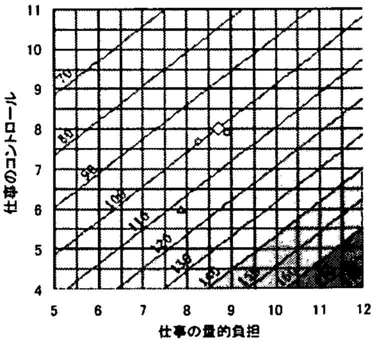
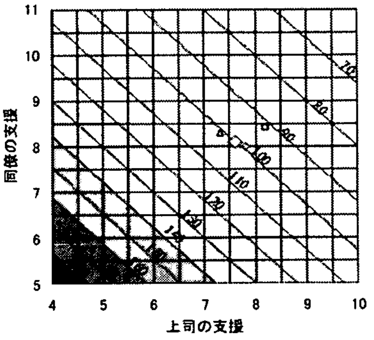
過重労働等ストレス健康リスク予知チャート（うつ病版）
各要因の評価方法

※詳細は、過重労働等ストレス健康リスク予知チャート素案活用マニュアルを参照ください。

【重要】うつ病発症リスクの推定の前に、産業医は対象者のうつ病の可能性を評価します。うつ病の可能性があれば、専門医への受診を勧めます。

1	超過勤務時間	対象者の、週40時間労働としての超過勤務時間を、45時間未満、45-79時間、80時間以上のいずれか選択してください
2	抑うつについて	抑うつについて、例えば「この1週間の気分についてうかがいます。ゆううつな気分は、1週間にどれくらいの頻度でありましたか。あったとしても1日もつづかないですか、週のうち1～2日でしたか、週のうち3～4日でしたか、週のうち5日以上でしたか。」とたずねます。週のうち3日以上なら「抑うつあり」とします。労働者の疲労蓄積度自己診断チェックリストの自覚症状の問4「ゆううつだ」の回答を用いてもかまいません。この場合、「ほとんどない」＝週1日未満、「時々ある」＝週1～2日、「よくある」＝週3日以上としてください。
3	疲労について	以下の2つの質問について、「1週間にどれくらいの頻度でありましたか。あったとしても1日もつづかないですか、週のうち1～2日でしたか、週のうち3～4日でしたか、週のうち5日以上でしたか。」とたずねます。 (1)朝、いつになく疲れていた。 判定方法: (ア)いずれか週のうち3日以上なら「疲労強い」とします。 (イ)いずれか週のうち1～2日以上なら「疲労中等度」とします。 (ウ)いずれも週のうち1日未満なら「疲労なし」とします。 労働者の疲労蓄積度自己診断チェックリストの自覚症状問11「へとへとだ」、問12「朝、起きた時、ぐったりした疲れを感じる」の回答を用いてもかまいません。この場合、「ほとんどない」＝週1日未満、「時々ある」＝週1～2日、「よくある」＝週3日以上としてください。
4	過去1年以内の異動あるいは仕事の変化	異動または仕事の変化があったと報告されれば、「あり」とします。
5	過去1年以内の仕事外の出来事	過去1年以内に、転居、結婚、本人または家族の病気など、仕事外の出来事がおきたかどうかたずねます。あった場合には「あり」とします。
6	婚姻状態	結婚しているかどうかたずねます。単身（独身）あるいは離・死別の場合にはリスク要因とみなします。結婚しているが単身赴任の場合や、結婚していないが同居生活を行っている場合は、ここでは「結婚している」に含めます。婚姻についてたずねにくい場合、婚姻状態が不明な場合には、「既婚」の方のチャートを使用してください。
7	飲酒	毎日かつ1日日本酒相当で3合以上の飲酒者か、それ以外かをたずねます。日本酒3合相当は、ビール大びん3本、ウイスキー水割り6杯に相当します。
8	仕事のストレス	上記2）の①で、抑うつが週2日未満の場合には、仕事のストレスと職場の支援度を評価し職業性ストレス簡易調査票から抜粋した仕事の要求度，仕事のコントロールについての6問の質問に回答してもらいます。仕事のストレス判定図の要求度ーコントロール判定図から、健康リスクの数値を読み取ります。これに加えて、職場の支援度に関する6問の質問に回答してもらいます。仕事のストレス判定図の職場の支援判定図から、健康リスクの数値を読み取ります。2つの健康リスクを掛け合わせます。計算された総合健康リスクが100未満の場合には、簡便のため100とします。   ※「仕事のストレス判定図」の詳細は、http://www.jstress.net　をご覧ください。

本チャートは、平成19年度労働安全衛生総合研究費「過重労働等による労働者のストレス負荷の評価に関する研究」（主任研究者　川上憲人）の研究成果です。本チャートの開発は、川上憲人（東京大学）が担当しています。

Ⅱ．研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
該当なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kobayashi Y, Hirose T, Tada Y, Tsutsumi A, Kawakami N.	Relationship between two job stress models and coronary risk factors among Japanese part-time female employees of a retail company	Journal of Occupational Health	47(3)	201-210	2005
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Ⅲ. 研究成果の刊行物・別刷

J Occup Health 2005; 47: 201–210

Journal of Occupational Health

Relationship between Two Job Stress Models and Coronary Risk Factors among Japanese Part-Time Female Employees of a Retail Company

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Abstract: Relationship between Two Job Stress Models and Coronary Risk Factors among Japanese Part-Time Female Employees of a Retail Company: Yuka Kobayashi, *et al.* Department of Hygiene and Preventive Medicine, Okayama University Graduate School of Medicine and Dentistry—The objective of this study was to explore the associations between two major job stress models (job strain and effort-reward imbalance) and coronary heart disease (CHD) risk factors (blood pressure; total, high- (HDL) and low-density lipoprotein (LDL) cholesterol; and triglycerides) in Japanese part-time female employees of a retail company. The study population was either 35 yr old or between 40 and 63 yr old. Data collection was carried out in 2002; a total of 1,401 subjects participated in a medical examination and completed a questionnaire. After adjusting for other covariates (age, relative weight, tobacco use, alcohol consumption, lack of exercise, education, marital status, history of child bearing, medical treatment for disease, and occupation), a significant association was found between the effort-reward imbalance, a "high-cost and low-gain" condition at work, and a high prevalence of low HDL cholesterol (Odds ratio = 4.4). A weak but unexpected association was found between job strain and low prevalence of low HDL cholesterol. In explanatory analysis with individual components of the two models, associations were evident between high extrinsic effort and high prevalence of low HDL cholesterol and low prevalence of high triglyceride, high job control and low prevalence of high systolic blood pressure, and high job demands and low prevalence of high systolic and diastolic blood pressure. In this cross-sectional study of Japanese part-time working women, a significant association was found between effort-reward imbalance and unfavorable HDL cholesterol profiles. The findings did not support the hypothesis that job strain is associated with CHD risk factors.
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Key words: Job strain, Effort-reward imbalance, Coronary risk factors, Part-time workers, Women, Japan

In the past two decades, a cumulative body of results has been reported showing an association between job strain defined in Karasek's job strain model[1] and coronary heart disease (CHD)[2–4] and its risk factors[5–17]. A high level of job strain, that is, a combination of high level of job demands and low level of job control, has been found to be associated with physiological CHD risk factors, such as high blood pressure in men[5–10] and women[11], high serum total cholesterol in men[9–12] and women[9], low high-density lipoprotein (HDL) cholesterol in men and women[11], and high triglycerides in men[8]. In addition, social support at work appears to reduce the effects of job strain on CHD risk factors, such as high blood pressure in women[18] and high serum total cholesterol in men[9]. However, previous studies have reported no clear association between job strain and high blood pressure in men[11, 14, 15, 19, 20] and women[6, 7, 9, 15, 17, 20], high serum total cholesterol in men[5, 8, 13, 14, 20] and women[12, 13, 17, 20], low HDL cholesterol in men[8, 11–13, 15, 20] and women[12, 13, 15, 17, 20], and high triglycerides in men[15, 20] and women[15, 17, 20].

Another more recently developed job stress model is the effort-reward imbalance model[21]. This model supposes that the source of stress in the workplace results from imbalance between individual recognition of extrinsic effort (e.g., high workload) and the extrinsic

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reward (e.g., money, esteem, and occupational status control), focusing on the negative trade-off between experienced costs and gains at work. However, this model has been studied much less than the job strain model, which shows that effort-reward imbalance also predicts CHD[22–24]. A significant association between effort-reward imbalance and high blood pressure, high serum total cholesterol, and high total / HDL cholesterol has been observed in men[25].

Information on women is sparse and inconsistent when compared to the data from studies of men[6, 9, 11–13, 15, 17, 20] with regard to the job strain model[6, 9, 11–13, 15, 17, 20], effort-reward imbalance model[25], and a combination of both[23]. These differences might be attributable to difficulties in finding associations owing to the protective function of female reproductive hormones and contamination of data from domestic work and job stress. Another important factor related to job stress is whether an individual is employed full- or part-time. Recently, the number of part-time working women has been increasing in Japan[26]; it has grown by approximately 1.4 times in the last decade. The results of studies in western countries indicate that part-time workers have lower levels of perceived job stress than full-time workers[27]. The low levels of job stress among part-time employees might be attributable to limited exposure to job stressors; however, a Japanese study showed lower levels of decision latitude in female temporary employees than permanent employees[28]. Furthermore, part-time employees experience more job insecurity and poorer prospects for promotion than full-timers. Although such differences in job stress are generally attributed to working conditions, it appears that the association between job stress and CHD risk factors in part-time employees has never been examined.

The questionnaires used for the job strain and effort-reward imbalance models are similar (i.e., job demands and extrinsic effort); however, the job strain model focuses more on task-oriented characteristics, while the effort-reward imbalance model deals with the broader occupational environment. Furthermore, the questionnaires show that the job strain scale makes use of objective job characteristics[29], while the effort-reward imbalance questionnaire measures the emotional aspects induced by stressful situations (see the Methods section). Thus, associations with biological CHD risk factors, if any, might be different between the two stress measures. Furthermore, application of the two stress models might provide more comprehensive features of the association between psychosocial job stress and coronary risks.

The objective of this study was to explore the associations between psychosocial work environments and CHD risk factors in a population of Japanese part-time female employees. Japanese retail companies hire many part-time females, and we used a large database of retailers. The two stress models and biological CHD risk factors were measured simultaneously.

Subjects and Methods

Subjects

The study population was recruited from a retail business in Miyagi Prefecture, Japan. A total of 5,635 employees were engaged in processing, sales, and the delivery of dairy goods, and about 80 percent of them were part-time employees. The target population included 3,510 female employees who worked four hours daily, 20 hours weekly, five days a week. They were selected from all part-time females (n=4,104), and the majority worked four-hour shifts.

A cross-sectional survey was carried out between July and December 2002 using a mailed questionnaire on demographic variables and the psychosocial work environment. Each employee was asked to complete the questionnaire. They also underwent an annual medical examination, which included a physical examination to determine blood pressure and blood tests. Blood samples were collected from participants aged 35 yr and from those aged 40 yr or above (n=2,798), according to the Industrial Safety and Health Law and related regulations. One thousand four hundred one participants completed both the questionnaire and medical examination, including the blood test (participation rate: 50%).

The study design and procedures were reviewed and approved by the Human Ethics Committee for Epidemiological Research at the Okayama University Graduate School of Medicine and Dentistry, Japan.

Procedures

CHD risk factors

The biological risk factors for CHD were measured as a part of the medical examination. The examination included measurements of blood pressure and serum lipids from blood samples, and took place during working hours (09:30 to 16:00).

The subject was seated, and then blood pressure was measured on the right arm once or twice by trained nurses. Measurements were obtained with a sphygmomanometer. The point at which the Korotkoff sounds disappeared (Swan's point 5) was recorded as the diastolic blood pressure. High systolic blood pressure was defined as 140 mmHg or greater and high diastolic blood pressure was defined as 90 mmHg or greater, according to the guidelines of The Japanese Society of Hypertension[30].

Serum total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were measured from the blood samples using high performance liquid chromatography. High serum total cholesterol was defined as 220 mg/d*l* or greater; low HDL cholesterol as under 40 mg/d*l*; high LDL cholesterol as 140 mg/d*l* or greater; and high triglycerides as 150 mg/d*l* or greater, according to the guidelines of the Japan Atherosclerosis

Society[31].

Psychosocial job stressors

Psychosocial job stressors were measured according to two major job stress models, the job strain[1] or demand-control-support model[4] and the effort-reward imbalance model[21]. The job strain model was measured using the Japanese version of the Job Content Questionnaire (JCQ), which contains 22 Likert-scaled items[32, 33]. Job strain score reflects a relatively objective work environment[29]. A scale of 1 to 4 was used to measure job strain. There were 5 items measuring "job demands" such as "working very fast"; nine items composed of two subscales for "job control": "skill discretion" with 6 items such as "opportunity to develop abilities", and "decision authority" with 3 items such as "allowed to make decisions"; four items for "supervisor support" such as "the supervisor pays attention to me"; and 4 items on "coworker support" such as "coworkers take an interest in me". The questions were designed to seek information about the existence of stressors in the workplace. A 4-point scale ranging from *strongly disagree* to *strongly agree* was developed, and the scores ranged from 12 to 48 for job demands, 24 to 96 for job control, 4 to 16 for supervisor support, and 4 to 16 for coworker support. The reliability coefficients of each subscale were job demands: 0.65, job control: 0.72, supervisor support: 0.90, and coworker support: 0.77. The quotient of job demands to job control was used as an indicator of "job strain" according to previous studies[19], and ranged from 0.1 to 2.0. The subjects were grouped into one of three strata for each psychosocial job stressor (low, medium or high) based on tertiles defined according to the distribution of scores: 15–31, 32–35, and 36 or greater, respectively, for job demands; 24–58, 59–66, and 67 or greater, respectively, for job control; 4–9, 10–11, and 12 or greater, respectively, for supervisor support; 4–10, 11, and 12 or greater, respectively, for coworker support; and 0.28–0.51, 0.51–0.61, and 0.61 or greater, respectively, for the job strain index.

The effort-reward imbalance model was measured using the Japanese version of the effort-reward imbalance questionnaire, which contains 17 Likert-scaled items[21, 34]. Two categories were used to measure these items. One was "extrinsic effort", which had 6 items such as "I am under constant time pressure due to my heavy work load", the other was "extrinsic reward", which had 11 items composed of three subscales. The subscales were as follows: "job promotion and salary" with 4 items such as "My job promotion prospects are poor"; "esteem" with 5 items such as "I receive the respect I deserve from my supervisors"; and "job instability" with 2 items such as "My job security is poor". The extrinsic effort and extrinsic reward categories were designed to seek information from respondents about the existence of stressful environmental conditions. If they *agree*, they are then asked to indicate the level of distress on a 4-point scale ranging from *very distressed* to *not at all distressed.* The total score used to measure these elements ranged from 6 to 30 for extrinsic effort and from 11 to 55 for extrinsic reward. The reliability coefficients of each subscale were 0.80 and 0.84 for extrinsic effort and extrinsic reward, respectively. The effort-reward imbalance index was calculated using the following formula, which ranged from 0.2 to 5:

$$\text{extrinsic effort} \times 11/((66-\text{extrinsic reward}) \times 0.5454)$$[35]

An effort-reward imbalance index was used to indicate "high-cost and low-gain", which reflects a subjective work environment. The subjects were grouped into one of three strata for each psychosocial job stressor (low, medium or high) based on tertiles defined according to the distribution of scores: 6–10, 11–14, and 15 or greater, respectively, for extrinsic effort; 11–14, 15–20, and 21 or greater, respectively, for extrinsic reward; and 0.20–0.37, 0.37–0.56, and 0.56 or greater, respectively, for the effort-reward imbalance index.

Covariates

Subjects were divided into three age groups according to age, 35 and 40–44, 45–49, and 50–63 yr old, and three occupational categories were used, laborers, clerks, or others. Other covariates included relative weight, health-related behaviors, and demographic variables. Height and weight were measured by trained nurses during the medical examination. The degree of relative weight was calculated as the relative excess in weight to a standard weight based on height ($22 \times \text{height (m)}^2$). Relative weight was divided into three categories: less than –10%, between –10 and 10%, and greater than 10%.

Health-related behaviors included tobacco use, alcohol consumption, and lack of exercise, and were self-reported. Tobacco use was determined according to whether individuals classified themselves as a current smoker, ex-smoker, or non-smoker; they were further divided into current or non-smokers. Alcohol consumption was determined according to how individuals classified their alcohol use: that is, daily, occasional, or rare; they were further divided into drinkers (those who answered "daily" or "occasional") and non-drinkers (those who answered "rare"). Frequency of exercise was determined by individual answers as follows: "more than once weekly", "sometimes", and "rarely"; subjects were then divided into one of two groups, "once weekly" or "less than once weekly"; the latter was defined as a lack of exercise.

Educational level was determined by years of school completed, and subjects were divided into two groups, 12 yr or less of schooling or more than 12 yr. Two categories were used for marital status, currently married or not married. Subjects also indicated whether or not they had children and whether they were being treated for CHD-related diseases, such as hypertension, hyperlipidemia, angina pectoris, myocardial infarction, and diabetes.

Statistical analysis

First, associations of psychosocial job stressors and tobacco use, alcohol consumption, lack of exercise, and relative weight were examined by the χ^2 test. Next, the associations between psychosocial job stressors and CHD risk factors were examined by multiple logistic regressions. Four psychosocial job stressors (job strain, supervisor support, coworker support, or effort-reward imbalance) were entered into the model to predict each CHD risk factor (the prevalence of high systolic/diastolic blood pressure, high total cholesterol, low HDL cholesterol, high LDL cholesterol, and high triglycerides), while controlling all covariates (age, tobacco use, alcohol consumption, lack of exercise, education, marital status, child bearing history, and medical treatment for disease) and occupation. As explanatory analyses, similar multiple logistic regression of each CHD risk factor were conducted with regards to job demands, job control, extrinsic effort, extrinsic reward, supervisor support, and coworker support, while controlling all covariates. All associations were inferred with an α level of 0.05. These were performed using SPSS computer program, version 11 (Chicago, IL, U.S.A.).

Results

The characteristics of the subjects are presented in Table 1. Compared with the excluded subjects, the number of clerical and married employees was higher (5 vs. 8%, χ^2=13.4; p=0.001, and 96 vs. 98%, χ^2=5.8; p= 0.016, respectively) among those analyzed. There were no differences between the analyzed and excluded subjects with regards to the other studied variables.

The associations of job stressors and tobacco use,

Table 1. Characteristics of the study sample

Variables	n	(%)
Sociodemographic data and health-related behaviors		
Age (years)		
35 or 40–44	337	(24.1)
45–49	465	(33.2)
50–63	599	(42.8)
Relative weight (relative excess in weight, see text)		
<–10%	209	(14.9)
–10–10%	776	(55.4)
10%<	416	(29.7)
Tabaccouse		
Current smoker	182	(13.0)
Never or ex-smoker	1219	(87.0)
Alcohol consumption		
Daily or sometimes	634	(45.3)
Rarely	767	(54.7)
Exercise		
Once weekly	346	(24.7)
Less than once weekly	1055	(75.3)
Education		
12 years or less	1015	(72.4)
More than 12 years	386	(27.6)
Marital status		
Married	1369	(97.7)
Not married	32	(2.3)
Childbearing		
Yes	768	(54.8)
No	633	(45.2)
Being treated for diseases[a]		
Yes	135	(9.6)
No	1266	(90.4)

(continued on next page)

(continued)
Table 1. Characteristics of the study sample

Variables	n	(%)
Occupation		
Production line workers	1241	(88.6)
Clerks	116	(8.3)
Others	44	(3.1)
Psychosocial job stressors (scores in the parentheses)		
Job strain (Job demands/Job control ratio)		
Low (.28–.51)	375	(26.8)
Medium (.51–.61)	489	(34.9)
High (.61–1.62)	537	(38.3)
Supervisor support		
High (12–16)	671	(47.9)
Medium (10–11)	305	(21.8)
Low (4–9)	425	(30.3)
Coworker support		
High (12–16)	726	(51.8)
Medium (11)	371	(26.5)
Low (4–10)	304	(21.7)
Effort-reward imbalance		
Low (.20–.37)	479	(34.2)
Medium (.37–.56)	460	(32.8)
High (.56–2.08)	462	(33.0)
CHD risk factors		
High systolic blood pressure (≥140 mmHg)	149	(10.6)
High diastolic blood pressure (≥90 mmHg)	136	(9.7)
High total cholesterol (≥220 mg/d*l*)	452	(32.3)
Low HDL cholesterol (<40mg/d*l*)	40	(2.9)
High LDL cholesterol (≥140 mg/d*l*)	434	(31.0)
High triglycerides (≥150 mg/d*l*)	175	(12.5)

a)"diseases" comprises hypertension, hyperlipidemia, angina pectoris, myocardial infarction, and diabetes.

alcohol consumption, lack of exercise, and relative weight are shown in Table 2. In our subjects, there were no statistically significant associations, although those who reported low coworker support tended to exercise less frequently (χ^2=5.6, p<0.10).

When four psychosocial job stressors and all other covariates were simultaneously entered into the multiple logistic regression model (Table 3), part-time women exposed to the highest effort-reward imbalance were four times as likely to be associated with high prevalence of low HDL cholesterol compared with those with the lowest effort-reward imbalance. On the other hand, although the association was weaker, the high job strain group had a significantly lower odds ratio (OR) of high prevalence of low HDL cholesterol. Associations between social support and CHD risk factors were apparent, but not statistically significant. Age and relative weight were significantly associated with all CHD risk factors except for HDL cholesterol; tobacco use was inversely associated with high prevalence of high total cholesterol; alcohol consumption was inversely associated with high prevalence of high total and LDL cholesterol; and lack of exercise was significantly associated with high prevalence of high systolic blood pressure. Additional controlling for occupation did not change the results.

Explanatory logistic regression analyses using job demands, job control, extrinsic effort, extrinsic reward, supervisor support, and coworker support as independent variables showed that high extrinsic effort was associated with high prevalence of low HDL cholesterol (OR =2.92, 95% confidence interval (CI)=1.04–8.19 for the medium group; OR=4.23, 95%CI=1.34–13.38 for the high group), and low prevalence of high triglycerides (OR=0.83, 95% CI=0.55–1.26 for the medium group; OR=0.46, 95% CI=0.27–0.78 for the high group). As expected, high job control was associated with low prevalence of high systolic blood pressure (OR=0.75, 95% CI=0.48–1.15 for the medium group; OR=0.43, 95% CI=0.26–0.71 for the

Table 2. Association of psychosocial job stressors with health-related behaviors (tobacco use, alcohol consumption, and lack of exercise) and relative weight status among part-time working women[a]

Job stressor (Range of scores)	Current smoker		Drinker (daily or sometimes)		Lack of exercise (Less than once weekly)		Relative weight[b]					
							<–10%		–10–10%		10%<	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Job strain (Job demands/Job control ratio)												
Low (.28–.51)	46	(12.3)	173	(46.1)	292	(77.9)	51	(13.6)	205	(54.7)	119	(31.7)
Medium (.51–.61)	69	(14.1)	218	(44.6)	356	(72.8)	75	(15.3)	283	(57.9)	131	(26.8)
High (.61–1.62)	67	(12.5)	243	(45.3)	407	(75.8)	83	(15.5)	288	(53.6)	166	(30.9)
Supervisor support												
High (12–16)	90	(13.4)	295	(44.0)	513	(76.5)	110	(16.4)	366	(54.5)	195	(29.1)
Medium (10–11)	37	(12.1)	147	(48.2)	232	(76.1)	45	(14.8)	164	(53.8)	96	(31.5)
Low (4–9)	55	(12.9)	192	(45.2)	310	(72.9)	54	(12.7)	246	(57.9)	125	(29.4)
Coworker support												
High (12–16)	92	(12.7)	321	(44.2)	549	(75.6)	118	(16.3)	393	(54.1)	215	(29.6)
Medium (11)	47	(12.7)	164	(44.2)	265	(71.4)	55	(14.8)	211	(56.9)	105	(28.3)
Low (4–10)	43	(14.1)	149	(49.0)	241	(79.3)	36	(11.8)	172	(56.6)	96	(31.6)
Effort–reward imbalance												
Low (.20–.37)	60	(12.5)	213	(44.5)	360	(75.2)	81	(16.9)	256	(53.4)	142	(29.6)
Medium (.37–.56)	62	(13.5)	211	(45.9)	359	(78.0)	67	(14.6)	269	(58.5)	124	(27.0)
High (.56–2.08)	60	(13.0)	210	(45.5)	336	(72.7)	61	(13.2)	251	(54.3)	150	(32.5)

a) No significant association was observed between job stressors and health-related behaviors (tobacco use, alcohol consumption, or lack of exercise) or relative weight status in crude or age-adjusted analysis (χ^2 test or multiple logistic regression, respectively, $p>0.05$).

b) Relative excess (%) in weight. See text.

high group), but unexpectedly high job demands were associated with low prevalence of high systolic blood pressure (OR=0.60, 95% CI=0.37–0.96 for the medium group; OR=0.71, 95% CI=0.44–1.16 for the high group) and low prevalence of high diastolic blood pressure (OR=0.45, 95% CI=0.27–0.76 for the medium group; OR=0.86, 95% CI=0.53–1.41 for the high group). Although not statistically significant, job demands showed a tendency to be associated with low prevalence of low HDL cholesterol (OR=0.92, 95% CI=0.36–2.36 for the medium group; OR=0.80, 95% CI=0.31–2.06 for the high group). Low coworker support was significantly associated with high prevalence of low HDL cholesterol (OR=2.21, 95% CI=1.03–4.76 for the medium group; OR=1.35, 95% CI=0.55–3.30 for the low group).

Discussion

Multivariate logistic regression analyses revealed a significant association between effort-reward imbalance and high prevalence of low HDL cholesterol in female part-time employees of a retail business, after adjusting for relevant confounding factors (age, relative weight, tobacco use, alcohol consumption, lack of exercise, education, marital status, child bearing, medical treatment of disease, and occupation). On the other hand, high job strain was associated with low prevalence of low HDL cholesterol. Explanatory analyses showed expected findings with regards to job control and support components, whereas demand components, extrinsic effort, and particularly, job demands had inverse associations with CHD risk factors. The associations between covariates and CHD risk factors were mostly as expected.

Effort-reward imbalance was associated with a large proportion of individuals with low HDL cholesterol. On the other hand, as in previous studies with inconsistent results ranging from a significantly adverse association[11] to almost no association[12, 13, 15, 17, 20] in women, this study showed high HDL cholesterol in the part-time workers exposed to job strain. These results might have been caused by differences in the aspects measured by both models. Emotional reactions to unpleasant situations might be an important variable in biochemical correlation studies of cholesterol[36], and lipid elevation appears to be more affected by perceived stress than objective stress[37]. The job strain model might be related more to objective measures of stressors than other questionnaires[29]; the subjects are questioned about their job characteristics, not about their feelings concerning stress. In contrast, the effort-reward questionnaire approaches more

Table 3. Associations between psychosocial job stressors and CHD risk factors among part-time working women: Results of fully adjusted multiple logistic regression analysis

	High systolic blood pressure			High diastolic blood pressure			High total cholesterol			Low HDL cholesterol			High LDL cholesterol			High triglycerides		
		95%CI[a]			95%CI			95%CI			95%CI			95%CI			95%CI	
Variables	Odds ratio	Lower	Upper	Odds ratio	Lower	Upper	Odds ratio	Lower	Upper	Odds ratio	Lower	Upper	Odds ratio	Lower	Upper	Odds ratio	Lower	Upper
Job strain (Job demand/Job control ratio)																		
Low (.28–.51)	1.00			1.00			1.00			1.00			1.00			1.00		
Medium (.51–.61)	0.78	0.49	1.26	0.79	0.48	1.28	1.01	0.74	1.38	0.71	0.32	1.58	1.03	0.75	1.41	0.90	0.58	1.39
High (.61–1.62)	1.12	0.71	1.77	1.02	0.64	1.64	1.02	0.75	1.40	0.40*	0.17	0.97	1.07	0.78	1.47	1.10	0.72	1.69
Supervisor support																		
High (12–16)	1.00			1.00			1.00			1.00			1.00			1.00		
Medium (10–11)	0.85	0.51	1.40	1.14	0.70	1.87	1.13	0.82	1.55	0.89	0.35	2.26	1.06	0.77	1.47	1.14	0.74	1.77
Low (4–9)	1.37	0.88	2.13	1.16	0.72	1.87	1.18	0.87	1.60	1.27	0.56	2.88	1.27	0.94	1.73	1.25	0.82	1.90
Coworker support																		
High (12–16)	1.00			1.00			1.00			1.00			1.00			1.00		
Medium (11)	1.38	0.91	2.09	1.06	0.68	1.65	1.09	0.82	1.44	2.14	1.00	4.58	1.07	0.81	1.43	1.24	0.83	1.85
Low (4–10)	0.96	0.59	1.57	0.98	0.60	1.62	1.04	0.75	1.44	1.29	0.54	3.08	0.93	0.67	1.30	1.44	0.94	2.22
Effort-reward imbalance																		
Low (.20–.37)	1.00			1.00			1.00			1.00			1.00			1.00		
Medium (.37–.56)	0.98	0.63	1.52	1.18	0.75	1.87	1.15	0.86	1.54	2.00	0.72	5.55	1.14	0.85	1.54	1.04	0.70	1.54
High (.56–2.08)	0.88	0.55	1.40	0.92	0.56	1.51	0.87	0.63	1.19	4.37**	1.63	11.73	0.88	0.64	1.21	0.63	0.41	0.99
Age (year)																		
35 or 40–44	1.00				1.00			1.00			1.00			1.00			1.00	
45–49	1.82	0.96	3.43	1.46	0.76	2.80	1.58*	1.09	2.28	0.80	0.34	1.93	1.59*	1.09	2.32	1.24	0.75	2.07
50–63	2.87**	1.46	5.64	2.52**	1.26	5.04	3.31**	2.20	4.98	0.44	0.15	1.34	2.90**	1.91	4.40	1.67	0.95	2.93
Relative weight (relative excess in weight)																		
<-10%	1.00			1.00			1.00			1.00			1.00			1.00		
–10–10%	1.79	0.89	3.58	1.54	0.77	3.11	1.93**	1.30	2.88	0.69	0.24	1.99	2.84**	1.80	4.48	2.19*	1.10	4.34
10%<	2.76**	1.36	5.60	2.56**	1.25	5.22	2.21**	1.44	3.37	2.09	0.74	5.94	4.73**	2.94	7.61	4.78**	2.39	9.56
Tobacco use (current smoker)	0.77	0.41	1.43	0.69	0.35	1.35	0.62*	0.41	0.94	1.35	0.54	3.36	0.84	0.56	1.25	1.61	1.00	2.59
Alcohol consumption (drinker)	1.02	0.71	1.48	1.26	0.86	1.84	0.77*	0.60	0.98	0.80	0.40	1.59	0.70**	0.54	0.89	1.00	0.71	1.41
Lack of exercise (less than once weekly)	1.71*	1.08	2.69	1.41	0.90	2.22	0.80	0.61	1.06	1.68	0.71	3.95	0.94	0.71	1.25	0.84	0.58	1.23
Education (more than 12 yr)	0.83	0.54	1.27	0.85	0.55	1.33	0.99	0.75	1.29	1.04	0.48	2.21	1.08	0.82	1.42	0.77	0.52	1.15
Marital status (not married)	0.61	0.17	2.18	1.12	0.36	3.47	1.33	0.61	2.90	0.00	0.00	7×10^{11}	1.26	0.57	2.75	1.24	0.44	3.49
Child bearing (yes)	0.87	0.55	1.38	0.85	0.52	1.37	1.06	0.78	1.44	0.62	0.26	1.52	0.89	0.65	1.21	1.11	0.72	1.70
Being treated for diseases (yes)	2.64**	1.67	4.18	3.21**	2.03	5.08	2.08**	1.41	3.05	0.36	0.08	1.60	1.33	0.91	1.96	2.37**	1.51	3.71

*: $p<.05$, **: $p<.01$, all variables were simultaneously entered in the model.

a) CI=Confidence Interval

cognitive levels of perceived job stress, and in this questionnaire the subjects are asked how they feel distressed.

The two stress models might provide an additional explanation for the results on lipid profiles. Previous investigations of occupational instability and job insecurity have frequently demonstrated increased total cholesterol levels[38, 39] and, to a lesser extent, high blood pressure levels[40]. Thus, perceived threat of job loss or poor job prospects could be a sensitive predictor of lipid deterioration, which might have been replicated in the effort-reward imbalance analysis. However, prevalence of low HDL cholesterol was very low; although relevant confounders were adjusted for in this study, the subjects with low HDL cholesterol may be a special group characterized by factors other than effort-reward imbalance, such as poor health practices or lifestyles. Further studies are necessary to explore the association between effort-reward imbalance and poor HDL cholesterol profiles.

The explanatory analysis revealed that the unexpected findings with regards to job strain appeared to be primarily attributable to the job demands component. The majority of recent evidence on job strain and CHD has not been able to confirm the full model, that is, the combination with high demands and low control[41]. Most recent studies have predicted an association between low control and CHD risk, whereas high demands were associated with decreased CHD risk. A demanding situation might not necessarily lead to adverse consequences in the current working world. This proposition might apply to Siegrist's effort component[21] to some extent (i.e., the unexpected observed association with triglycerides), and it requires more study. As expected, however, part-time women with high job control had low prevalence of high systolic blood pressure. Extrinsic effort was also associated with unfavorable HDL profiles, but the combination of high extrinsic effort and low extrinsic reward showed a clearer association, as postulated by the model[21].

Many tests showed no statistically significant associations, not only in our main hypothesis between job stressors and biological CHD risk factors but also in the associations between job stressors and health-related behaviors, which are possible mediators through which job stressors lead to biological CHD risk factors. These findings might be related to the specific characteristics of the sample studied. Part-time workers in retail businesses, such as the one studied here, consist of a central work force. While career development is limited, employees do not face a severe threat of job loss. In addition, exposure to adverse conditions is limited because of the limited working hours. Thus, it should be taken into account that the sample did not necessarily represent part-time employees who hypothetically experience harsh working conditions in terms of low occupational rewards.

The following limitations of the present study need to be discussed. First, because of the cross-sectional design of the study, a causal relationship was not determined by these results. Another shortcoming due to the study design is related to the employees' response to psychosocial job characteristics. Most employees have an annual physical checkup and were aware of their health status. Those who were aware that their health status was poor might have let their health situation be affected by external work conditions. More definite evidence would be obtained from a longitudinal study[24].

The low response rate might also have limited the validity of this study. The study population was slightly over-representative of clerical and married workers in the target population. However, there were no differences in independent and dependent indices (job stressors and CHD risk factor levels) as well as other demographic/behavioral variables between the analyzed and excluded workers. Thus, it was unlikely that the selection had a large effect on the results.

Third, blood pressure data were obtained by casual blood pressure measurements. Casual blood pressure measurements are less sensitive than ambulatory blood pressure monitoring in determining an association between psychosocial job characteristics and blood pressure[42–44]. In addition, serum samples were not collected after fasting in the present study, which might have resulted in measurement errors for serum lipids. Therefore, it is possible that the associations among psychosocial job stressors and CHD risk factors were underestimated in this study.

Fourth, not much consideration was given in this study to the following confounding factors. In this study sample, most workers carried domestic burdens as housekeepers, child care providers, or elderly care providers. Such domestic burdens might have affected the physiological data and shown a relationship with job stress. This study did not measure physical activity at work to adjust for other factors, which limits our interpretation of the unexpected associations of extrinsic effort and job strain with CHD risk factors. It is clear that there are other important possibly confounding factors, which were not included in the present analysis, such as family income, menstruation, dietary pattern, and sedentary lifestyle.

Finally, problems might have resulted due to multiple testing. In this study, the associations between multiple indicators were tested: four to six at once with regards to job stressors and six CHD risk factors. This possibly would increase the α error. Some subtle associations might have been observed as statistically significant.

Our findings did not fully support the hypothesis that an adverse psychosocial work environment is associated with unfavorable CHD risk factors. However, this does not mean that the association is not worthy of further study. Rather, our trial should be replicated using a larger employee sample engaged in contingent work characterized by low-wages and poor work prospects and performed mainly by women.

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Classical conditioned response of rectosigmoid motility and regional cerebral activity in humans

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Abstract *The relationship between the central processes of classical conditioning and conditioned responses of the gastrointestinal function is incompletely understood in humans. We tested the hypothesis that the rectosigmoid motility becomes conditioned with anticipatory painful somatosensory stimulus and that characteristic brain areas become activated during anticipation. In nine right-handed healthy male subjects, a loud buzzer (CS, conditional stimulus) was paired with painful transcutaneus electrical nerve stimulation to the right hand (unconditional stimulus). Rectosigmoid muscle tone measured by the barostat as the intrabag volume, phasic contractions of the bowel measured as the number of phasic volume events (PVEs), and regional cerebral blood flow assessed by positron emission tomography (PET), were measured before and after conditioning. Following conditional trials, the bag volume after CS alone did not show significant changes between before and after the stimulus, but the number of PVEs after 2-minute interval of the CS alone was significantly greater than that before the stimulus ($P < 0.05$). The PET data showed the conditioning elicited significant cerebral activation of the prefrontal, anterior cingulate, parietal and insula cortices ($P \leq 0.001$, uncorrected). Rectosigmoid motility can be conditioned with increase in phasic contractions in humans.*

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INTRODUCTION

In classical or Pavlovian conditioning, the conditional stimulus (CS), which is a neutral stimulus paired with an uncomfortable unconditional stimulus (US) previously, comes to elicit behavioural and physiological responses and the US alone.[1–3] This learning process provides a model to understand anticipatory reports of pain and anticipatory gastrointestinal symptoms in situations that are not objectively threatening or painful.[4]

Little is known about the process of anticipatory response in gastrointestinal motility in humans. Physical and psychological actual stress induces significant changes in gastrointestinal motility, which includes smooth muscle tone and phasic contractions of the gastrointestinal tract.[5] Patients with irritable bowel syndrome (IBS) show greater responses with abnormal patterns in the duodenal and colonic motility than healthy subjects during stress.[6] The studies of the Pavlovian conditioning paradigm in the animal model revealed that the anticipatory stimulus elicited the same gastrointestinal responses as a delivered actual stimulus.[7] In this model, the CS caused a significant increase in colonic spike burst frequency compared to basal values after repeated foot shock.[7] Moreover, epidemiological studies revealed that post-traumatic stress disorder (PTSD)[8] and a history of sexual or physical abuse,[9] which tend to be accompanied with anticipatory fear/anxiety,[10] had a high prevalence in patients with IBS. These phenomena suggest that central enhancement induced by associative learning may affect changes in gastrointestinal function.[11]

Classical conditioning is considered to be a model to understand anticipatory responses to aversive events, which is an essential component of how the brain–gut interaction develops in functional gastrointestinal disorders. Recently, central process of anticipatory responses has been investigated by several paradigm of brain imaging studies.[12–15] In spite of research progress of brain imaging studies, there have been few studies to observe conditioned response in both brain and gastrointestinal motility function. It has been established that conditioned response can be observed by pairing a painful somatosensory stimulus with a neutral stimulus.[16] In this study, we tested the following hypothesis: (i) the rectosigmoid motility becomes conditioned with increasing smooth muscle tone and increasing number of phasic contractions in humans and (ii) characteristic brain areas become activated during anticipation regardless of the stimulus intensity.

METHODS

Subjects

Nine right-handed healthy male subjects (mean age 24 ± 1 years; 19–29 years) were recruited from Tohoku University Campus in Sendai, Japan. All participants were free of gastrointestinal complaints and had not taken any medications within 4 weeks prior to testing. Each participant in this study underwent a medical history evaluation and was given a physical examination. Written informed consent was obtained from all participants, and this study was approved by the Tohoku University Ethics Committee.

Measurement of rectosigmoid function

The experiment was performed after a fasting period of at least 9 h. The subjects were placed in supine position and were instructed not to move during each session because of positron emission tomography (PET) scanning at the same time. A computer-driven barostat (Synectics Visceral Stimulator; Synectics, Stockholm, Sweden) was used to assess the rectosigmoid function.[17–19] A polyethylene bag (diameter, 9 cm; length, 9 cm; volume, 0–500 mL), which was tightly fixed at both ends to a catheter, was inserted into the rectosigmoid colon of each subject and placed with distal end of the bag 10 cm from the anal verge 30 min before the study. The biomechanical properties of the bag were determined by pressure–volume measurements with the bag outside of a subject (*ex vivo*; Fig. 1). At volumes of less than 430 mL, the bag itself did not contribute to resistance to inflation.

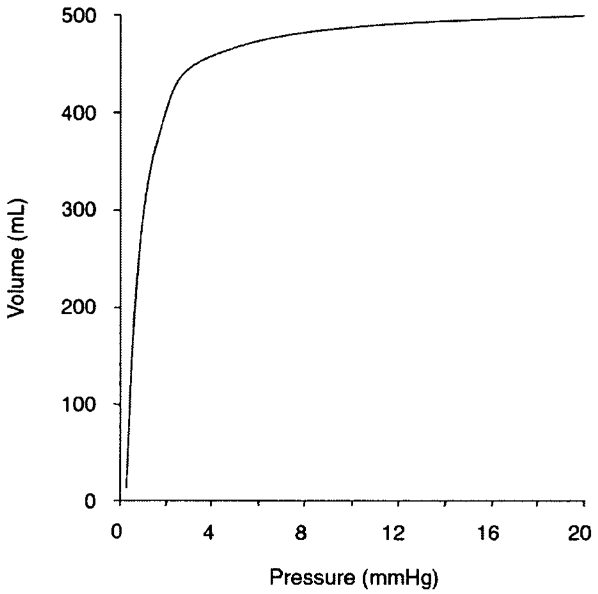

Figure 1 Barostat bag compliance measured *ex vivo*. The pressure–volume curve demonstrated operation in the low-elastance portion for operating volumes <430 mL. In this range, the bag itself did not contribute to resistance to inflation, assuring that barostat measurements reflect the mechanical characteristics of the surrounding tissue.

Before the protocol, an initial distension in which the balloon pressure was increased from 0 to 40 mm Hg in 2 mm Hg steps at 10-second intervals was performed to reduce variability in compliance and to confirm the reproducibility. Thereafter rectal compliance was assessed by graded inflation until the first painful sensation or a maximal pressure of 40 mm Hg in the same way of the initial distension. During the protocol, the intra-operating pressure of the barostat bag was kept constant at 10 mm Hg as one of the standard methods for measuring colonic tone.[19] On the other hand, there is the other standard method to consider the minimal distending pressure as the intra-operating pressure.[17–19] However, no subjects in the present study showed that each minimal distending pressure (median 8 mm Hg; 6–8 mm Hg) exceeded the operating pressure. Besides, the operating pressure was much lower compared with the threshold of the first painful sensation (median 30 mm Hg; 22 to >40 mm Hg), which showed reproducibility in each subject.

Measurement of brain activation

Using a similar technique, which we have described in the previous report,[20] regional cerebral blood flow (rCBF) was measured. Subjects were instructed to lie on their back in the PET scanner and to minimize head movement and keep their eyes closed during the scanning (for 70 s). Using a ^{68}Ge/^{68}Ga radiation source, transmission scans were carried out prior to PET scanning. [^{15}O]-labelled water (Tohoku University Cyclotron Radioisotope Center) was injected into the right arm vein 10 s before the beginning of each stimulus session. Ten seconds later, the radioactivity in the brain reached a plateau and an increase in rCBF was detected by the PET scanning as an index of neural activity evoked by the stimulus. As shown in Fig. 2, five scans of rCBF in each subject were measured using PET scanner in three-dimensional sampling mode (HEADTOME V SET-2400W, Shimadzu, Kyoto, Japan).[21] The scanner produced 63 horizontal slices with a separation of 3.125 mm, an axial field of view of 200 mm, an in-plane resolution of 590 mm, a full width at half maximum (FWHM) and an axial resolution of 3.9 mm FWHM. To ensure that radioactivity levels in each subject returned to baseline before starting a new scan, a 10-minute interval was given between successive scans.

Protocol

The protocol for the present study is shown in Fig. 2. There were three sessions; preconditioning, conditional and postconditioning trials. Subjects were exposed seven times to a loud buzzer (500 Hz with an intensity of 87 dB) lasting 1 s and being followed by a 9 s break. This sequence served as the CS. For the first sequence, only the CS tones were administrated as a preconditioning trial.

The US, which followed the CS during the conditional trials and a part of the postconditioning trials, was composed of transcutaneous electrical nerve stimulations (TENS; OG GIKEN AUDIO TREATER EF-501, Okayama, Japan) delivered to the back of the right hand at a frequency of 15 Hz with two different levels of intensity (7 or 4 mA). The US started just after each tone was finished and the stimulus period lasted 70 s (Fig. 2). After three sets of the CS or the postconditioning CS sequence, high-mA TENS was applied as the US. After the postconditioning CS sequence, low-mA TENS was applied as weak US. After the pre- or postconditioning CS-alone sequence, the US was not applied. In the postconditioning session, stimulus intensities of 0 (sham), 4 and 7 mA were given in random order.

The PET scanning was performed at the resting period as a background, and the pre- and postconditioning trials for each subject (five injections per scans, see Fig. 2). Each combination of the stimulus (the CS with/without the US) with break (10-second duration) was repeated seven times because the PET technique requires a 70-second recording window for each scan. The intra-bag pressure of barostat was kept at 10 mm Hg to measure changes in the bag volume in the rectosigmoid colon.

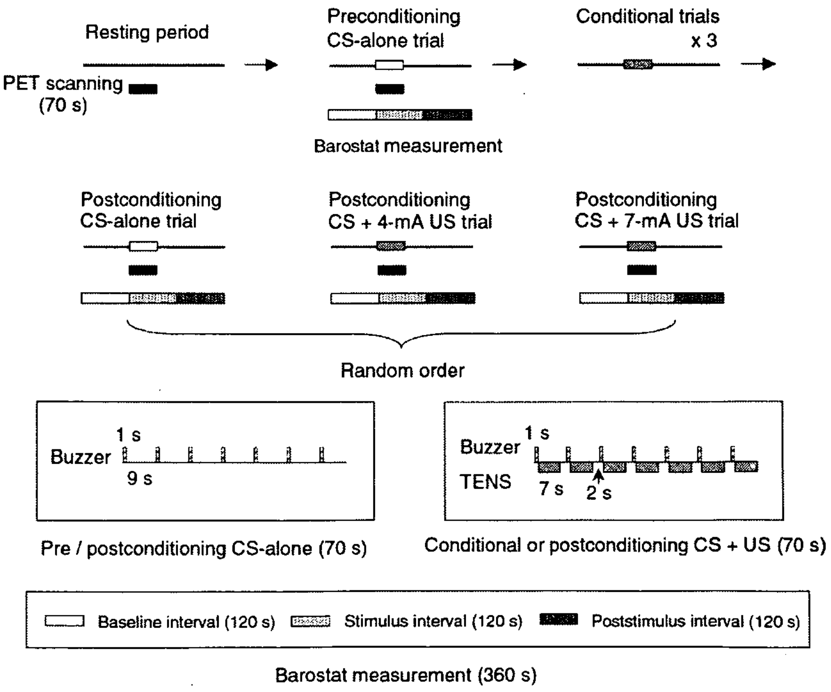

Figure 2 The protocol in this study. Simple tones of buzzer horn were used as conditional stimulus (CS) and following transcutaneus electrical stimulation (TENS) to the right hand were used as unconditional stimulus (US). Only the CS tones were administrated as a preconditioning trial. After three 70-second sequences of conditional trials in which the CS was paired with the US, three additional test sequences were presented in random order; they consisted of the CS presented alone, CS paired with 7-mA US, or CS paired with 4-mA US as postconditioning trials. Subjects were exposed seven times to a loud buzzer in each trial. The US was started just after each tone was finished (no overlap). PET scanning was performed at the resting period as a background, and the pre- and postconditioning trials.

The subjects were also asked in the scanner to verbally rate the intensity of overall anxiety on a 0–10 point scale, with 0 representing no anxiety and 10 being the most anxious, before and after all series of the sessions.

Analysis

The intrabag volume in the rectosigmoid colon was measured continuously and its variations were visually analysed. Mean bag volume over each 2-minute interval served as a measure of muscle tone, and number of phasic volume events (PVEs), served as a measure of phasic contractions according to the reported standard method.[17,18] In the present study, 2-minute interval for the analysis of barostat measurement was selected not to fail to observe changes in the rapid volume waves.[17] To control for occasional, minor changes in colorectal tone, the volume had to differ more than 10% from the baseline tone occurring at a frequency of 1–4 min^{-1} to be characterized as a change[17] (see Fig. 3). Movement artifacts were defined as sudden changes in bag volume that did not continue for more than 15 s and/or did not differ more than 10% from baseline;[17] these artifacts were excluded from data analysis. Changes in the bag volume or number of PVEs from each 2-minute baseline interval just before the stimulus (baseline interval) to each 2-minute interval just after the beginning of the stimulus (stimulus interval), and each following 2-minute interval (poststimulus interval), were considered to represent the colorectal wall reactivity to the CS with/without the US (Fig. 3). The paired Student's *t*-test or Wilcoxon's rank-sum test was used for comparing the rectosigmoid function in the 2-minute baseline, stimulus and poststimulus intervals of each trial. Alpha level was set at 5% for these statistical analyses.

The PET data were transferred to a super computer (NEC SX-4/128H4, Tokyo, Japan) at the computer centre of Tohoku University through the optical network. The image reconstruction of all brain area was carried out using the three-dimensional filtered back projection algorithm.[22] The PET image data were analysed using standard software (Statistical Parametric Mapping; SPM99, The Welcome Department of Cognitive Neurology, London) according to the method of Friston *et al.*[23] All brain slices were analysed. The PET images were realigned, spatially normalized and

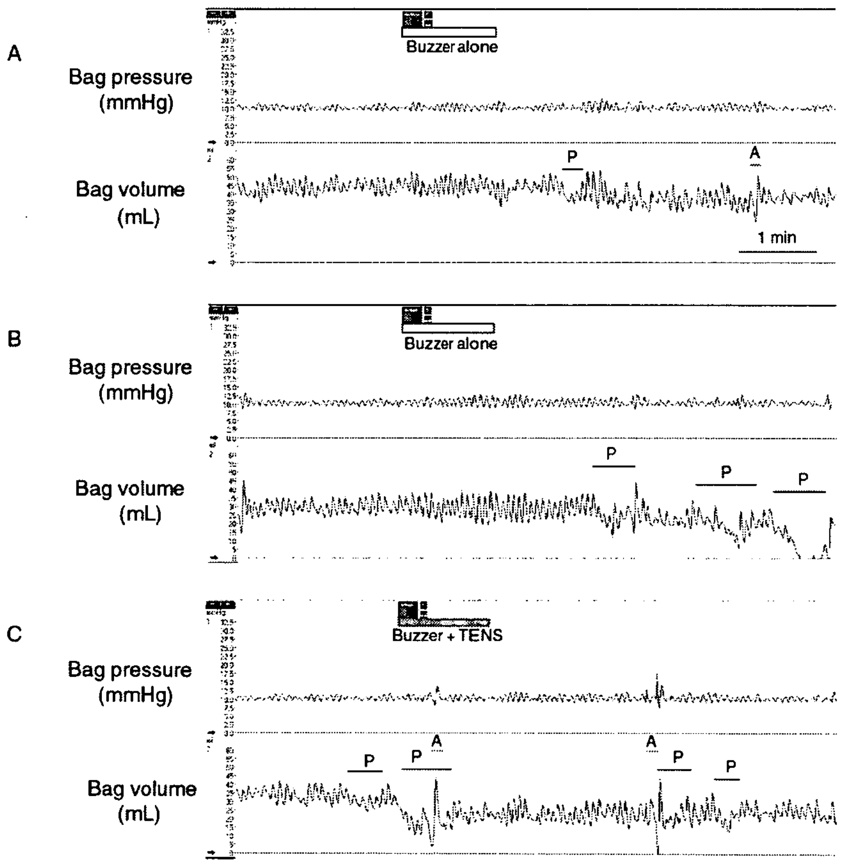

Figure 3 Examples of tracings of the barostat. Changes in the rectosigmoid bag volume were measured during the preconditioning trial (top; A), the postconditioning CS-alone trial (middle; B) and the postconditioning CS/US trial (bottom; C) using the barostat. The tracings that were obtained from one of the healthy 26-year-old male subjects were shown as the intrabag pressure (at the top) and the intrabag volume (at the bottom), respectively. Phasic volume events (P) were considered to be minor changes in colorectal tone, which differed more than 10% from the baseline tone. Artifacts (A) were considered to be sharp waves, that were parenthetically observed and that did not continue for more than 15 s and/or did not differ more than 10% from baseline tone.

transformed into an approximate Talairach–Tournoux stereotactic space, 3D Gaussian filtered (FWHM; 13 mm) and proportionally scaled to account for global confounders. The size of each voxel was set at 2 × 2 × 2 mm. A t-test was used to compare rCBF differences between the pre- and postconditioning CS-alone trials as a primal analysis for the effect of the conditioning. In addition, rCBF during the post-conditioning CS with high- or low-mA TENS trial was compared with that during the preconditioning CS-alone trial as secondary analyses for the effect of both nociception and conditioning. As an additional analysis, brain regions manifesting linear correlations to the mean bag volumes or the number of PVEs on the barostat measurement were also examined using simple regression analysis in SPM99. According to the reported methods of the 3D brain imaging studies,[22,23] we set alpha equal to 0.1% (uncorrected for multiple comparisons) as the region of significant differences. The region, which showed the significant activity correlations, was identified on the basis of Talairach co-ordinates.

RESULTS

No subjects had a history of functional/organic gastrointestinal disorders, psychiatric/psychological disorders or physical/sexual abuse. No abnormality was found on physical examination including failure to anal relaxation with a rectal digital examination in each subject. All subjects completed the full protocol. All the subjects reported pain to the right hand and different given stimulus intensities during the post-conditioning buzzer (CS) with high- or low-mA stimulus (US) trials. They did not report any pain or discomfort to the right hand in the buzzer-alone test trials. The buzzer with TENS or the buzzer alone did not induce any gastrointestinal symptoms. The anxiety scores did not show a significant change between before and after the protocol [median 4 (0–10) *vs* 2 (0–10), $P > 0.1$].

Assessment of rectosigmoid function

The rectosigmoid pressure and volume measurements were recorded at each distension step in the bag were plotted as mean values for the subjects in Fig. 3. The mean bag volume during 2-minute baseline interval was not significantly different among the sessions before and after the conditioning (Table 1). Example of actual barostat traces during the pre/postconditioning CS-alone (buzzer-alone) trials and the postconditioning CS with the US (buzzer with TENS) trials are shown in Fig. 4. In the postconditioning CS + high-mA US trial, the mean bag volume during 2-minute poststimulus

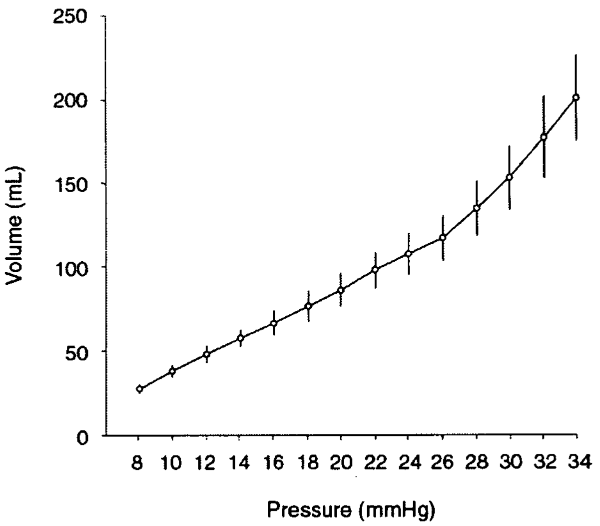

Figure 4 Pressure–volume curve reflecting the rectal compliance during intermittent isobaric distension in the subjects. The curve represents the mean value of the barostat bag volume (±SE) for each step of distension.

Table 1 Mean bag volume and number of PVEs in the rectosigmoid colon during pre- and postconditioning trials

	Mean bag volume (mL)			Number of PVEs (min^{-1})		
	Baseline interval	Stimulus interval	Poststimulus interval	Baseline interval	Stimulus interval	Poststimulus interval
CS alone/preconditioning	43 ± 8	41 ± 8	40 ± 8	0 (0–1.5)	0.5 (0–1.5)	0.5 (0–1.5)
CS alone/postconditioning	36 ± 11	36 ± 11	34 ± 13	0 (0–2)	0.5 (0–3)	1 (0–2.5)*
CS + US (4 mA)/postconditioning	48 ± 20	44 ± 15	38 ± 11	0.5 (0–1.5)	1 (0.5–2)	1 (0.5–2)*
CS + US (7 mA)/postconditioning	65 ± 29	63 ± 30	47 ± 18*	0 (0–1.5)	1 (0–3)	1 (0–2.5)*

CS, conditional stimulus; US, unconditional stimulus; PVEs, phasic volume events.
The duration of each interval is 2 min. Data were shown as mean ± SE or median with range. *$P < 0.05$ *vs* baseline interval (Student's t-test or Wilcoxon's rank-sum test).

interval was significantly smaller than that during 2-minute baseline interval ($P < 0.05$, Table 1). In the preconditioning trial and the postconditioning CS-alone and CS + low-mA US trials, the mean bag volume during the stimulus or poststimulus intervals did not show significant difference compared to that during each baseline interval. Thus, no conditioned effect was demonstrated for rectosigmoid muscle tone.

In the postconditioning CS-alone trial, the number of PVEs during the 2-minute poststimulus interval was significantly greater than that during the immediately preceding 2-minute baseline interval ($P < 0.05$, Table 1). The number of PVEs during the poststimulus intervals were significantly greater than those during the baseline intervals in the postconditioning CS + low-mA US ($P < 0.05$) and CS + high-mA US ($P < 0.05$) trials, respectively. There were no significant differences in the number of PVEs in the preconditioning trial (Table 1). These data support a conditioning effect for colonic phasic contractions.

Assessment of central activation

The average PET data from all the subjects showed the conditioning elicited significant activation of the left lateral prefrontal, right anterior cingulate, bilateral parietal cortices, right insula, right pons and left cerebellum ($P \le 0.001$, uncorrected; Table 2 and Fig. 5) when comparing rCBF differences between pre- and postconditioning CS-alone trials of PET images. Comparing the postconditioning CS with 7-mA US with the preconditioning CS-alone trials, there was significant more activation of the bilateral primary sensory, left frontal, temporal, posterior cingulate and occipital cortices and bilateral pons ($P \le 0.001$, uncorrected; Table 3). Comparing the postconditioning CS with 4-mA US with the preconditioning CS-alone trials, there was significant more activation of the left primary sensory, prefrontal, anterior cingulate, parietal and primary motor cortices, bilateral precentral gyrus, left putamen and left pons ($P \le 0.001$, uncorrected; Table 4).

Table 2 Areas of rCBF significantly increased in the post-conditioning CS-alone trial compared to the preconditioning CS-alone trial ($P \le 0.001$, uncorrected)

		Talairach co-ordinate			
Area (Broadmann area)	Hemi-sphere	*x*	*Y*	*Z*	*Z*-score
Prefrontal cortex (46)	Left	−42	40	10	4.1
Anterior cingulate cortex (32)	Right	14	34	30	3.4
Insula (13)	Right	36	2	−4	3.8
Parietal cortex (40)	Left	−34	−32	40	3.6
	Right	54	−40	30	3.2
Pons*	Right	14	−26	−42	3.4
	Right	12	−14	−28	3.8
Cerebellum	Left	−28	−54	−40	3.2

rCBF, regional cerebral blood flow.
*Two different activated areas in the right pons were discriminated.

For the postconditioning CS-alone trial, there were no significant correlations between rCBF in any region and the mean bag volumes or the number of PVEs.

DISCUSSION

In the present study, the loud buzzer used prior to conditioning as a conditioned stimulus (CS) did not cause any alteration in rectosigmoid motility. However, following a series of conditional trials in which the buzzer was paired with painful electrical stimulation to the right hand, the buzzer-alone elicited increases in the phasic contractions of the rectosigmoid colon, which were similar to those seen following the conditioned stimulus plus the US. This provides evidence for Pavlovian conditioning of phasic motor responses. However, we did not find evidence for conditioning of the tonic motor response (barostat volume) or subjective pain; following conditional trials, the CS alone did not elicit changes in barostat volumes or reports of any gastrointestinal symptoms in the healthy subjects.

Little has been known about the anticipatory motor response in digestive system in humans. Previously, Naliboff *et al.*[15] and our group[20] reported that healthy human subjects reported slight unpleasantness/pain in response to sham distention of the colon after actual painful distention, and Mertz *et al.*[24] reported the same for sham distention of the stomach in patients with functional dyspepsia. However, these reports have not investigated gastrointestinal motility function. Only the animal study with rat model revealed that conditioned fear after repeated foot shock as US caused a significant increase in colonic spike burst frequency but failed to affect jejunal motility.[7] The colonic motility changes that have been identified in the present study are considered to be as one of secondary phenomena that would occur during the anticipation of pain. Anticipation affects the autonomic nervous function. The observation that anticipation of painful/aversive stimulus resulted in changes in heart rate was confirmed by several studies in both human and animal models.[25–27] Tests with drugs blocking the sympathetic or parasympathetic fibres revealed that