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Detection of Exaggerated Blood Pressure Response Using Laboratory of Physical Science Protocol and Risk of Future Hypertension

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Abstract: Detection of Exaggerated Blood Pressure Response Using Laboratory of Physical Science Protocol and Risk of Future Hypertension: Tsutomu ODAHARA, *et al*. Kagoshima Occupational Environmental Health Center—Objective: To assess the usefulness of the Laboratory of Physical Science (LOPS) protocol for detecting exaggerated blood pressure (BP) response as a risk factor for future hypertension when controlling for work and personal factors. **Methods**: Subjects were 815 healthy normotensive men (mean age, 43.1 ± 6.76 yr; range, 29–64 yr) who participated in the LOPS protocol, a graded 4-stage exercise test undertaken for the measurement of 40–70% of maximum oxygen consumption. A hypertensive response was defined as systolic blood pressure (SBP) of 250 mmHg or diastolic blood pressure (DBP) of 120 mmHg during the exercise test. **Results**: New-onset hypertension or the initiation of antihypertensive drug treatment had occurred in 108 men (13.3%) after 7 yr of follow-up. Cox proportional survival analysis revealed significantly increased risks of developing hypertension were associated with exaggerated BP response to exercise (hazard ratio, 2.3; 95% confidence interval, 1.4–3.7) and higher frequency of business trips (hazard ratio, 1.7; 95% confidence interval, 1.2–2.5) after multivariable adjustments for work and personal-related risk factors. **Conclusions**: These results suggest that the LOPS protocol is effective for detecting exaggerated BP response as a risk factor for future hypertension when controlling for work and personal-related risk factors. Exaggerated BP response to exercise and higher frequency of business trips are risk factors for developing future hypertension.
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Hypertension is the most prevalent disease among Japanese workers and a key risk factor for cardiovascular and cerebrovascular disease morbidity and mortality. In Japan, roughly 40 million adults have hypertension[1)], and prevention of target organ damage resulting from hypertension may be an effective strategy for addressing escalating health care costs, the increase in hypertension-related mortality and the need for nursing care. Earlier detection of hypertension, strict management of blood pressure (BP) and prevention of hypertension are therefore needed. Hypertension is considered a work-related disease, and working factors may affect hypertension independently and significantly. Most studies have controlled for age, sex, body weight, physical fitness and alcohol consumption but have failed to control for working factors such as overtime and work posture.

Identification of the risk factors of hypertension may allow for earlier detection and possible prevention of this condition. Several prospective studies have identified BP response to postural change, loud noise, cold water immersion, mental arithmetic tasks and both isometric and dynamic physical stress tests as predictors of hypertension[2–6)]. The graded exercise test for the detection of individuals at risk of future hypertension and cardiovascular disease is widely used as a screening method for coronary artery disease[7–13)].

Benbassat *et al*.[4)] reviewed 11 articles and suggested that normotensive participants with an exaggerated BP response to exercise were 2.06–3.39 times at greater risk of future hypertension 0.5–15 yr later than participants with a normal BP response to exercise. However, there was no standardization of the exercise testing protocols. Moreover, the definitions of hypertensive response varied among the previous studies. Some authors have defined a hypertensive response to exercise as an increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during exercise compared with that in normotensive subjects[8,9]. Others have suggested that hypertensive patients respond to exercise with an increase in SBP, while in normotensive subjects DBP is either reduced or unchanged[13].

Among various protocols, the ramp protocol is generally employed, but the initial workload applied in this protocol may already be too heavy for those with low physical strength, because the workload is increased mechanically. The Laboratory of Physical Science (LOPS) protocol was developed and is currently used in Japan. This protocol, in which the maximal workload is set at a presumed 70–80% maximal oxygen intake, is a graded 4-stage test[14]. The advantage of the LOPS protocol is that physiological responses can be assessed independent of individual differences, because workload is determined based on the physical strength of individuals. As an exaggerated BP response, the end point of hypertension is used, which is defined as SBP of 250 mmHg or DBP of 120 mmHg during the exercise test.

The objective of this study was to determine the effectiveness of the LOPS protocol for detecting future hypertension when controlling for personal and work-related factors.

Materials and Methods

Study population

A total of 1,534 men participated in annual medical examinations conducted at the Hitachi Health Care Center in 1997, and eligible individuals for this study were followed for 7 yr through the company's annual medical examination program. The annual medical examination was offered to employees as part of the regular medical examination prescribed by the Industrial Safety and Health Act. Details of the examination and its ethical aspects were assessed, and then approved by the Safety and Health Committee, in advance. A questionnaire was directly handed to each participant by the Hitachi Health Care Center. A completed questionnaire in a securely sealed envelope was returned to the center by each participant on the day of the annual medical examination. The questionnaire clearly stated that participation in this study was voluntary, data provided by participants were strictly for research use only, and data provided by the participants would be presented as part of statistical data without specifying the identities of the participants. Medical evaluation included a physical examination, graded exercise test, blood chemistry analysis and assessment of health habits and personal and family health histories. Subjects were excluded if they (1) had a history of cardiovascular disease or cerebrovascular disease, (2) had electrocardiographic evidence of coronary heart disease or cardiac arrhythmia, or (3) were hypertensive, as defined by the current use of any antihypertensive medication or a resting BP of 140/90 mmHg. Consequently, 1,008 subjects free of cardiovascular disease and with normal ECG results were eligible for this study. Based on the exercise test results, BP and heart rate (HR) responses to exercise were evaluated.

Table 1. Clinical characteristics of healthy normotensive male subjects (n=815)

Variable	
Age, year	43.1 ± 6.76
Body mass index, kg/m^2	25.6 ± 2.63
Systolic blood pressure, mmHg	122.5 ± 10.01
Diastolic blood pressure, mmHg	77.5 ± 6.93
Fasting blood sugar, mg/d*l*	108.5 ± 16.40
Hemoglobin A1c, %	5.7 ± 0.80
Total cholesterol, mg/d*l*	209.5 ± 38.22
HDL cholesterol, mg/d*l*	50.6 ± 12.40
Triglyceride, mg/d*l*	174.0 ± 121.27
Concomitant disease (yes), %	9.4
Parental history of hypertension (present), %	29.4
Current smoker (yes), %	52.1
Alcohol consumption	
None, %	21.0
1–4 times/wk, %	35.8
≥5 times/wk, %	43.2
No regular sports activities (yes), %	87.6
Working posture (desk work), %	71.4
Irregular working h (present), %	15.2
Frequency of business trips (≥8 times/mo), %	46.7
Overtime work (≥60 h/mo), %	22.0

Values are expressed as mean ± standard error or percentage. Those subjects undergoing treatment for diabetes or dyslipidemia were defined as subjects with concomitant disease.

After the exercise test at baseline, we followed 815 subjects until 2005; 193 subjects who terminated exercise for a reason other than an increase in blood pressure were not followed. Among the 815 subjects, 263 subjects who did not complete the full follow-up course (including retirees) were categorized as incomplete subjects in the analysis of this study. Clinical characteristics of the study sample are shown in Table 1.

Questionnaire

A questionnaire designed by the Hitachi Health Care Center was completed by all subjects. It contained four work-related items, namely, irregularity of working hours, involvement in business trips, average overtime work and work posture. The detailed multiple-choice questions used and the corresponding answers (given in parentheses) were as follows: whether work involved irregular working hours (1. yes, or 2. no); whether work involved business trips (1. rarely, 2. <8 times/month(mo), 3. ≥8 times/mo, 4. a long-term business trip of over 1 mo); average overtime work hours in the past few months (1. <45 hour (h)/mo, 2. 45–59 h/mo, 3. 60–99 h/mo, or 4. ≥100 h/mo); posture during work (1. desk work (mostly sitting), or 2. other (work involving considerable amounts of standing, walking and moving)). With respect to the frequency of business trips, the subjects were classified into two groups (<8 times/mo, or ≥8 times/mo). Similarly, the subjects were categorized into two groups (<60 h/mo, or ≥60 h/mo) according to average overtime work hours. Furthermore, subjects were divided into two groups based on smoking habit (smoker or non-smoker), and into three groups based on alcohol intake habit (none, 1–4 days/wk, or ≥5 days/wk). For physical activities, the types of activities, time spent in one session and the number of sessions per month were determined, and the subjects who exercised ≥10 days/mo were categorized as the regular physical activities group. Those subjects undergoing treatment for diabetes or dyslipidemia were defined as subjects with concomitant diseases, and categorized in the concomitant disease group, while those with a family history of hypertension were categorized as the family history group. The definition of concomitant diseases was purely based on those undergoing treatment, regardless of clinical evidence of diabetes or dyslipidemia.

Exercise protocol and hemodynamic measurement

A graded exercise test was performed on an electronically braked bicycle ergometer (Fukuda Denshi, ML-1800) using the LOPS protocol. This protocol has four stages,each with a duration of 4 minutes (min). Using the LOPS protocol, in order to determine performance capacity ($\dot{V}o_2max/wt$) and to calculate maximum oxygen consumption ($\dot{V}o_2max$) and maximum amount of exercise (Wmax) based on body weight, we first established standards for the extent of exercise performed by subjects in their daily routine based on the following: i) those who were prone to illness and consequently had limits placed on their daily routine of physical activity, ii) those who predominantly sat during their work, iii) those who walked for about 10 min at one time, including shopping or commuting, iv) those who participated in endurance exercise totaling around 180 min each wk, and v) those whose weekly endurance exercise totals were around 300 min. Regardless of future contraindicated activities, there is minimal risk to asymptomatic patients with a disorder, and it is thought that it is possible to start the exercise with any subject at a load of 40% $\dot{V}o_2max$, and then increase the load in 4 intervals up to 70% $\dot{V}o_2max$[14].

During the test, HR and BP were recorded every 2 min. A graded uninterrupted exercise test was started at a workload of 40% predicted $\dot{V}o_2max$. After 2 min of initial load, the workload was progressively increased to change HR. In the second stage, workload was increased towards a HR of 50% $\dot{V}o_2max$. After 2 min of the second stage, workload was increased if HR did not sufficiently increase. In the third stage, workload was increased towards a HR of 60% $\dot{V}o_2max$. After 2 min of the third stage, workload was increased toward the target HR if it was insufficient. In the fourth stage, the target HR was 70% $\dot{V}o_2max$. After 2 min, workload was adjusted to the target HR. The recovery phase was 3 min at half of the first stage workload (Fig. 1).

As for the criteria for terminating exercise, we used subjective symptoms such as chest pain, dizziness and discomfort, as well as changes in electrocardiogram findings, such as frequent or continuous ventricular arrhythmia, ischemic ST-segment changes, atrial flutter and fibrillation; 85% of the maximal HR determined by the Blackburn method (220 – age) was set as the target HR. In terms of BP, the general criteria for terminating exercise were a maximal SBP of 250 mmHg and/or a DBP of 120 mmHg.

Throughout the test, ECG-led V3 and HR were monitored continuously, and BP was recorded every 2 min noninvasively with an automated sphygmomanometer (Nippon Colin, STBP-780B). The device was an auscultatory unit using R-wave gating to identify Korotkoff sounds.

Exaggerated blood pressure

Subjects categorized as having an exaggerated BP response group were those showing abnormal BP increases (SBP of 250 mmHg and/or DBP of 120 mmHg) and interruption of the examination due to high SBP and/or DBP exceeding normal limits.

Hypertensive status at follow-up

During the follow-up period, hypertensive treatment of the subjects was ascertained based on responses to a questionnaire regarding medical histories and BP measurements conducted at the biannual medical examination. Subjects were considered hypertensive (hypertensive group) if the resting BP was 140/90 mmHg and did not return to the normotensive status or they had started antihypertensive medication during the follow-up period. The normotensive group was defined as the group showing BP in the normal range 7 yr after the test.

Data analyses

Baseline descriptive variables were compared across the normotensive and hypertensive groups after using the *t*-test and chi-square test.

Personal factor variables used were as follows: age (1-year intervals); BMI; resting SBP and DBP; levels of fasting blood sugar (FBS), hemoglobin A1c (HbA1c), total cholesterol (TC), HDL cholesterol (HDL) and

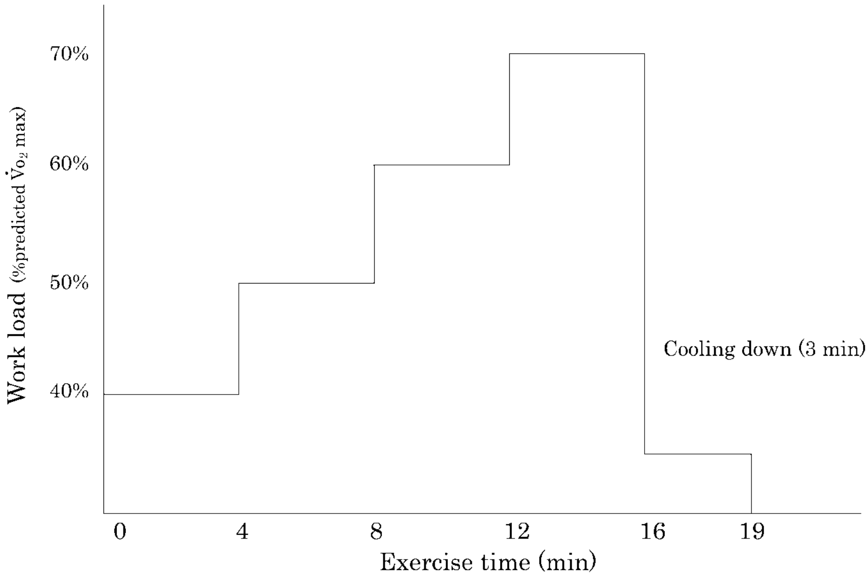

Fig. 1. LOPS protocol used in this study. Percent (%) predicted $\dot{V}o_2$ max is stress intensity as a proportion of predicted maximal oxygen intake.

tryglyceride (TG); an exaggerated BP response to exercise (present or not); concomitant disease (present or not); parental history of hypertension (present or not); present smoking habit (smoker or non-smoker); frequency of drinking (none, 1–4 days/wk, or ≥5 days/wk); and regular exercise habit (present or not). Work-related factors used were as follows: work posture (desk work or not); irregularity of working hours such as night work and shift work (presence or not); frequency of business trips (<8 times/mo or ≥8 times/mo); and overtime work (<60 h/mo or ≥60 h/mo).

Associations between work-related risk, personal risk and future development of hypertension were evaluated by estimation with Cox proportional hazard models using the backward elimination stepwise method. In this analysis, subjects were divided into 2 subcategories based on whether or not they had complete BP measurement data: the complete exercise group was composed of those who completed the final workload at the fourth stages and the incomplete exercise BP measurement data group was composed of those who discontinued taking the exercise test before the final workload due to an increase in BP. Hazard ratio with corresponding 95% confidence intervals were estimated in this model and used for quantifying the association between exaggerated BP response and hypertensive status. Data analysis was performed using the SPSS statistical package 12.0 for Windows (SPSS Software).

Results

The number of subjects who completed the workload test (i.e. the complete group) was 747 (91.7% of the total), while the number of subjects who discontinued the test (i.e. the incomplete group) due to SBP or DBP exceeding 250 mmHg or 120 mmHg, respectively, was 61 (8.3%). Clinical characteristics of the complete and incomplete exercise groups are shown in Table 2.

At 7 yr follow-up, 108 subjects (13.3%) had developed to hypertension (hypertensive group) and 707 subject (86.7%) had normal blood pressure (normotensive group). Comparisons of measures between the normotensive and hypertensive groups are shown in Table 3. Compared with the normotensive group, the hypertensive group had significantly higher age, higher BMI, higher SBP, higher DBP, abnormal BP response, parental history of hypertension and higher frequency of business trips. The two groups did not differ in terms of working posture, irregular working hours or overtime work.

Multiple Cox hazard analysis found the following independent variables to be significantly associated with hypertension outcome: exaggerated BP response, resting SBP and DBP, TC, age, parental history of hypertension and frequency of business trips, as shown in Table 4. Compared with a normal pressure response, the hazard ratios were 2.264 (95% confidence interval, 1.373–3.734) for the exaggerated BP response group, 1.047 (1.010–1.085) for resting SBP, 1.106 (1.048–1.168) for resting DBP, 0.993 (0.988 – 0.998) for TC, 1.043 (1.012–1.075) for age, 1.500 (1.018–2.211) for parental history of hypertension and 1.691(1.153–2.482) for frequency of business trips. BMI was not a significant factor in this model.

Table 2. Clinical characteristics of the complete and incomplete groups

Variable	Complete group (n=754)	Incomplete group (n=61)
Age, year	42.9 ± 6.70	45.3 ± 7.20**
Body mass index, kg/m²	25.6 ± 2.61	25.1 ± 2.86
Systolic blood pressure, mmHg	122.3 ± 10.00	125.2 ± 10.00*
Diastolic blood pressure, mmHg	77.3 ± 6.84	80.5 ± 7.41**
Fasting blood sugar, mg/d*l*	108.2 ± 15.92	112.8 ± 21.11
Hemoglobin A1c, %	5.6 ± 0.73	6.0 ± 1.32*
Total cholesterol, mg/d*l*	208.8 ± 38.50	219.2 ± 33.40*
HDL cholesterol, mg/d*l*	50.7 ± 12.34	50.5 ± 12.84
Triglyceride, mg/d*l*	173.2 ± 120.51	184.3 ± 130.94
Concomitant disease (yes), %	9.0	14.8
Parental history of hypertension (present), %	29.7	26.2
Current smoker (yes), %	52.1	52.5
Alcohol consumption		
None, %	20.8	23.0
1–4 times/wk, %	35.9	34.4
≥5 times/wk, %	43.2	42.6
No regular sports activities (yes), %	87.4	90.2
Working posture (desk work), %	72.7	55.7**
Irregular working hours (present), %	15.0	18.0
Frequency of business trips (≥8 times/mo) , %	47.1	42.6
Overtime work (≥60 h/mo), %	22.4	16.4

Values are expressed as mean ± standard error or percentage. * $p<0.05$; ** $p< 0.01$. Those subjects undergoing treatment for diabetes or dyslipidemia were defined as subjects with concomitant disease.

Discussion

The results of this study indicate that the LOPS protocol is a useful means for detecting normotensive men who later develop hypertension. Compared with the group that completed the LOPS-employed exercise stress test using a bicycle ergometer, the retired group, having an increase in SBP to ≥250 mmHg and/or an increase in DBP to ≥120 mmHg during the test, had developed hypertension 7 yr after the test with a hazard ratio of 2.3. Because workload is adjusted according to the physical strength of each participant, the LOPS protocol is relatively safe, and can be easily employed at general health check facilities (which are not as well equipped as medical hospitals), and we experienced no cardiovascular accidents requiring an emergency transfer during the 7-year study period.

Merits of the LOPS protocol

A multi-step loading protocol in which the initial workload of 25–50 Watts is increased by 25 Watts at 3-minute intervals is most commonly used for the cycle ergometer test. With respect to the end-point of workload, the maximal load test and the submaximal load test are used. In the maximal load test, exercise continues until oxygen consumption reaches $\dot{V}o_2max$ (the point when oxygen consumption becomes unchanged despite an increase in workload), whereas in the submaximal load test, exercise will be terminated when oxygen consumption reaches 80–90% $\dot{V}o_2max$ regardless of symptoms and signs of myocardial ischemia. Considering the risk of complications due to excessive workload and no further improvement in accuracy by continuing the test after 80–90% $\dot{V}o_2max$, the submaximal load test is the preferred method[15]. A gradual elevation in workload from the light initial workload and quick completion of assessment are the advantages of a multi-step loading protocol, but parameters, such as the initial workload, workload increment and duration of exercise at each workload level, are difficult to establish. On the other hand, in the LOPS protocol, $\dot{V}o_2max$ is estimated based on age, amount of daily exercise and weight of each participant, and workload at each stage is determined as % $\dot{V}o_2max$. Therefore, differences in physiological and biochemical responses among participants are small[14]. It has been reported that the LOPS protocol is not symptom limited, and is thus weak as a protocol for detecting silent myocardial ischemia[16]. Nevertheless, the

Table 3. Comparison of subject characteristics according to hypertensive status at 7 yr of follow-up

Variable	Normotension (n=707)	Hypertension (n=108)
Age, year	42.9 ± 6.72	44.5 ± 6.85*
Body mass index, kg/m^2	25.5 ± 2.58	26.1 ± 2.93*
Systolic blood pressure, mmHg	121.4 ± 10.0	129.7 ± 6.52**
Diastolic blood pressure, mmHg	76.7 ± 6.77	83.1 ± 5.19**
Fasting blood sugar, mg/d*l*	108.2 ± 16.50	110.5 ± 15.63
Hemoglobin A1c, %	5.6 ± 0.81	5.7 ± 0.72
Total cholesterol, mg/d*l*	210.3 ± 37.7	204.7 ± 41.11
HDL cholesterol, mg/d*l*	50.8 ± 12.45	49.4 ± 11.79
Triglyceride, mg/d*l*	171.9 ± 124.35	188.0 ± 98.10
Abnormal blood pressure response (present), %	5.7	19.4**
Concomitant disease (yes), %	9.5	9.3
Parental history of hypertension (present), %	27.6	41.7**
Current smoker (yes), %	52.1	52.8
Alcohol consumption		
None, %	21.4	18.5
1–4 times/wk, %	36.9	28.7
≥5 times/wk, %	41.7	52.8
No regular sports activities (yes), %	87.4	88.9
Working posture (desk work), %	71.7	69.4
Irregular working hours (present), %	15.6	13.0
Frequency of business trips (≥8 times/mo), %	45.5	54.6*
Overtime work (≥60 h/mo), %	22.1	21.3

*$p < 0.05$; **$p < 0.01$. Those subjects undergoing treatment for diabetes or dyslipidemia were defined as subjects with concomitant disease.

Table 4. Multiple adjusted associations for work-related risk, personal risks and hypertensive status

Variable	β	SE	*p* value	Hazard ratio (95% CI)
Abnormal blood pressure response (present vs. not)	0.817	0.255	0.001	2.264 (1.373 – 3.734)
Systolic blood pressure (1 mmHg)	0.046	0.018	0.013	1.047 (1.010–1.085)
Diastolic blood pressure (1 mmHg)	0.101	0.028	0.000	1.106 (1.048–1.168)
Total cholesterol (1 mg/d*l*)	–0.007	0.003	0.010	0.993 (0.988–0.998)
Age (1 yr)	0.042	0.016	0.007	1.043 (1.012–1.075)
Parental history of hypertension (present vs. not)	0.405	0.198	0.040	1.500 (1.018–2.211)
Frequency of business trips (present vs. not)	0.526	0.196	0.007	1.691 (1.153–2.482)

β=partial regression coefficient; SE=standard error of the β coefficient; 95% CI=95% confidence intervals. Variables considered in the model are exaggerated blood pressure response (present or not), resting systolic blood pressure and diastolic blood pressure, entry age, body mass index, fasting blood sugar, hemoglobin A1c, total cholesterol, HDL cholesterol, triglyceride, parental history of hypertension (present or not), concomitant disease (diabetes or dyslipidemia, present or not), current smoker (yes or no), alcohol consumption (none, 1–4 times/wk, ≥5 times/wk) , no regular sports activities (yes or no), working posture (desk work or not), irregular working hours (present or not), frequency of business trips (≥8 times/mo or <8 times/mo), and overtime work (≥60 h/mo or <60 h/mo).

LOPS protocol enables the assessment of BP responses to relative workloads lower than 70% $\dot{V}o_2max$, which is an advantage of the protocol.

Exaggerated blood pressure as a predictive factor

A wide fluctuation in BP during activities of daily living are commonly observed in hypertensive patients, and several fluctuation patterns were revealed by BP measurement using a home-use BP monitor and by ambulatory blood pressure monitoring. Diagnosis of hypertension now tends to use classifications such as normotension, white coat hypertension, masked hypertension and (persistent) hypertension, based on the BP measurement using the above-mentioned devices combined with in-clinic BP measurement[17]. Considering that BP fluctuates more widely during the day when BP elevates more in response to exercise workload[18], it was suggested that normotensive individuals who show abnormal BP responses to stress during an exercise test are highly likely to be subjects with masked hypertension, who are normotensive in the clinic but hypertensive outside the clinic.

BP rises immediately after the start of exercise. In general, SBP, but not DBP, rises in response to dynamic exercise such as jogging, walking and swimming, while both SBP and DBP rise in response to static exercise such as pushing, pulling and lifting. It is considered that increases in cardiac output and HR cause elevation in SBP in response to dynamic exercise[19]. Decreased parasympathetic nerve activity and increased sympathetic nerve activity occurring in response to elevation in exercise intensity cause an increase in HR, resulting in increases in skeletal muscle blood flow and in the supply of oxygen and energy to the exercising muscles[20, 21]. In a healthy individual, peripheral vascular resistance decreases with an increase in HR, and this prevents elevation in DBP. Many reports have shown that an exaggerated BP response to workload indicates abnormal hemodynamics caused by exercise, and is indeed a predictor of future hypertension. In general, a person with normal resting BP shows an exaggerated BP response to exercise due to an increase in sympathetic nerve activity during exercise, an enhanced vascular response to norepinephrine, and slight thickening of the arterial wall[22–25]. Therefore, a suitable assessment of these conditions would contribute to the identification of the normotensive group at high risk prior to the onset of hypertension.

Definitions of an exaggerated BP response to exercise vary among researchers. Many define it with absolute values, such as SBP of ≥250 mmHg and/or DBP of ≥120 mmHg during exercise[8]. Others argue that absolute values of BP elevation in response to exercise are difficult to normalize as they show significant positive correlation with resting BP, suggesting that BP increments, independent of resting BP, are more appropriate standards for assessment[7]. However, there is no consensus on the criteria of BP change. Therefore, in the present study, an exaggerated BP response was defined by absolute standard values. The workload in the final fourth stage of the LOPS protocol is 70% $\dot{V}o_2max$. Elevation in SBP to 250 mmHg and/or in DBP to 120 mmHg before this stage means that an exaggerated BP response occurred at a load of ≤70% $\dot{V}o_2max$, indicating a new definition of an exaggerated BP response to exercise. According to a follow-up study over a period of 3–5 yr by Benbassat *et al*.[4], the relative risk of the normotensive participants developing hypertension in the resting condition was in the range of 1.44–3.4. Our follow-up study over a period of 7 yr showed a hazard ratio of 2.3, which is within this range. Considering that our study population was relatively young (mean age, 43.1 yr) and that the workload applied during the exercise test was light (≤70% $\dot{V}o_2max$), this hazard ratio is considered to be appropriate for a relatively long follow-up study of over 7 yr. It is necessary to study whether the time for a normotensive individual to develop hypertension depends on the level of workload (%$\dot{V}o_2max$) causing an exaggerated BP response (SBP of ≥250 mmHg and/or DBP of ≥120 mmHg).

Work place hypertension

Multivariable analysis also revealed that frequent business trips (≥8 times/mo) increased the risk of future hypertension. Hypertension is an occupational disease, and stress at work accelerates its onset and progression.

In recent years, workplace hypertension that is normotensive during clinical assessment but hypertensive at work has been recognized as a type of masked hypertension. Stress increases BP, and many men and women with high levels of work stress appear to have higher BP during working hours than at the time of a group medical examination[26]. Also, it was reported that those who work long hours due to overtime work are consequently exposed to stress for long periods and tend to retain relatively high BP[27]. Furthermore, those who have frequent business trips must work long hours, including traveling time, and tend to have frequent hotel stays and dine out. In addition, the possibility of BP elevation the day after a business trip, attributed to short sleeping time, is undeniable[28]. Therefore, our finding that the frequency of business trips is a new work-related risk factor for the development of future hypertension has important significance.

Many shift workers are known to have a tendency towards high BP because of disrupted circadian rhythm[29]. Also, a 14-year follow-up study showed that the odds ratio for hypertension is high among shift workers[30]. Although we did not identify irregular working hours as a significant independent factor, probably due to the short follow-up period, it is highly likely to be a risk factor for the development of future hypertension, and thus further follow-up studies are warranted.

Obesity and family history of hypertension are characteristics of individuals with workplace hypertension[31]. In the present study, obesity was also a significant factor according to univariate analysis, although an insignificant independent factor according to multivariate analysis. On the other hand, family history of hypertension was a significant independent factor according to multivariate analysis.

Patients with masked hypertension, including workplace hypertension, are more likely to have metabolic disorders than normotensive individuals, and show hypertension-associated organ damage such as left ventricular hypertrophy and carotid stenosis, regardless of treatment status[32].

The present study found that the exercise test can detect the group with a high risk of future hypertension, and moreover, with a risk of cardiovascular events, at the early stage. It also revealed that appropriate business trip management can reduce the risk of future hypertension. The Total Health Promotion Plan (THP), a promotion activity for the maintenance of workers' health, has been implemented since 1988 in Japan, but activities such as physical fitness measurements are not as frequently organized as before. It appears necessary to revise the THP as an antihypertensive measure.

Limitations and advantages of the present study

There are some limitations to this study. First, the data was based on male employees working in the manufacturing industry in a certain region, and thus the study population might be representative of a selective group and not of general occupations in various sectors. Second, work-related factors such as working posture, irregularity in work pattern, hours of overwork and frequency of business trips were used, but psychological stress factors and factors related to working environment were not evaluated. Third, considering that the mean age of the study population was 43.1 yr at the beginning of the study, a period of 7 yr was possibly too short a duration of follow-up.

On the other hand, the health examination used to assess the participants in this study was a duty of the employer under the Industrial Safety and Health Act, Article 66. This means that the participants, if not retired, were monitored throughout the follow-up period, achieving a relatively complete study. In addition, because the participants worked for the same company and experienced little change in job type, work-related factors were relatively unaltered during the follow-up period. Considering the young population (mean age, 43.1 yr) examined in this study, more participants may develop hypertension in an extended follow-up period. We consider that using the LOPS protocol with an extended follow-up period, the detection rate of the high-risk group for future hypertension would improve.

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