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ORIGINAL ARTICLE

Association of blood pressure levels with the effects of alcohol intake on the vasculature in Japanese men

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The association of blood pressure levels with the effects of alcohol intake on the vasculature has not been clarified. We evaluated the differential effects of alcohol intake on the vasculature of subjects with optimal or normal blood pressure (ONbp) and those with high normal blood pressure or higher (HNHbp) in a 6-year follow-up study. The pulse wave velocity (PWV) was measured on three occasions at an interval of 3 years in 1185 middle-aged Japanese men (age 41 ± 8 years). In subjects with ONbp (n=677), a U-shaped relationship between alcohol intake (non-drinker, and light-to-moderate and heavy alcohol intake groups) and the increase in the adjusted value of PWV was observed at the end of 6 years' observation. On the other hand, in subjects with HNHbp (n=508), a U-shaped relationship was not observed. At the end of 6 years' observation, the increase in PWV was significantly more in the heavy intake group than in the light-to-moderate intake group or the non-drinker group, even after adjustment for changes in blood pressure and prescribed medication ($P<0.01$). In conclusion, blood pressure levels may modulate the effects of alcohol intake on the vasculature in middle-aged Japanese subjects. In subjects with ONbp, light-to-moderate alcohol intake appeared to have a possible vasculoprotective effect; on the other hand, in subjects with NHNbp, heavy alcohol intake seemed to exert a detrimental effect on the vasculature.
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INTRODUCTION

Several epidemiological studies have shown an inverse or J-shaped association between alcohol intake and cardiovascular morbidity and mortality.[1–4] Atherosclerosis produces not only vascular endothelial damage but also vascular wall damage (that is, arteriosclerosis), which causes increased arterial stiffness.[5–9] Carotid intima-media thickness assessed by ultrasound examination and pulse wave velocity (PWV), which reflects arterial stiffness, are thought to be markers of arterial damage.[5–10] However, conflicting results have been reported on the relationship between alcohol intake and these markers.[11–14] Thus, the vasculoprotective effects of alcohol intake have not been fully shown. Regular alcohol intake has been reported to be associated with a dose-related increase in blood pressure,[15] and some studies have suggested that the increase in blood pressure due to alcohol intake is a risk factor for cardiovascular events.[3,4,15,16] Therefore, the inconsistent findings with regard to the relationship between alcohol intake and vascular damage might be attributable, at least in part, to the differences in blood pressure levels of the study subjects. Recently, we showed that even increased blood pressure (⩾130/85 mm Hg) levels are associated with accelerated arterial stiffening.[9] Therefore, it might be possible that the relationship between alcohol intake and vascular damage differs between subjects with optimal or normal blood pressure (ONbp) and those with high-normal or high blood pressure (HNHbp).

The differential effects of alcohol intake on the vasculature of middle-aged Japanese men with ONbp and those with HNHbp were evaluated by assessing changes in the brachial–ankle PWV in this 6-year follow-up study.

METHODS

Study cohort

All the study subjects were enrolled in this observational study protocol in 2000 and were followed up until 2006. The details of this study protocol are described elsewhere.[9] Briefly, the subjects underwent a routine annual health check, including evaluation of known atherosclerotic risk factors (body mass index (BMI), serum levels of triglycerides (TG), high-density lipoprotein (HDL) cholesterol and total cholesterol (TC), fasting blood glucose and blood pressure), and brachial–ankle PWV was also measured on three occasions, that is, at the beginning (first examination: 2000), after 3 years (second examination: 2003), and at the 6-year follow-up (third examination: 2006). In the treatment protocol, subjects with atherosclerotic risk factors were advised to visit the Health Care Center of their construction company as a first step, and a management plan was drawn up for each subject. The patients were provided guidance with regard to therapeutic lifestyle modifications, including recommendation of less-than-moderate intake of alcohol, by the doctor, nurse, and nutritionist team at the Health Care Center. In subjects who were judged as requiring medication for abnormalities, appropriate medication was prescribed at either the Health Care Center or at other clinics; each patient was given the freedom to choose his/her own doctor for such treatment. Verbal informed

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consent was obtained from all participants before their participation in this study. The study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University.

Subjects meeting the following criteria were considered to be ineligible for the study: an ankle/brachial systolic blood pressure index (ABI) of <0.95, atrial fibrillation, and undergoing regular hemodialysis. The reliability of the brachial–ankle PWV measurements in the presence of these conditions is considered to be questionable.[8,9] In addition, subjects in the non-drinker or light-to-moderate alcohol intake groups with serum γ-glutamyltransferase levels of $>100\,\text{units}\,\text{l}^{-1}$ were excluded from the study, so as to avoid a misclassification.

In 2000, 2184 subjects working at the company headquarters were enrolled in this follow-up study protocol. Of these, 1879 subjects were successfully followed up until 2006, but 305 were lost to follow-up because of migration from the company headquarters to branch offices, change of job, or retirement. Of the 1879 subjects, 407 were excluded because of failure to obtain data for 2003 ($n=240$), loss of interview records determining the daily alcohol intake ($n=24$), poor reliability of brachial–ankle PWV measurements (ABI <0.95, $n=32$; atrial fibrillation $n=6$; undergoing regular hemodialysis $n=2$), and subjects with serum levels of γ-glutamyltransferase of $>100\,\text{units}\,\text{l}^{-1}$ ($n=103$). In addition, 287 women were excluded from the analysis because the number of women categorized into the HNHbp group was too small to allow reliable analysis ($n=55$). Finally, the data of 1185 men were successfully entered for the analysis.

Measurements

Alcohol intake. Habitual alcohol intake was assessed using a self-administered questionnaire. The level of alcohol intake was evaluated using two parameters: average drinking frequency (days/week) and average amount consumed each week (ml). The average daily alcohol intake ($\text{g}\,\text{day}^{-1}$, ethanol equivalent) was then calculated for each subject. Some of the subjects, selected based on their responses to the questionnaire, were provided guidance with regard to therapeutic lifestyle modifications at the Health Care Center, including recommendations for limitation of alcohol intake. In this study cohort assessing the reproducibility of the questionnaire, assessment of alcohol intake was conducted twice at an interval of 1 month for 3095 subjects working at the company headquarters in 2002. The correlation co-efficient and κ-value for alcohol intake between the first and second questionnaire was $r=0.91$ and $\kappa=0.77$; $P<0.01$ for drinking frequency, and $r=0.86$ and $\kappa=0.64$; $P<0.01$ for the average amount consumed. Further, the subjects were categorized according to their daily alcohol intake as estimated from their responses to the questionnaire, as follows: 0 (non-drinker group), 1–29 $\text{g}\,\text{day}^{-1}$ (light-to-moderate alcohol intake group), and $>30\,\text{g}\,\text{day}^{-1}$ (heavy alcohol intake group).

We assessed alcohol intake at the first, second, and third examinations. According to these assessments, we defined the mean alcohol intake during the study period as follows: non-drinker: categorized as a non-drinker at least twice; light-to-moderate alcohol intake: categorized into the light-to-moderate alcohol intake group at least twice; and heavy alcohol intake: categorized into the heavy alcohol intake group at least twice.

PWV

The brachial–ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI, Colin Co. Ltd, Komaki, Japan), in accordance with a previously described methodology.[8,9] Briefly, electrocardiographic electrodes were placed on both wrists, and a microphone for the phonocardiogram was attached to the left side of the chest. Electrocardiograms and phonocardiograms served as the time markers for the device. Occlusion cuffs, which were connected to both plethysmographic and oscillometric sensors, were tied around both upper arms and ankles, with the subjects lying in a supine position. The brachial and post-tibial arterial pressures were measured using the oscillometric sensor. The brachial and post-tibial arterial pressure waveforms determined by the plethysmographic sensor were recorded for 10 s and stored. The measurements were conducted after the subject had rested for at least 5 min in a supine position, in an air-conditioned room (24–26 °C) earmarked exclusively for this purpose. The interobserver and intraobserver coefficients of variation for the brachial–ankle PWV have been reported to be 8.4 and 10.0%, respectively.[8]

Laboratory measurements

The TG, HDL cholesterol, TC, fasting blood glucose, and serum creatinine levels were measured using enzymatic methods (Falco Biosystems Co. Ltd, Tokyo). The interassay coefficients of variation for the laboratory measurements were as follows: TG 1.5%, HDL cholesterol 1.9%, TC 0.4%, plasma glucose 0.8%, and serum creatinine 0.5%. All the blood samples were obtained in the morning after the patients had fasted overnight.

Definitions

Blood pressure was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer. Then, HNHbp was defined as $\geqslant 130/85$ mm Hg.

Statistical analysis

Data were expressed as means ± s.d. The significance of the effect of blood pressure class (ONbp *vs.* HNHbp) and that of light-to-moderate alcohol intake status (light-to-moderate alcohol intake *vs.* other alcohol intake categories) on the changes in the brachial–ankle PWV during the study period was assessed by multivariate linear regression analysis. The differences in the variables between the first and the third examinations in each group were assessed by paired *t*-test. For assessment of the differences in status of each variable among the groups, a one-way analysis of variance with Bonfferoni's adjustment was applied for continuous variables, and the χ^2 test was applied for categorical variables. In addition, the differences in changes in the brachial–ankle PWV during the study period were compared across the six subject groups divided based on daily alcohol intake level and blood pressure using a general linear model univariate analysis with control for covariates. All analyses were conducted using the SPSS software for Windows (version 11.0J, SPSS, Chicago, IL, USA). A *P*-value of <0.05 was considered to denote statistical significance.

RESULTS

A multivariate linear regression analysis showed that blood pressure class (ONbp *vs.* HNHbp) and mild-to-moderate alcohol intake status (light-to-moderate alcohol intake *vs.* other alcohol intake categories) were independently related to changes in the brachial–ankle PWV during the study period (Table 1). Although the prevalence of subjects who smoked was higher in the heavy drinker group than in the other group classified according to alcohol intake status, smoking status was not found to be significantly related to changes in the brachial–ankle PWV during the study period (Table 1).

Study subjects were classified based on blood pressure levels at the first examination and mean alcohol intake during the study period. Table 2 shows the clinical characteristics of the subjects and their changes during the follow-up period. From the first through the third examination, the brachial–ankle PWV and the serum HDL cholesterol level, but not the plasma glucose level, significantly increased in all subject groups. In subjects with HNHbp, systolic blood pressure decreased in all alcohol intake groups, although we could not explain the reason why blood pressure decreased in these groups.

Figure 1 shows the changes in the adjusted values of the differences in the brachial–ankle PWV during 6-years study periods (that is, between the first and third examination) in the six groups adjusted for continuous variables (the values at the first examination—age, BMI, brachial–ankle PWV, heart rate, TC, HDL cholesterol, TG, fasting plasma glucose, and serum creatinine—and changes in body weight, mean arterial pressure, heart rate, TC, HDL cholesterol, TG, fasting plasma glucose, and serum creatinine, during the study period) and categorical variables (smoking status at the first examination, change in smoking status during the study period and medication for hypertension, dyslipidemia, diabetes mellitus, heart

Table 1 The results of multivariate linear regression analysis to assess the significance of the effect of blood pressure classification and that of light-to-moderate alcohol intake status on changes in brachial–ankle pulse wave velocity during the 6-years study period

Variable	β	t-*value*	P-*value*
BP classification	0.05	1.96	0.04
LiMo Alc intake	−0.05	2.10	0.03
Age (years)	0.11	4.04	<0.01
BMI (kg/m^2)	−0.01	−0.30	0.76
Smoking	0.03	1.24	0.22
baPWV 1st	−0.23	−7.46	<0.01
TC 1st	−0.01	−0.04	0.97
HDL 1st	−0.04	−1.29	0.15
TG 1st	−0.01	−0.19	0.85
FBS 1st	0.09	2.41	0.01
Cr 1st	−0.05	−1.92	0.05
HR 1st	0.10	3.43	<0.01
delMBP	0.45	17.30	<0.01
delHR	0.21	7.71	<0.01
delSmoking	0.01	0.03	0.98
delBW	0.03	1.07	0.28
delTC	−0.01	−0.24	0.81
delHDL	0.11	3.61	<0.01
delFBS	0.14	4.12	<0.01
delCr	−0.01	−0.30	0.76
HBP	0.06	2.26	0.02
Lipid	−0.06	−2.20	0.02
DM	0.02	0.53	0.60
Heart	0.02	1.01	0.31
Stroke	−0.03	−1.32	0.19
Kidney	−0.02	−0.77	0.44

Abbreviations: 1st, the initial of study period; baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; BP classification, blood pressure classification into two groups (that is., optimal or normal blood pressure and high normal blood pressure or higher); BW, body weight; Cr, serum creatinine; del, changes in variables during the study period; DM, number of patient prescribing drugs for diabetes mellitus; FPG, fasting plasma glucose; HBP, number of patient prescribing drugs for hypertension; HDL, serum high-density lipoprotein cholesterol; heart, number of patients prescribing drugs for heart disease; HR, heart rate; kidney, number of patient prescribing drugs for chronic kidney disease; LiMo Alc intake, light-to-moderate alcohol intake; lipid, number of patients prescribing drugs for dyslipidemia; stroke, number of patients prescribing drugs for stroke; TC, serum total cholesterol; TG, serum triglycerides.
R^2=0.37.

disease, stroke, and chronic kidney disease). Among the groups, the increase in the adjusted value of the brachial–ankle PWV was significantly lower in the ONbp/light-to-moderate alcohol intake group than in the ONbp/non-drinker group (Figure 1). However, this adjusted value was similar among the HNHbp/light-to-moderate alcohol intake group, ONbp/non-drinker group, and HNHbp/non-drinker group (Figure 1). By contrast, this adjusted value was higher in the HNHbp/heavy alcohol intake group than in any of the other five groups (Figure 1). This finding was also confirmed in subjects not receiving medication for risk factors for cardiovascular disease (n=988) (data not shown).

In subjects who were non-smokers (n=733), although similar tendencies were observed, because the number of study subjects decreased, the difference in the increase of brachial–ankle PWV during the study period between ONbp/non-drinker and ONbp/light-to-moderate alcohol intake groups did not reach statistical significance. However, this value in the HNHbp/heavy alcohol intake group was larger than that in any of the other five groups (data not shown).

DISCUSSION

Although some cross-sectional studies have shown an inverse or J-shaped relationship of alcohol intake with either carotid intima-media thickness or PWV,[12,13] prospective studies could not confirm such a relationship.[14,17] However, these prospective studies did not examine the influence of blood pressure levels on such relationship.[14,17] Furthermore, these studies might have had a major limitation: they assessed only the alcohol intake at baseline. This study evaluated the relationship between the mean alcohol intake during the study period and the progression of arterial stiffness between the subjects with and without raised blood pressure after adjustment for changes in blood pressure and medication. To our knowledge, this was the first observational study to show that the relationship between alcohol intake and progression of vascular damage assessed by brachial–ankle PWV during the study period differs between subjects with ONbp and those with HNHbp.

A recent Japanese prospective study indicated that heavy alcohol intake is associated with increased mortality from total stroke and total cardiovascular disease in men.[18] Several studies showed that increased central arterial stiffness is an independent risk for cardiovascular events.[6,7,19] Carotid-femoral PWV is an established marker of this central arterial stiffness.[7] However, although brachial–ankle PWV includes both central and peripheral arterial components,[8,9] some studies have also shown that the brachial–ankle PWV is a marker of prognosis.[20,21] In subjects with HNHbp, the increase in arterial stiffness was greater in the heavy alcohol intake group than that in any of the other groups, even after the adjustment including the changes in blood pressure and medication. Thus, the results of this study suggested that increased arterial stiffness might contribute, at least in part, to increased cardiovascular mortality resulting from heavy alcohol intake.

Arterial stiffening is caused by functional changes, such as increased arterial wall tension related to elevated blood pressure and/or structural changes in the arterial wall, such as disease of the medial layer related to arteriosclerosis.[5,6] Several mechanisms, such as hypertrophy of the tunica media of the arteries, the renin–angiotensin system, and endothelial dysfunction, have been thought to be involved in the increased arterial stiffening related to elevated blood pressure.[5,6] At the third examination, blood pressure, plasma glucose level, and TG were higher in the former group than those in the latter group. Therefore, these atherogenic abnormalities related to heavy alcohol intake might have some contribution to the progression of vascular damage in these subjects.

According to the results of our study, light-to-moderate alcohol intake attenuated the progression of arterial stiffness in subjects with ONbp, even after the adjustment for changes in blood pressure and medication over the 6-year period. The present results suggest that light-to-moderate alcohol intake might have a possible protective effect against the progression of vascular damage in subjects with ONbp. Until now, no study has clarified whether the relationship between alcohol intake and cardiovascular events might differ between subjects with and without hypertension. Therefore, the next logical step would be to clarify whether the differential effects of alcohol intake on arterial stiffness among subjects with different blood pressure levels might also affect the cardiovascular outcomes.

It is thought that the reduction in inflammation, oxidative stress and/or metalloprotease activity, and the improvement of HDL cholesterol and/or glucose metabolism may have some role in the light-to-moderate alcohol intake-related attenuation of structural arterial stiffening.[13,22–24] In this study, however, the serum HDL cholesterol level, but not the plasma glucose level, was similarly increased in all

Table 2 Clinical characteristics and their changes of the subjects classified based on the blood pressure levels at the 1st examination and the mean alcohol intake during the study period

Gp-category	*ONbpNon*		*ONbpLi-Mo*		*ONbpHeavy*		*HNHbpNon*		*HNHbpLi-Mo*		*HNHbpHeavy*	
Number	*111*		*397*		*169*		*66*		*253*		*189*	
Ex-time	*1st*	*3rd*	*1st*	*3rd*	*1st*	*3rd*	*1st*	*3rd*	*1st*	*3rd*	*1st*	*3rd*
Age (years)	40 ± 8		39 ± 8		41 ± 8†		44 ± 7*,†,‡		42 ± 8*,†		45 ± 7$^{*,\dagger,\ddagger,\text{♪}}$	
BMI (kg m^{-2})	22.7 ± 2.9	23.3 ± 3.2$^{\int}$	22.9 ± 2.5	23.4 ± 2.6$^{\int}$	23.4 ± 2.5*,†	23.9 ± 2.5$^{\int,\dagger}$	24.7 ± 2.9*,†,‡	25.3 ± 3.6$^{\int,*,\dagger,\ddagger}$	24.2 ± 2.9*,†,‡	24.4 ± 3.2$^{\int,*,\dagger,\ddagger}$	24.7 ± 2.8*,†,‡	24.9 ± 2.8$^{\int,*,\dagger,\ddagger}$
Smoking (%)	39 (35)	35 (32)	142 (36)	99 (25)	97 (57)*,†	78 (46)*,†	15 (23)‡	13 (20)‡	73 (29)*,‡	62 (25)‡	86 (46)$^{*,\dagger,\ddagger,\P,\text{♪}}$	64 (34)$^{\dagger,\ddagger,\P,\text{♪}}$
SBP (mm Hg)	114 ± 8	116 ± 10$^{\int}$	115 ± 8	118 ± 11$^{\int}$	117 ± 8†	122 ± 12$^{\int,*,\dagger}$	139 ± 15*,†,‡	130 ± 12$^{\int,*,\dagger,\ddagger}$	137 ± 9*,†,‡	131 ± 10$^{\int,*,\dagger,\ddagger}$	138 ± 11*,†,‡	134 ± 9$^{\int,*,\dagger,\ddagger,\P,\text{♪}}$
DBP (mm Hg)	70 ± 7	71 ± 9$^{\int}$	70 ± 7	72 ± 9$^{\int}$	72 ± 7	75 ± 9$^{\int,*,\dagger}$	86 ± 12*,†,‡	80 ± 10$^{\int,*,\dagger,\ddagger}$	85 ± 10*,†,‡	81 ± 10$^{\int,*,\dagger,\ddagger}$	86 ± 10*,†,‡	84 ± 10$^{\int,*,\dagger,\ddagger,\P,\text{♪}}$
HR (b.p.m.)	64 ± 10	66 ± 9$^{\int}$	63 ± 8	65 ± 9$^{\int}$	63 ± 9	67 ± 10$^{\int,\dagger}$	68 ± 10 *,†,‡	70 ± 11$^{\int,*,\dagger}$	67 ± 10*,†,‡	69 ± 11$^{\int,*,\dagger}$	68 ± 10*,†,‡	71 ± 10$^{\int,*,\dagger,\ddagger}$
TC (mmol l^{-1})	5.1 ± 0.9	5.5 ± 1.0$^{\int}$	4.9 ± 0.8	5.2 ± 0.8$^{\int,*}$	4.9 ± 0.9	5.2 ± 0.9$^{\int,*}$	5.5 ± 0.9*,†,‡	5.5 ± 1.0†,‡	5.2 ± 0.8†,‡	5.4 ± 0.8$^{\int,\dagger}$	5.2 ± 0.9†,‡,¶	5.4 ± 0.9$^{\int,\dagger,\ddagger}$
HDL (mmol l^{-1})	1.3 ± 0.3	1.4 ± 0.4$^{\int}$	1.4 ± 0.3*	1.5 ± 0.4$^{\int,*}$	1.5 ± 0.3*,†	1.6 ± 0.4$^{\int,*}$	1.2 ± 0.2*,†,‡	1.3 ± 0.3$^{\int,\dagger,\ddagger}$	1.4 ± 0.3*,†,‡,¶	1.5 ± 0.4$^{\int,\dagger}$	1.5 ± 0.3$^{*,\dagger,\P,\text{♪}}$	1.7 ± 0.4$^{\int,\dagger,\ddagger}$
TG (mmol l^{-1})	1.4 ± 1.8	1.5 ± 1.8$^{\int}$	1.2 ± 0.8*	1.2 ± 1.2*	1.4 ± 1.0†	1.6 ± 1.6$^{\int,\dagger}$	1.6 ± 0.8†	1.5 ± 0.8	1.3 ± 0.8†	1.4 ± 1.0	1.6 ± 1.0$^{\dagger,\ddagger,\text{♪}}$	1.6 ± 1.0$^{\dagger,\text{♪}}$
FPG (mmol l^{-1})	5.1 ± 0.6	5.1 ± 0.6	5.1 ± 0.7	5.1 ± 0.7	5.2 ± 0.9	5.3 ± 0.9$^{\int,*,\dagger}$	5.6 ± 0.9*,†,‡	5.6 ± 0.9*,†,‡	5.3 ± 0.7†,¶	5.3 ± 0.7*,†,¶	5.6 ± 0.9$^{*,\dagger,\ddagger,\text{♪}}$	5.5 ± 0.9$^{*,\dagger,\ddagger,\text{♪}}$
Cr (mmol l^{-1})	72 ± 8	72 ± 9	73 ± 8	73 ± 9	71 ± 9†	71 ± 9	75 ± 9*,‡	76 ± 10*,†,‡	74 ± 8‡	74 ± 9‡	71 ± 9$^{\dagger,\P,\text{♪}}$	69 ± 10$^{\int,*,\dagger,\P,\text{♪}}$
BaPWV (cm s^{-1})	1148 ± 125	1227 ± 130$^{\int}$	1181 ± 129*	1246 ± 133$^{\int}$	1235 ± 145*,†	1307 ± 169$^{\int,*,\dagger}$	1368 ± 219*,†,‡	1420 ± 237$^{\int,*,\dagger,\ddagger}$	1322 ± 164*,†,‡,¶	1370 ± 192$^{\int,*,\dagger,\ddagger,\P}$	1394 ± 195$^{*,\dagger,\ddagger,\text{♪}}$	1487 ± 246$^{\int,*,\dagger,\ddagger,\P,\text{♪}}$
Medication												
HBP	0	0	0	3	0	3	8*,†,‡	18*,†,‡	24*,†,‡	51*,†,‡	22*,†,‡	47*,†,‡
Lipid	1	2	3	10	2	5	1	9*†‡	4	8¶	0	11†,¶
DM	0	1	3	6	0	4	3	7*†‡	1	3¶	3	11$^{*,\dagger,\ddagger,\text{♪}}$
Heart	0	0	2	2	1	2	1	1	2	4	1	3
Stroke	0	0	0	0	0	0	0	1	0	0	0	0
Kidney	0	1	0	1	0	1	1	1	0	1	0	2

Abbreviations: 1st, the first examination; 3rd, the third examination; baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; Cr, serum creatinine; DBP, diastolic blood pressure; DM, number of patients prescribing drugs for diabetes mellitus; FPG, fasting plasma glucose; Gp-category, group category of alcohol intake and blood pressure; HBP, number of patients prescribing drugs for hypertension; HDL, serum high-density lipoprotein cholesterol; heart, number of patients prescribing drugs for heart disease; HMHbpNon, high normal blood pressure or higher group with non-drinker; HNHbpHeav, high normal blood pressure or higher group heavy alcohol intake; HNHbpLiMo, high normal blood pressure or higher group with light-to-moderate alcohol intake; HR, heart rate; kidney, number of patients prescribing drugs for chronic kidney disease; lipid, number of patients prescribing drugs for dyslipidemia; OnbpHeav, optimal or normal blood pressure group with heavy alcohol intake; OnbpLiMo, optimal or normal blood pressure group with light-to-moderate alcohol intake; ONbpNon, optimal or normal blood pressure group with non drinker; SBP, systolic blood pressure; stroke, number of patients prescribing drugs for stroke; TC, serum total cholesterol; TG, serum triglycerides.$^{*}P<0.05$ *vs.* optimal or normal blood pressure group with non-drinker; $^{\dagger}P<0.05$ *vs.* optimal or normal blood pressure group with light-to-moderate alcohol intake; $^{\ddagger}P<0.05$ *vs.* optimal or normal blood pressure group with heavy alcohol intake; $^{\P}P<0.05$ *vs.* high normal blood pressure or higher group with non-drinker; $^{\text{♪}}P<0.05$ *vs.* high normal blood pressure or higher group with light-to-moderate alcohol intake; $^{\int}P<0.05$ *vs.* the first examination.

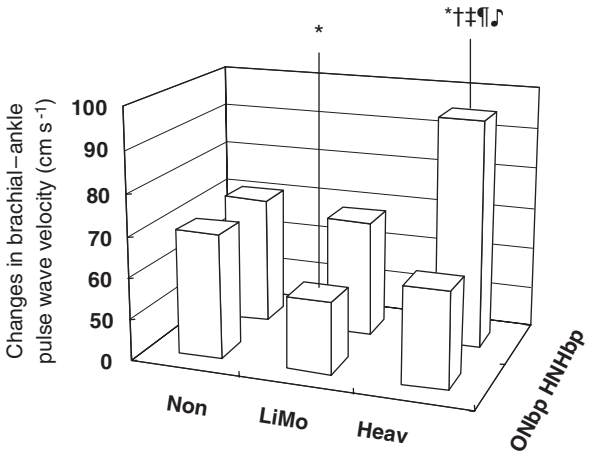

Figure 1 The adjusted value of the changes in the brachial–ankle pulse wave velocity during the 6-year study period in all the subject groups classified according to the mean daily alcohol intake level and blood pressure. Abbreviations: Non, non-drinker; LiMo, light-to-moderate alcohol intake group; Heav, heavy alcohol intake group; ONbp, subjects with optimal or normal blood pressure; HNHbp, subjects with high normal blood pressure or higher; *$P<0.05$ *vs.* ONbp/non-drinker group; †$P<0.05$ *vs.* ONbp/light-to-moderate alcohol intake group; ‡$P<0.05$ *vs.* ONbp/heavy alcohol intake group; ¶$P<0.05$ *vs.* HNbp/non-drinker group; ♪$P<0.05$ *vs.* HNbp/light-to-moderate alcohol intake group.

the subject groups. Therefore, the precise mechanisms underlying this attenuation could not be clarified in the present study. On the other hand, the value of brachial–ankle PWV at the first examination was similar between the non-drinker group and light-to-moderate alcohol intake group. This study also could not clarify the underlying mechanisms of this discrepancy (that is, although light-to-moderate alcohol intake attenuated the progression of arterial stiffening, the value of brachial–ankle PWV at the first examination was similar between the non-drinker and light-to-moderate alcohol intake groups). One possible explanation is that the extent of alcohol intake before entering this protocol might affect the value of brachial–ankle PWV at the first examination.

This study had several limitations. First, the self-reporting of alcohol intake by participants may have led to some underestimation of the daily alcohol consumption by the subjects.[25] Although it is difficult to validate self-reporting of alcohol intake, the questionnaire assessment of alcohol intake repeated twice at an interval of 1 month in a part of the study cohort showed satisfactory reproducibility. In addition, this method has actually been validated in a previous study.[25] Second, we did not analyze the type of alcoholic beverage consumed by the subjects. Thirdly, we did not analyze the confounding of the results by lifestyle variables; for example, (1) non-drinkers are less likely to exercise regularly,[26] and this has been shown to affect the rate of progression of arterial stiffening;[6,7] (2) a high salt intake related to heavy drinking may act to increase the arterial stiffness;[27,28] (3) although smoking was not found to be significantly related to the changes in the brachial–ankle PWV during the study period in this study, it is thought to increase the rate of arterial stiffness.[29] Because of the limited number of study subjects who did not smoke in this study, a study to examine the interaction of the effect of alcohol intake and that of smoking on the rate of progression of arterial stiffness is proposed. Fourthly, in relation to the lifestyle modifications in this study protocol, only 10% (40/378) of the subjects classified into the heavy alcohol intake group succeeded in lowering their alcohol intake and thus in shifting to the moderate alcohol intake group. Fifthly, the difference in the relationship between alcohol intake and central arterial stiffness among different blood pressure levels should be confirmed by carotid-femoral PWV.

In conclusion, blood pressure levels may modulate the effects of alcohol intake on the vasculature in middle-aged Japanese subjects. In subjects with ONbp, light-to-moderate alcohol intake appeared to have a possible vasculoprotective effect; on the other hand, in subjects with NHNbp, heavy alcohol intake seemed to exert a detrimental effect on the vasculature.

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