Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function

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SUMMARY The diagnosis of autonomic neuropathy frequently depends on results of tests which elicit reflex changes in heart rate. Few well-documented normal ranges are available for these tests. The present study was designed to investigate the effect of age upon heart rate variability at rest and in response to a single deep breath, the Valsalva manoeuvre, and standing. A computerised method of measurement of R-R interval variation was used to study heart rate responses in 310 healthy subjects aged 18-85 years.

Heart rate variation during each procedure showed a skewed distribution and a statistically significant negative correlation with age. Normal ranges (90% and 95% confidence limits) for subjects aged 20-75 years were calculated for heart rate difference (max-min) and ratio (max/min) and standard deviation (SD). Heart rate responses were less than the 95th centile in at least one of the four procedures in 39 (12.6%) out of the 310 subjects, and were below this limit in two or more tests in five (1.6%) subjects. In view of the decline in heart rate variation with increasing age, normal ranges for tests of autonomic function must be related to the age of the subject.

In recent years several simple, non-invasive tests of autonomic function have been described.^{1,2} These tests are based on measurement of reflex changes in heart rate in response to standardised stimuli, such as the Valsalva manoeuvre,³ single⁴ or repeated deep breaths,⁵ passive tilting, or standing.^{6,7} More complex procedures, such as lower body negative pressure⁸ and injection of pressor agents,⁹ provide additional information about autonomic control of the cardiovascular system but are not suitable for routine clinical use.

Assessment of heart rate variability in subjects of all ages is, however, complicated by changes that occur in the autonomic nervous system with advancing age.¹⁰ These changes include a gradual increase in basal and stimulated plasma noradrenaline concentrations,¹¹ altered adrenoceptor function,¹² and diminished responsiveness to adrenergic agonists and antagonists.¹³ The heart rate response to the

Valsalva manoeuvre and deep breathing tests declines with age in normal subjects.^{3,14} Consequently normal ranges for such procedures that quote a single limit for all ages,¹⁵ with or without a borderline range, are inappropriate and will result in errors in diagnosis, particularly in the elderly.

The present study was undertaken to evaluate the effect of age upon heart rate variation in a large group of healthy subjects, and thus to establish confidence limits for the heart rate response to standard tests of autonomic function.

Subjects and methods

SUBJECTS

A total of 310 healthy normal subjects, 147 males and 163 females, were studied. The age range was 18-85 years (mean (SD) 48 (17)); in each decade from 20 to 70 years of age there was a minimum of 50 subjects, approximately 50% males and 50% females (Table 1). Most of those aged less than 65 were factory employees, a few were hospital staff and healthy outpatients attending the physiotherapy department. Those aged 65-85 years were volun-

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Table 1 Age and sex distribution of subjects

Sex	18-29 yr	30-39 yr	40-49 yr	50-59 yr	60-69 yr	70-85 yr
M	32	31	23	29	24	8
F	23	27	29	27	29	28
Total (%)	55 (17.7)	58 (18.7)	52 (16.8)	56 (18.1)	53 (17.1)	36 (11.6)

teers from day centres for the elderly in Bristol. Diabetic patients were excluded, as were those with cardiac failure, angina, cerebrovascular disease, and those taking drugs known to affect heart rate. None of the subjects had glycosuria.

METHODS

Changes in heart rate were measured with an instantaneous cardiac ratemeter (Lectromed type 4522 model A) interfaced with a microcomputer (Commodore 4008N). Details of the method have been reported elsewhere.¹⁰ The computer was programmed to record heart rate in either beats per minute or milliseconds per beat. A signal generated by an R wave simulator set at a rate of 60 min⁻¹ was measured with 100% accuracy over a period of two minutes.

Heart rate was measured continuously during four procedures in each subject as follows: (a) quiet supine rest for 60 s; (b) a single deep breath—the subject was asked to inhale deeply over 5 s and then to exhale over 5 s; (c) Valsalva manoeuvre—the subject was asked to maintain a pressure of 40 mm Hg for 15 s by means of forced expiration into a mouth-piece connected to a sphygmomanometer, the subject then lay quietly while heart rate was recorded for a further 45 s; (d) standing for 60 s (in this case the recording was started immediately the subject was erect). These are referred to hereafter as *resting*, *inspiration*, *Valsalva*, and *standing*. Subjects were

supine or semirecumbent during (a)–(c). In addition blood pressure over the brachial artery was measured with a standard sphygmomanometer before and after the subject had stood for 60 s. All studies were performed by a single investigator (IAD O'B).

The following data were recorded from each test: maximum, minimum, mean, and SD of heart rate in beats/min. The values of the 15th and 30th beats after standing were noted also.¹¹ From these results, we derived the following indices of heart rate variation: heart rate difference (max – min), heart rate ratio (max/min), heart rate SD, and 30:15 ratio.

STATISTICAL ANALYSIS

The influence of age and other variables on heart rate variation was examined by non-parametric techniques. Multiple correlation analysis was used to study the relation of age, resting heart rate, and blood pressure to heart rate variation. The difference in heart rate variability between males and females was compared by unpaired *t* tests. To derive confidence limits for indices of heart rate variation it was necessary to use a transformation technique because of the skewed distribution of results and the non-linear relation with age. Thus the original data were transformed to normality by the method of Box and Cox, in which a general power transformation is used to convert the original data to normality.¹² Confidence limits were then calculated and the data were transformed back.

Table 2 The relative contribution of age, systolic blood pressure (BP), and basal heart rate to heart rate variation at rest and in response to the Valsalva manoeuvre, a single deep breath, and standing (values given are those of the change in *R*² at each stage in multiple correlation analysis)

Index	Age	Systolic BP	Mean heart rate
Heart rate difference:			
Resting	23.0%	—	0.2%
Inspiration	32.6%	—	—
Valsalva	20.5%	0.8%	4.0%
Standing	33%	—	—
Heart rate ratio:			
Resting	23.4%	—	2.7%
Inspiration	29.2%	—	3.3%
Valsalva	19.5%	1.6%	—
Standing	29.1%	—	1.3%
Heart rate SD:			
Resting	15.4%	—	—
Inspiration	30.5%	—	—
Valsalva	17.9%	1.1%	0.8%
Standing	33.1%	—	—

Results

The correlation coefficient of heart rate indices with age ranged from -0.45 ($p < 0.001$) for resting heart rate SD to -0.60 ($p < 0.001$) for standing heart rate difference. Heart rate difference and SD were independent of resting heart rate in all tests, whereas heart rate ratio showed a weak correlation with resting heart rate in all procedures except for the Valsalva manoeuvre. There was also a significant negative correlation of heart rate variability with supine systolic blood pressure; however, this was due almost entirely to the dependence of blood pressure on age ($r = 0.59$, $p < 0.001$). Multiple correlation analysis showed that age accounted for 15–33% of

Fig. 1 Heart rate differences in normal subjects measured at rest, during a single deep breath, Valsalva manoeuvre, and standing ($n = 310$).

variation in heart rate responsiveness in normal subjects, and that less than 4% was attributable to basal heart rate or blood pressure (Table 2).

Comparison of heart rate results between males and females was confined to subjects aged < 70 years because of a preponderance of females above this age. Heart rate variability was generally less in women than in men; however, with the exception of heart rate ratio at rest ($p = 0.004$), the difference did not reach statistical significance. Therefore, results from both sexes were analysed together.

The relative change in heart rate in response to the various procedures was Valsalva $>$ standing $>$ inspiration $>$ resting. All indices of heart rate variability showed unimodal, positively skewed distributions. For example, Fig. 1 shows data for heart rate difference. Figure 2 shows the asymmetrical scatter of Valsalva ratios. It also illustrates the non-linear decline in heart rate responsiveness with increasing age and the 90% and 95% confidence limits derived by the transformation technique described above. The values of 90% and 95% confidence limits for heart rate difference, ratio, and SD in response to each procedure are given in Table 3.

Individual subjects rarely had results outside these limits in more than one test. Heart rate responses were less than the 95th centile in at least one of the four procedures in 39 (12.6%) out of 310 subjects. In the entire group heart rate difference results were outside the lower 95% confidence limit in two or more of the four tests in only two out of the 310 subjects (0.6%). Similarly, only three subjects (0.9%) had two or more abnormal heart rate ratios or SDs.

Fig. 2 Age-related decline in the Valsalva ratio in normal subjects ($n = 310$) and 90% and 95% confidence limits.

Table 3 Normal ranges for heart rate responses in normal subjects aged 20–75 years. Values given are (a) the lower 95% and (b) the lower 90% confidence limits

	20 yr	25 yr	30 yr	35 yr	40 yr	45 yr	50 yr	55 yr	60 yr	65 yr	70 yr	75 yr
Heart rate difference:												
Resting												
(a)	7	7	6	6	5	5	5	4	4	4	3	3
(b)	9	8	7	7	6	6	5	5	5	4	4	4
Inspiration												
(a)	11	10	9	8	7	6	5	5	4	3	3	2
(b)	13	12	11	10	9	8	7	6	5	4	4	3
Valsalva												
(a)	22	20	19	17	16	15	13	12	11	19	9	8
(b)	25	23	22	20	19	17	16	15	13	12	11	10
Standing												
(a)	15	13	12	11	9	8	7	6	5	5	4	3
(b)	17	16	14	13	11	10	9	8	7	6	5	4
Heart rate ratio:												
Resting												
(a)	1.12	1.11	1.10	1.09	1.08	1.07	1.06	1.05	1.04	1.04	1.03	1.02
(b)	1.14	1.12	1.11	1.10	1.09	1.08	1.07	1.07	1.06	1.05	1.04	1.03
Inspiration												
(a)	1.17	1.15	1.13	1.12	1.10	1.08	1.07	1.06	1.04	1.03	1.02	1.00
(b)	1.20	1.18	1.16	1.14	1.13	1.11	1.09	1.08	1.06	1.05	1.04	1.02
Valsalva												
(a)	1.35	1.32	1.30	1.27	1.24	1.24	1.20	1.17	1.15	1.13	1.11	1.09
(b)	1.41	1.38	1.35	1.32	1.29	1.27	1.24	1.22	1.19	1.17	1.15	1.13
Standing												
(a)	1.20	1.17	1.15	1.13	1.12	1.10	1.08	1.06	1.05	1.03	1.02	1.01
(b)	1.23	1.21	1.19	1.16	1.14	1.13	1.11	1.09	1.07	1.06	1.04	1.03
Heart rate SD:												
Resting												
(a)	1.6	1.5	1.4	1.3	1.3	1.2	1.1	1.1	1.0	1.0	0.9	0.9
(b)	1.8	1.7	1.6	1.5	1.4	1.4	1.3	1.2	1.1	1.1	1.0	1.0
Inspiration												
(a)	3.6	3.2	2.9	2.5	2.2	1.9	1.6	1.4	1.2	0.9	0.8	0.6
(b)	4.3	3.9	3.5	3.1	2.7	2.4	2.1	1.8	1.5	1.3	1.1	0.9
Valsalva												
(a)	6.0	5.6	5.1	4.7	4.3	3.9	3.5	3.2	2.9	2.6	2.3	2.1
(b)	7.2	6.6	6.1	5.6	5.1	4.7	4.3	3.9	3.6	3.2	2.9	2.6
Standing												
(a)	3.6	3.3	2.9	2.6	2.3	2.0	1.7	1.5	1.3	1.1	0.9	0.8
(b)	4.3	3.9	3.5	3.1	2.7	2.4	2.1	1.9	1.6	1.4	1.2	1.0

The timing of maximum and minimum heart rates on standing was determined in 219 subjects: maximum heart rate occurred within 10 s in 77%. In contrast, the timing of minimum rate showed a much wider scatter. The 30:15 ratio was compared with (max/min) heart rate ratio on standing in 294 subjects. There was a significant correlation between both measurements ($r=0.45$, $p<0.001$). The 30:15 ratio was <1.00 in 43%, however, and thus this derived index consistently underestimated the true max/min ratio.

As expected, supine systolic blood pressure was positively correlated with age ($r=0.59$, $p<0.001$). The difference between supine and standing systolic blood pressure was independent of age ($r=-0.01$, p NS). Four subjects, all of whom were aged 60–65 years, had a fall in systolic pressure on standing of 20–25 mm Hg.

The reproducibility of the heart rate response to each procedure was assessed in a separate study of six healthy male subjects aged 20–35 years, each of whom was studied on five separate occasions over

three days. Heart rate ratios were found to have a lower coefficient of variation than heart rate differences or SDs (Table 4).

Discussion

Variation in heart rate, whether at rest or in response to a stimulus, is mediated by the combined effects of cardiac vagal and sympathetic nerves acting upon the sinoatrial node. The aim of simple clinical tests, such as were used in the present study, in which the

Table 4 Coefficients of variation (mean (range)) of heart rate measurements in six normal subjects

	Heart rate		SD
	Difference	Ratio	
Resting	29% (18–44%)	7% (6–9%)	25% (12–34%)
Inspiration	16% (7–28%)	6% (2–9%)	21% (13–34%)
Valsalva	17% (4–29%)	9% (4–16%)	21% (2–27%)
Standing	26% (12–31%)	9% (4–16%)	24% (10–41%)

chronotropic response to standardised manoeuvres is measured, is to investigate the integrity of these autonomic control mechanisms. Assessment of heart rate variability is, however, complicated by changes in the autonomic nervous system that occur with advancing age.¹³ These functional changes include a gradual increase in basal and stimulated plasma nor-adrenaline concentrations,¹⁴ altered adrenoceptor function,¹⁵ and diminished responsiveness to adrenergic agonists and antagonists.¹⁶ The results of the present study demonstrate that age is an important determinant of heart rate variability in normal subjects. Thus, unless allowance is made for the physiological effects of aging, diminished heart rate variability in older subjects may be attributed incorrectly to disease.

In this study of more than 300 healthy subjects, care was taken to ensure an even distribution of age and sex. It was necessary to use a transformation technique to analyse the data because the distribution of results was skewed, and the decline in heart rate responsiveness with age was non-linear. Alternative transformation methods were used by Smith and Wieling to derive normal ranges for heart rate variation at rest¹⁷ and in response to deep breathing,^{17,18} the Valsalva manoeuvre,¹⁹ and standing.¹⁸ We have obtained slightly lower limits, probably due to the larger number and more uniform age distribution of our subjects. Many previous studies of cardiovascular autonomic function tests, particularly those of diabetic autonomic neuropathy, have been of small groups of subjects or narrow age ranges or both.^{11,20,21} In some instances recommended normal limits have not taken account of observed reductions in heart rate variability in older subjects^{3,22,23}; in others normal ranges have been defined "arbitrarily".²⁴

Sinus arrhythmia is enhanced during β adrenergic blockade²⁵ and is abolished by atropine.⁵ Thus, although the precise mechanisms responsible for sinus arrhythmia are not fully understood, the efferent pathway is via cardiac vagal fibres. Respiratory-induced changes in heart rate are reduced in the elderly.^{4,17,18,26,27} This may be due to altered vagal activity, since the chronotropic response to atropine is also reduced in older subjects.²⁸ Bennett *et al*, in a comparative study of cardiac autonomic function tests, found that resting R-R interval SD correlated negatively with mean heart rate, and that R-R interval SD was not useful in detecting subjects with impaired heart rate responsiveness.⁹ In the present study, heart rate variability during quiet and deep breathing was independent of mean heart rate, and it was possible to derive age-related limits for resting heart rate variation. In studying the response to deep breath-

ing we used a single breath rather than repeated breaths, since the magnitude of the change in rate is often greater during the first breath and diminishes thereafter.⁹ Ewing and Clarke have recommended a normal range of >15 beats/min for heart rate difference during deep breathing, with 11–14 as borderline and <11 as abnormal.²⁹ Our results indicate that these limits are not applicable to subjects of all ages; our results (Table 3) are, however, similar to the limits obtained by Mackay *et al* and Sundkvist *et al* in subjects aged <50 years.^{22,30}

The Valsalva manoeuvre elicits a complex series of haemodynamic events that result in activation of sympathetic and parasympathetic neurones. It has been suggested that the cardiac response to Valsalva should be represented by the increase or decrease in rate relative to the initial heart rate.³¹ Both these indices, however, correlate closely with the Valsalva ratio, and the latter has the advantage of being independent of basal heart rate. In a study of 200 normal subjects by Levin, the Valsalva ratio decreased with age and 96% had ratios >1.5.³ The normal ranges that we have calculated for the Valsalva ratio are lower than 1.5 at all ages, and are generally higher than the limit of 1.10 set by Ewing and Clarke.²⁹ Our results are, however, similar to the range found by Dyrberg *et al* in subjects aged 30–48.²⁰

The increase in heart rate on standing diminishes with age²⁶ (Table 3). The ratio of the R-R intervals of the 30th and 15th beats after standing, the 30:15 ratio, has been proposed as an index of the reflex heart rate response to standing.¹¹ The mechanisms underlying the immediate heart rate response to standing are complex,⁷ and the present data indicate that these changes in rate are not accurately represented by the 30:15 ratio because of the high frequency of false positive results. Others have also found the 30:15 ratio to be unhelpful and to underestimate the true max/min ratio.^{18,32}

Postural hypotension is a relatively common finding in the elderly. Caird *et al* found that 16% of 494 people aged more than 65 have a systolic fall >20 mm Hg on standing.³³ This degree of postural hypotension was less common among our subjects, occurring in only 4.5% of those aged 60 or more. This may have been due to differences in the study populations, since contributory factors were identified in 40% of Caird's subjects with postural hypotension and such individuals would have been excluded from the present study.

It is a contentious issue whether the response to tests of autonomic function should be expressed as the difference or the ratio of the induced change in heart rate (or R-R interval). Although the relation between these two indices is linear, the slope is dependent on basal heart rate (Fig. 3). Thus, if a

Fig. 3 The effect of basal heart rate upon the relation between heart rate difference (max-min) and heart rate ratio (max/min).

particular test induces a heart rate difference of 20 beats/min the corresponding heart rate ratio will be 1.33 for a basal heart rate of 60, 1.20 for a basal rate of 100, and 1.17 for a basal rate of 120. Furthermore, it is not known whether a change in heart rate from 60 to 80 is comparable physiologically to a change in rate from 100 to 120. Since there is no consensus on which index should be used to express the heart rate response, we have presented all our data after all three methods of analysis. The expression of heart rate data as either ratios or differences may also be relevant to the diagnosis of diabetic autonomic neuropathy. It is well documented that heart rates are, in general, faster in diabetics than in non-diabetics.^{2 5 9 20} Consequently, autonomic dysfunction may be diagnosed more frequently if ratios rather than differences are used.

It is important to recognise that a diagnosis of autonomic neuropathy cannot be substantiated on the basis of the results from a single test.²⁹ Among the reasons for this are the variability of results in healthy subjects, the different physiological basis of the various tests, and, in the case of disease states, the patchy distribution of lesions within the autonomic nervous system. Using a combination of four simple procedures we have shown that <2% of a normal population will have more than one abnormal test result. We suggest, therefore, that abnormal autonomic control of heart rate can be diagnosed with confidence using these tests with age-related normal ranges.

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