Hormonal Responses to Cold Exposure in Subjects with Vibration Syndrome

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Summary: Responses of the autonomic nervous system and the endocrine system to cold exposure were investigated. The subjects were all males, between 41 and 69 years of age. Seventy subjects with the vibration syndrome and vibration-induced white finger (VWF(+)) group, 70 subjects with the vibration syndrome without VWF (VWF(-)) group and 70 healthy subjects (control group) were individually matched according to age. The subjects remained in a cold room at 7°C for 30 minutes. Catecholamines, cyclic nucleotides, thyroid hormones, ACTH and cortisol were measured before and during cold exposure. The VWF(+) group and the VWF(-) group had larger % increases of plasma norepinephrine, cyclic AMP, cyclic GMP, T₃ and T₄ levels than the control group. These findings indicate that the responses of the autonomic nervous system and the thyroid system to cold exposure are greater in the subjects with the vibration syndrome.

Key words: plasma level—catecholamines—cyclic nucleotides—thyroid hormones—ACTH—cortisol—vibration-induced white finger

Introduction

The effects of occupational hand-arm vibration on the regulatory systems of the body were investigated by monitoring autonomic nervous function and endocrine function using electrophysiological methods and blood chemical analyses during exposure to cold. This included heart rate variation obtained from an electrocardiogram (Harada et al. 1987) and a power spectrum of the microvibration on the thenar eminence (Harada and Kondo, 1986). Dopamine-beta-hydroxylase activity (Harada et al. 1989), cyclic nucleotides (Harada et al. 1985), catecholamines, pituitary hormones, thyroid hormones and cortisol (Kondo, 1988; Harada et al. 1988) were measured in the blood. The results

indicated that the basal activity of the regulatory systems and the responses to cold exposure were different for subjects with vibration syndrome and control subjects.

A further investigation was performed using not only these methods, but also indices of the central nervous system on a large number of subjects with age-matched controls. The data are still being analyzed. In this paper, the changes of hormonal substances in the blood, such as catecholamines (norepinephrine, epinephrine), plasma cyclic nucleotides (cyclic adenosine 3' 5'-monophosphate, cyclic AMP; and cyclic guanosine 3' 5'-monophosphate, cyclic GMP), thyroid hormones (triiodothyronine, T₃; thyroxine, T₄), adrenocorticotrophic hormone (ACTH) and

cortisol, during exposure to cold are described.

Subjects and Methods

Eighty-six subjects with the vibration syndrome and vibration-induced white finger (VWF, VWF(+) group), 97 subjects with the vibration syndrome without VWF (VWF(-) group) and 84 healthy subjects (control group) were examined in four areas of western Japan. All subjects were males, between 41 and 69 years of age, who did not have pneumoconiosis, diabetes mellitus, hypertension, heart disease, liver disease nor a history of cerebrovascular disease. They were individually matched according to age, within a 5 year range, among the three groups. Also, when comparing the VWF(+) and VWF(-) groups, the subjects were individually matched within a 3 year range according to the number of years which had elapsed since ceasing the operation of vibratory tools.

As a result of the selection process, 70 subjects with the vibration syndrome and VWF, 70 subjects with the vibration syndrome without VWF and 70 healthy subjects were obtained. Means of age, body height, body weight, years of exposure to vibration and years after ceasing the operation of vibratory tools were not significantly different for the three groups (Table 1). The most common tools which

had been operated by the subjects of the VWF(+) and VWF(-) groups were chain-saws (61 workers, 44%) and rock drills (42 workers, 30%). The number of matched sets which were actually analyzed were different for each hormonal substance because it was not possible to measure catecholamines and T_4 in some samples, and measurements of ACTH and cortisol were limited to one of the four geographic areas.

Blood samples were taken under two conditions. At first, the subject was required to sit in a room at a temperature of $25 \pm 1^\circ\text{C}$ and blood was drawn after 25 minutes. Then the subject moved and sat down in a cold room in which the temperature was controlled at $7 \pm 1.5^\circ\text{C}$ and blood was drawn after 25 minutes (cold exposure test). For this test, the subjects wore two pieces of clothing on the upper and lower half of the body. The plasma was separated from the blood using a centrifugal separator at 4°C and was frozen at -70°C . Catecholamines were analyzed using HPLC with the THI method. Other hormones were analyzed using an RI assay kit (Yamasa for cyclic nucleotides, Dainabot for T_3 , cortisol and T_4 and CIS for ACTH). Drawing of blood was performed from 9:30 am to 12:30 am from October, 1987 to March, 1988. For 7 days before the tests, all drug treatments were terminated. For the statistical test, the Wilcoxon signed-rank test was used and the significance levels were 0.05 and 0.01.

TABLE 1

Number of subjects, ages, body dimensions, periods of exposure to vibration and periods since ceasing the operation of vibratory tools.

	n	age (yr)	height (cm)	weight (kg)	years of exposure	years after ceasing ^A
VWF (+) group	70	55.9 $\pm$ 5.6	161.7 $\pm$ 5.4	58.6 $\pm$ 7.3	21.2 $\pm$ 7.8	5.6 $\pm$ 3.5
VWF (-) group	70	55.9 $\pm$ 5.9	160.4 $\pm$ 6.3	59.7 $\pm$ 8.4	19.8 $\pm$ 7.5	5.5 $\pm$ 3.6
control group	70	55.7 $\pm$ 6.1	161.0 $\pm$ 6.7	60.8 $\pm$ 9.1		

Mean $\pm$ SD; ^A excluding 37 subjects in each group who are still operating tools.

Results

Table 2 shows the changes of plasma norepinephrine levels during cold exposure. The plasma norepinephrine increased during cold exposure in all three groups ($p < 0.01$). The % increase for the VWF (+) group was the largest and the increase for the VWF (-) group was next. The % increases of the VWF (+) and VWF (-) groups were significantly different from the control group ($p < 0.01$, $p < 0.05$). Table

3 shows the changes of plasma epinephrine during cold exposure. The plasma epinephrine in the VWF (-) and control groups decreased during cold exposure ($p < 0.01$), while the level in the VWF (+) group did not change significantly.

Table 4 shows the changes of plasma cyclic AMP concentrations during cold exposure. The increase in cyclic AMP induced by cold exposure was statistically significant in all three groups ($p < 0.01$), however the % increases in the VWF (+)

TABLE 2

Responses of plasma norepinephrine levels ($\mu\text{g/ml}$) to a cold exposure test of the whole body at 7°C.

	n	rest	exposure	% increase
VWF (+) group	65	326 $\pm$ 133	1027 $\pm$ 384##	234 $\pm$ 119**
VWF (-) group	65	320 $\pm$ 120	951 $\pm$ 391##	205 $\pm$ 91*
control group	65	352 $\pm$ 121	926 $\pm$ 296##	173 $\pm$ 72

Mean $\pm$ SD; ## $p < 0.01$ comparison between rest and exposure.

* $p < 0.05$, ** $p < 0.01$ compared with the control group.

TABLE 3

Responses of plasma epinephrine levels ($\mu\text{g/ml}$) to a cold exposure test of the whole body at 7°C.

	n	rest	exposure	% increase
VWF (+) group	65	91.3 $\pm$ 53.2	81.0 $\pm$ 47.7	3.2 $\pm$ 58.2
VWF (-) group	65	87.4 $\pm$ 49.0	73.9 $\pm$ 38.0##	- 8.5 $\pm$ 34.5
control group	65	96.2 $\pm$ 70.5	72.2 $\pm$ 42.0##	-13.4 $\pm$ 33.6

Mean $\pm$ SD; ## $p < 0.01$ comparison between rest and exposure.

TABLE 4

Responses of plasma cyclic AMP levels (pmol/ml) to a cold exposure test of the whole body at 7°C.

	n	rest	exposure	% increase
VWF (+) group	70	16.3 $\pm$ 4.0	19.1 $\pm$ 5.4##	17.7 $\pm$ 16.5*
VWF (-) group	70	15.4 $\pm$ 3.9**	18.3 $\pm$ 5.0##	19.0 $\pm$ 17.6*
control group	70	16.6 $\pm$ 4.3	18.7 $\pm$ 5.1##	12.9 $\pm$ 17.5

Mean $\pm$ SD; ## $p < 0.01$ comparison between rest and exposure.

* $p < 0.05$, ** $p < 0.01$ compared with the control group.

and VWF(-) groups were larger than that of the control group ($p<0.05$). Table 5 shows the changes of cyclic GMP during cold exposure. The increase of cyclic GMP induced by cold exposure was statistically significant in all three groups ($p<0.01$). The % increases in the VWF(+) and VWF(-) groups tended to be larger than that of the control group, however the differences were not statistically significant.

Table 6 shows the changes of plasma

T_3 during cold exposure. The plasma T_3 concentrations for the VWF(+) and VWF(-) groups at rest tended to be smaller than for the control group. Cold exposure induced an increase of plasma T_3 in all three groups ($p<0.01$). The % increases for the VWF(+) and VWF(-) groups were larger than the increases in the control group ($p<0.05$). Table 7 shows the changes of plasma T_4 during cold exposure. The plasma T_4 concentrations in the VWF(+) and VWF(-) groups at

TABLE 5
Responses of plasma cyclic GMP levels (pmol/ml) to a cold exposure test of the whole body at 7°C.

	n	rest	exposure	% increase
VWF(+) group	70	3.02±1.39	3.70±1.68##	35.2±81.2
VWF(-) group	70	2.96±1.47	3.75±2.48##	34.3±84.4
control group	70	2.95±1.52	3.41±1.59##	24.9±43.7

Mean±SD; ## $p<0.01$ comparison between rest and exposure.

TABLE 6
Responses of plasma T_3 levels (ng/ml) to a cold exposure test of the whole body at 7°C.

	n	rest	exposure	% increase
VWF(+) group	70	1.14±0.55	1.29±0.60##	17.6±19.5*
VWF(-) group	70	1.15±0.53	1.30±0.55##	16.6±22.0*
control group	70	1.24±0.53	1.34±0.59##	10.2±20.1

Mean±SD; ## $p<0.01$ comparison between rest and exposure.

* $p<0.05$ compared with the control group.

TABLE 7
Responses of plasma T_4 levels (μ g/100ml) to a cold exposure test of the whole body at 7°C.

	n	rest	exposure	% increase
VWF(+) group	69	9.91±4.72	11.44±5.97##	14.0±17.3
VWF(-) group	69	9.46±4.60*	11.22±5.58##	19.6±22.5**
control group	69	10.94±4.67	12.16±6.23##	10.7±18.5

Mean±SD; ## $p<0.01$ comparison between rest and exposure.

* $p<0.05$, ** $p<0.01$ compared with the control group.

rest and during cold exposure tended to be smaller than those in the control group. An increase of plasma T_4 induced by cold exposure was observed in all three groups ($p < 0.01$). The % increases for the VWF(+) and VWF(-) groups tended to be larger than those in the control group. The difference between the VWF(-) group and the control group was statistically significant ($p < 0.01$).

Table 8 shows the changes of plasma ACTH during cold exposure. The plasma ACTH of the VWF(+) group was the lowest and that of the VWF(-) group was intermediate for each condition. The difference of plasma ACTH during rest for the VWF(+) group and the control group was statistically significant ($p < 0.05$). Cold exposure induced a decrease of the

plasma ACTH in all three groups, however only the decrease in the control group was statistically significant ($p < 0.05$). The change of plasma ACTH in the VWF(+) group was the smallest and that in the VWF(-) group was intermediate; however the differences between these changes and the change for the control group were not statistically significant. Table 9 shows the changes of plasma cortisol during cold exposure. The concentrations of plasma cortisol for the three groups at rest were almost the same. The absolute plasma cortisol concentration and the % increase during cold exposure tended to be larger in the VWF(-) group than in the other two groups; however the differences were not statistically significant.

TABLE 8

Responses of plasma ACTH levels (pg/ml) to a cold exposure test of the whole body at 7°C.

	n	rest	exposure	% increase
VWF (+) group	12	26.3 ± 20.1*	23.6 ± 19.8	- 6.6 ± 42.0
VWF (-) group	12	34.3 ± 26.6	29.0 ± 20.7	- 9.9 ± 62.7
control group	12	43.2 ± 19.8	33.3 ± 15.7#	-19.9 ± 28.1

Mean ± SD; # $p < 0.05$ comparison between rest and exposure.

* $p < 0.05$ compared with the control group.

TABLE 9

Responses of plasma cortisol levels (pg/ml) to a cold exposure test of the whole body at 7°C.

	n	rest	exposure	% increase
VWF (+) group	12	125.2 ± 39.8	119.9 ± 35.6	0.0 ± 32.1
VWF (-) group	12	127.8 ± 48.9	132.2 ± 40.9	11.8 ± 48.7
control group	12	129.3 ± 51.4	123.4 ± 50.2	-3.4 ± 19.4

Discussion

To evaluate plasma levels of hormones, the circadian rhythm must be considered. This is especially important for plasma cortisol levels (Weitzman et al. 1975). In this study, blood samples were taken during a three hour interval before noon, and differences of plasma levels before and during cold exposure were evaluated. Therefore, the effects of the circadian rhythm on the results should be small.

Table 10 summarizes the hormonal responses to cold exposure in subjects with vibration syndrome and in healthy controls. Evaluation of the responses is based on the statistical significance of the differences of the results during rest and during cold exposure and comparison of the % increases with the control group. Cold exposure induced increases of plasma norepinephrine, cyclic AMP, cyclic GMP, T_3 and T_4 , and decreases of plasma epinephrine and ACTH in the control group. The increases were usually larger in the VWF (+) and VWF (-) groups and a decrease for these two groups was only observed for the plasma epinephrine level of the VWF (-) group.

Plasma norepinephrine is maintained by release from the sympathetic nerve

endings and is a sensitive indicator of sympathetic nerve function. The results with plasma norepinephrine indicate that the sympathetic nervous system in subjects with the vibration syndrome is easily activated by cold exposure. It is interesting that norepinephrine has a strong action to contract the smooth muscle of vessels and that VWF is provoked when the whole body is exposed to cold.

The plasma epinephrine levels in the VWF (-) and control groups decreased during cold exposure. Epinephrine is secreted primarily by the adrenal medulla and the control of release is not the same as the control for norepinephrine release. The discrepancy between the responses of plasma norepinephrine and epinephrine to cold exposure can be explained by this "selective control" (Brück, 1983). The fact that a significant decrease of plasma epinephrine was not observed in the VWF (+) group may be related to a hypersensitivity of the VWF (+) subjects to cold.

Cyclic AMP and cyclic GMP are second messengers in cells, and changes in blood concentrations during physiological stress are pointed out to reflect sympathetic beta receptor function and sympathetic alpha or parasympathetic muscarinic receptor

TABLE 10

Summary of hormonal responses to cold exposure in subjects with the vibration syndrome and control subjects.

	catecholamines		cyclic nucleotides		thyroid hormones		ACTH	cortisol
	NE	EP	cAMP	cGMP	T_3	T_4		
n of each group	65	65	70	70	70	69	12	12
VWF (+) group	↑↑↑	—	↑↑	↑	↑↑	↑	—	—
VWF (-) group	↑↑	↓	↑↑	↑	↑↑	↑↑	—	—
control group	↑	↓	↑	↑	↑	↑	↓	—

↑ increase; ↓ decrease; — no change.

NE norepinephrine; EP epinephrine; cAMP cyclic AMP; cGMP cyclic GMP.

Evaluations were based on the statistical significance of each difference between rest and exposure conditions, and the comparison of the % increase with the control group.

functions, respectively (Okada et al. 1980; Ui et al. 1980). It has been reported that an increase in plasma cyclic GMP was induced by immersing a hand in cold water in vibration syndrome patients but not in healthy controls (Okada et al. 1983). The changes of plasma cyclic AMP and cyclic GMP levels indicate that the response of receptors on nerve endings to cold exposure in subjects with the vibration syndrome are larger. These phenomena probably relate to a hyperfunction of the autonomic nervous system.

Cold exposure induces an enhancement of T_3 - and T_4 - production in laboratory animals. It was pointed out that similar responses of plasma T_3 and T_4 to acute cold exposure had not been confirmed in man (Sterling and Lazarus, 1977). However, a recent study showed that cold exposure of healthy subjects to 4°C for 30 minutes induced a rise of circulating T_3 and T_4 levels. This rise was interpreted to be the result of a direct effect of increased norepinephrine on the thyroid gland (O'Malley BP et al. 1984). These findings coincide with the present results. Significant increases of plasma T_3 and T_4 levels were induced by cold exposure in all three groups. The % increases in the VWF(+) and VWF(-) groups were larger than for the control group. These results indicate that the sensitivity to cold of subjects with the vibration syndrome is higher than the sensitivity of control subjects.

The plasma ACTH levels tended to decrease during cold exposure and the plasma cortisol levels did not change significantly in any of the groups. Many acute stresses can increase the secretion of ACTH from the pituitary, which then activates the adrenal cortex. The following reasons may account for the fact that positive results were not observed. First, the number of subjects in which plasma ACTH and cortisol levels were measured was small. Second, the severity of cold

stress in this study may not have been sufficient to induce an "alarm response" in the pituitary-adrenal cortical system.

Conclusion

The VWF(+) and VWF(-) groups had larger % increases of plasma norepinephrine, cyclic AMP, cyclic GMP, T_3 and T_4 levels than the control group. These findings indicate that the responses of the autonomic nervous system and the thyroid system to cold exposure are enhanced in subjects with the vibration syndrome.

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