ELSEVIER

Journal of the Autonomic Nervous System 48 (1994) 105–111

Journal of the
Autonomic
Nervous
System

Autonomic neurotoxicity of alcohol assessed by heart rate variability

Katsuyuki Murata [a], Shunichi Araki [a,*], Kazuhito Yokoyama [a], Fumihiro Sata [a], Kohei Yamashita [a], Yasuhiko Ono [b]

[a] *Department of Public Health, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan;*
[b] *Department of Pediatrics, Nagasaki University Faculty of Medicine, 7-1 Sakamoto, Nagasaki 852, Japan*

(Received 15 April 1993; revision received and accepted 2 September 1993)

Abstract

Measurement of heart rate variability ($CV_{R\text{-}R}$) provides a promising approach for evaluation of the autonomic nervous function. Specifically, high- and low-frequency component coefficients of variation of the $CV_{R\text{-}R}$ ($C\text{-}CV_{HF}$ and $C\text{-}CV_{LF}$), computed from component spectral powers by autoregressive spectral and component analyses, are inferred to reflect parasympathetic and sympathetic activities, respectively. To assess the acute and chronic effects of alcohol on parasympathetic and sympathetic activities, ECGs in the supine posture were obtained in 11 male healthy volunteers, and in 23 male patients with severe alcoholic dependency together with the same number of age-matched healthy men. Significant changes in the $CV_{R\text{-}R}$ and heart rate were found 1 h after ethanol intake in the volunteers; also, the 1-h alteration in heart rate after intake was inversely correlated with that in the $C\text{-}CV_{HF}$. The $CV_{R\text{-}R}$, $C\text{-}CV_{HF}$ and $C\text{-}CV_{LF}$ were significantly depressed in the alcoholics compared to the matched controls. In the alcoholics, the age-adjusted correlation coefficients between not only the $CV_{R\text{-}R}$ but also $C\text{-}CV_{HF}$ and heart rate were negatively significant. These data suggest that acute and habitual intake of alcohol affects cardiac autonomic functions including sympathetic and parasympathetic activities; and, increase of heart rate in relation to alcohol, at least in alcoholics, seems to occur through reducing the parasympathetic activity.

Key words: Alcohol (ethanol); R-R interval variability; Parasympathetic and sympathetic activity; Heart rate; Human

1. Introduction

There is evidence that chronic excessive use of alcohol or acute intoxication from alcohol causes dysfunctions of the autonomic nervous system: impaired autonomic function has been shown in alcoholics assessed by sympathetic skin response [33], heart rate variation [4,11,17,36] and pathological findings in the vagus nerve and the sympathetic trunk [7,25]. With the exception of such extreme cases, however, attempts to establish links between sympathetic nervous activity and cardiovascular changes after alcohol administration have proved inconclusive [13]. For example, acute ingestion of alcohol has been reported to be associated with an early increase in heart rate [14,29,31,37]; in another study, the heart rate

* Corresponding author.

SSDI 0165-1838(93)E0124-N

remained unaltered after alcohol consumption while heart rate variability was reduced immediately [34]. Further study will be required to clarify the actions of the parasympathetic and sympathetic activities on heart rate following alcohol intake.

Previous work with alcohol intake has concentrated on sympathetic depression since the first observation by Barraclough and Sharpey-Schafer [3,11]. On the other hand, parasympathetic activity appears to be more susceptible to several hazardous factors in the environment than does sympathetic [9,19–21,24]. Such discussion might differ with the methods used, e.g., hormonal examinations vs. tests of heart rate variability. In this sense, it would be valuable to confirm the acute and chronic effects of alcohol on sympathetic and parasympathetic activities, by using tests offering objective and reproducible information on the functional status of the autonomic nervous system.

The measurement of the coefficient of variation in the electrocardiographic R-R intervals ($CV_{R\text{-}R}$) at rest provides a promising approach for evaluation of cardiac autonomic function in clinical investigations [5,16,27,34,36]. Furthermore, two major components, the high-frequency (HF) and low-frequency (LF) components which are dissociated from the R-R interval variability using spectral analyses, seem to reflect parasympathetic and sympathetic activities, respectively [1,5,8,10,22,26–28]: (1) intravenous atropine (i.e., parasympathetic blocker) abolishes the HF component but propranolol (i.e., beta-sympathetic blocker) has no effect on it; (2) the LF component is considered to be derived from the fluctuation in the vasomotor activity through the baroreflex mechanism and shows a β-adrenergically mediated increase in the standing posture; and (3) the value, normalized by average R-R, of the LF component in the supine posture is independent of that of the HF component among healthy men and has a positive relation to heart rate. Despite the limitations and potential uncertainties in analytical process of the R-R intervals [5], accordingly, this method is expected to be useful for objective assessment of parasympathetic and sympathetic dysfunction resulting from environmental substances. In the present study, this technique was applied to two studies of R-R intervals obtained from healthy volunteers and patients diagnosed as alcohol dependent.

2. Materials and methods

2.1. Study of acute effects

The subjects consisted of 11 male students, aged 20 to 25 (mean 22) years; they consented readily to become volunteers for this study. All these subjects had a history of alcohol-induced facial flushing. They drank alcohol equivalent to 0–300 (mean 68) ml of 100% ethanol per week and smoked 0–20 (mean 2) cigarettes per day. They had never suffered from neurologic, endocrinologic or psychiatric disorders. None of them took drugs, alcohol or other beverages containing caffeine in the afternoon of the examination day.

ECG testing for the 11 healthy volunteers was conducted by ingesting 200 ml Japanese spirits (containing 25% ethanol, 0.54–0.66 g of ethanol/kg body weight) at 4:50–5:00 p.m.; the R-R intervals on ECG were measured in the same subjects at 4:30–4:50 p.m., at 6:00–6:20 p.m. and at 7:00–7:20 p.m. (i.e., before and 1 and 2 h after alcohol ingestion), totally three times on the same day. Moreover, the ECG testing was done again for 9 of those 11 subjects in the same manner, by ingesting 200 ml orange juice, on another day for reference to circadian rhythm within the same time period, 4:30–7:00 p.m.

2.2. Study of chronic effects

The subjects were 23 male patients who had been diagnosed as alcohol-dependent by one psychiatrist according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised [2]. All patients had drunk alcohol (more than 700 ml of 100% ethanol per week) over 10 years. Their ages ranged from 30 to 64 (mean 50) years. They smoked 0–40 (mean 17) cigarettes per day. None of them had suffered from endocrinological disorders, or had been ex-

posed to heavy metals or solvents occupationally. Four patients had subjective symptoms of sensory abnormalities such as paresthesia and pain in their legs at the time of the examination [6]. None of them had taken either drugs or alcohol for at least 8 h before the ECG measurement.

The control subjects were 23 healthy men, matched to each patient by age (3 years span), i.e., 30–63 (mean 49) years. Their alcohol and tobacco consumption ranged from 0 to 540 (mean 225) ml/week and from 0 to 40 (mean 10) cigarettes/day, respectively. None of the controls had ever been exposed to neurotoxic substances occupationally, and none had ever suffered from neurologic, cardiovascular or other potentially confounding disorders. There was no significant difference in age or tobacco consumption between the controls and the alcoholic patients (paired sample t-test, $t = 0.92$ and 2.06; $P > 0.05$).

The nature of the procedure used in the present study was fully explained to all subjects, and the study was carried out with their informed consent.

2.3. Electrocardiographic study

The examination was carried out using an ECG-amplifier (NEC-Sanei 1271SP) and a microcomputer (NEC PC9801UV2) with an analog-to-digital converter (Neolog PCN-2198; sampling time, 1 ms) according to our method reported previously [22]. After the subject had lain quietly supine for 10 min, 300 R-R intervals on the ECG were measured in real time and stored on floppy disk; consecutive 100 R-R intervals without an extreme trend or very large respiratory changes were extracted from the obtained data to avoid non-stationarities. The $CV_{R\text{-}R}$ was defined as the ratio of the standard deviation of the R-R intervals to their average value ($R\text{-}R_{mean}$, ms). The power spectrum of R-R intervals was computed by autoregressive spectral analysis. The spectrum of each of two components, i.e., the high-frequency (HF) component at the center frequency of 0.15–0.3 Hz and low-frequency (LF) component at 0.05 to 0.15 Hz, was separated by component analysis [5,8,19–22]. As the square root of the total power spectral density is equal to the standard deviation of the R-R intervals, each component coefficient of variation (i.e., $C\text{-}CV_{HF}$ and $C\text{-}CV_{LF}$) was defined as the ratio of the square root of each component power spectral density (PSD_k, ms^2) to the $R\text{-}R_{mean}$: $C\text{-}CV_k = 100 \cdot (PSD_k)^{1/2}/R\text{-}R_{mean}$, where k = HF or LF. In addition, the LF/HF ratio was calculated from the PSD_{LF} and PSD_{HF} to obtain the infor-

Table 1
$CV_{R\text{-}R}$, $C\text{-}CV_{HF}$, $C\text{-}CV_{LF}$, LF/HF ratio and heart rate (mean ± SD) before and 1 and 2 h after alcohol or juice ingestion in 11 male healthy subjects: results of analysis of repeated measurement [a]

	Before	1 h	2 h	F value
Alcohol ingestion				
$CV_{R\text{-}R}$ (%)	7.20 ± 3.03	5.29 ± 2.29 [c]	5.38 ± 2.26 [c]	4.95 [d]
$C\text{-}CV_{HF}$ (%)	3.94 ± 1.47	3.45 ± 2.56	2.76 ± 0.89	1.97
$C\text{-}CV_{LF}$ (%)	4.56 ± 3.35	2.71 ± 1.32	3.55 ± 2.12	2.22
LF/HF ratio	1.38 ± 1.08	2.31 ± 4.30	1.79 ± 1.42	0.35
Heart rate (/min)	60 ± 8	71 ± 19 [c]	67 ± 19	4.42 [d]
Juice ingestion [b]				
$CV_{R\text{-}R}$ (%)	6.20 ± 1.95	6.08 ± 2.58	5.83 ± 1.96	0.16
$C\text{-}CV_{HF}$ (%)	4.12 ± 2.02	3.45 ± 2.26	3.60 ± 2.26	0.80
$C\text{-}CV_{LF}$ (%)	3.29 ± 1.26	3.21 ± 2.26	2.73 ± 1.16	0.40
LF/HF ratio	0.97 ± 0.73	1.36 ± 1.66	1.19 ± 1.24	0.60
Heart rate (min)	62 ± 13	58 ± 11	57 ± 8 [c]	5.22 [e]

[a] Abbreviations same as in text.
[b] The sample number was 9 of the 11 healthy subjects.
[c] $P < 0.05$ (results of Scheffe multiple comparison as compared with the value prior to alcohol or juice ingestion).
[d] $P < 0.05$ (Analysis of variance, $df_1 = 2$ and $df_2 = 20$).
[e] $P < 0.05$ (Analysis of variance, $df_1 = 2$ and $df_2 = 16$).

mation on sympatho-vagal balance [26,27]. The daily variation in the $CV_{R\text{-}R}$ in a healthy 30-year-old man examined repeatedly over an 18-day-period was found to be 7.5% [22]. The C-CV_{HF} and C-CV_{LF} are thought to reflect parasympathetic and sympathetic activities, respectively [1,5,8,10,22,26,27]; also, the $CV_{R\text{-}R}$ reveals higher functions of the autonomic nervous system [15], as well as both activities.

2.4. Statistical analysis

Regarding evaluation of acute effect of alcohol the significance level of repeated measurements in each of CV parameters (i.e., $CV_{R\text{-}R}$, C-CV_{HF}, C-CV_{LF} and LF/HF ratio) on the same day was analyzed by two-way analysis of variance; and, when the F-value was statistically significant ($P < 0.05$), the Scheffe multiple comparison was conducted to assess the differences among values measured on the three different times. The relation of the changes in the CV parameters after alcohol ingestion to both ethanol dose per body weight and the change in heart rate was tested by the Spearman's rank correlation coefficient. With respect to evaluation of chronic effect of alcohol, the paired sample t-test and the Hotelling T^2 statistic were used to determine the significance of the matched differences between the patients with alcohol dependency and the age-matched controls [18]. The correlations between CV parameters and heart rate in each of two groups were analyzed by the age-adjusted (partial) correlation coefficient because of the wide age range. All analyses were performed using the Statistical Packages for the Biosciences (SPBS, Uni-Science Co.).

3. Results

3.1. Acute effects of alcohol

Significant changes in the $CV_{R\text{-}R}$ and heart rate were found after alcohol ingestion in the 11 healthy subjects (Table 1). The $CV_{R\text{-}R}$ was significantly reduced at 1 and 2 h after alcohol ingestion, and heart rate increased significantly 1 h later. The 1-h change in the heart rate was negatively correlated with the 1-h change in the C-CV_{HF} (Fig. 1); but, no significant correlation was seen between ethanol dose per body weight and any changes in the $CV_{R\text{-}R}$, C-CV_{HF}, C-CV_{LF}, LF/HF ratio or heart rate ($P > 0.05$).

In 9 of the 11 healthy subjects, the heart rate significantly decreased 2 h after ingestion of orange juice (Table 1). However, there were no significant changes in the $CV_{R\text{-}R}$, C-CV_{HF}, C-CV_{LF} or LF/HF ratio due to juice intake.

3.2. Chronic effects of alcohol

The $CV_{R\text{-}R}$, C-CV_{HF} and C-CV_{LF} in the 23 patients with alcoholic dependency were signifi-

Table 2
Differences in $CV_{R\text{-}R}$, C-CV_{HF}, C-CV_{LF}, LF/HF ratio and heart rate between 23 male patients with alcohol dependency and same number of age-matched control subjects (means with ranges in parentheses) [a]

	Patients	Controls	Matched differences [b]
$CV_{R\text{-}R}$ (%) [c]	2.50 (1.32–4.63)	3.75 (1.59–5.89)	−1.25 ± 1.04 [d]
C-CV_{HF} (%) [c]	1.33 (0.68–2.92)	1.76 (0.54–4.55)	−0.43 ± 0.97 [e]
C-CV_{LF} (%) [c]	1.24 (0.20–4.40)	1.79 (0.51–4.40)	−0.55 ± 1.14 [e]
LF/HF ratio	2.64 (0.04–38.4)	1.70 (0.15–11.7)	0.94 ± 8.21
Heart rate (min)	69 (46–94)	65 (52–88)	4 ± 16

[a] Abbreviations same as in text.
[b] Mean and standard deviation of matched differences.
[c] The Hotelling T^2 statistic between the patients and controls among the $CV_{R\text{-}R}$, C-CV_{HF} and C-CV_{LF} was 34.1 [$F(3,20) = 10.3$, $P < 0.01$].
[d] $P < 0.001$.
[e] $P < 0.05$ (paired sample t-test).

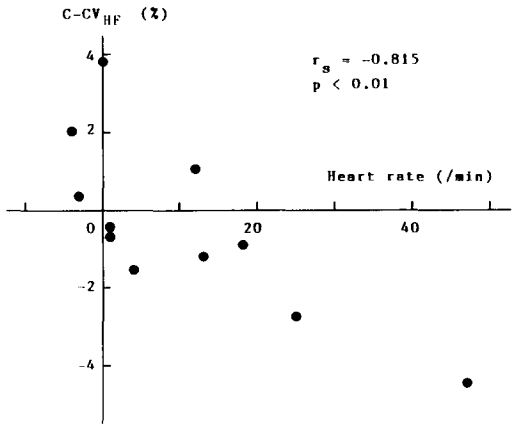

Fig. 1. Relationship between 1-h changes of the C-CV_{HF} and heart rate after alcohol ingestion among 11 male healthy subjects. r_s represents the Spearman's rank correlation coefficient.

cantly depressed as compared with those in the same number of control subjects, whereas there was no significant difference in LF/HF ratio or heart rate between them (Table 2). Also, only two partial correlation coefficients, i.e., both between the CV_{R-R} and heart rate and between the C-CV_{HF} and heart rate in the patients, were statistically significant (Table 3).

4. Discussion

In the present study of 11 healthy volunteers with facial flushing, the CV_{R-R} decreased significantly 1 and 2 h after ethanol intake of 0.54–0.66 (mean 0.61) g/kg body weight, despite the absence of significant changes in any CV parameters after juice intake. The CV_{R-R} change agrees with the data of Weise et al. [34], who found a significant decrease in heart rate variability at 30 and 60 min after 8 healthy volunteers ingested 0.7 g of ethanol/kg body weight. Blood ethanol concentration reaches the peak at 30–60 min after intake [14,37]; its immediate effects on the circulation are relatively minor but the polysynaptic structures of the reticular activating system and certain cortical sites are particularly susceptible to ethanol [29]. In an investigation of solvent workers there is an assumption that depression of the CV_{R-R} and C-CV_{HF} due to mixed organic solvents may originate from impairment of the higher autonomic centers rather than of the heart [20]. Based upon these findings, ethanol may affect higher centers of the autonomic nervous system transiently, as well as the highly integrated function that can be evaluated by the P300 latency of event-related potentials [23,30].

Table 3
Age-adjusted (partial) and simple correlation coefficients (r_p and r_s) between the CV parameters (CV_{R-R}, C-CV_{HF} and C-CV_{LF}) and heart rate in 23 male patients with alcohol dependency and in 23 age-matched control subjects [a]

Correlation to heart rate	Patients		Controls	
	r_p	(r_s)	r_p	(r_s)
CV_{R-R}	−0.598 [b]	(−0.485) [c]	0.120	(−0.057)
C-CV_{HF}	−0.423 [c]	(−0.348)	−0.052	(−0.097)
C-CV_{LF}	−0.206	(−0.137)	−0.041	(−0.178)

[a] Abbreviations same as in text.
[b] $P < 0.01$.
[c] $P < 0.05$ (t-test).

Significant increase of heart rate associated with acute consumption of alcohol (Table 1), in contrast to the decrease of heart rate when juice was administered, is consistent with several previous observations [14,29,31,37]. This change has been thought to be attributable to the increased sympathetic activity in the literature [12,13], inasmuch as ethanol does not affect the heart rate response to atropine. Also, Zilm speculated that the increase in heart rate reflected an initial effect of alcohol on the medullary vasomotor centers, and that the lasting effect could probably be accounted for by secondary effects of alcohol mediated through the adrenergic and/or cholinergic neurotransmitter system [37].

However, the C-CV_{HF} and C-CV_{LF} at 1 and 2 h after alcohol intake were depressed in our healthy volunteers, even though the differences were not statistically significant. And, a significant correlation was found between the C-CV_{HF} and heart rate in the alcoholic patients (Table 3), as reviewed by Johnson et al. [13]. It appears likely that the functional state of the vasomotor center can be influenced by impulses from the relatively nearby respiratory centers [35]. Accordingly, the significant and negative relationship

observed between 1-h changes of the C-CV_{HF} and heart rate (Fig. 1) suggests that increase of heart rate due to alcohol ingestion might have occurred through reducing parasympathetic impulses that are conducted to the heart by the vagus nerve. The explication of this physiological mechanism awaits further research with adequate animal models.

In the current study, the C-CV_{HF} and C-CV_{LF}, as well as the CV_{R-R} were significantly depressed in the patients with alcoholic dependency, in whom the faster myelinated fibers of the median nerve have been suspected of being impaired in our previous investigation using the distribution of nerve conduction velocities [6]. Similar autonomic dysfunctions in alcoholics have been previously reported, implying the largely irreversible deleterious effects on the heart [32], degeneration of the myelinated fibers in the vagus nerve and thoracic paravertebral sympathetic trunk [7,25], the depressed CV_{R-R} [4,17,36], and depression of the sympathetic sudomotor activity in the hand [33]. On the other hand, some recent work has demonstrated that occupational exposure to lead, mixed organic solvents or hand-arm vibration influences the CV_{R-R} mainly through depression of parasympathetic activity (e.g., C-CV_{HF}) [9,19–21,24], suggesting that the parasympathetic function is more vulnerable to such environmental insults than the sympathetic one. In case of chronic excessive ingestion, therefore, alcohol appears to be one of potent neurotoxicants that give rise to the sympathetic other than parasympathetic dysfunctions.

Finally, no dose–effect relationship was found between alcohol dose per body weight and any CV parameters among the 11 healthy volunteers. The effects of alcohol on the central nervous system are well known to be proportional to its concentration in the blood [23,29]. Two explanations are possible for this disagreement. At first, the sample size and the range of alcohol dose, of our study, might not have been sufficiently large to observe that relation. Secondly, the effects of alcohol on the autonomic nervous system may differ from those on the central nervous system, because the former maximal response to alcohol emerges earlier than the latter. Indeed, it took at least 2 h to exhibit the maximal prolongation in P300 latency after alcohol intake in healthy subjects [23]. In future studies, it would be valuable to compare autonomic nervous system measures to a set of measures of central nervous system.

Acknowledgment

We thank Mr. Shigeru Handa, Yashio Hospital, for his technical collaboration.

References

[1] Akselrod, S., Gordon, D., Madwed, J.B., Snidman, M.C., Shannon, D.C. and Cohen, R.J., Hemodynamic regulation: investigation by spectral analysis, Am. J. Physiol., 249 (1985) H867–875.

[2] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised, American Psychiatric Association, Washington DC, 1987, pp. 165–186.

[3] Barraclough, M.A. and Sharpey-Schafer, E.P., Hypotension from absent circulatory reflexes: effects of alcohol, barbiturates, psycho therapeutic drugs and other mechanisms, Lancet, ii (1963) 1121–1126.

[4] Duncan, G., Johnson, R.H., Lambie, D.G. and Whiteside, E.A., Evidence of vagal neuropathy in chronic alcoholics, Lancet, ii (1980) 1053–1057.

[5] Ewing, D.J., Analysis of heart rate variability and other non-invasive tests with special reference to diabetes mellitus. In R. Bannister and C.J. Mathias (Eds.), Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System, 3rd edn, Oxford University Press, Oxford, 1992, pp. 312–333.

[6] Fujimura, Y., Araki, S., Murata, K., Yokoyama, K. and Handa, S., Assessment of the distribution of nerve conduction velocities in alcoholics, Environ. Res., 61 (1993) 317–322.

[7] Guo, Y.P., McLeod, J.G. and Baverstock, J., Pathological changes in the vagus nerve in diabetes and chronic alcoholism, J. Neurol. Neurosurg. Psychiat., 50 (1987) 1449–1453.

[8] 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.

[9] 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.

[10] 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.
[11] Johnson, R.H., Autonomic failure in alcoholics. In R. Bannister (Ed.), Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System, 2nd edn, Oxford University Press, Oxford, 1988, pp. 690–714.
[12] Johnson, R.H., Lambie, D.G. and Eisenhofer, G., The effects of acute and chronic ingestion of ethanol on the autonomic nervous system. Drug. Alcohol Depend., 18 (1987) 319–328.
[13] Johnson, R.H., Lambie, D.G. and Eisenhofer, G., Effects of ethanol on autonomic function. In K.E. Crow and R.D. Batt (Eds.), Human Metabolism of Alcohol, Volume III: Metabolic and Physiological Effects of Alcohol, CRC Press, Boca Raton, 1989, pp. 189–203.
[14] Kupari, M., Acute cardiovascular effects of ethanol: a controlled non- invasive study, Br. Heart J., 49 (1983) 174–182.
[15] Lacroix, D., Logier, R., Kacet, S., Hazard, J-R., Dagano, J. and Lekieffre, J., Effects of consecutive administration of central and peripheral anticholinergic agents on respiratory sinus arrhythmia in normal subjects, J. Auton. Nerv. Syst., 39 (1992) 211–218.
[16] Mackay, J.D., Page, M.Mc.B., Cambridge, J. and Watkins, P.J., Diabetic autonomic neuropathy: the diagnostic value of heart rate monitoring, Diabetologia, 18 (1980) 471–478.
[17] Malpas, S.C., Whiteside, E.A. and Maling, T.J.B., Heart rate variability and cardiac autonomic function in men with chronic alcohol dependence, Br. Heart J., 65 (1991) 84–88.
[18] Morrison, D.F., Multivariate Statistical Methods, McGraw-Hill Book Co., New York, 1976, pp. 128–169.
[19] 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.
[20] Murata, K., Araki, S., Yokoyama, K. and Maeda, K., Autonomic and peripheral nervous system dysfunction in workers exposed to mixed organic solvents, Int. Arch. Occup. Environ. Health, 63 (1991) 335–340.
[21] 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.
[22] Murata, K., Landrigan, P.J. and Araki, S., Effects of age, heart rate, gender, tobacco and alcohol ingestion on R-R interval variability in human ECG, J. Auton. Nerv. Syst., 37 (1992) 199–206.
[23] Murata, K., Araki, S., Tanigawa, T. and Uchida, E., Acute effects of alcohol on cognitive function and central nervous system assessed by auditory event-related potentials, Jpn. J. Hyg., 47 (1992) 958–964.
[24] Murata, K., Araki, S., Yokoyama, K., Tanigawa, T., Yamashita, K., Okajima, F., Sakai, T., Matsunaga, C. and Suwa, K., Cardiac autonomic dysfunction in rotogravure printers exposed to toluene in relation to peripheral nerve conduction, Ind. Health, 31 (1993) 79–90.
[25] Novak, D.J. and Victor, M., The vagus and sympathetic nerves in alcoholic polyneuropathy, Arch. Neurol., 30 (1974) 273–284.
[26] 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-vagus interaction in man and conscious dog, Circ. Res., 59 (1986) 178–193.
[27] 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.
[28] 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.
[29] Rall, T.W., Hypnotics and sedatives: ethanol. In A.G. Gilman, T.W. Rall, A.S. Nies, and P. Taylor (Eds.), Goodman and Gilman's the Pharma cological Basis of Therapeutics, 8th edn, Pergamon Press, New York, 1990, pp. 1345–1385.
[30] Rohrbaugh, J.W., Stapleton, J.M., Parasuraman, R., Zubovic, E.A., Frowein, H.W., Varner, J.L., Adinoff, B., Lane, E.A., Eckardt, M.J. and Linnoila, M., Dose-related effects of ethanol on visual sustained attention and event-related potentials, Alcohol, 4 (1987) 293–300.
[31] Tanaka, T. and Mukasa, H., The individual differences in responses after alcohol ingestion, Jpn. J. Alcohol Drug Depend., 20 (1985) 375–387. (in Japanese with English abstract)
[32] Urbano-Marquez, A., Estruch, R., Navarro-Lopez, F., Grau, J.M., Mont, L. and Rubin, E., The effects of alcoholism on skeletal and cardiac muscle, N. Engl. J. Med., 320 (1989) 409–415.
[33] Valls-Sole, J., Monforte, R. and Estruch, R., Abnormal sympathetic skin response in alcoholic subjects, J. Neurol. Sci., 102 (1991) 233–237.
[34] Weise, F., Krell, D. and Brinkhoff, N., Acute alcohol ingestion reduces heart rate variability, Drug Alcohol Depend., 17 (1986) 89–91.
[35] Witzleb, E., Functions of the vascular system. In R.F. Schmidt and G. Thews (Eds.), Human Physiology, Springer, Berlin, 1987, pp. 480–542.
[36] Yokoyama, A., Takagi, T., Ishii, H., Muramatsu, T., Akai, J., Kato, S., Hori, S., Maruyama, K., Kono, H. and Tsuchiya, M., Impaired autonomic nervous system in alcoholics assessed by heart rate variation, Alcohol. Clin. Exp. Res., 15 (1991) 761–765.
[37] Zilm, D.H., Ethanol-induced spontaneous and evoked EEG, heart rate, and respiration rate changes in man, Clin. Toxicol., 18 (1981) 549–563.