the National Cardiovascular Center in Osaka and treated by implementation of standard lifestyle and pharmacological measures. CVD events of interest in this study were acute myocardial infarction, stroke, aortic dissection, CHF requiring hospitalization, and cardiovascular death. The occurrence of myocardial infarction was confirmed if symptoms met the criteria of the World Health Organization and if the event was associated with abnormal levels of cardiac enzymes and diagnostic electrocardiographic criteria. Stroke was confirmed if the participant had a new neurologic deficit that persisted for >24 h. Computed tomographic scans or magnetic resonance images were available for all the events and were used to distinguish hemorrhagic from ischemic events. Aortic dissection was defined as any nontraumatic dissection when a participant was admitted to hospital with a dissection that required intervention, and diagnosis was based on confirmatory imaging, intraoperative visualization, or autopsy. CHF was defined by the Framingham Heart Study criteria,[33] which require the simultaneous presence of at least two major criteria, or one major criterion in conjunction with two minor criteria, and requiring treatment with a diuretic, vasodilator, or antihypertensive drug. The cause of death was classified as CVD if there was sudden death from CVD. All CVD events were determined by an independent review panel of physicians who were unaware of the echocardiographic and clinical findings. Events that were more equivocal, such as unrecognized myocardial infarction, were not included as CVD for this analysis. Furthermore, patients with clinical evidence of pneumonia or uremia were excluded. For patients who experienced multiple nonfatal episodes of CVD, the analysis included only the first event.

Statistical analysis. Statistical analyses were performed with SPSS, version 15.0 (SPSS, Chicago, IL). Data are presented as mean ± s.d. for continuous variables and as proportions for categorical variables. First, we divided the participants into four groups according to the presence/absence of MetS and/or CKD. Differences in baseline characteristics among the four groups were determined by one-way analysis of variance (ANOVA) with Dunnett's multiple comparison post-test for continuous variables, and χ^2 test for categorical variables. Because of the right skew in CRP distribution, levels of CRP were log-transformed to examine the significance of any difference between groups. The number of subjects in whom CRP was measured was small (n = 997) compared with the total number of study subjects. Therefore, CRP was not included in the following analysis.

We used logistic regression analysis to determine the odds ratio (OR) of LVH as a function of MetS or CKD. In multivariate models, we entered both MetS and CKD into the same model, and included variables that might confound the relation between LVH and MetS or CKD: age, sex, duration of hypertension, systolic BP, smoking status, previous CVD, and receiving antihypertensive medication. We next divided the subjects into four groups according to the presence/absence of MetS and/or CKD, and the relative ORs of LVH were assessed in crude, age- and sex-adjusted, and multivariate regression models (adjusting for the same variables as listed above). Relative ORs were calculated using the MetS$^-$/CKD$^-$ group as a reference for each.

Survival analysis was performed using cumulative event-free Kaplan–Meier curves according to the presence/absence of MetS or CKD, and the groups were compared by Mantel log-rank test. Cox proportional hazard analysis was used to examine the association between variables and the cumulative incidence of CVD in crude and multivariate models. In multivariate models, both MetS and CKD were entered into the same model after accounting for relevant variables, using a P value of <0.05 as the selection criterion. These effects were measured by the hazard ratio (HR) and 95% confidence interval (CI) based on Cox regression models.

We then evaluated the joint associations of MetS and CKD with incident CVD by dividing the subjects into four groups according to the presence/absence of MetS and/or CKD. Event-free survival analysis was performed using the Kaplan–Meier method to plot the cumulative incidence of CVD. The relative risk of CVD events in Cox proportional hazard analysis was assessed in crude and multivariate models, and the cumulative incidence of CVD was calculated using the MetS$^-$/CKD$^-$ group as a reference for each. In these analyses, HRs of CVD were calculated using the whole participants or excluding subjects with previous CVD and/or diabetes from the analysis. A P value <0.05 was considered to be statistically significant.

RESULTS

Characteristics of study subjects

The baseline clinical and biochemical characteristics of the study subjects are shown in Table 1. Their mean age was 63.3 ± 11.2 years, and 53.0% were men. Overall, 42.4% had MetS, and 50.6% had CKD. We first divided the subjects into four groups according to the presence/absence of MetS and/or CKD. As a result, the total subjects were divided into four groups as follows; no MetS and no CKD (MetS$^-$/CKD$^-$), MetS without CKD (MetS$^+$/CKD$^-$), CKD without MetS (MetS$^-$/CKD$^+$), and MetS and CKD (MetS$^+$/CKD$^+$). As shown in Table 1, compared with the MetS$^-$/CKD$^-$ group, the MetS$^+$/CKD$^+$ group showed an increased risk of cardiovascular morbidity, such as significantly longer duration of hypertension, higher prevalence of previous CVD, diabetes, and current-smoking, higher age, BMI, systolic BP, fasting glucose, and CRP, worse dyslipidemia, and lower eGFR. In addition, the MetS$^+$/CKD$^+$ group showed a significantly longer duration of hypertension, lower eGFR, and higher CRP than the MetS$^+$/CKD$^-$ group, and a significantly higher prevalence of diabetes, higher BMI, fasting glucose, and CRP, and worse dyslipidemia than the MetS$^-$/CKD$^+$ group.

Relations of MetS and CKD to LVH

The baseline echocardiographic characteristics of the study subjects are shown in Table 2. At baseline, 58.3% of the total subjects were found to have LVH. Univariate logistic

Table 1 | Baseline clinical characteristics of study subjects

Variables	Total	MetS$^-$/CKD$^-$	MetS$^+$/CKD$^-$	MetS$^-$/CKD$^+$	MetS$^+$/CKD$^+$
n	1,160	344	243	324	249
Age, years	63.3 ± 11.2	61.4 ± 11.4‡	60.4 ± 10.3‡	66.5 ± 10.9**,†	64.6 ± 10.7**,†
Male, %	53.0	46.5†	59.3**	50.3	59.4**
Duration of hypertension, years	16.2 ± 10.9	14.3 ± 10.3††	15.8 ± 10.8	16.4 ± 11.1*	18.8 ± 11.1**,†,††
Previous CVD, %	25.5	15.7‡	22.6††	31.8**,***	33.7**,***
Diabetes, %	25.0	6.4†	38.3**,‡	12.0†	54.6**,‡
Smoking status, % (never/past/current)	50.9/28.6/20.4	62.5†/21.2***/16.3†	39.9**,‡/31.3*/28.8**,‡	53.9†/28.8/17.3†	42.2/35.7**/22.1
BMI, kg/m^2	24.2 ± 3.4	23.4 ± 2.7†,‡	26.8 ± 3.2**,‡	22.3 ± 2.7**,†	25.4 ± 3.2**,‡
Systolic BP, mm Hg	145.2 ± 15.6	145.8 ± 14.6†	140.9 ± 13.4**,‡	148.0 ± 17.8†	147.8 ± 17.1†
Diastolic BP, mm Hg	81.6 ± 10.6	83.6 ± 10.9***,††	81.4 ± 9.4*	80.9 ± 10.7**	80.3 ± 10.9**
Pulse rate, bpm	66.6 ± 8.2	67.1 ± 8.5	66.2 ± 7.8	66.4 ± 8.4	66.4 ± 7.8
Triglycerides, mg/dl	138 ± 90	105 ± 48†	178 ± 124**,‡	105 ± 44†	187 ± 103**,‡
HDL-cholesterol, mg/dl	49.88 ± 15.08	57.62 ± 14.31†,††	42.15 ± 10.05**,‡	54.91 ± 15.08*,†	39.83 ± 11.60**,‡
Fasting glucose, mg/dl	102 ± 24	97 ± 15†	113 ± 30**,‡	94 ± 19†	108 ± 27**,***,‡
eGFR, ml/min/1.73 m^2	64.4 ± 31.3	82.0 ± 18.1***,‡	87.1 ± 22.8*,‡	44.3 ± 25.4**,†	44.0 ± 30.2**,†
CRP (mg/l), median (IQR), *n* = 997	0.70 (0.30–1.80)	0.50 (0.30–1.00)†,‡	1.00 (0.31–2.00)**	0.70 (0.28–1.70)**	1.20 (0.30–2.50)**,***,††
MetS components, %					
Obesity	36.1	19.2†	72.4**,‡	12.0†	55.4**,†,‡
Elevated triglycerides	31.9	9.0†	58.9**,‡	10.5†	65.1**,‡
Low HDL-cholesterol	40.1	12.2†	67.9**,‡	19.4†	78.3**,***,‡
Impaired fasting glucose	31.4	11.9†	50.2**,‡	15.1†	61.0**,†,‡
CKD stages					
High blood pressure	15.3	26.2‡	35.8‡	0**,†	0**,†
High blood pressure with reduced GFR	35.3	73.8‡	64.2‡	0**,†	0**,†
Stages 1 and 2	9.5	0‡	0‡	17.0**,†	22.1**,†
Stage 3	23.4	0‡	0‡	52.5**,†	40.6**,†,‡
Stages 4 and 5	16.6	0‡	0‡	30.5**,†	37.3**,†,††
Antihypertensive medication, %					
Calcium-channel blockers	68.2	54.1†,‡	68.3**	71.0**	83.9**,†,‡
β-Blockers	30.1	24.4	32.1	31.5	34.1*
ACE inhibitors or ARB	35.1	30.8	32.5	34.3	44.6**,***,††
Diuretics	18.1	10.2‡	10.3‡	25.3**,†	27.3**,†
No. of CVD events	172	21***,‡	33*	53**	65**,†,‡

Values are mean ± s.d. or frequency (%). IQR is 25th to 75th percentile.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-cholesterol, high-density lipoprotein cholesterol; MetS, metabolic syndrome.
$^{*}P < 0.05$ and $^{**}P < 0.01$ vs. MetS$^-$/CKD$^-$. $^{***}P < 0.05$ and $^{‡}P < 0.01$ vs. MetS$^-$/CKD$^-$. $^{††}P < 0.05$ and $^{†}P < 0.01$ vs. MetS$^-$/CKD$^+$.

regression analysis found that the presence of MetS as well as CKD was each associated with an increased risk of LVH (MetS: OR 1.54, 95% CI 1.21–1.95; CKD: OR 1.83, 95% CI 1.44–2.31, $P < 0.01$, respectively). When MetS and CKD were entered into the same model, the results of multivariate logistic regression analysis showed that MetS as well as CKD was each an independent risk for LVH (MetS: adjusted-OR 1.58, 95% CI 1.22–2.05; CKD: adjusted-OR 1.52, 95% CI 1.18–1.96, $P < 0.01$, respectively).

We then divided the total subjects into four groups, and found that echocardiographic characteristics also differed between the groups, with the MetS$^+$/CKD$^+$ group

Table 2 | Echocardiographic characteristics of study subjects according to presence/absence of MetS and/or CKD

Variables	Total	MetS$^-$/CKD$^-$	MetS$^+$/CKD$^-$	MetS$^-$/CKD$^+$	MetS$^+$/CKD$^+$
% Fractional shortening, %	41.2 ± 6.9	41.8 ± 6.7	41.6 ± 7.0	40.8 ± 6.8	40.3 ± 7.2*
LV mass index, g/m^2					
Male	138.4 ± 38.1	122.1 ± 26.0***,‡	131.5 ± 29.4*,‡	148.4 ± 43.4**,†	150.2 ± 40.6**,†
Female	120.8 ± 33.2	111.8 ± 24.5***,††	121.0 ± 27.6*	120.0 ± 33.9*	137.8 ± 42.5**,†,‡
LV hypertrophy, %	58.3	46.2***,‡	57.5*	61.0**	71.5**,†,††
Relative wall thickness	0.48 ± 0.09	0.46 ± 0.08‡	0.48 ± 0.08	0.48 ± 0.09**	0.50 ± 0.09**
LV geometric patterns, %					
Normal geometry	21.4	30.2†,††	17.9**	21.0*	13.6**
Concentric remodeling	20.4	23.6	24.6	18.0	14.9*,***
Eccentric hypertrophy	17.9	15.7	19.2	19.5	18.5
Concentric hypertrophy	40.3	30.5††	38.3	41.5*	53.0**,†,††
E/A ratio	0.85 ± 0.25	0.91 ± 0.28‡	0.87 ± 0.24	0.84 ± 0.24**	0.80 ± 0.24**,†
DcT, ms	229.7 ± 51.8	221.7 ± 46.9	225.3 ± 47.8	230.3 ± 50.8	244.4 ± 62.0**,†,††

Values are mean ± s.d. or frequency (in %).
CKD, chronic kidney disease; DcT, deceleration time of early diastolic LV filling; *E/A*, ratio of peak early-to-late diastolic filling velocity; LV, left ventricular; MetS, metabolic syndrome.
*P < 0.05 and **P < 0.01 vs. MetS$^-$/CKD$^-$, ***P < 0.05 and †P < 0.01 vs. MetS$^+$/CKD$^-$, and ††P < 0.05 and ‡P < 0.01 vs. MetS$^-$/CKD$^+$.

Table 3 | Results of crude and multivariate logistic regression analysis relating MetS and CKD to LVH

	MetS$^-$/CKD$^-$	MetS$^+$/CKD$^-$	MetS$^-$/CKD$^+$	MetS$^+$/CKD$^+$
Crude	1 (reference)	1.55 (1.11–2.17)**	1.81 (1.33–2.47)**	2.91 (2.05–4.12)**
Age- and sex-adjusted	1 (reference)	1.59 (1.14–2.22)**	1.69 (1.24–2.32)**	2.80 (1.97–3.99)**
Multivariate-adjusted[a]	1 (reference)	1.58 (1.11–2.24)*	1.51 (1.09–2.10)*	2.40 (1.66–3.48)**

Values are odds ratio (95% CI).
CKD, chronic kidney disease; LVH, left ventricular hypertrophy; MetS, metabolic syndrome.
[a]Adjusted for age, sex, duration of hypertension, systolic BP, smoking status, previous CVD, and receiving antihypertensive medication.
*P < 0.05 and **P < 0.01 vs. MetS$^-$/CKD$^-$.

demonstrating significantly lower % fractional shortening and *E/A*, higher LVMI and RWT, lower prevalence of normal geometry, higher prevalence of concentric remodeling and concentric hypertrophy, and longer deceleration time of early diastolic LV filling than the MetS$^-$/CKD$^-$ group (Table 2). In addition, the MetS$^+$/CKD$^+$ group showed significantly longer deceleration time of early diastolic LV filling than the MetS$^+$/CKD$^-$ group as well as the MetS$^-$/CKD$^+$ group. The prevalence of LVH also significantly differed among groups, with the highest prevalence of LVH in the MetS$^+$/CKD$^+$ group. As shown in Table 3, concomitance of MetS and CKD was significantly associated with increased odds ratios of LVH. Multivariate analysis showed that the odds ratio of LVH was 2.4-fold higher in the MetS$^+$/CKD$^+$ group compared with the MetS$^-$/CKD$^-$ group.

Predictive value of MetS and CKD for CVD

During a mean (±s.d.) follow-up of 4.8 ± 2.7 years, 172 patients (14.8%, 70 female) developed CVD. Specifically, there were 38 patients with nonfatal CHF, 65 with cerebral infarction, 14 with intracerebral hemorrhage, 3 with subarachnoid hemorrhage, 18 with myocardial infarction, 6 with aortic dissection, and 28 patients died from CVD causes.

MetS and CKD were both associated with incident CVD events, with significance in log-rank tests of $P < 0.001$. A univariate Cox proportional hazard model showed that both MetS (HR 1.83, 95% CI 1.35–2.48, $P < 0.01$) and CKD (HR 2.71, 95% CI 1.96–3.74, $P < 0.01$) were each significant predictors of CVD events. Other variables in this study that significantly predicted CVD events included age, sex, duration of hypertension, previous CVD, smoking habit, systolic BP, LVMI (Table 4), antihypertensive medication (HR 1.81 for yes, 95% CI 1.07–3.07, $P < 0.01$), and LV geometry (concentric remodeling: HR 1.74, 95% CI 1.04–2.91, $P < 0.05$; eccentric hypertrophy: HR 1.22, 95% CI 0.69–2.14, NS; concentric hypertrophy: HR 2.19, 95% CI 1.39–3.43, $P < 0.01$). When MetS and CKD were entered into the same model, the results of multivariate Cox regression analysis including age, sex, duration of hypertension, previous CVD, smoking habit, systolic BP, LVMI, and antihypertensive medications found that the presence of MetS (HR 1.90, 95% CI 1.38–2.63, $P < 0.01$) as well as CKD (HR 1.82, 95% CI 1.29–2.59, $P < 0.01$) was each an independent predictor of CVD events. Furthermore, adjustment for LV geometry instead of LVMI did not meaningfully influence the results (MetS: HR 1.82, 95% CI 1.32–2.50; CKD: HR 2.02, 95% CI 1.43–2.84, $P < 0.01$, respectively).

Table 4 | Crude and multivariate-adjusted HRs of CVD events associated with MetS and CKD

	Total subjects						Subjects without previous CVD and/or diabetes ($n = 745$)					
	Crude		Multivariate adjusted[a]		Plus LVMI		Crude		Multivariate adjusted[b]		Plus LVMI	
Variables, unit of increase	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
MetS and CKD												
MetS$^-$/CKD$^-$	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
MetS$^+$/CKD$^-$	2.31 (1.34–4.00)	0.003	2.09 (1.19–3.66)	0.010	2.03 (1.16–3.57)	0.013	2.64 (1.30–5.35)	0.007	2.74 (1.34–5.62)	0.006	2.65 (1.29–5.44)	0.008
MetS$^-$/CKD$^+$	3.32 (2.00–5.50)	<0.001	2.21 (1.31–3.71)	0.003	2.08 (1.23–3.51)	0.006	3.22 (1.69–6.15)	<0.001	2.40 (1.23–4.62)	0.009	2.31 (1.19–4.46)	0.013
MetS$^+$/CKD$^+$	5.21 (3.19–8.53)	<0.001	3.85 (2.33–6.37)	<0.001	3.58 (2.16–5.95)	<0.001	5.25 (2.77–9.94)	<0.001	4.42 (2.32–8.42)	<0.001	4.16 (2.16–8.02)	<0.001
Age, 1 year	1.07 (1.05–1.09)	<0.001	1.06 (1.04–1.08)	<0.001	1.06 (1.04–1.08)	<0.001	1.08 (1.05–1.11)	<0.001	1.07 (1.05–1.10)	<0.001	1.07 (1.05–1.10)	<0.001
Sex, male	1.71 (1.26–2.33)	0.001	1.28 (0.84–1.95)	0.25	1.19 (0.78–1.81)	0.43	1.13 (0.74–1.72)	0.57				
Duration of hypertension, 1 year	1.02 (1.01–1.04)	0.001	1.01 (0.99–1.02)	0.45	1.00 (0.99–1.02)	0.56	1.02 (1.00–1.04)	0.08				
Previous CVD, yes	2.43 (1.79–3.29)	<0.001	1.69 (1.23–2.33)	0.010	1.67 (1.21–2.29)	0.002						
Smoking status												
Never	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Past	1.76 (1.25–2.49)	0.001	1.27 (0.82–1.96)	0.29	1.27 (0.82–1.95)	0.28	1.34 (0.81–2.21)	0.25	1.20 (0.73–1.99)	0.47	1.18 (0.71–1.95)	0.53
Current	1.81 (1.23–2.66)	0.002	1.69 (1.06–2.71)	0.029	1.58 (0.99–2.52)	0.06	1.69 (1.00–2.86)	0.049	1.63 (0.95–2.78)	0.08	1.53 (0.89–2.65)	0.13
Systolic BP, 10 mm Hg	1.14 (1.05–1.25)	0.003	1.10 (1.00–1.21)	0.041	1.07 (0.97–1.17)	0.18	1.16 (1.03–1.30)	0.018	1.12 (1.00–1.26)	0.05	1.10 (0.98–1.25)	0.12
Pulse rate, 10 bpm	1.13 (0.94–1.28)	0.17					1.16 (0.89–1.36)	0.23				
LVMI, 10 g/m^2	1.09 (1.05–1.12)	<0.001			1.05 (1.01–1.09)	0.024	1.08 (1.03–1.13)	0.001			1.06 (1.00–1.12)	0.045

Values are hazard ratio (95% CI).
[a]Adjusted for age, sex, duration of hypertension, previous CVD, smoking status, and systolic BP. [b]Adjusted for age, smoking status, and systolic BP.
BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; LVMI, left ventricular mass index; MetS, metabolic syndrome.

Joint effect of MetS and CKD on CVD

To explore the combined effects of MetS and CKD, we divided the total subjects into four groups on the basis of the presence or absence of MetS and/or the presence or absence of CKD at baseline. Life table analyses of CVD throughout the follow-up period in the four groups are plotted in Figure 1. These curves show significantly poorer survival in the MetS$^+$/CKD$^+$ group. Table 4 shows the results from a series of crude and multivariate regression analysis, showing how the association of MetS and CKD with CVD risk changed as groups of CVD risk factors were added to the regression model. In the crude model, the risk for CVD was significantly higher in the MetS$^+$/CKD$^+$ group compared with the MetS$^-$/CKD$^-$ group (HR 5.21). The relative risk in the MetS$^+$/CKD$^+$ group remained highly significant in the multivariate model (HR 3.85). The further addition of LVMI to the model reduced the relative risk in the MetS$^+$/CKD$^+$ group to 3.58. Furthermore, when compared with the MetS$^+$/CKD$^-$ group or with the MetS$^-$/CKD$^+$ group, the risk of CVD events was significantly higher in the MetS$^+$/CKD$^+$ group in univariate Cox regression analysis (vs. MetS$^+$/CKD$^-$ group: HR 2.26, 95% CI 1.48–3.43, $P < 0.01$; vs. MetS$^-$/CKD$^+$ group: HR 1.57, 95% CI 1.09–2.26, $P = 0.01$) and in multivariate Cox regression analysis including LVMI (vs. MetS$^+$/CKD$^-$ group: HR 1.97, 95% CI 1.29–3.02; vs. MetS$^-$/CKD$^+$ group: HR 1.72, 95% CI 1.18–2.51, $P < 0.01$ respectively).

We performed several additional analyses to address the robustness of these findings. Because patients with previous CVD and/or diabetes were more frequent in the MetS$^+$/CKD$^+$ group, we repeated our analysis for the 745 patients without previous CVD and/or diabetes. In this analysis, 87 CVD events

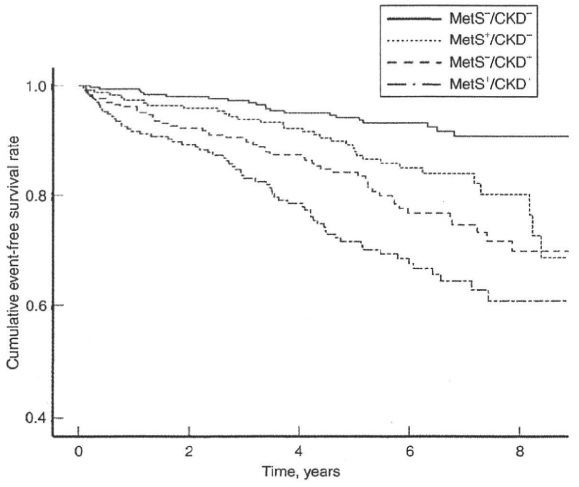

Figure 1 | Kaplan–Meier plots showing cumulative CVD event-free survival in subjects in four groups divided by presence or absence of MetS and presence or absence of CKD (log-rank $\chi^2 = 54.55$; $P < 0.001$). CKD, chronic kidney disease; CVD, cardiovascular disease; MetS, metabolic syndrome.

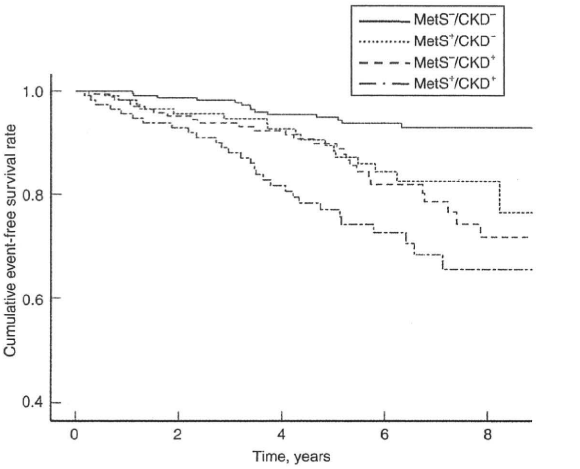

Figure 2 | Kaplan–Meier plots for CVD event-free survival in subgroup without previous CVD and or diabetes ($n = 745$) (log-rank $\chi^2 = 30.67$; $P < 0.001$). CKD, chronic kidney disease; CVD, cardiovascular disease; MetS, metabolic syndrome.

(11.7%, 47 female) occurred during the follow-up period. As shown in Figure 2 and Table 4, the independent predictive value of MetS$^+$/CKD$^+$ for CVD events was also confirmed by the Kaplan–Meier method and by multivariate Cox regression analysis including LVMI. Furthermore, even when compared with the MetS$^+$/CKD$^-$ group or with the MetS$^-$/CKD$^+$ group, the risk of CVD events was significantly higher in the MetS$^+$/CKD$^+$ group in the multivariate model including LVMI (vs. MetS$^+$/CKD$^-$ group: HR 1.57, 95% CI 1.01–3.43, $P < 0.05$; vs. MetS$^-$/CKD$^+$ group: HR 1.81, 95% CI 1.06–3.08, $P = 0.03$).

DISCUSSION

This study identified a significant positive relationship between the combination of MetS and CKD and risk for LVH. This relationship was independent of age, sex, and other potential risk factors for LVH, such as smoking. We also examined the associations of the presence of MetS and CKD, alone and in combination, with incident CVD over a follow-up period, and found that the presence of MetS as well as CKD was each associated with CVD, with a joint effect that was greater than the individual effect of either disease separately. Despite previous studies suggesting a link between these two diseases,[9–11] these two risk factors interact to substantially increase the risk of CVD.

Our findings confirm previous investigations by documenting that the prevalence of LVH is higher in subjects with MetS or CKD than in those without these diseases.[16–20] Little information is available on the association of the combination of MetS and CKD with LVH, especially in essential hypertensives. In our study, LVH and altered LV patterns were more frequent in the MetS$^+$/CKD$^+$ group than in the MetS$^-$/CKD$^-$ group. Even after adjustment for confounding factors, MetS$^+$/CKD$^+$ was associated with a 2.4-fold higher risk of LVH than was MetS$^-$/CKD$^-$. The mechanism by which the concomitance of MetS and CKD is a strong risk for LVH remains hypothetical, but is likely multifactorial. Hypertension is the fundamental trigger of the sequence of biologic events that lead to the development of LVH. In addition, demographic characteristics (i.e., age and gender), volume overload, inotropy, obesity, and arterial compliance also are important determinants of the development and degree of LVH. In MetS, among the main nonhemodynamic factors that may contribute to the development of LVH, the most likely candidates are insulin resistance, activated sympathetic nervous system, increased arterial stiffness,[18,34] and inflammation.[35] In CKD, increased activity of the renin–angiotensin–aldosterone system and sympathetic nervous system, hypervolemia, hyperparathyroidism, abnormalities of calcium-phosphate homeostasis, and anemia may all contribute to the increase in LV mass.[36,37] Consequently, hemodynamic changes, such as increased peripheral resistance and hypervolemia, and nonhemodynamic factors including metabolic and hormonal factors have been proposed as possible factors contributing to LVH in subjects with MetS$^+$/CKD$^+$. Conversely, because the balance between the two fundamental hemodynamic stimuli (pressure and volume) also determines the predominant type of LV geometry, our result that a high prevalence of concentric hypertrophy was found in the MetS$^+$/CKD$^+$ group suggests the presence of increased total peripheral resistance[38] and activation of the renin–angiotensin–aldosterone system[39] in this group.

Our results were partially in accordance with the previous report that MetS is associated with subsequent CVD, independent of traditional CVD risk factors including LVH defined by electrocardiogram and serum creatinine.[40] We also found that, in essential hypertensives, the presence of MetS as well as CKD was each an independent predictor of CVD, and the combination of MetS and CKD was a strong and significant predictor of CVD. Moreover, the increased risk for CVD was evident even after excluding subjects with previous CVD and/or diabetes. Our results suggest that these diseases jointly contribute to the development of CVD, and the adverse prognostic effect of the combination of MetS and CKD was independent of traditional

CVD risk factors including LVMI. Hypertension is a potential cause and consequence of CVD, and thus, our results indicate the need for metabolic screening as well as the assessment of renal function in hypertensive patients. Several LVH-related factors may also ultimately contribute to the development of CVD, and a number of underlying biochemical derangements may exist in hypertensive patients with MetS and CKD.

One notable result of this study is that, in the case of concomitant MetS and CKD, the risk of CVD became higher than that in the presence of MetS or CKD alone. Apart from renal and metabolic profiles, there are other possible mechanisms by which the risk for CVD became higher with concomitant MetS and CKD. Inflammation and oxidative stress have been implicated in the pathogenesis of CVD. Even though preliminary data, our results showed a significantly higher CRP level in the $MetS^+/CKD^+$ group than in the $MetS^+/CKD^-$ group as well as in the $MetS^-/CKD^+$ group. In addition, more severe impairment of LV relaxation was observed in the $MetS^+/CKD^+$ group, and this impaired relaxation is known to be associated with increased risk of CVD.[27,41] Consequently, we propose that, in the case of concomitant MetS and CKD, further activation of inflammation and the renin–angiotensin system,[39] increased total peripheral resistance,[38] and impaired relaxation may be caused, and thus enhance the risk of CVD.

Our study has several limitations. First, we used eGFR rather than directly measured GFR to define CKD. Although serum creatinine has been widely used in clinical practice for evaluating renal function, misclassification of individuals with borderline CKD also may have resulted in biased estimates. Second, the study subjects were a hospital-based rather than population-based cohort. Third, only baseline measurements of risk factors such as eGFR, lipids, and drug use were available for the present analysis. The metabolic profile may deteriorate over time, and, as a result, drug use may increase substantially during the follow-up period. Fourth, because waist circumference was not available in this study, we used BMI to establish the diagnosis of obesity, with adjustment for the Japanese population, as a component of MetS. However, a recent meta-analysis reported no difference in outcomes irrespective of whether waist circumference or BMI was used in the criteria for MetS to predict CVD events.[42]

We found that the combination of MetS and CKD represents a strong risk for LVH in essential hypertension. In addition, both MetS and CKD predict CVD, with their combination further increasing the risk, independent of baseline confounding factors including LVMI. From a practical standpoint, physicians should be aware that hypertensive patients with concomitant MetS and CKD are at increased risk for the development of CVD. In hypertension, assessment of MetS as well as CKD has appeal for improving the risk stratification for CVD in daily practice. A large prospective population-based study will be important to confirm our preliminary observations, and future studies should investigate whether aggressive pharmacological and lifestyle interventions in hypertensive patients with concomitant MetS and CKD can reduce their substantial CVD risk.

Disclosure: The authors declared no conflict of interest.

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Hypertension Research (2010) 33, 181–191

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REVIEW

Physio-pathological effects of alcohol on the cardiovascular system: its role in hypertension and cardiovascular disease

Yuhei Kawano

Alcohol has complex effects on the cardiovascular system. The purpose of this article is to review physio-pathological effects of alcohol on cardiovascular and related systems and to describe its role in hypertension and cardiovascular disease. The relationship between alcohol and hypertension is well known, and a reduction in the alcohol intake is widely recommended in the management of hypertension. Moreover, alcohol has both pressor and depressor actions. The latter actions are clear in Oriental subjects, especially in those who show alcohol flush because of the genetic variation in aldehyde dehydrogenase activity. Repeated alcohol intake in the evening causes an elevation in daytime and a reduction in nighttime blood pressure (BP), with little change in the average 24-h BP in Japanese men. Thus, the hypertensive effect of alcohol seems to be overestimated by the measurement of casual BP during the day. Heavy alcohol intake seems to increase the risk of several cardiovascular diseases, such as hemorrhagic stroke, arrhythmia and heart failure. On the other hand, alcohol may act to prevent atherosclerosis and to decrease the risk of ischemic heart disease, mainly by increasing HDL cholesterol and inhibiting thrombus formation. A J- or U-shaped relationship has been observed between the level of alcohol intake and risk of cardiovascular mortality and total mortality. It is reasonable to reduce the alcohol intake to less than 30 ml per day for men and 15 ml per day for women in the management of hypertension. As a small amount of alcohol seems to be beneficial, abstinence from alcohol is not recommended to prevent cardiovascular disease.
Hypertension Research (2010) **33,** 181–191; doi:10.1038/hr.2009.226; published online 15 January 2010

Keywords: alcohol; blood pressure; cardiovascular disease

INTRODUCTION

Alcohol has complex effects on the cardiovascular system. The relationship between alcohol and hypertension is well known, and a restriction of alcohol intake is widely recommended as a part of lifestyle modifications in the management of hypertension.[1–6] Alcohol has both pressor and depressor actions, however, and the genetic susceptibility regarding alcohol metabolism influences the cardiovascular effect of alcohol.[3,7] The effect of alcohol on blood pressure (BP) is also modified by several factors, such as the level of consumption, time period after the last drink and overall drinking behavior.

Alcohol consumption is associated with several cardiovascular diseases, such as brain hemorrhage, heart failure and arrhythmia, as well as with other disorders.[3,8–11] Heavy drinking and alcoholism not only lead to medical problems but are also serious social concerns. However, alcohol also seems to have beneficial effects, including the prevention of ischemic heart disease. It has been shown that cardiovascular and all-cause mortality is lower in light drinkers compared with nondrinkers.[3,8–12]

The purpose of this article is to review physio-pathological effects of alcohol on cardiovascular and related systems and to describe its role in hypertension and cardiovascular disease. I will outline the cardiovascular actions of alcohol, the effects of alcohol on BP and hypertension, including changes in 24-h BP, and the relationship between alcohol and cardiovascular diseases.

CARDIOVASCULAR ACTIONS OF ALCOHOL

Acute effect on BP

The effect of a single intake of alcohol on BP in normal subjects is not consistent among studies. Some studies have shown an increase in BP,[13,14] whereas it decreased[15,16] or remained unchanged[17,18] in others. In hypertensive patients, the BP also became elevated[19] or fell[20] after a single ingestion of alcohol.

In studies showing the pressor effect of alcohol, a BP increase was observed within 1 h after drinking; however, the increase was not sustained.[3] On the other hand, BP usually fell or remained unchanged after alcohol consumption in studies with prolonged observation periods. Stott *et al.*[21] reported that BP levels increased at 1 h after drinking but tended to decrease over the next 7 h in normotensive subjects.

We examined the effect of a single intake of alcohol (1 ml kg^{-1}) on BP using ambulatory BP monitoring (ABPM) in hypertensive

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Received 24 June 2009; revised 8 November 2009; accepted 29 November 2009; published online 15 January 2010

Japanese men.[7] As shown in Figure 1, the BP decreased and the heart rate increased for several hours after drinking alcohol. This alcohol-induced hypotension was marked in subjects showing facial flush identified by visual inspection after drinking, and was mild in those who did not show such flush. A transient pressor response to alcohol consumption was not observed in our study, and BP values the day after drinking were comparable to those on the control day.

Minami *et al.*[22] also studied the effect of a single intake of alcohol on ambulatory BP in normotensive and hypertensive Japanese men in relation to the genotype of aldehyde dehydrogenase 2 (ALDH2). In their study, BP decreased significantly after alcohol ingestion in the inactive ALDH2 group (heterozygotes and a homozygote for ALDH2*2), whereas the reduction in BP was small but significant only for diastolic BP in the active ALDH2 group (homozygotes for ALDH2*1).

A single intake of alcohol therefore mainly acts to lower the BP, at least in Japanese men. As this depressor effect varies according to race and the presence and absence of alcohol flush, genetic variation in ALDH2 activity seems to have a major function. It has been shown that subjects with the ALDH2*2 genotype, which is common in Mongoloids but rare in Caucasians and Africans, show facial flush after drinking alcohol because of the accumulation of vasodilative acetaldehyde.[3,22–24] The mechanisms causing a transient pressor response to alcohol are not clear. An emotional change or gastric irritation rather than a direct effect of alcohol, however, may be involved in the pressor response because it takes several hours for blood alcohol to disappear after a single intake.[3,21]

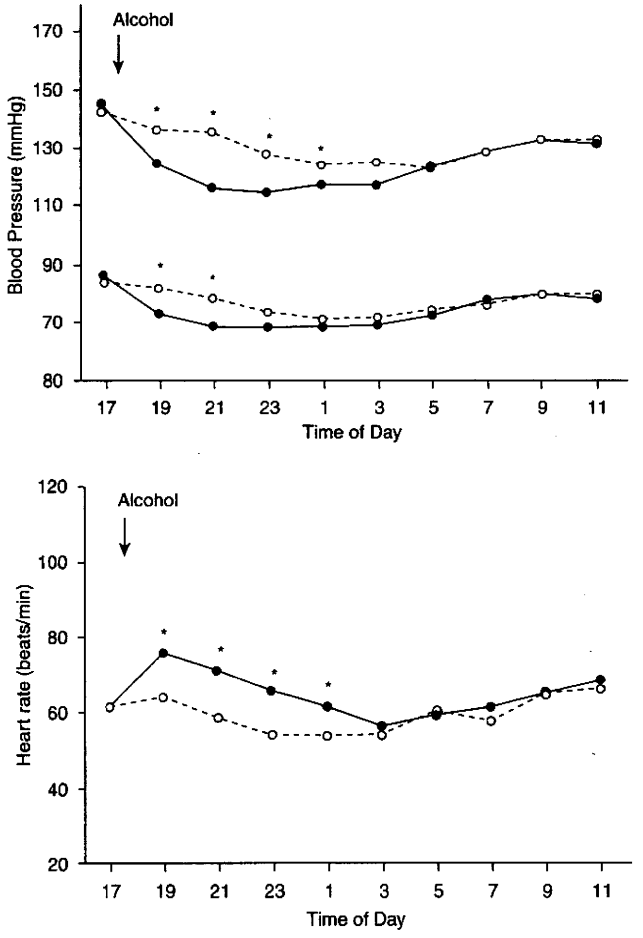

Figure 1 Ambulatory blood pressure (BP) and heart rate during the alcohol intake day (●) and the control day (○). *: $P<0.05$ between the two periods (adopted from Kawano *et al.*[7] with permission).

Vascular actions

The action of alcohol on the vasculature is variable according to its concentration and the kind of blood vessel.[25,26] High concentrations of alcohol constrict most blood vessels. This vasoconstriction depends on calcium ions and is inhibited by calcium channel blockers. Alcohol also acts to augment the vasoconstriction caused by catecholamines and vasopressin and inhibits endothelium-dependent vasodilation.[27,28] It has been suggested that endothelin and nitric oxide are involved in alcohol-induced vasoconstriction.[29] Soardo *et al.*[30] observed that alcohol increased the levels of endothelin-1, nitric oxide, plasminogen activator inhibitor-1 and oxidative stress both *in vivo* and *in vitro*. As the scavengers of oxidants prevented those changes, oxidative stress may have a role in the alcohol-induced endothelial dysfunction.[30] It was, however, reported that the flow-mediated dilation of the brachial artery and blood markers of endothelial function were similar between the usual drinking period and the alcohol restriction period in healthy men.[31]

On the other hand, low concentrations of alcohol usually dilate blood vessels.[25,26] This effect also seems to be mediated by calcium ions and endothelium-derived nitric oxide. It has been shown that low doses of alcohol increase the release of nitric oxide and augment endothelium-dependent vasodilation.[32] Criscione *et al.*[27] reported that ethanol inhibits norepinephrine-induced vasoconstriction in the rat mesenteric artery. They also observed that norepinephrine-induced vasoconstriction is enhanced after the withdrawal of alcohol. These results seem to be consistent with the time-dependent BP changes after alcohol consumption in humans.

Acetaldehyde, a metabolite of alcohol, acts as a vasodilator.[17] Subjects with low-active aldehyde dehydrogenase (ALDH2*2) show facial flush after alcohol ingestion because of the accumulation of acetaldehyde in the blood. Such subjects, especially those homozygous for the ALDH2*2 genotype, show marked tachycardia and hypotension after alcohol consumption.[3,23]

In our study, the alcohol-induced BP reduction in hypertensive patients was due to a decrease in peripheral vascular resistance (Table 1).[7] We also observed that the intracellular sodium concentration in red blood cells decreases after alcohol ingestion.[33] This change may also act to dilate blood vessels through a decrease in the intracellular calcium concentration.

Table 1 Hemodynamic variables after alcohol intake in hypertensive patients (adopted from Kawano *et al.* with permission)

	Control day		*Alcohol intake day*	
Variables	*5 PM*	*7 PM*	*5 PM*	*7 PM*
MBP (mm Hg)	109±4	100±4	106±5	89±3*†
HR (b.p.m.)	54±2	56±2	52±3	68±5*†
CI ($l\,min^{-1}\,m^{-1}$)	2.6±0.2	2.9±0.3	2.6±0.2	3.3±0.3*†
PVR ($dyn\,s^{-1}\,cm^{-5}$)	2061±208	1791±225	2096±268	1305±114*†
LVFS (%)	34±2	37±2	35±1	43±2*†
LVESWS ($10^3\,dyn\,cm^{-2}$)	67±10	56±7	62±5	37±5*†

Abbreviations: b.p.m., beats per minute; CI, cardiac index; HR, heart rate; LVESWS, left ventricular end-systolic wall stress; LVFS, left ventricular fractional shortening; MBP, mean blood pressure; PVR, peripheral vascular resistance.
*$P<0.05$ *vs.* the control day, †$P<0.05$ *vs.* 5 PM on the alcohol intake day.

Taken together, alcohol has both constrictive and dilative actions on blood vessels, and these effects may be dependent on race, the dose and timing of alcohol consumption.

Cardiac actions

The effects of alcohol on the heart are also complex.[3,8,34] It has been shown that alcohol directly inhibits the contractility of cardiac muscle in a dose-dependent manner.[18,26] This negative inotropic action is apparent in the isolated heart or after blocking of the autonomic nervous system.[18]

Cardiac function, however, does not often change or even increase after the administration of alcohol in normal humans and animals. Kupari *et al.*[23] reported that both the heart rate and cardiac output increased whereas systemic vascular resistance decreased after alcohol ingestion in healthy volunteers.[15] They also observed that those changes were small in subjects who did not show facial flush, but were marked in subjects who showed flush after drinking. In our study, the heart rate and cardiac output also increased significantly after alcohol ingestion in hypertensive patients[7] (Table 1). The activation of the sympathetic nervous system seems to mask the direct inhibitory action of alcohol on the heart. Indeed, we have observed that the alcohol-induced increases in heart rate and cardiac output are attenuated after the administration of a beta blocker.[35]

The adverse influence of alcohol on the heart is clear after the consumption of large amounts for many years. It has been shown that the total alcohol intake is positively related to the left ventricular mass and negatively related to the left ventricular ejection fraction.[36] Structural changes in cardiac muscle were also observed in heavy drinkers [37] as well as in ethanol-fed rats.[38] These changes may be involved in alcohol-induced cardiomyopathy, heart failure and arrhythmia.

Alcohol withdrawal syndrome

Chronic heavy drinkers, such as alcoholic patients, show alcohol withdrawal syndrome, which is characterized by psycho-neurological symptoms and signs after the sudden cessation of alcohol consumption. This syndrome includes elevation of the BP and heart rate because of activation of the sympathetic nervous system.[26] The pressor response during alcohol withdrawal reaches a peak the day after cessation.[39] In this case, the BP decreased to a lower level compared with baseline within several days after alcohol withdrawal in heavy drinkers.[40] As habitual drinkers experience a mild degree of repeated alcohol withdrawal in daily life, it is possible that this withdrawal phenomenon contributes to alcohol-related hypertension.

NEUROHORMONAL ACTIONS OF ALCOHOL

Actions on the autonomic nervous system

It has been shown that alcohol activates the sympathetic nervous system.[3,26] Van de Borne *et al.*[41] observed an increase in muscle sympathetic nerve activity after a single intake of alcohol in normal men. In their study, BP did not change, although the heart rate increased significantly. In our study, plasma catecholamines increased but BP decreased after alcohol ingestion in hypertensive patients, and the increase in plasma catecholamines was more pronounced in subjects with a large BP reduction.[7,42] These results suggest that the activation of the sympathetic nervous system occurs in response to BP change and acts to compensate for any further BP reduction.

Experimental studies have shown that alcohol suppresses the baroreceptor reflex.[43] Narkiewicz *et al.*[44] reported that alcohol enhances the hypotension induced by lower body negative pressure. The combination of impairment of the baroreceptor reflex and systemic vasodilation acts to potentiate orthostatic hypotension and may induce syncope after drinking in susceptible subjects.

Actions on the endocrine system

It is known that alcohol increases plasma renin activity.[7,26,42] As the increase in renin activity was suppressed by pretreatment with propranolol in our study,[35] it seems to be mediated by the sympathetic nervous system. Alcohol also stimulated the release of adrenocorticotropic hormone, and increases in plasma cortisol and aldosterone were observed after drinking.[26] It has been reported that dexamethasone inhibited the BP elevation and sympathetic activation after alcohol ingestion.[45] We and others, however, have failed to observe significant changes in adrenocorticotropic hormone, cortisol or aldosterone.[21,42]

Alcohol suppresses the release of vasopressin; however, this change does not seem to mediate the acute depressor effect of alcohol.[21,26,42] Several depressor hormones and substances, such as atrial natriuretic peptide, prostaglandin E_2, beta endorphin and cyclic GMP, did not change after alcohol ingestion.[42] Although data relating alcohol intake to plasma atrial natriuretic peptide have been inconsistent, Djousse *et al.*[46] observed a positive relationship after adjusting for several confounding factors.

The level of plasma insulin increases after alcohol intake; however, the change is less than that induced by an isocaloric control drink.[42] It has been shown that a light-to-moderate intake of alcohol enhances insulin sensitivity[47] and reduces the risk of type 2 diabetes mellitus.[48] Alcohol therefore seems to have a beneficial effect on insulin and glucose metabolism.

Taken together, alcohol causes various changes in the autonomic nervous system and endocrine system, but these changes do not seem to have a major role in the pressor or depressor effect of alcohol except in the case of alcohol withdrawal syndrome.

ACTIONS OF ALCOHOL ON WATER AND ELECTROLYTE METABOLISM

Alcohol also exhibits actions on water and electrolyte metabolism. Urinary excretion increases after alcohol ingestion.[49,50] The increase in urine volume seems to be caused by fluid intake and the suppression of vasopressin.[21,27]

We have studied the effect of repeated alcohol intake for 7 days on the urine volume and sodium excretion in hypertensive patients.[51] Urine volume increased on days 3–5 but not on day 1. Urinary sodium excretion decreased in the early phase but increased in the late phase. The average BP also decreased in the early phase and then returned toward the baseline levels. The initial BP reduction may mask the alcohol-induced diuresis and causes sodium retention, which may be involved in subsequent BP elevation.

It has been shown that urinary potassium excretion decreases after alcohol ingestion.[48,49] In our study, the serum potassium level decreased after a single intake of alcohol.[7,35] This change in serum potassium seems to be mediated by the sympathetic nervous system, as propranolol attenuated alcohol-induced hypokalemia.[35] Conversely, alcohol increases the urinary excretion of magnesium and calcium.[49,50,52] It is possible that magnesium and calcium are depleted in habitual drinkers, and the alcohol-induced changes in these minerals may contribute to BP elevation and arrhythmia.[3,53]

ALCOHOL AND HYPERTENSION

Epidemiological studies

Numerous epidemiological observational studies have examined the relationship between alcohol consumption and BP or hypertension. Almost all of them have shown that habitual drinkers have a higher BP

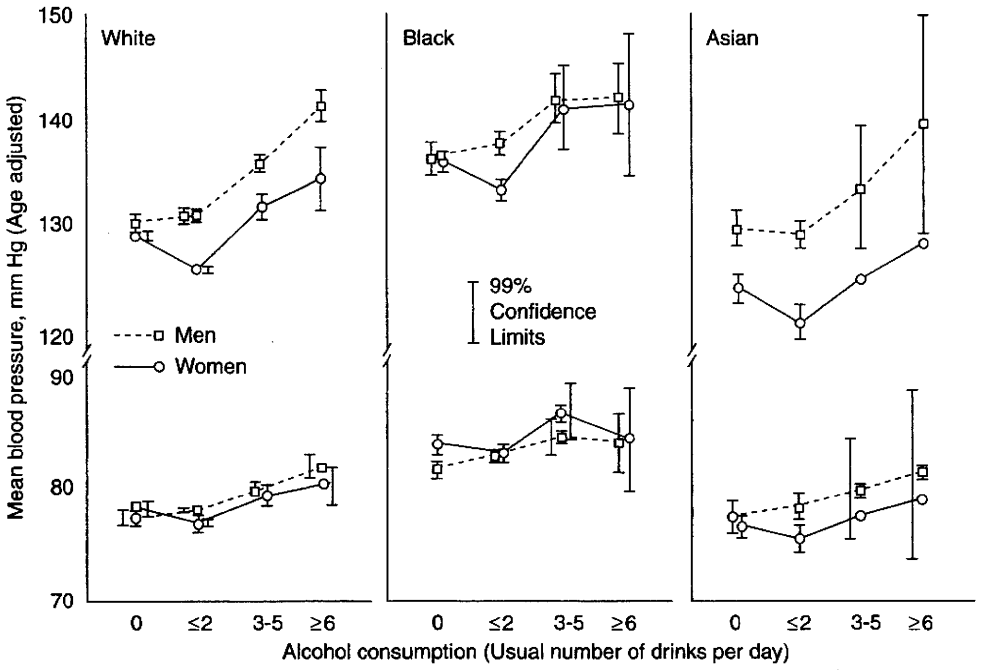

Figure 2 Mean systolic and diastolic BPs for White, Black or Asian men and women for known drinking habits (adopted from Klatsky *et al.*[54] with permission).

and higher prevalence of hypertension than nondrinkers.[1–3,54–58] These associations have been observed regardless of race, gender, age and the type of alcohol (Figure 2). Although some studies suggest the presence of a threshold regarding the pressor effect of alcohol,[59,60] the relationship between the level of alcohol consumption and BP is usually linear. In cross-sectional studies, the systolic BP increased by 3–4 mm Hg and diastolic BP increased by 1–2 mm Hg per three drinks per day (one drink contained 10–15 ml, or 8–12 g of alcohol).[1] Intake of 10 ml per day of alcohol therefore seems to elevate the systolic BP by about 1 mm Hg in humans. It has been estimated that about 10% of hypertension in the general population can be attributed to alcohol.[1–3]

The relationship between alcohol and BP seems to be independent of confounding variables. Increases in the body weight and abdominal fat associated with alcohol consumption, however, may have a role in alcohol-related hypertension. Suter *et al.*[61] observed that both the BP and waist/hip ratio increased with the level of alcohol intake, and there was a positive association between changes in body weight and alcohol consumption.

The hypertensive effect of alcohol has also been shown in longitudinal studies.[62–64] Tsuruta *et al.*[62] reported that the probability of the development of hypertension in heavy drinkers (alcohol consumption ≧46 g per day) was about twice that of the rest of the population after a 12-year follow-up among normotensive men. Fuchs *et al.*[63] showed that the consumption of alcohol at ≧30 g per day was an independent risk factor among participants in the Atherosclerosis Risk in Communities (ARIC) study. Nakanishi *et al.*[64] also observed that the risk for hypertension increased in a dose-dependent manner with increases in alcohol intake among Japanese men in a longitudinal study.

Although epidemiological studies have clearly shown the hypertensive effect of alcohol, most studies did not consider the time-related effect of alcohol on BP. This fact may be important because BP measurement has been carried out during the daytime, whereas alcohol is usually consumed at night. Moreira *et al.*[65] reported that the BP in habitual drinkers was higher at 13–24 h after the last drink compared with that within 3 h or at more than 24 h. Kawabe *et al.*[66] observed that the evening home BP was lower but the morning home BP was higher on drinking compared with nondrinking days in Japanese volunteers. These findings suggest that the BP in habitual drinkers is overestimated by casual BP measurement taken during the day.

Clinical studies

Clinical intervention studies have also revealed an increase in BP with alcohol consumption and a BP decrease with alcohol restriction. Howes and Reid,[67] observed a BP increase after repeated alcohol consumption for 7 days in normotensive subjects. Potter and Beevers,[68] reported a BP increase after alcohol intake for 4 days in hypertensive patients. Using a crossover design, Puddey *et al.*[69,70] compared BP values during a 6-week period of unrestricted alcohol consumption and that of alcohol restriction in normotensive and hypertensive subjects. The average level of alcohol consumption was 50 ml per day during the unrestricted period and 10 ml per day during the restricted period, and the BP was 3/2 mm Hg higher in the former than in the latter period in normotensive subjects.[69] In hypertensive subjects, the BP was 5/3 mm Hg higher in the unrestricted than during the restricted period.[70] Ueshima *et al.*[71] also examined the effect of a 2-week period of alcohol intake and restriction using a crossover method in Japanese hypertensive patients and observed a similar BP elevation with alcohol consumption.

According to a meta-analysis of 15 randomized controlled trials, BP significantly decreased with alcohol restriction[72] (Figure 3). The mean BP reduction was 3.3/2.0 mm Hg, and there was a dose–response relationship between alcohol reduction and decrease in BP. The effects of intervention were enhanced in studies with a higher baseline BP. The results of this meta-analysis support the importance of alcohol reduction in the management of hypertension among heavy drinkers.

Most clinical studies have not considered the timing of alcohol intake and BP measurement. We studied the effect of repeated episodes of alcohol consumption on BP with ABPM under standar-

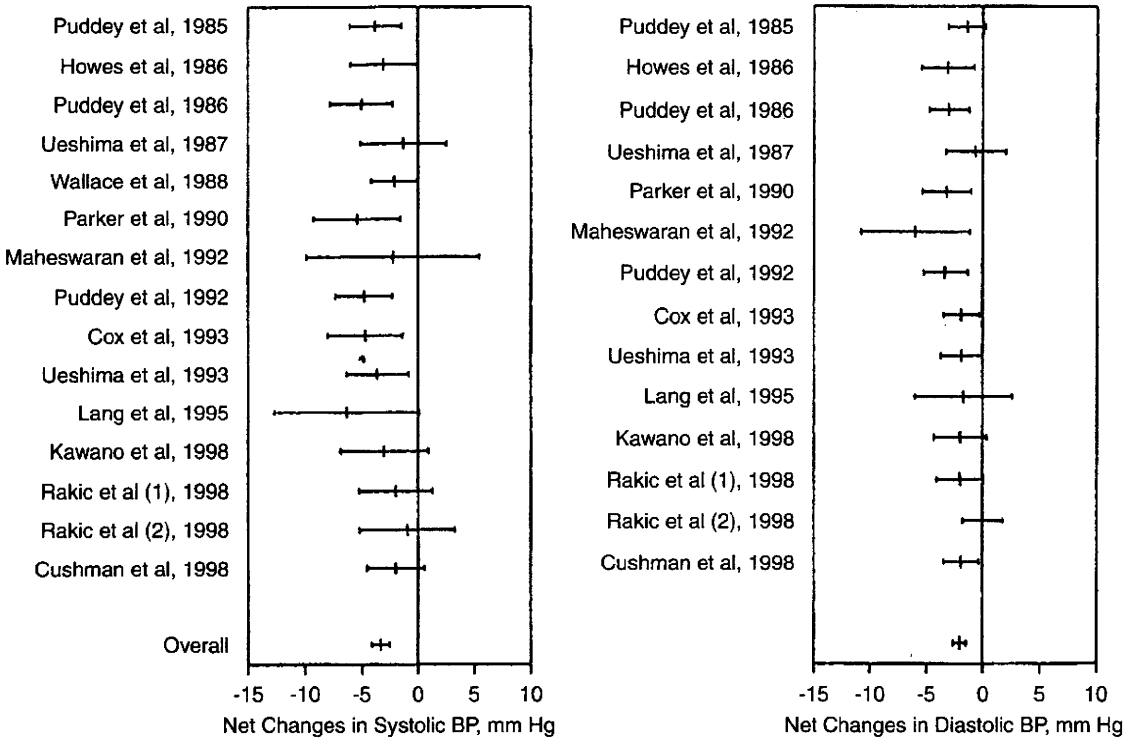

Figure 3 Average net changes in systolic and diastolic BPs and corresponding 95% CIs related to alcohol reduction intervention in 15 randomized controlled trials (adopted from Xin *et al.*[72] with permission).

dized conditions in Japanese men with hypertension.[73] After several days of the control period, the subjects consumed 1 ml kg^{-1} of alcohol with an evening meal for 7 days. Evening BP values decreased for several hours after alcohol consumption on both days 1 and 7, whereas morning BP was unchanged on day 1 but increased on day 7. The average 24-h BP was lower on day 1 and was the same on day 7 compared with the control period. A short-term repeated intake of alcohol therefore causes biphasic changes in BP without altering the average 24-h BP, at least in Japanese men.

We also examined the effect of a 4-week period of unrestricted alcohol consumption and that of alcohol restriction on the 24-h BP in hypertensive patients in a randomized crossover study.[74] The average level of daily alcohol intake was 66 ml in the unrestricted period and 11 ml in the restricted period. The daytime BP was 3/2 mm Hg higher in the unrestricted period than in the restricted period, but the nighttime BP was 4/2 mm Hg lower in the former (Figure 4). The average 24-h BP was comparable between the two periods. These effects of alcohol resulted in changes in the dipping pattern of the 24-h BP. Half of those who did not show a dip in BP during the restricted period changed and showed a dip in the unrestricted period, and half of those that showed a dip showed an extreme dip during this period.

On the other hand, Minami *et al.*[75] observed reductions in the daytime (−3.4 mm Hg) and 24-h (−3.2 mm Hg) systolic BPs after 3 weeks of alcohol restriction in Japanese men. In their study, daytime, nighttime and 24-h diastolic BPs did not change with alcohol reduction (−1.1, +2.1 and −0.3 mm Hg, respectively).

The effect of alcohol on the 24-h BP may differ between Orientals and Caucasians. Howes *et al.*[76] observed that short-term alcohol intake increased BP variability without changing the average BP in Australian subjects. However, Rakic *et al.*[77] showed that the average 24-h BP increased significantly after 4 weeks of alcohol consumption in Australian men. In their study, the average 24-h systolic BP was 2–3 mm Hg higher and the nighttime BP was not lower in the unrestricted compared with the restricted period. It was also reported that the average 24-h BP decreased after abstinence in alcoholic patients.[78]

In a systematic review, McFadden *et al.*[79] analyzed clinical trials that examined the BP after a period of sustained alcohol intake. In this review, the pressor effect of alcohol was evident in non-ABPM studies, but not in ABPM studies. An early effect of reducing the BP and a later effect of raising the BP led to smaller differences in the net effect of alcohol on BP values in ABPM studies.

We also studied changes in morning and evening home BP measurements during each of the 4 weeks of unrestricted consumption and restriction in hypertensive patients.[80] In this study, the morning BP increased by 4.4 mm Hg but late evening BP decreased by 7.4 mm Hg at the end of the unrestricted alcohol intake period. The pressor effect was significant from week 2, whereas the depressor effect was evident from day 1. These results indicate that the status of alcohol intake influences the morning–evening BP difference, and that slow pressor mechanism(s) are involved in alcohol-induced BP elevation.

It is therefore clear that alcohol consumption contributes to hypertension, and alcohol restriction decreases the daytime BP. It should be noted, however, that the effects of alcohol on BP vary according to the level and duration of consumption and the time from the last drink. Alcohol seems to exert a marked influence on circadian BP variation, whereas its influence on the average 24-h BP seems to be small. The mechanisms of the pressor effects of alcohol have not been fully clarified; however, changes in vascular reactivity and sympathetic nerve activity related to intermittent alcohol withdrawal seem to be more important than the direct actions of alcohol. Deficiencies in

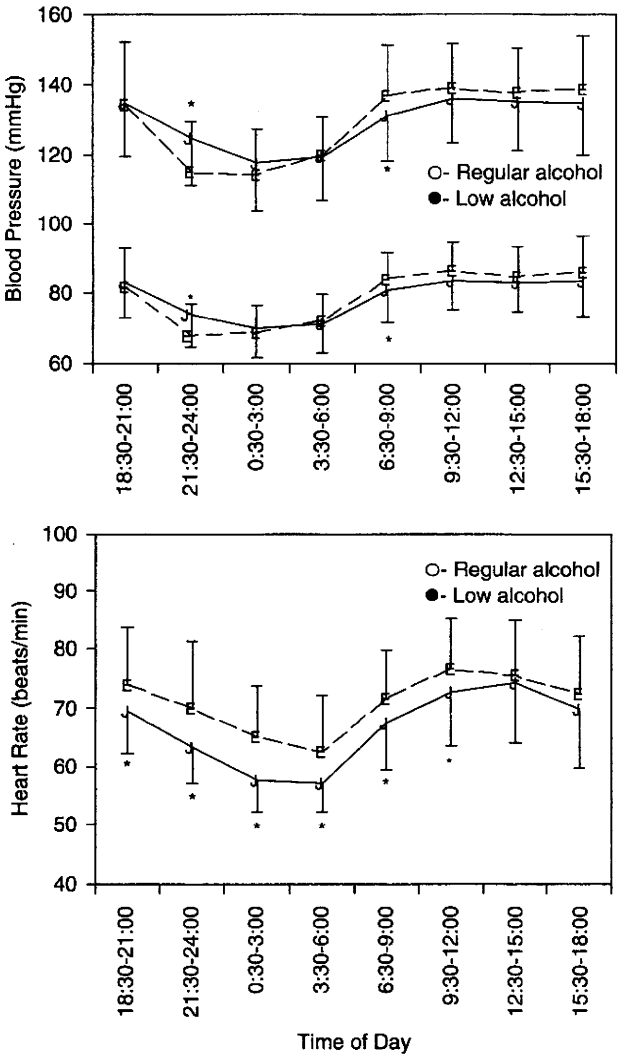

Figure 4 Profile of 24-h BP and heart rate at the end of the regular-alcohol period and the low-alcohol period in hypertensive patients. $*P<0.05$ between the two periods (adopted from Kawano *et al.*[74] with permission).

magnesium and calcium may contribute to BP elevation after chronic alcohol consumption. Increases in the caloric intake through consuming alcoholic beverages and elevated salt intake associated with drinking may also be involved in alcohol-related hypertension.

Experimental studies

Many experimental studies have examined the effect of chronic administration of alcohol on BP; however, the results have been inconsistent.

Strickland and Wooles,[81] reported an elevation of BP after ethanol administration (5–20% in drinking water) for 4 weeks in rats. In their study, the plasma level of norepinephrine was decreased in ethanol-fed animals. Vasdev *et al.*[82] observed BP elevation after 1 week during the administration of ethanol (5–10%) to Wister Kyoto rats. They noted increases in the concentration of platelet intracellular calcium ions and the uptake of calcium in the aorta. Hsieh *et al.*[53] identified increases in BP and intracellular calcium ions and a decrease in intracellular magnesium ions after 4 weeks of ethanol administration (15%) to rats. They suggested a role of magnesium deficiency in ethanol-induced hypertension as the BP elevation was attenuated by magnesium supplementation. Puddey *et al.*[83] reported a BP elevation of ~10 mm Hg and decreases in the level of phospholipids and the ratio of unsaturated/saturated fatty acids in the aorta and kidney after the chronic administration of alcohol to rats. Harada *et al.*[84] also observed increases in the BP and platelet-free calcium concentration with ethanol consumption (15%) in Wister Kyoto rats.

In some studies, the BP did not change after the chronic administration of alcohol to animals. Abdel-Rahman[85] reported that the BP increase was not different between ethanol-fed (5–20% in drinking water) spontaneously hypertensive (SH) rats and control SH rats during a 13-week observation period. The depressor effect of clonidine, however, was reduced in the ethanol-fed SH rats, suggesting a change in the neural regulation of BP.

Several studies have shown that chronic alcohol intake decreases BP in animals. Howe *et al.*[86] reported that BP values in alcohol-fed (5–20% in drinking water) Wister Kyoto, SH and stroke-prone SH rats were lower than those of respective control rats during a 6-month observation period. Hatton *et al.*[87] observed a BP decrease during chronic ethanol administration (36% in a liquid diet) for 18 weeks in Wistar rats. The vasoconstrictor response of resistant arteries to norepinephrine was enhanced and the vasodilator response to alcohol was attenuated in their study. Beilin *et al.*[88] reported a decrease in the resting BP of Wister Kyoto and SH rats after 12 weeks of ethanol administration (20% in drinking water), although cardiovascular reactivity to noise-related stress was augmented in the ethanol-fed SH rats. El-Mas and Abdel-Rahman[89] also observed a lower BP in freely moving, ethanol-fed (5% in a liquid diet) rats compared with control rats based on telemonitoring of the BP.

The reasons for the inconsistent results in experimental studies are not clear, but cannot be explained by differences in daily doses of alcohol administration. The periods of alcohol administration, however, are generally longer in studies showing BP reduction than those showing BP elevation. The timing of BP measurement may be important, such as in clinical studies. Crandall *et al.*[90] administered 30% alcohol twice daily ($7–8\,g\,kg^{-1}$) for 10 weeks to rats and examined the levels of BP and blood alcohol. In their study, BP was normal at the time of the peak blood alcohol level but was elevated at 24 h after alcohol consumption, when alcohol was not detected in the plasma. Their results suggest that alcohol-induced hypertension is not because of its direct action but to alcohol withdrawal.

The harmful effects of large doses of alcohol, such as cardiac dysfunction, have been shown in experimental studies.[91] Schlicht *et al.*[92] however, reported that the lifespan of SH rats was prolonged by the chronic administration of ethanol. These observations are important, as both the adverse effects of a large amount of alcohol and the beneficial effects of a moderate amount on cardiovascular disease and total mortality have been shown in large-scale epidemiological studies.[8–12]

Interaction with antihypertensive drugs

Alcohol interacts with several antihypertensive agents. Experimental studies have shown that alcohol attenuates the effect of centrally acting antihypertensive drugs such as clonidine.[86] Heavy drinking is recognized as one of the factors responsible for resistant hypertension. The interaction between alcohol and antihypertensive drugs and the hypertensive effect of alcohol may have a role in alcohol-related resistant hypertension. In addition, heavy drinkers often show poor adherence to both pharmacological treatment and lifestyle modifications. Habitual drinkers taking antihypertensive drugs are also prone to morning hypertension.[93]

Table 2 Moderation of alcohol consumption recommended by hypertension treatment guidelines

JNC-7 (2003)	*ESH-ESC 2007*	*JSH 2009*
Men: ≦2 drinks per day (≦30 ml per day)	Men: ≦20–30 g per day	Men: ≦20–30 ml per day
Women, light weight person: ≦1 drink per day (≦15 ml per day)	Women: ≦10–20 g per day	Women: ≦10–20 ml per day

Expressed as amount of ethanol. ESH-ESC 2007, European Society of Hypertension–European Society of Cardiology guidelines;[5] JNC-7, Joint National Committee 7th report (Chobanian *et al.*[4]); JSH 2009, Japanese Society of Hypertension guidelines (Ogihara *et al.*[6]).

The combination of alcohol and antihypertensive drugs may also lead to a marked BP reduction. This phenomenon has been known; however, few clinical studies have addressed this interaction. It is possible that sympatholytic drugs augment the depressor effect of alcohol, as alcohol-induced hypotension is associated with the reflex activation of the sympathetic nervous system.[7] In our studies, alcohol and a beta blocker, propranolol, additively lowered the nighttime BP,[35] whereas alcohol and an alpha blocker, prazosin, synergistically acted to lower the BP in hypertensive patients.[94] It has also been reported that alcohol enhances the depressor effect of the calcium antagonist felodipine.[95] Changes in the type and timing of antihypertensive medication along with the moderation of alcohol consumption should be considered to treat hypertensive patients with a drinking habit.

Hypertension treatment guidelines

As an excess consumption of alcohol is a risk factor for hypertension, all hypertension treatment guidelines recommend the moderation of alcohol intake as a part of lifestyle modifications for the management of hypertension (Table 2). The 7th report of the Joint National Committee in the United States (JNC-7) recommends the limitation of daily alcohol consumption to no more than two drinks (30 ml) for most men and to no more than one drink (15 ml) for women and light-weight men.[4] According to the European guidelines (European Society of Hypertension–European Society of Cardiology guidelines, ESH–ESC 2007), the upper limit is 20–30 g per day for men and 10–20 g per day for women. The Japanese guidelines provide similar recommendations (20–30 ml per day for men and 10–20 ml per day for women). Of note, 600 ml of beer or 250 ml of wine contains about 30 ml of ethanol.

These recommendations put forward by the guidelines are appropriate because small doses of alcohol exert little adverse effects on BP and the cardiovascular system. There are, however, some concerns regarding the efficacy of alcohol restriction on BP because the effect of alcohol on average 24-h BP levels seems to be very small. In our studies, salt restriction and weight reduction substantially decreased the BP for 24 h, but the effect of alcohol restriction on average 24-h BP was not significant.[96–98] As light drinking has beneficial effects on the cardiovascular system, as described later, abstinence from alcohol should not be imposed on hypertensive individuals except for patients with special conditions.

ALCOHOL AND CARDIOVASCULAR DISEASE

Cardiac disease

Heart failure. A heavy alcohol intake is associated with cardiac hypertrophy and the risk of cardiomyopathy and heart failure.[8,36,37] It has been shown that the total consumption of alcohol is positively related to a left ventricular mass and is negatively associated with the ejection fraction in asymptomatic alcoholic subjects.[37] Recent epidemiological studies, however, have shown that moderate alcohol consumption is associated with a lower risk of heart failure.[99,100] Klatsky *et al.*[101] reported that heavy drinkers had an increased risk of heart failure because of noncoronary artery disease, whereas alcohol drinking was inversely related to the risk of heart failure because of coronary artery disease. Heavy drinking therefore seems to increase the risk of heart failure but light-to-moderate drinking may decrease the risk, probably because of its favorable association with coronary artery disease.

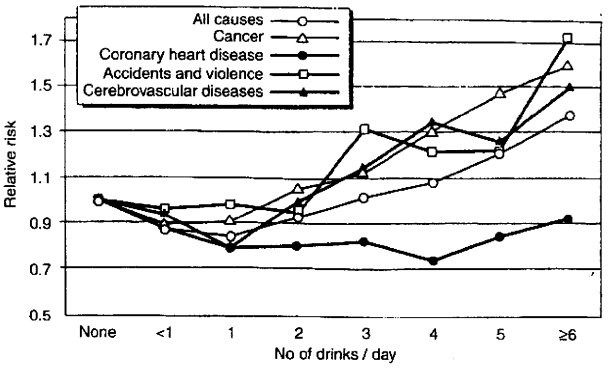

Figure 5 Alcohol consumption and relative risk of death over 12 years in American Cancer Society prospective study of 276 802 men aged 40–59 (adopted from Boffetta *et al.*[105] with permission).

Arrhythmia. Alcohol intake is associated with the risk of tachyarrhythmia, such as ventricular and supraventricular premature contractions and atrial fibrillation.[8,102–104] In the Danish Diet, Cancer and Health study, moderate-to-heavy consumption of alcohol was associated with an increased risk of atrial fibrillation.[103,104] Such alcohol-induced arrhythmia often occurs after binge drinking. Activation of the sympathetic nervous system and a decrease in the serum potassium level after drinking may trigger this arrhythmia.[3] Cardiac functional and structural changes because of chronic alcohol consumption also seem to have a role in arrhythmia.[37]

Coronary heart disease. Alcohol seems to have a beneficial effect on coronary heart disease.[8,9] It has been shown that the risk of myocardial infarction is 20–50% lower in habitual compared with nondrinkers.[9,105–108] This risk reduction is dose-dependent up to the level of moderate drinking, but further risk reduction has not been observed in heavy drinkers (Figure 5). A U-shaped relationship has been observed between the level of alcohol consumption and degree of coronary calcification in a general population.[109] In some studies, such as the Japan Collaborative Cohort Study,[110] the beneficial effect of alcohol on coronary heart disease was modest and not significant (Table 3).

The mechanisms behind the inverse association of alcohol with coronary heart disease have not been fully clarified. The alcohol-induced increase in HDL cholesterol, however, seems to be the most important mechanism.[107,111] The inhibitory effect of alcohol on blood coagulation also contributes to the lower risk of myocardial infarction.[107] In addition, it has been shown that moderate alcohol consumption is associated with a lower plasma level of C-reactive protein, suggesting an anti-inflammatory action of alcohol.[112] The weak effect of alcohol on the average 24-h BP may also have a role as a high BP is a strong risk factor for coronary heart disease.[74,79]

Red wine contains polyphenols that act to prevent atherosclerosis because of their antioxidant effect. Several studies have shown that

Table 3 Mortality from stroke, coronary heart disease and total cardiovascular disease by alcohol consumption category in men in the Japan Collaborative Cohort Study (adopted from Ikehara *et al.*[110] with modification)

			Ethanol intake, g per day			
	Nondrinkers	*Ex-drinkers*	*0.1–22.9*	*23.0–45.9*	*46.0–68.9*	*≧69.0*
Person–years	96423	25919	78478	101256	90000	41588
Total stroke	200	126	114	168	173	83
Age-adjusted HR	1.00	1.93[a]	0.91	0.98	1.46[a]	1.89[a]
Multivariable HR	1.00	1.90[a]	0.95	0.96	1.39[a]	1.71[a]
Hemorrhagic stroke	55	31	41	52	60	37
Age-adjusted HR	1.00	1.80[a]	1.09	1.02	1.51[a]	2.30[a]
Multivariable HR	1.00	1.79[a]	1.16	1.02	1.47	2.16[a]
Ischemic stroke	126	88	60	101	95	37
Age-adjusted HR	1.00	2.12[a]	0.80	0.99	1.44[a]	1.60[a]
Multivariable HR	1.00	2.11[a]	0.81	0.94	1.34[a]	1.39
Coronary heart disease	116	56	71	90	65	33
Age-adjusted HR	1.00	1.50[a]	0.94	88	0.87	1.16
Multivariable HR	1.00	1.35	0.96	0.82	0.76	0.95
Total cardiovascular disease	487	282	269	379	342	162
Age-adjusted HR	1.00	1.77[a]	0.88	0.90	1.16[a]	1.47[a]
Multivariable HR	1.00	1.66[a]	0.90	0.87	1.07	1.28[a]

Abbreviation: HR, hazard ratio.
[a]Significant *vs.* nondrinkers.

people who mainly drink red wine have a lower risk of cardiovascular disease than those who drink other kinds of alcoholic beverage.[113,114] It is suggested, however, that the low incidence of myocardial infarction in habitual drinkers is largely attributed to the effect of alcohol itself.[115]

Cerebrovascular disease

The relationship between alcohol consumption and total cerebrovascular disease is generally J-shaped, although it differs according to subtypes of stroke [105,116] (Figure 5). It is clear that alcohol is a risk factor for hemorrhagic stroke. A positive linear relationship has been observed between the level of alcohol consumption and risk of brain or subarachnoid hemorrhage.[8,110,116,117] Actions on the BP and blood coagulation system seem to be underlying mechanisms for this adverse influence of alcohol.

On the other hand, the relationship between alcohol consumption and the risk of ischemic stroke has been found to be J- or U-shaped.[110,116–118] The low risk in light drinkers seems to be due to the lower degree of atherosclerosis and the inhibition of blood coagulation, as in the case of ischemic heart disease. The increased risk in heavy drinkers is probably related to increases in the level and variability of the BP, hemoconcentration because of dehydration and thromboembolism associated with alcohol-induced atrial fibrillation. Regarding alcoholic beverage types, wine drinkers seem to have a lower risk of ischemic stroke.[119,120]

The favorable association of light-to-moderate drinking with the risk of ischemic stroke seems to be more apparent in Caucasians than in Japanese, although the results of epidemiological studies have been inconsistent in both populations. The racial differences may be related to variation in the frequencies of stroke subtypes. Atherothrombotic brain infarction is common in Caucasians, whereas lacunar stroke is more common in Japanese.

Several studies have examined the relationship between alcohol intake and subclinical findings on magnetic resonance imaging of the brain in general populations. In the Cardiovascular Study, a U-shaped relationship was observed between alcohol consumption and white matter abnormalities. Moreover, moderate drinking was also associated with a lower risk of lacunar infarction compared with abstainers.[121] Such risk reduction with moderate drinking, however, was not observed in the ARIC study, and an increased level of alcohol intake was associated with brain atrophy.[122]

Peripheral arterial disease and atherosclerosis

As light-to-moderate consumption of alcohol seems to act to suppress the progression of atherosclerosis, it may also have a favorable influence on peripheral arterial disease. The Edinburgh Artery Study supported the protective effect of alcohol, as there was a positive association between the level of alcohol intake and the ankle brachial index.[123] In the Physicians' Health Study, habitual drinkers showed a 26% lower incidence of peripheral arterial disease compared with nondrinkers after adjustment for confounding factors.[124] Similar results were also shown in the Framingham Heart Study and the ARIC study.[125,126]

Regarding the association of alcohol and carotid atherosclerosis, an inverse relationship was noted in the Lausanne Stroke Registry.[127] On the other hand, there was no significant association between alcohol intake and the carotid artery thickness in the ARIC study.[128] A U- or J-shaped relationship was observed between the level of alcohol intake and severity of carotid atherosclerosis in the Bruneck Study and the Study of Health in Pomerania.[129,130] Although the results of epidemiological studies have been inconsistent, light-to-moderate consumption seems to inhibit the development of carotid atherosclerosis.

Several studies examined the relationship between alcohol consumption and arterial stiffness by measuring the pulse wave velocity.

Sierksma *et al.*[131] identified a U-shaped relationship between alcohol consumption and the aortic pulse wave velocity. van den Elzen *et al.*[132] observed an inverse relationship between the alcohol intake and pulse wave velocity in young men and women. On the other hand, Kurihara *et al.*[133] reported that the brachial–ankle pulse wave velocity was elevated in heavy drinkers. These studies also support the favorable effect of moderate and the harmful effect of heavy drinking on large arteries.

Cardiovascular mortality and total mortality

As described earlier, alcohol seems to exert both beneficial and adverse effects on cardiovascular diseases. The relationship between alcohol consumption and total cardiovascular mortality has been shown to be J-, U- or L-shaped. A J-shaped relationship was observed in the Japan Collaborative Cohort Study; however, the beneficial effect of light-to-moderate drinking was not significant.[110] On the other hand, in very large longitudinal studies conducted by the American Cancer Society, a U-shaped relationship was observed in the original study,[105] and the relationship was L-shape (nondrinkers showed the highest cardiovascular mortality) in Study II.[10] In a meta-analysis conducted by Di Castelnuovo *et al.*,[114] a light-to-moderate consumption of wine or beer was associated with lower cardiovascular risk. A drinking habit, particularly wine consumption, has been shown as a part of a lifestyle associated with low cardiovascular risk.[134,135] It has also been suggested that the risk reduction associated with alcohol consumption is low in individuals without cardiovascular risk factors but is high in those with a marked cardiovascular risk. Taken together, light-to-moderate alcohol consumption seems to decrease cardiovascular mortality, whereas heavy drinking may result in poor cardiovascular outcomes compared with abstainers.

Alcohol is also related to several cancers, liver disease, psychiatric and neurological disorders and injury, and it seems to influence total mortality. A J- or U-shaped relationship has been observed between the level of alcohol intake and total mortality.[10,11,105,136,137] It has been suggested that all-cause mortality is the lowest among subjects who consume about one drink per day. In the American Cancer Society Prospective Study II, total mortality was lower in drinkers than in nondrinkers.[10] It has also been shown that wine drinkers have a lower mortality rate than drinkers who avoid wine.[136] In a meta-analysis of 34 studies including more than one million individuals, a J-shaped relationship was found between alcohol consumption and total mortality.[11] In this analysis, low levels of alcohol intake (one to two drinks per day for women and two to four drinks per day for men) were inversely associated with total mortality, although higher levels of alcohol increased mortality. Those findings suggest that a light-to-moderate intake of alcohol decreases but heavy consumption increases total mortality compared to nondrinking.

CONCLUSIONS

Alcohol has complex effects on the cardiovascular system. It is clear that alcohol consumption is related to hypertension, and therefore the restriction of alcohol intake is recommended in the management of hypertension. Alcohol and its metabolites, however, also exhibit a vasodilatory action, and the BP usually decreased after alcohol ingestion, especially in Orientals who show alcohol flush. Mechanisms for the pressor action of alcohol have not been completely clarified; however, an increase in the vascular sensitivity, activation of the sympathetic nervous system and depletion of magnesium and calcium may be involved. The depressor action of alcohol is due to a decrease in systemic vascular resistance that may be related to the attenuation of vascular sensitivity and production of nitric oxide. The pressor effect of alcohol consumed in the evening is apparent during the day, but its effect on average 24-h BP seems to be very small. It should be mentioned that casual BP measurement may lead to overestimating the hypertensive effect of alcohol.

Alcohol seems to exert both harmful and beneficial effects on cardiovascular disease. An excessive intake of alcohol is associated with increased risks of heart failure, arrhythmia and hemorrhagic stroke and causes an increase in total mortality. Light-to-moderate drinkers, however, show lower rates of atherosclerosis and lower risks of coronary heart disease, heart failure, ischemic stroke, peripheral artery disease and cardiovascular and total mortality compared with nondrinkers. As the aim of the management of hypertension is the prevention of cardiovascular disease and premature death, moderation of alcohol intake is to be recommended to hypertensive patients, but abstinence from alcohol should not be insisted on unless there are specific indications for it.

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Journal of Human Hypertension (2010) 24, 320–326

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ORIGINAL ARTICLE

Association of insulin-like growth factor-1 receptor gene polymorphisms with left ventricular mass and geometry in essential hypertension

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Stimulation of insulin-like growth factor (IGF)-1 receptor by IGF-1 and insulin strongly induces cardiomyocyte hypertrophy. In this study, we assessed the hypothesis that genetic variations of the IGF-1 receptor may be linked to the diversity of left ventricular (LV) structure in hypertensive patients. Genotypes in 12 single nucleotide polymorphisms (SNPs) of the IGF-1 receptor gene identified by direct sequencing were determined in 795 Japanese patients with essential hypertension. In echocardiographic examinations, LV mass index (LVMI) and relative wall thickness (RWT) were measured. Among 12 SNPs, promoter −328C>T and intron-13 275124A>C polymorphisms were significantly associated with LV hypertrophy (LVMI ⩾125 g m^{-2}) and concentric change (RWT ⩾0.44), respectively. In allele frequencies, the C allele of −328C>T was related to LV hypertrophy, and the A allele of 275124A>C was related to LV concentric change. In fact, LVMI and prevalence of LV hypertrophy increased in CC genotype of −328C>T. RWT and prevalence of LV concentric change increased in AA genotype of 275124A>C. A multiple logistic regression analysis revealed that the presence of CC genotype of −328C>T or AA genotype of 275124A>C was an independent determinant for LV hypertrophy or concentric change, respectively. Furthermore, the combination of CC of −328C>T and AA of 275124A>C genotypes was significantly associated with abnormal LV geometry, especially concentric hypertrophy. Our findings show that two SNPs of the IGF-1 receptor gene are related to LV hypertrophy in patients with essential hypertension, suggesting that the genetic variation of the IGF-1 receptor may be involved in the diversity of LV structure in hypertensives.

Journal of Human Hypertension (2010) **24**, 320–326; doi:10.1038/jhh.2009.73; published online 17 September 2009

Keywords: insulin-like growth factor; receptor; gene polymorphism; hypertrophy

Introduction

Left ventricular (LV) hypertrophy, the most common cardiac consequence of hypertension, is considered as a maladaptation to the increased afterload, because it is one of the independent risk factors for cardiovascular morbidity and mortality.[1] However, the haemodynamic load is not the only determinant of LV hypertrophy, because for similar elevations of blood pressure, a wide range of severities and types of LV hypertrophy have been observed.[2,3] Many studies have shown that blood pressure explains only 10 to 25% of the variation in LV mass, supporting the hypothesis that several non-haemodynamic factors, such as genetic and metabolic factors, are involved in the cardiac growth in human hypertension.[4–6]

Hypertension is one of the components of the metabolic syndrome, which is characterized by insulin-resistance and hyperinsulinemia. An earlier study has shown that circulating levels of insulin and insulin-like growth factor (IGF)-1 are associated with LV hypertrophy and geometric change in hypertensive subjects.[7] IGF-1 is a well-known strong promoter of cardiomyocyte growth through its receptors abundantly expressed in myocardium.[8] Insulin may also stimulate cardiomyocyte hypertrophy by binding to the IGF-1 receptors because of the structural similarity between the two molecules.[9,10]

The above considerations prompted us to hypothesize that the genetic variation of the IGF-1 receptor may be linked to the diversity of LV structure in hypertensives. Thus, this study analysed the association of IGF-1 receptor gene polymorphisms with LV mass and geometry in patients with essential hypertension.

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Received 12 June 2009; accepted 15 July 2009; published online 17 September 2009

Materials and methods

Subjects

A total of 795 Japanese patients with essential hypertension (438 men and 357 women; mean age, 65 ± 11 years) were enroled in this study. Patients with secondary hypertension, myocardial infarction, valvular heart disease, congestive heart failure, atrial fibrillation, or unsatisfactory B-mode and Doppler echocardiograms were excluded from this study. Hypertension was defined as a systolic blood pressure of ⩾140 mm Hg and/or a diastolic blood pressure of ⩾90 mm Hg by repeated measurements or when medication was taken for treatment of hypertension. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria, such as a fasting plasma glucose of ⩾126 mg per 100 ml and/or a plasma glucose level at 2 h after a 75 g oral glucose load of ⩾200 mg per 100 ml, or when medication was taken for treatment of hyperglycaemia.

Among the 795 patients, 726 (91%) were receiving antihypertensive drugs, including combination therapy in some cases. In total, 574 patients (72%) were treated with calcium channel blockers, 407 (51%) with renin angiotensin system inhibitors (that is, angiotensin II receptor blockers and angiotensin converting enzyme inhibitors), 285 (36%) with β-blockers, 181 (23%) with diuretics and 113 (14%) with other classes of agents. In all, 69 patients (9%) were treated with diet and/or exercise therapy (without antihypertensive medication).

All subjects gave their informed consent to participate in this study. The study protocol was approved by the ethical review committee of the National Cardiovascular Center.

Clinical parameters

At the time of the physical examination, blood pressure, heart rate, body mass index and biochemical profiles were determined. Blood pressure and heart rate were measured in the subjects after at least 10 min of rest in a sitting position. Peripheral blood samples were obtained in the morning after an overnight fast. Total cholesterol, triglycerides, fasting plasma glucose, haemoglobin A1c and serum creatinine levels were determined by standard laboratory measurements.

Echocardiographic measurement

A comprehensive two-dimensional echocardiography was performed using a cardiac ultrasound unit (Sonos 5500; Philips Medical Systems, Andover, MA, USA) as described earlier.[11,12] Echocardiographic parameters were measured by the consensus of two experienced investigators who were blinded to the clinical data of the subjects. Measurements, such as interventricular septal thickness (IVSTd), posterior wall thickness (PWTd), LV diameter at end-diastole (LVDd) and LV diameter at end-systole (LVDs). Fractional shortening was calculated as (LVDd–LVDs)/LVDd. Relative wall thickness (RWT) was calculated as (IVSTd + PWTd)/LVDd. LV mass was estimated using the formula validated by Devereux and Reichek:[13] LV mass (g) = $1.04 \times \{(\mathrm{IVSTd} + \mathrm{PWTd} + \mathrm{LVDd})^3 - \mathrm{LVDd}^3\} - 13.6$. LV mass was normalized for body surface area and expressed as LV mass index (LVMI). LV hypertrophy and LV concentric change were defined as a LVMI of ⩾125 g m^{-2} and a RWT of ⩾0.44, respectively.[2,3] The geometry of LV was stratified into four different patterns according to the values of LVMI (< or ⩾125 g m^{-2}) and RWT (< or ⩾0.44). Patients with increased LVMI and increased RWT were considered to have concentric hypertrophy, and those with increased LVMI and normal RWT were considered to have eccentric hypertrophy. Those with normal LVMI and increased or normal RWT were considered to have concentric remodelling or normal geometry, respectively.

To assess LV diastolic function, the diastolic filling of LV (LV inflow) was examined using Doppler echocardiography.[14] The peak velocity of early diastolic filling (*E*) and the peak velocity of atrial filling (*A*) were recorded and the *E* to *A* ratio (*E*/*A*) was calculated. The deceleration time was measured as the time between the top of the *E* wave and the point at which the descending part of the *E* wave or its asymptote crossed the zero line.

Detection and genotyping of single nucleotide polymorphisms (SNPs)

First, peripheral blood samples were obtained from 96 patients with essential hypertension, and all exons, part of the intron segments, and the promoter regions of the IGF-1 receptor gene were sequenced for the detection of SNPs. The method of direct sequencing has been described earlier.[15,16] The identified polymorphisms were numbered from the *A* of the initiator codon (ATG), according to the recommendations of the Nomenclature Working Group for human gene mutations.[17] Among all SNPs identified by sequencing, common SNPs with a minor allele frequency of >5% were chosen, and one SNP from several SNPs with tight linkage disequilibrium ($r^2 \geqslant 0.5$) was selected for genotyping. As a result, 12 SNPs were genotyped using the TaqMan-polymerase chain reaction system for all patients, as described earlier.[18,19]

Statistical analysis

The values are expressed as mean ± s.d. To assess the association of IGF-1 receptor SNPs with LV structural change, differences in frequency among the groups were tested by χ^2 analysis. An unpaired Student's *t*-test was used for comparison of clinical and echocardiographic parameters between the two groups with different SNP genotypes. A multiple