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Effects of age, heart rate, gender, tobacco and alcohol ingestion on R-R interval variability in human ECG

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Abstract

To evaluate the possibly confounding effects of age, gender, heart rate, tobacco and alcohol ingestion on the coefficient of variation of the electrocardiographic R-R interval (CV_{RR}), ECGs in the supine posture were obtained in 68 healthy men and 33 healthy women. The $C\text{-}CV_{RSA}$ and $C\text{-}CV_{MWSA}$ (two component CVs reflecting respiratory sinus arrhythmia and Mayer wave related sinus arrhythmia, respectively) were computed in each subject from component spectral powers using autoregressive spectral and component analyses. Results of multiple regression analysis indicated that age was inversely related to CV_{RR}, $C\text{-}CV_{RSA}$ and $C\text{-}CV_{MWSA}$ in both sexes. Heart rate was positively related to $C\text{-}CV_{MWSA}$ in males. However, no significant difference in the CV_{RR}, $C\text{-}CV_{RSA}$ or $C\text{-}CV_{MWSA}$ was found between males and females. The $C\text{-}CV_{MWSA}$ was not correlated with the $C\text{-}CV_{RSA}$ in either males or females. These data indicate that the CV_{RR}, $C\text{-}CV_{RSA}$ and $C\text{-}CV_{MWSA}$ are affected by age and partly by heart rate; gender, moderate smoking or drinking habits might not strongly influence autonomic nervous system function. On the other hand, the $C\text{-}CV_{RSA}$ in the supine posture appears to be independent of the $C\text{-}CV_{MWSA}$. The positive relationship observed between the $C\text{-}CV_{MWSA}$ and heart rate suggests that the $C\text{-}CV_{MWSA}$ may be associated with sympathetic activity.

Introduction

Little information has been developed on the basic covariates of autonomic nervous system measures except age, although measurement of variability in heart rate at rest, specifically determination of the coefficient of variation in the electrocardiographic R-R interval (CV_{RR}) provides a useful approach for objective assessment of autonomic nervous system function. Wheeler and Watkins [32] observed a striking reduction or absence of the CV_{RR} with both quiet and deep breathing in nine diabetics with autonomic neuropathy, in which the beat-to-beat variation was inversely correlated with age in healthy subjects. Other researchers also confirmed the negative relation of the CV_{RR} to age [7,8,22,28]. On the other hand, acute or heavy smoking seemed to be associated with dysfunction of the autonomic nervous system in the previous literature [9,15,18,26, 31]. Depression of R-R interval variability was seen in patients with alcoholic dependency [15].

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As Stockard et al. [29] have reported a small but significant effect of gender on latency of visual evoked potential, the difference in the autonomic nervous system function is likely to be found between both sexes. Further study with large populations would be necessary to verify whether age, gender, smoking and drinking affect the autonomic nervous system function.

Since the early 1970s, spectral analysis with fast Fourier transformation (FFT) has been used to evaluate R-R interval variability in the ECG [2,3,10,11,13,19,25,27,28]. Two main components in this variation — high frequency component (respiratory sinus arrhythmia, RSA) at a center frequency of about 0.3 Hz, and low frequency component (Mayer wave related sinus arrhythmia, MWSA) at a frequency of 0.1 Hz — have been identified as meaningful on the basis of physiological and pharmacological studies. In the standing posture, the spectral powers for the high and low frequency components are reduced by parasympathetic and beta-sympathetic blocking drugs, respectively.

Autoregressive spectral analysis has been utilized more recently instead of spectral analysis based on FFT to evaluate CV_{RR} [8,9,22–24], because the power spectrum obtained by FFT cannot be partitioned into independent components as can the spectrum derived from the autoregressive model. In particular, two newly developed parameters (C-CV_{RSA} and C-CV_{MWSA}) that can be computed from each component power spectral density of the RSA and MWSA using component analysis after autoregressive spectral analysis, are expressed as the ratio of the square root of power spectral density to the average value of R-R intervals [8,9,15–17]. Thus, these parameters may be expected to be unaffected by heart rate, in contrast to the component power spectral densities (absolute powers) of RSA and MWSA.

In the present study, the autoregressive spectral model technique was applied to the study of R-R intervals obtained from healthy men and women under stable conditions to ascertain the effects of age, gender, heart rate, tobacco and alcohol ingestion on the autonomic nervous system function.

Materials and Methods

Subjects

The subjects examined in this study consisted of 68 healthy men, aged 22–75 (mean 45) years, and 33 healthy women, aged 21–66 (mean 38) years: they participated voluntarily in the ECG study that was conducted in conjunction with a routine health checkup at a regional health institute. Males smoked 0–50 (mean 13) cigarettes per day and drank alcohol equivalent to 0–975 (mean 201) ml of 100% ethanol per week; females smoked 0–20 (mean 1) cigarettes per day and drank 0–380 (mean 21) ml per week of 100% ethanol. None were occupationally exposed to neurotoxic substances such as lead or solvents, and none had ever suffered from cardiovascular, endocrinological, neurological or psychological disorders such as arrhythmia, hypotension, hypertension, heart failure, diabetes mellitus, brain cancer or alcoholic dependency. Subjects consumed neither drugs nor alcohol for at least 12 h before the ECG; they also did not smoke for at least 4 h prior to testing.

Electrocardiographic study

The examination was carried out using a NEC-Sanei ECG-amplifier 1271SP and a NEC PC-9801UV2 microcomputer with a Neolog PCN-2198 analog-to-digital converter (sampling time, 1 ms) as shown in Fig. 1. After the subject had lain quietly supine for 10 min, 300 R-R intervals were measured in real time and stored on a floppy disk. Then, consecutive 100 R-R intervals without either an extreme trend or large respiratory changes were extracted from the obtained data in order to avoid non-stationarities as possible (Fig. 1A); such a trend or change in R-R intervals would produce an increase of the very-low-frequency (0 Hz) component. The CV_{RR} was defined as the ratio of the standard deviation of the R-R intervals to their average value (RR_{mean}, ms). The power spectrum of R-R intervals was calculated by autoregressive spectral analysis (Fig. 1B) [1,8,22]. The spectra of the high frequency (RSA) and low frequency (MWSA) components were separated by component analysis (Fig. 1C). The validity of autoregressive model fitting of

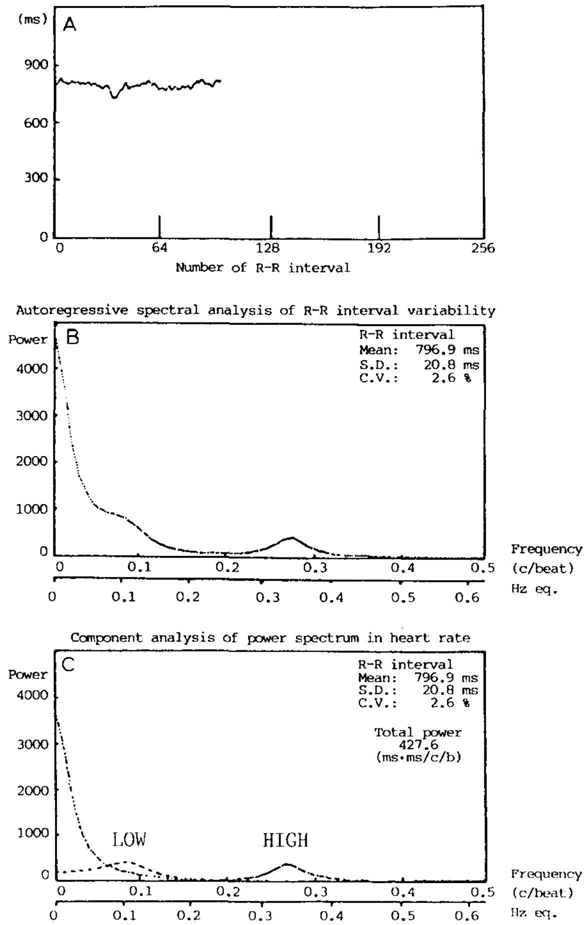

Fig. 1. Outline of the autoregressive spectral analysis of R-R interval variability. Time series of R-R intervals was measured automatically as a function of beat number (**A**). The power spectrum was computed by autoregressive spectral analysis and plotted (**B**). Then, the spectra of individual spectral components were calculated with their center frequencies, associated powers and component coefficients of variation (C-CV) by component analysis (**C**). HIGH and LOW represent the high frequency (respiratory sinus arrhythmia, RSA) and low frequency (Mayer wave related sinus arrhythmia, MWSA) components, respectively.

R-R intervals has been described [8,9,22]. As the square root of the total power spectral density (sum of each component power) is equal to the standard deviation of the R-R intervals (the numerator for calculation of the CV_{RR}), each component coefficient of variation (i.e., $C\text{-}CV_{RSA}$ and $C\text{-}CV_{MWSA}$) was defined as the ratio of the square root of each component power spectral density (PSD_k, ms^2) to the RR_{mean}:

$$C\text{-}CV_k = 100 \cdot (PSD_k)^{1/2} / RR_{mean}$$

where k = RSA or MWSA. RR_{mean} was utilized as the denominator in this equation in order to produce dimensional equivalency between $C\text{-}CV_k$ and CV_{RR} (i.e., expressed as percentage). Daily variation in the CV_{RR} in a healthy 30-year-old man examined repeatedly over an 18-day period was found to be 7.5% [16,17].

Statistical analysis

Differences in the CV parameters (CV_{RR}, $C\text{-}CV_{RSA}$ and $C\text{-}CV_{MWSA}$) and their corresponding power spectral densities (PSD_{RR}, PSD_{RSA} and PSD_{MWSA}) between males and females were tested by analysis of covariance to adjust for the effect of age. Differences between males and females in regression coefficients (gradients) estimated for age were analyzed by the *F*-test for each of the CV parameters. Multiple regression analysis was performed to examine the effects of age, heart rate, tobacco and alcohol ingestion on the CV or PSD parameters in males and females, separately. Simple correlation coefficient was calculated to examine the relations among the CV parameters; moreover, the age-adjusted (i.e., partial) correlation coefficient was analyzed to adjust for the effect of age. All analyses were performed using the Statistical Packages for the Biosciences (SPBS) (Uni-Science Co.).

Results

Table I shows the mean values and standard deviations of the CV and PSD parameters as well as heart rate measured in the 68 healthy men and 33 healthy women, who were the subjects of this study. No significant differences in either CV or PSD parameters or in heart rate were seen between the males and females. There were no significant differences in the regression coefficients (i.e., gradients) estimated for age between males and females for CV_{RR}, $C\text{-}CV_{RSA}$ or C-

CV_{MWSA} ($F = 0.77$, 1.92 and 0.81, respectively, $P > 0.05$; Fig. 2). The PSD distributions were highly skewed to the left and had the large standard deviations relative to the means. In the following analysis, accordingly, these values were transformed into common logarithmic values ($\log_{10}$[PSD]) to approximate normal distributions.

Results of multiple regression analysis indicated that age was negatively related to CV_{RR}, C-CV_{RSA} and C-CV_{MWSA} in both males and females (Table II); heart rate was positively related to C-CV_{MWSA} in males only (Table II and Fig. 3). In the multiple regression analysis of the PSD parameters, age was negatively related to PSD_{RR}, PSD_{RSA} and PSD_{MWSA} in both sexes (Table III); also, heart rate was negatively related to PSD_{RR} and PSD_{RSA} in both sexes.

All of the simple correlation coefficients were statistically significant for the CV_{RR}, C-CV_{RSA} and C-CV_{MWSA} (Table IV), except that between the C-CV_{RSA} and C-CV_{MWSA} in females. However, in the age-adjusted correlation coefficients no significant relationship was found between the C-CV_{RSA} and C-CV_{MWSA} in either males or females.

Discussion

In this study, age was found to be a significant covariate of CV_{RR}, C-CV_{RSA} and C-CV_{MWSA} in the supine posture in both males and females. Similarly, the corresponding PSD parameters (PSD_{RR}, PSD_{RSA} and PSD_{MWSA}) were negatively related to age. These results agree with previously reported studies using the CV_{RR} [7,8,32] and PSD parameters [22,28]. Similar age-dependent changes have been observed in peripheral and central nervous system function [4,14]. Age should, therefore, be included as a principal covariate in human studies of autonomic nervous system function.

In the present study, the effects of heart rate on the CV parameters differed from its effects on the PSD parameters. Specifically, the PSD_{RR} and PSD_{RSA} were negatively related to heart rate in both sexes, while no significant relationships were seen between heart rate and the corresponding CV parameters. Assuming that the CV_{RR} is dependent only on age (in fact, none of the potential covariates examined in this study except age was significantly related to the CV_{RR}), the PSD parameters may increase as the RR_{mean} (i.e., the reciprocal number of heart rate) becomes longer. Thus, these CV parameters (except C-CV_{MWSA}) are less markedly affected by heart rate than the PSD parameters. However, the PSD_{MWSA} seems to be unaffected by heart rate.

A number of investigators have demonstrated that the high frequency (RSA) component of CV_{RR} is mediated by parasympathetic activity [2,3,6,11,25,27], indicating that the C-CV_{RSA} re-

TABLE I

CV parameters (CV_{RR}, C-CV_{RSA} and C-CV_{MWSA}), power spectral densities (PSD_{RR}, PSD_{RSA} and PSD_{MWSA}) corresponding to CV parameters and heart rate in 68 healthy men and 33 healthy women [a]

	Men	Women	Analysis of covariance (F value) [b]
	Mean ± SD	Mean ± SD	
Age (years)	45 ± 11	38 ± 12	
CV_{RR} (%)	3.96 ± 1.52	4.58 ± 1.80	0.05
C-CV_{RSA} (%)	1.79 ± 0.94	2.25 ± 1.32	0.20
C-CV_{MWSA} (%)	2.11 ± 1.64	2.17 ± 1.34	2.24
PSD_{RR} (ms^2)	1457.3 ± 994.8	1993.4 ± 1687.7	0.14
PSD_{RSA} (ms^2)	338.3 ± 376.0	570.1 ± 763.3	0.85
PSD_{MWSA} (ms^2)	512.2 ± 760.7	499.8 ± 716.1	2.13
Heart rate (/min)	67 ± 9	69 ± 10	0.47

[a] Abbreviations same as in text.
[b] $P > 0.05$ (the effect of age was eliminated).

TABLE II

Effects of age, heart rate, tobacco and alcohol ingestion on CV parameters (CV_{RR}, $C\text{-}CV_{RSA}$ and $C\text{-}CV_{MWSA}$) [a] in 68 healthy men and 33 healthy women; results of multiple regression analysis

	Multiple correlation coefficient	Standardized regression coefficient			
		Age	Heart rate	Tobacco	Alcohol
Men:					
CV_{RR}	0.674 [d]	−0.672 [d]	0.084	0.089	0.068
$C\text{-}CV_{RSA}$	0.543 [d]	−0.496 [d]	0.048	0.025	−0.148
$C\text{-}CV_{MWSA}$	0.624 [d]	−0.532 [d]	0.277 [c]	0.070	0.111
Women:					
CV_{RR}	0.739 [d]	−0.707 [d]	−0.108	0.460	−0.526
$C\text{-}CV_{RSA}$	0.619 [c]	−0.587 [d]	−0.164	−0.032	0.023
$C\text{-}CV_{MWSA}$	0.550 [b]	−0.520 [c]	0.187	0.223	−0.324

[a] Abbreviations same as in text.
[b] $P < 0.05$, [c] $P < 0.01$ and [d] $P < 0.001$.

flects the parasympathetic activity. Administration of atropine causes a significant reduction of the RSA component power in both the supine and standing postures, although propranolol given alone has no effect on this component. The low frequency (MWSA) component, by contrast, has been considered to be mediated jointly by sympathetic and parasympathetic activities [2,3,11,22,25]. In this study, no significant correlation between the $C\text{-}CV_{RSA}$ and $C\text{-}CV_{MWSA}$ was found in either males or females when the effect of age was controlled. This finding suggests that the $C\text{-}CV_{MWSA}$ is independent of the $C\text{-}CV_{RSA}$ in human autonomic nervous system function, at least in the supine posture. Thus, the physiological function of $C\text{-}CV_{MWSA}$ measured under static conditions may not always correspond to that shown by pharmacologically induced changes; nevertheless, the CV_{RR} appears to represent both parasympathetic and sympathetic activities, inasmuch as it is composed of the RSA, MWSA and other components. Actually, the CV_{RR} was signif-

TABLE III

Effects of age, heart rate, tobacco and alcohol ingestion on power spectral densities (transformed values, $\log_{10}[PSD]$) corresponding to CV_{RR}, $C\text{-}CV_{RSA}$ and $C\text{-}CV_{MWSA}$ in 68 healthy men and 33 healthy women: results of multiple regression analysis [a]

	Multiple correlation coefficient	Standardized regression coefficient			
		Age	Heart rate	Tobacco	Alcohol
Men:					
PSD_{RR}	0.713 [d]	−0.694 [d]	−0.332 [d]	0.061	0.104
PSD_{RSA}	0.583 [d]	−0.556 [d]	−0.250 [b]	0.032	−0.071
PSD_{MWSA}	0.586 [d]	−0.595 [d]	−0.013	0.020	0.135
Women:					
PSD_{RR}	0.826 [d]	−0.626 [d]	−0.471 [d]	0.573	−0.594
PSD_{RSA}	0.775 [d]	−0.652 [d]	−0.392 [c]	0.159	−0.124
PSD_{MWSA}	0.572 [b]	−0.552 [c]	−0.086	0.153	−0.217

[a] Abbreviations same as in text.
[b] $P < 0.05$, [c] $P < 0.01$ and [d] $P < 0.001$.

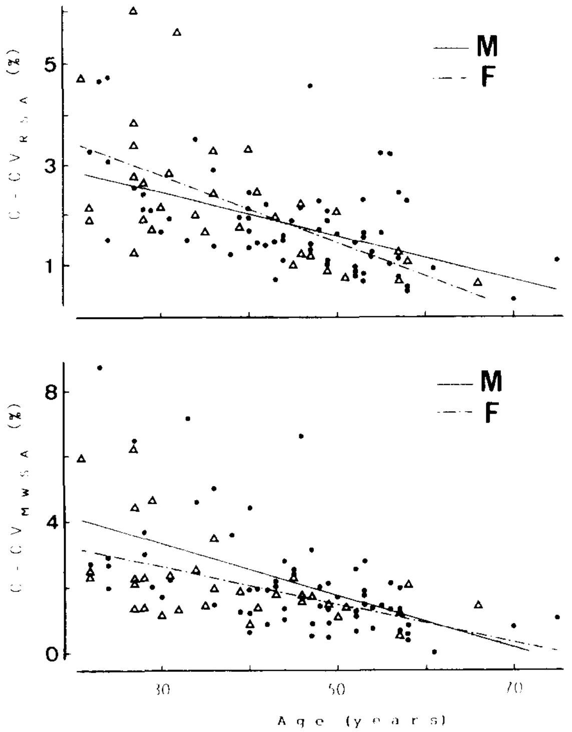

Fig. 2. Relationship between CV parameters (C-CV_{RSA} and C-CV_{MWSA}) and age in 68 healthy men (●) and in 33 healthy women (△). Correlation coefficient (r), regression equation and significance level for each relationship were as follows: $r = -0.658$, $Y = 7.96 - 0.088 \cdot$Age and $P < 0.001$ for the male CV_{RR}; $r = -0.709$, $Y = 8.68 - 0.108 \cdot$Age and $P < 0.001$ for the female CV_{RR}; $r = -0.522$, $Y = 3.74 - 0.043 \cdot$Age and $P < 0.001$ for the male C-CV_{RSA}; $r = -0.596$, $Y = 4.77 - 0.066 \cdot$Age and $P < 0.001$ for the female C-CV_{RSA}; $r = -0.545$, $Y = 5.69 - 0.079 \cdot$Age and $P < 0.001$ for the male C-CV_{MWSA}; and, $r = -0.510$, $Y = 4.35 - 0.057 \cdot$Age and $P < 0.01$ for the female C-CV_{MWSA}.

icantly correlated in this study with both the C-CV_{RSA} and C-CV_{MWSA}.

In males, the C-CV_{MWSA} was positively related to heart rate (Table II and Fig. 3) in contrast with the negative relationships between the PSD parameters and heart rate observed in both sexes. Conversely, this relation was not statistically significant in women, but the sample size of the female group was much smaller than that of the male group. The present finding in males suggests that the C-CV_{MWSA} is more closely associated with sympathetic activity than with parasympathetic activity, because heart rate is raised when

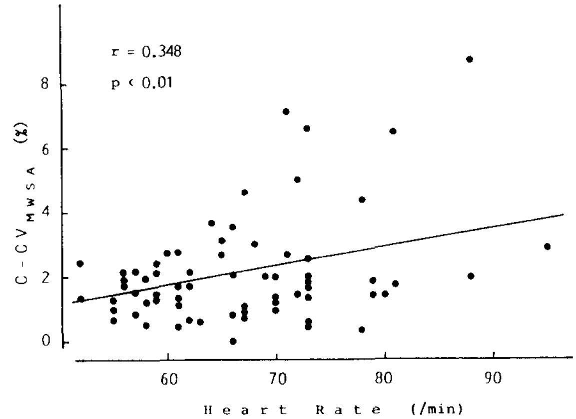

Fig. 3. Relationship between the C-CV_{MWSA} and heart rate in 68 healthy men. r indicates a simple correlation coefficient. The age-adjusted (partial) correlation coefficient was 0.319 ($P < 0.01$). Regression equation was given by $Y = -2.09 + 0.063 \cdot$(Heart rate).

fewer nerve impulses are conducted to the heart by the vagal nerve [5,30]. Additional study with an adequate animal model will be needed to re-examine the physiological role of sympathetic activity on heart rate.

In the current study, no significant differences between males and females were seen either in the CV parameters or in heart rate when adjustment for the effect of age was made. In addition,

TABLE IV

Relations among CV_{RR}, C-CV_{RSA} and C-CV_{MWSA} in 68 healthy men and 33 healthy women: results of simple and age-adjusted (i.e., partial) correlation coefficients [a,b]

	CV_{RR}	C-CV_{RSA}	C-CV_{MWSA}
Men:			
CV_{RR}		0.672 [d]	0.803 [d]
C-CV_{RSA}	0.511 [d]		0.446 [d]
C-CV_{MWSA}	0.704 [d]	0.226	
Women:			
CV_{RR}		0.709 [d]	0.660 [d]
C-CV_{RSA}	0.506 [c]		0.266
C-CV_{MWSA}	0.491 [c]	−0.055	

[a] Simple correlation coefficients are shown above the diagonal and partial correlation coefficients are shown below the diagonal.

[b] Abbreviations same as in text.

[c] $P < 0.01$ and [d] $P < 0.001$.

there were no significant differences between both sexes in the regression coefficients relating age to CV_{RR}, C-CV_{RSA} or C-CV_{MWSA}. Most electrophysiological measures including cerebral evoked potentials, do not appear to be significantly different between males and females [4], with the exception of the latency of visual evoked potentials [29]. Thus, measures of R-R interval variability might be expected to be uninfluenced by gender.

Tobacco or alcohol ingestion was not found to be a significant covariate of R-R interval variability parameters in the present study. The CV_{RR}, C-CV_{RSA} and C-CV_{MWSA}, however, have been observed to be significantly reduced in male patients with alcoholic dependency as compared with sex- and age-matched controls [15]; also, acute ethanol intake was connected with an early increase in heart rate [33]. The subjects who smoke more than one cigarette per day have shown significant depression of the CV_{RR} in comparison to non-smokers, although no significant dose–effect relationship was observed [18]; especially, heavy smoking (> 25 cigarettes/day) seems to cause long-term reduction in vagal cardiac control [9]. Furthermore, chemical substances such as nicotine or carbon monoxide are well-known to influence the cardiovascular system acutely [5,9,12,26]. There are two possible explanations for our not having observed significant effects of tobacco and alcohol ingestion on the CV parameters: (1) The daily dose of tobacco and alcohol that our subjects consumed in recent years was used as an independent variable in the present analysis, as the subjects' estimated total doses were not always definite. This daily dose may not fully reflect the chronic effects of tobacco or alcohol ingestion. (2) The subjects assembled in this study may have avoided excessive drinking or smoking, since they were much concerned with their health. Indeed, all the subjects had normal liver function in the biochemical examination conducted concurrently, and the number of heavy smokers (> 25 cigarettes/day) was 14 (35% of all the smokers). Further epidemiological study will be required to clarify whether long-term use of tobacco or alcohol causes dysfunction of the autonomic nervous system.

To be useful for evaluation of autonomic nervous system dysfunction resulting from environmental insult, tests should provide standardized, reliable, objective, and valid measures [21]. Other features desirable in worker assessments are that tests should be non-invasive and simple [20]. Electrocardiographic assessment of variability in RR intervals (CV_{RR}), despite its limitations and potential uncertainties in analytical process [24], fulfills not only these latter criteria, but also seems to provide objective and reproducible information on the functional status of the autonomic nervous system; at the same time, researchers' attention should be directed to both age and heart rate to preserve the comparability of the ECG data between case and control groups, which possibly applies to other methods, as introduced by Pagani et al. [22–24], of normalizing spectral component. On the other hand, the contribution ratio (i.e., the square of the multiple regression coefficients in Table II), explained by age, heart rate, tobacco and alcohol ingestion in this study, ranged from 30 to 55%, indicating that other factors such as blood pressure [22] or body temperature [27], probably related to the very-low-frequency component, may influence these parameters.

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References

1 Akaike, H., Fitting autoregressive models for prediction, Ann. Inst. Stat. Math., 21 (1969) 243–247.
2 Akselrod, S., Gordon, D., Ubel, F.A., Shannon, D.C., Barger, A.C. and Cohen, R.J., Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control, Science, 213 (1981) 220–222.
3 Akselrod, S., Gordon, D., Madwed, J.B., Snidman, N.C., Shannon, D.C. and Cohen, R.J., Hemodynamic regulation: investigation by spectral analysis, Am. J. Physiol., 249 (1985) H867–875.

4 Aminoff, M.J., Electrodiagnosis in Clinical Neurology, Churchill Livingstone, New York, 1986.

5 Braunwald, F. (Ed.), Heart Disease (3rd edn.), Saunders, Philadelphia, 1983, pp. 401–414.

6 Eckberg, D.L., Human sinus arrhythmia as an index of vagal cardiac outflow, J. Appl. Physiol., 54 (1983) 961–966.

7 Harada, N., Yoshida, I. and Kimura, K., Heart rate variation and serum dopamine-beta-hydroxylase activity in workers exposed to vibration, Int. Arch. Occup. Environ. Health, 61 (1989) 369–373.

8 Hayano, J., Quantitative assessment of autonomic function by autoregressive spectral analysis of heart rate variability: effect of posture, respiratory frequency, and age, Jiritsushinkei, 25 (1988) 334–344.

9 Hayano, J., Yamada, M., Sakakibara, Y., Fujinami, T., Yokoyama, K., Watanabe, Y. and Takata, K., Short- and long-term effects of cigarette smoking on heart rate variability, Am. J. Cardiol. 65 (1990) 84–88.

10 Heinonen, E., Farkkila, M., Forsstrom, J., Antila, K., Jalonen, J., Korhonen, O. and Pyykko, I., Autonomic neuropathy and vibration exposure in forestry workers, Br. J. Ind. Med. 44 (1987) 412–416.

11 Japundzic, N., Grichois, M-L., Zitoun, P., Laude, D. and Elghozi, J-L., Spectral analysis of blood pressure and heart rate in conscious rats: effects of autonomic blockers, J. Auton. Nerv. Syst., 30 (1990) 91–100.

12 LaDou, J. (Ed.), Occupational Medicine, Appleton & Lange, Norwalk, 1990.

13 Lishner, M., Akselrod, S., Mor Avi, V., Oz, O., Divon, M. and Ravid, M., Spectral analysis of heart rate fluctuations: a non-invasive, sensitive method for the early diagnosis of autonomic neuropathy in diabetes mellitus, J. Auton. Nerv. Syst., 19 (1987) 119–125.

14 Murata, K. and Araki, S., Effects of age, height and skin temperature on latencies of short-latency somatosensory evoked potentials, Jpn J. EEG EMG, 13 (1985) 152–158.

15 Murata, K., Yokoyama, K. and Araki, S., Analyses of the distribution of nerve conduction velocities (DCV) and electrocardiographic R-R interval variability in patients with alcoholic dependency, Jpn J. Hyg., 45 (1990) 351 (in Japanese).

16 Murata, K., Araki, S. and Maeda, K., Autonomic and peripheral nervous system dysfunction in workers exposed to hand-arm vibration: a study of R-R interval variability and distribution of nerve conduction velocities, Int. Arch. Occup. Environ. Health, 63 (1991) 205–211.

17 Murata, K. and Araki, S., Autonomic nervous system dysfunction in workers exposed to lead, zinc and copper in relation to peripheral nerve conduction: a study of R-R interval variability, Am. J. Ind. Med., 20 (1991) 663–671.

18 Muto, T., Omae, K. and Sakurai, H., Effects of smoking on the autonomic nervous system: a study of electrocardiographic R-R interval variation, Jpn J. Public Health, 34 (1987) 388–390 (in Japanese).

19 Myers, G.A., Martin, G.J., Magid, N.M., Barnett, P.S., Schaad, J.W., Weiss, J.S., Lesch, M. and Singer, D.H., Power spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods, IEEE Trans. Biomed. Eng., BME-33 (1986) 1149–1156.

20 NIOSH, Criteria for a Recommended Standard: Occupational Exposure to Hand-Arm Vibration, U.S. Department of Health and Human Services, Cincinnati, 1989 (DHHS Publication No. 89–106).

21 Otto, D.A., The use of sensory evoked potentials in neurotoxicity testing of workers, Seminars Occup. Med., 1 (1986) 175–183.

22 Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., Piccaluga, E., Turiel, M., Baselli, G., Cerutti, S. and Malliani, A., Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog, Circ. Res., 59 (1986) 178–193.

23 Pagani, M., Malfatto, G., Pierini, S., Casati, R., Masu, A.M., Poli, M., Guzzetti, S., Lombardi, F., Cerutti, S. and Malliani, A., Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy, J. Auton. Nerv. Syst., 23 (1988) 143–153.

24 Pagani, M., Rimoldi, O., Pizzinelli, P., Furlan, R., Crivellaro, W., Liberati, D., Cerutti, S. and Malliani, A., Assessment of the neural control of the circulation during psychological stress, J. Auton. Nerv. Syst., 35 (1991) 33–42.

25 Pomerantz, B., Macaulay, R.J.B., Caudill, M.A., Kutz, I., Adam, D., Gordon, D., Kilborn, K.M., Barger, A.C., Shannon, D.C., Cohen, R.J. and Benson, H., Assessment of autonomic function in humans by heart rate spectral analysis, Am. J. Physiol., 249 (1985) H151–153.

26 Robertson, D., Tseng, C.J. and Appalsamy, M., Smoking and mechanisms of cardiovascular control, Am. Heart J., 115 (1988) 258–263.

27 Sayers, B.Mc.A., Analysis of heart rate variability, Ergonomics, 16 (1973) 17–32.

28 Shannon, D.C., Carley, D.W. and Benson, H., Aging of modulation of heart rate, Am. J. Physiol., 253 (1987) H874–877.

29 Stockard, J.J., Hughes, J.F. and Sharbrough, F.W., Visually evoked potentials to electronic pattern reversal: latency variations with gender, age and technical factors, Am. J. EEG Technol., 19 (1979) 171–204.

30 Thews, G. and Vaupel, P., Autonomic Functions in Human Physiology, Springer-Verlag, Berlin, 1985.

31 Trap-Tensen, J., Effects of smoking on the heart and peripheral circulation, Am. Heart J., 115 (1988) 263–267.

32 Wheeler, T. and Watkins, P.J., Cardiac denervation in diabetes, Br. Med. J., 8 (1973) 584–586.

33 Zilm, D.H., Ethanol-induced spontaneous and evoked EEG, heart rate, and respiration rate changes in man, Clin. Toxicol., 18 (1981) 549–563.