous measures of intra-arterial BP.

Five cardiovascular function tests were performed, as described by Ewing et al. (1): the HR response to a Valsalva maneuver, the HR response to deep breathing, the HR response to standing up, the systolic blood pressure (sBP) response to standing up, and the diastolic blood pressure (dBP) response to a sustained handgrip. Each of the scores was classified as normal, borderline, or abnormal, and was coded by 0, 0.5, and 1, respectively (1). The sum of the five scores is the total score. A total score of >1 defines an autonomic neuropathy, considered as severe if the total score is >2.

Data analysis

We used the runs test (3) to assess the randomness of dichotomous sequences. Consider, for example, three sequences of signs:

+ - + - + - + - + - + - + - (1)
+ + + + + + + + + + + + + + (2)
+ + + - - - + - + + - - - - (3)

In a sequence, each group of the same sign is called a run. Let r be the number

Table 1—*Body habitus, office BP, beat-to-beat BP and HR, z values of HR and BP changes in normal subjects and subjects with diabetes*

	Normal subjects	Diabetic subjects	*P* value
n	44	60	—
Sex (M/F)	34/10	44/16	—
Age (years)	33 ± 17	56 ± 13	<0.0001
Weight (kg)	65 ± 11	79 ± 14	<0.0001
Office sBP (mmHg)	130 ± 10	137 ± 20	<0.01
Office dBP (mmHg)	74 ± 10	80 ± 10	<0.01
Age at diabetes onset (years)	—	13 ± 9	—
Microalbumin > 30 mg/24 h (*n*)	—	14	—
Insulin-dependent diabetes (*n*)	—	23	—
Finapres sBP (mmHg)	113 ± 13	124 ± 15	0.0003
Finapres dBP (mmHg)	59 ± 12	71 ± 14	0.0003
Finapres HR (b/min)	71 ± 11	71 ± 9	NS
SD of Finapres sBP (mmHg)	5.7 ± 2.0	6. ± 2.2	NS
SD of beat-to-beat dBP (mmHg)	3.3 ± 1.2	3.1 ± 1.4	NS
SD of Finapres HR (b/min)	4.5 ± 2.3	3.0 ± 1.4	0.0001
z value of sBP changes	−7.74 ± 4.35	−8.68 ± 5.20	NS
z value of HR changes	3.54 ± 0.97	2.98 ± 0.97	0.0040

Data are means ± SD.

of runs of the sequence. The highest r value (case 1, $r = 14$) characterizes a sequence with systematic change in sign, and the lowest r value (case 2, $r = 1$) characterizes a sequence with no change in sign. For r values in between (case 3, $r = 6$), the sequences are less organized. In the runs test, a z statistic is derived from the r value (3). It characterizes the randomness of the sequence. Let (y_i) be a sequence of HR. We applied the runs test to the sequence (Δy_i), defined by $\Delta y_i = y_{i+1} - y_i$. All Δy_i above (resp. below) the mean value of the total sequences were coded by + (resp. −). The z value was used as a score to assess the quality of the heartbeat control.

RESULTS— Table 1 displays the main characteristics of the subjects in the normal and diabetic groups. The Finapres BP was lower than the office BP ($P < 0.001$). The variability of BP (assessed by its standard deviation) was the same in normal and diabetic subjects. In contrast, the variability of HR was lower in diabetic compared with normal subjects (3.0 ± 1.4 vs. 4.5 ± 2.3 beats/min, $P < 0.0001$).

The Ewing score in diabetic subjects was correlated to age ($P = 0.003$), office sBP ($P < 0.004$), and office dBP ($P < 0.03$). The z value was significantly lower in diabetic compared with normal subjects (2.98 ± 0.97 vs. 3.54 ± 0.97, $P < 0.004$). It was not correlated to age in normal subjects ($P = 0.06$) but closely correlated to age in diabetic subjects ($r = -0.57$, $P < 0.0001$). In diabetic subjects, the z value of HR fluctuations was closely correlated to the global score of disautonomy ($r = -0.48$, $P < 0.0002$). The z value and the score of disautonomy were both related to age ($r = -0.57$, $P < 0.0001$ and $r = 0.40$, $P < 0.003$, respectively). The partial correlation between the z value and the score of disautonomy, assuming a constant age, was $r = -0.66$ ($P < 0.0001$).

The z value of HR changes was significantly related to the office sBP ($r = -0.43$, $P < 0.001$). Figure 1 dis-

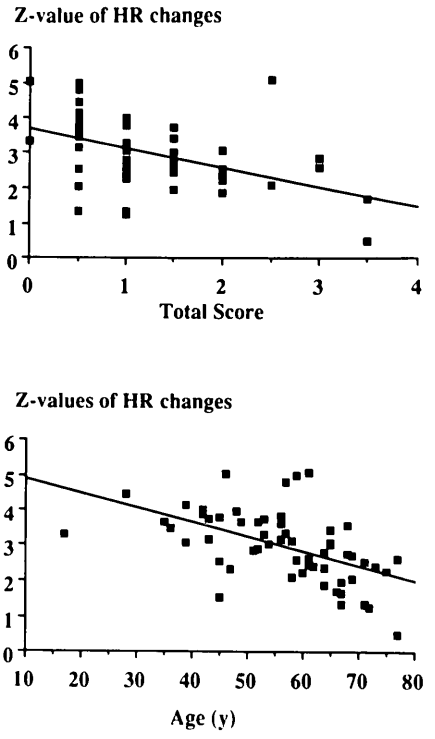

Figure 1—*Relationships between age, score of disautonomy, and z value of HR changes.*

plays the relationships between score of disautonomy, age, and z value of the HR changes in diabetic subjects.

CONCLUSIONS — The z value of HR changes is lower in diabetic compared with normal subjects. Although the two groups are different both in age and in health status, the disease might be the dominant factor because the z value is only weakly dependent on age in the normal subjects.

It is a striking result that the z value of HR changes is so closely correlated to the Ewing score. The z value of the HR changes might be a marker of autonomic neuropathy. However, the role of age must be more precisely evaluated. Because the power of the runs test is lacking (3), the interpretation of the z value in the light of pattern, fractal, and chaos theories might help. It is not impossible that the z value is still more closely related to the Ewing score when the latter is performed by the Finapres system itself.

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