Diabetologia (1982) 22: 163–166

Diabetologia

Reflex Control of Heart Rate in Normal Subjects in Relation to Age: A Data Base for Cardiac Vagal Neuropathy

W. Wieling, J. F. M. van Brederode, L. G. de Rijk, C. Borst and A. J. Dunning

Department of Medicine, Academic Medical Centre, and Department of Physiology, University of Amsterdam, Amsterdam, The Netherlands

Summary. We examined the heart rate changes induced by forced breathing and by standing up in 133 healthy subjects in the age range 10–65 years in order to establish a data base for studies on parasympathetic heart rate control in autonomic neuropathy. Test results declined with age. Log-transformation was used to define the lower limit of normal ($P_{0.10}$) and an uncertainty range (values between $P_{0.10}$ and $P_{0.025}$). The lower limit of normal decreased from 22 to 11 beats/min for forced breathing and from 26 to 16 beats/min for standing up, with age increasing from 10 to 65 years. No subject scored below and only two subjects scored in or below the uncertainty range for both tests. Lack of correlation between both tests ($r = 0.17$) documents the different afferent mechanisms of the reflex heart rate changes. In combination these two tests form a simple and reliable bedside method to establish cardiac vagal neuropathy.

Key words: Diabetic autonomic neuropathy, vagal heart rate control, forced breathing, orthostatic reflexes.

Impaired vagal control of heart rate (HR) has been described in a variety of diseases, such as diabetes mellitus [1–3], uraemia [4] and rheumatoid arthritis [5]. In patients with diabetes mellitus, cardiac vagal dysfunction is most often detected in longstanding disease, but damage to the autonomic nervous system may even be present at diagnosis [6]. Abnormal autonomic cardiac function is prognostically important because it may be associated with a high mortality [7]. Instantaneous HR changes with forced breathing [1–3, 6, 8–10] and after the transition from lying to standing [7, 8, 10–12] are used as simple bedside tests to assess vagal HR control. In order to establish a data base for delineating abnormal vagal HR control from normal, we compared instantaneous HR changes with forced breathing and after standing up in 133 healthy volunteers in the age range 10–65 years.

Subjects and Methods

Normal subjects consisted of medical students, hospital personnel and community volunteers. No medication other than oral contraceptives was used. Subjects were grouped according to age: 10–29 years ($n = 64$), 30–49 years ($n = 48$), 50–65 years ($n = 21$). Values for resting HR, blood pressure, weight and height are given in Table 1. Subjects were examined in the morning (70%) or in the afternoon (30%), at least 1 h after the last meal. They were requested to abstain from coffee and cigarettes on the day of the experiment. The instantaneous HR (beats/min) was determined by a cardiotachometer and monitored on a pen recorder (Servogor RE 511). The subjects rested in a supine position for at least 5 min before the measurements were started. The resting HR was taken as the mean value over a 30-s period preceding the tests.

Forced Respiratory Sinus Arrhythmia

The subject was instructed to perform six consecutive maximal inspirations in the supine position at a rate of 6 breaths/min [1–3, 6, 8]. From the pen recording we measured the mean difference between the maximum and minimum instantaneous HR during each of six consecutive cycles of forced inspiration and expiration: the I–E difference (beats/min) [1–3, 6, 8].

Standing Up from the Supine Position in 3–5 s

A marker connected to the pen recorder was used to identify the moment the subject began to stand up (time $t = 0$ in RR-interval number RR_0). A correction of 1 s was made to allow for the reaction time of the subject and the fact the cardiotachometer lagged one cardiac cycle. The following measurements were made:

(a) ΔHR_{max} (beats/min), T_{max} (s) and the number of the corresponding shortest RR-interval RR_{min} [8,12,13]

(b) ΔHR_{min}, T_{min} and the number of the corresponding longest RR-interval RR_{max} [8,12,13]

For comparison with other studies [8,12,13] we also determined the RR_{30}/RR_{15} ratio and the RR_{max}/RR_{min} ratio. Blood pressure was measured at rest and after 1 min in the erect posture.

Table 1. Physical characteristics of male and female subjects in the three age groups

Age (years)	10–29		30–49		50–65	
Sex	M	F	M	F	M	F
Number of subjects	40	24	26	22	9	12
Height (cm)	176 ± 12	168 ± 8	179 ± 8	168 ± 7	178 ± 6	170 ± 6
Weight (kg)	66 ± 12	60 ± 7	74 ± 10	62 ± 11	77 ± 3	63 ± 4
Resting heart rate (beats/min)	70 ± 12	73 ± 13	65 ± 10	67 ± 9	67 ± 9	67 ± 13
Systolic blood pressure (mmHg)	123 ± 11	120 ± 9	123 ± 12	114 ± 10	127 ± 19	135 ± 16
Diastolic blood pressure (mmHg)	74 ± 4	75 ± 6	76 ± 6	72 ± 6	80 ± 9	80 ± 7

Results expressed as mean ± SD

Table 2. RR-interval changes in the first 30 s after standing up

Age (years)	10–29	30–49	50–65
Number of subjects	$n = 64$	$n = 48$	$n = 21$
T_{max} (s)	12.0 ± 2.8	11.0 ± 2.8	12.0 ± 3.4
T_{min} (s)	21.2 ± 4.0	21.3 ± 3.4	23.5 ± 3.5
RR_{max} (interval number)	17 ± 5	15 ± 4	15 ± 4
RR_{min} (interval number)	31 ± 7	29 ± 4	30 ± 5
$\frac{RR_{30}}{RR_{15}}$	1.27 ± 0.20	1.30 ± 0.16	1.17 ± 0.12
$\frac{RR_{max}}{RR_{min}}$	1.49 ± 0.21	1.44 ± 0.17	1.31 ± 0.14

Results expressed as mean ± SD

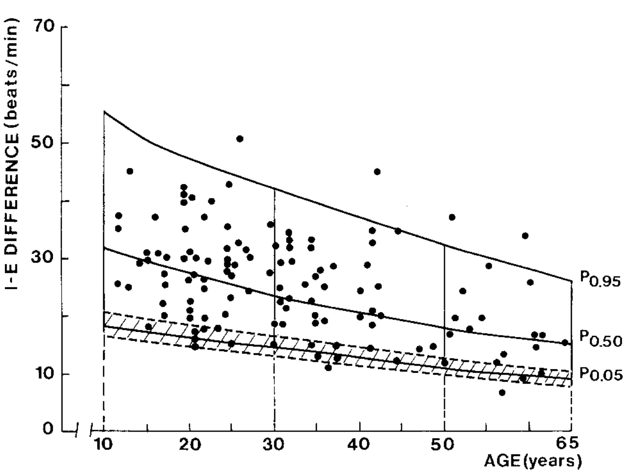

Fig. 1. Forced respiratory sinus arrhythmia (I–E difference) in relation to age. The regression line ($P_{0.50}$) and the 90% confidence limits (solid lines) were calculated from log-transformed values (see Methods). The hatched area indicates the uncertainty range; values below it are considered abnormally small, values above it are considered normal

Statistical Analysis

Test results were log-transformed because the data from each age group gave positively skewed distributions [14]. The log-normal data were fitted to the linear regression model log $\hat{Y} = a + bX$ ($\hat{Y}$ stands for test score, X for age). We calculated the 90% confidence limits for individual observations [14]. In order to establish a range of values from probably normal to probably abnormal – an uncertainty range – we also calculated the lower one-sided 90% and 97.5% confidence limits ($P_{0.10}$ and $P_{0.025}$). The regression coefficient (b) was tested for deviation from zero. Differences between group means were tested using Student's 't' test. The regression equation and the confidence limits were transformed back into normal scale. Correlation was calculated using Pearson's product moment correlation *(r)*. A $p < 0.05$ was considered to indicate a significant difference.

Results

No influence of sex was found. Test results in the morning and afternoon did not differ significantly. Consequently all results were pooled.

Forced Respiratory Sinus Arrhythmia

The I–E difference ranged from 7 to 51 beats/min and declined with age (Fig. 1). The regression of the I–E difference with age is described by the equation log I–E difference = 1.5732 – 0.0060 × age. The regression coefficient was significantly different from 0 ($p < 0.001$). The median I–E difference decreased from 33 to 15 with age increasing from 10 to 65 years. The lower limit of the 90% confidence interval ($P_{0.05}$) decreased from 19 at the age of 10 years to 9 at the age of 65 years. The uncertainty range ($P_{0.025}$ to $P_{0.10}$; Fig. 1, hatched area) shifted from 17–21 to 8–10. Two subjects scored below and 18 subjects scored within the uncertainty range. Correlation between I–E difference and resting HR was very poor ($r = 0.31$).

Immediate Heart Rate Changes After Standing Up

Orthostatic hypotension (systolic pressure fall ⩾30 mmHg) was not observed. The time course of instantaneous HR changes showed a very characteristic response: an abrupt HR rise starting after ⩽1 s, a peak around $t = 12$ s and a trough around $t = 22$ s (Table 2). HR continued to increase very little (<5 beats/min) in only 11 subjects after 15 s of standing up. For practical purposes the highest HR in the first 15 s was used as a measure for the initial peak HR rise to standing.

The ΔHR_{max} ranged from 14 to 47 beats/min and declined with age (Fig. 2). The regression of ΔHR_{max} with age is described by the equation log ΔHR_{max} = 1.5864 – 0.0039 × age. The regression coefficient was significantly different from 0 ($p < 0.001$).

The median ΔHR_{max} decreased from 35 to 22, $P_{0.05}$ from 22 to 13 and the uncertainty range (Fig. 2, hatched area) shifted from 20–25 to 12–15 with age increasing from 10 to 65 years. No subject scored below and 17 subjects scored within the uncertainty range. The correlation between ΔHR_{max} and resting HR was very poor (r = 0.23). On average ΔHR_{max} was reached around RR_{15} and ΔHR_{min} around RR_{30}. However, since there were considerable individual differences, the RR_{30}/RR_{15} ratio underestimated the RR_{max}/RR_{min} ratio (Table 2).

The RR_{max}/RR_{min} ratio ranged from 1.08 to 1.98 and declined with age. The regression of the RR_{max}/RR_{min} ratio with age is dercribed by the equation log RR_{max}/RR_{min} = 0.2009 – 0.0014 × age. The regression coefficient was significantly different from 0 ($p < 0.001$). The median RR_{max}/RR_{min} decreased from 1.54 to 1.29, $P_{0.05}$ from 1.25 to 1.05 and the uncertainty range shifted from 1.31 – 1.20 to 1.09 – 1.01 with age increasing from 10 to 65 years. Three subjects scored below and 8 subjects scored within the uncertainty range. The correlation between the RR_{max}/RR_{min} ratio and resting HR was very poor (r = 0.19).

Correlation Between HR Changes After Forced Breathing and Standing Up

The correlation between I–E difference and ΔHR_{max} (r = 0.17) and I–E difference and RR_{max}/RR_{min} ratio (r = 0.14) was very poor. Two out of 133 subjects scored in or below the uncertainty range for the I–E difference and ΔHR_{max}, and only one in the uncertainty range for the I–E difference and the RR_{max}/RR_{min} ratio. No subject scored below the uncertainty range for both tests.

Discussion

Instantaneous HR changes induced by deep breathing and standing up are commonly used to assess vagal damage in diabetic autonomic neuropathy. The principal results of the present investigation in a large number of healthy subjects are: test results showed a huge scatter (for instance largest I–E difference seven times smallest difference) and skewed distributions. Analysis of test results after log-transformation enabled defining an 'uncertainty range' based on parametric statistics. Only two subjects scored within or

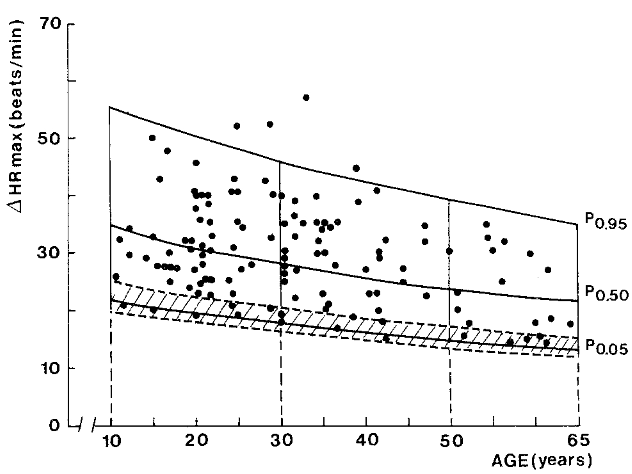

Fig. 2. Immediate HR increase after standing up (ΔHR_{max}) in relation to age. The hatched area indicates the uncertainty range (see legend to Fig. 1)

Table 3. Lowest normal value for I–E difference, ΔHR_{max} and RR_{max}/RR_{min} ratio

Author	No. of subjects	Age (years)	I–E difference (beats/min)	ΔHR_{max} (beats/min)	RR_{max}/RR_{min} ratio
This study	64	10–29	20 (15–19)	24 (19–23)	1.28 (1.17–1.27)[a]
	48	30–49	15 (11–14)	20 (16–19)	1.20 (1.09–1.19)
	21	50–65	12 (9–11)	17 (13–16)	1.13 (1.03–1.12)
Mackay et al. [8]	54	20–49	13 (9–12)	16 (12–15)	1.12 (1.04–1.11)
Wheeler and Watkins [1]	17	20–50	11		
Page and Watkins [2]	39	< 50	16	16	
Hilsted and Jensen [9]	10	20–40	16		
Dyrberg et al. [10]	28	30–48	9		

Values in parentheses are the boundary values of the uncertainty range in the present study and the borderline values reported by other authors. The uncertainty range is calculated for the midpoint of the three age groups

[a] After log-transformed data

below the uncertainty range in both tests. The HR changes evoked by forced breathing and by standing up declined with age [2, 8].

The present results are in general agreement with previous studies [1–3, 8–10], but comparison of tests scores considered to be the lower limit of normal by different authors (Table 3) shows that the more rigorous analysis in the present study improved the criteria for delineating abnormal from normal in individual testing of reflex vagal heart rate control. The very poor correlation between the HR changes with forced breathing and after standing up emphasizes that different afferent mechanisms are involved [3]. If we assume that these are entirely independent, there is a 1% chance that a healthy individual would score within or below the uncertainty range in both tests, and a 0.06% chance that scores below the uncertainty range would be obtained. Thus, in combination these two tests are eminently suited for bed-side screening of cardiac vagal neuropathy. No subjects had orthostatic hypotension after 1 min of standing. The immediate HR response to standing showed a striking pattern in time: the peak HR rise was found after about 12 s, the subsequent relative minimum after about 22 s (Table 2), values almost identical to those reported in previous studies [12,15,16]. Ewing et al. [12] characterized the HR response by calculating the ratio between the 30th and 15th RR-interval. Although the maximal HR was reached near RR_{15} and minimal HR near RR_{30} (Table 2), there were considerable individual differences and the RR_{30}/RR_{15} ratio was lower than the RR_{max}/RR_{min} ratio (Table 2). Thus, the RR_{max}/RR_{min} ratio is superior [5, 8] to the RR_{30}/RR_{15} ratio [10, 17] for testing abnormal vagal HR control in diabetic patients.

Acknowledgements. We would like to express our appreciation to J. M. Karemaker, Department of Physiology for critical suggestions, and to J. Oosting and A. A. M. Hart, Department of Medical Physics for statistical advice.

References

1. Wheeler T, Watkins PJ (1973) Cardiac denervation in diabetes. Br Med J 4: 584–586
2. Page MMcB, Watkins PJ (1977) The heart in diabetes: autonomic neuropathy and cardiomyopathy. Clin Endocrinol Metab 6: 377–388
3. Bennett T, Faquhar IK, Hosking DJ, Hampton JR (1978) Assessment of methods for estimating autonomic nervous control of the heart in patients with diabetes mellitus. Diabetes 27: 1167–1174
4. Naik RB, Mathias CJ, Wilson CA, Reid JL, Warren DJ (1981) Cardiovascular and autonomic reflexes in haemodialysis patients. Clin Sci 60: 165–170
5. Edmonds ME, Jones TC, Saunders WA, Sturrock RD (1979) Autonomic neuropathy in rheumatoid arthritis. Br Med J 2: 173–175
6. Watkins PJ, Mackay JD (1979) Cardiac denervation in diabetic neuropathy. Ann Intern Med 92: 304–307
7. Ewing DJ, Campbell IW, Clarke BF (1979) Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med 92: 308–311
8. Mackay JD, Page MMcB, Cambridge J, Watkins PJ (1980) Diabetic autonomic neuropathy: the diagnostic value of heart rate monitoring. Diabetologia 18: 471–478
9. Hilsted J, Jensen SB (1979) A simple test for autonomic neuropathy in juvenile diabetics. Acta Med Scand 205: 385–387
10. Dyrberg T, Bern J, Christiansen JS, Hilsted J, Nerup J (1981) Prevalence of diabetic autonomic neuropathy measured by simple bedside tests. Diabetologia 20: 190–194
11. Clarke BF, Ewing DJ, Campbell IW (1979) Diabetic autonomic neuropathy. Diabetologia 17: 195–212
12. Ewing DJ, Campbell JW, Murray A, Neilson JMM, Clarke BF (1978) Immediate heart rate response to standing: simple test for autonomic neuropathy in diabetes. Br Med J 1: 145–147
13. Ewing DJ, Hume L, Campbell JW, Murray A, Neilson JMM, Clarke BF (1980) Autonomic mechanisms in the initial heart rate response to standing. J Appl Physiol 49: 809–814
14. Armitage P (1971) Statistical methods in medical research. Blackwell Scientific Publications, Oxford, pp 163–166, 352
15. Drischel H von, Fanter H, Gürtler H, Labitzke H, Priegnitz H (1963) Das Verhalten der Herzfrequenz gesunder Menschen beim Übergang vom Liegen zum Stehen. Archiv für Kreislaufforschung 40: 135–167
16. White NJ (1980) Heart rate changes on standing in elderly patients with orthostatic hypotension. Clin Sci 58: 411–413
17. Ewing DJ, Campbell JW, Clarke BF (1978) Heart rate response to standing as a test for autonomic neuropathy. Br Med J 1: 1700

Received: 19 May 1981
and in revised form: 4 August 1981

Wouter Wieling, M. D.
Department of Medicine
Academic Medical Centre
Meibergdreef 9
NL-1105 AZ Amsterdam The Netherlands