Biphasic Effects of Repeated Alcohol Intake on 24-Hour Blood Pressure in Hypertensive Patients

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Background The association between alcohol and blood pressure (BP) may be related to the temporal sequencing of alcohol use and BP measurement. We investigated the effects of single and repeated intakes of alcohol on 24-hour BP.

Methods and Results Fourteen male habitual drinkers with essential hypertension were placed sequentially on a 4-day control phase: a nonalcoholic drink with the same calories as alcohol was given at dinner (5 PM to 6 PM) and a 7-day drinking phase: alcohol (ethanol, 1 mL/kg) was given at dinner under standardized conditions. Ambulatory BP measurements were performed on day 3 of the control phase and on days 1 and 7 of the alcohol phase. The average 24-hour systolic and diastolic BPs on day 1 were significantly lower than those in the control phase and on day 7. Between 6 PM and midnight, both systolic and diastolic BPs on days 1 and 7 (121±2/73±1 and 126±4/75±2 mm Hg, respectively) were significantly lower than those in the control phase (139±4/83±2 mm Hg). Between midnight and 8 AM (6 to 14 hours after the last drink), both systolic and diastolic BPs on day 7 (138±4/83±2 mm Hg) were significantly higher than those in the control phase (131±4/79±2 mm Hg) and day 1 (129±3/77±1 mm Hg). Between 8 AM and 3 PM, BPs showed no difference among the three phases.

Conclusions A single intake of alcohol has a depressor effect on BP that lasts for several hours after drinking, while repeated intakes for 7 days have both depressor and pressor effects according to the differences in time intervals after the last drink. This study suggests that the chronic effects of alcohol on BP might be overestimated when based on casual BP measurements alone. (Circulation. 1994;89:2626-2633.)

Key Words • alcohol • hypertension • blood pressure

Results of cross-sectional epidemiological studies are largely consistent in demonstrating a positive correlation between blood pressure (BP) and alcohol consumption independent of a variety of confounding factors such as age, sex, race, and obesity.1-6 Few prospective clinical studies have been performed to investigate the association between alcohol and hypertension and to demonstrate a pressor effect of alcohol.7,8 It has been estimated that between 5% and 39% of hypertension cases may be attributable to alcohol.9,10 The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommended that those who drink in excess should reduce their alcohol consumption to <30 mL per day.11 However, this recommendation is based on the results of studies that estimated BP mainly by casual measurements, not by 24-hour BP measurements.

Recently, home and ambulatory BP recorders provide further information on BP variability and circadian BP patterns in normal and hypertensive subjects.12-14 Analysis relating the different measures of BP to hypertensive target organ damage has been performed. These results indicate that home or ambulatory BP is related more closely to hypertensive target organ damage than office BP.15-17 This suggests that home or ambulatory BP readings are more representative than office BP readings.

A considerable amount of clinical data has indicated that the BP of alcoholics is highest during withdrawal18,19; however, little attention has been directed to the effects on 24-hour BP profiles, taking periodic sequencing of alcohol intake and BP measurement into consideration. We previously reported decreased BP for several hours after a single intake of alcohol in hypertensive patients with drinking habits.20 Thus, the BP circadian pattern with repeated intake of alcohol may differ from that with a single intake, since many studies have suggested a pressor action of alcohol. For this reason, we investigated and compared the effects of single and repeated consumptions of alcohol on 24-hour BP in hypertensive patients with drinking habits.

Methods

Subjects

We studied 14 men with essential hypertension and drinking habits with reported alcohol consumption of 30 to 120 mL/day. Clinical characteristics of these subjects are shown in Table 1. After a detailed history was obtained and a physical examination was performed, appropriate laboratory studies were made to exclude secondary hypertension and cardiovascular, renal, hepatic, metabolic, and endocrine disorders. All the patients were diagnosed as having mild to moderate essential hypertension, and none had serious cardiovascular, hepatic, or renal disorders. The study protocol was approved by the Ethics Committee of the National Cardiovascular Center, and informed consent was obtained from each subject.
TABLE 1. Clinical Characteristics of 14 Men With Essential Hypertension

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168±1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>57±2</td>
</tr>
<tr>
<td>Habitual alcohol intake, mL/d</td>
<td>71±6</td>
</tr>
<tr>
<td>Previous antihypertensive therapy, n</td>
<td>12/14</td>
</tr>
<tr>
<td>SBP on admission, mm Hg</td>
<td>148±4</td>
</tr>
<tr>
<td>DBP on admission, mm Hg</td>
<td>95±3</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

Protocol

Subjects abstained from alcoholic drinks and stopped antihypertensive medications for at least 1 week before the study. The studies were conducted in a standardized condition, and subjects were hospitalized in a ward of the National Cardiovascular Center where they spent the entire 24-hour test period and ate a regular hospital diet (salt, 10 g/d; calories, 1500 per day). Before entering the protocol, subjects stayed in the ward for several days to minimize the effect of hospitalization on BP during the study protocol.

The experiment was divided into two consecutive phases: control phase—a 4-day period during which nonalcoholic drinks containing the same amount of calories as alcohol were added to dinners (5 PM to 6 PM) and drinking phase—a 7-day period during which 1 mL/kg of ethanol was administered with dinner, in the form of vodka, lime juice, and water. Subjects were allowed approximately 60 minutes to consume the alcohol. BP recordings, echocardiographic examinations, blood samplings, and urine collections for 24 hours were performed on day 3 of the control phase and on days 1 and 7 of the drinking phase.

Twenty-four-hour BP recordings were performed from 3 PM to 3 PM. Echocardiographic examinations and subsequent venous blood samplings were performed before dinner (4:30 PM to 5 PM) and 90 to 120 minutes after dinner (6:30 PM to 7 PM). Additional blood samples were collected the next morning before breakfast (8 AM). Each blood sampling was performed after 30 minutes of recumbency.

BP Measurement and Analysis

Intermittent readings of BP and pulse rate were taken, at intervals of 30 minutes throughout 24 hours, by an oscillometric method using the Colin ABPM 630 (Nippon Colin). The accuracy of each recorder was checked by simultaneous measurement with a mercury sphygmomanometer, and all recorders showed a difference of <10 mm Hg. The same recorder was used in each patient for the entire protocol to avoid different BP readings caused by different recorders. There is a limit to precise estimations of the actual 24-hour BP variability by ambulatory BP readings that have only 48 measurements; thus, it would be best not to rely on a single BP measurement but rather to emphasize the mean of several measurements. For this reason, BP analysis was done using the mean of several measurements. BP circadian patterns were constructed using mean BPs calculated every 2 hours. According to the BP circadian pattern, BP was averaged for three time intervals: for 6 hours from 6 PM to midnight, for 8 hours from midnight to 8 AM, and for 7 hours from 8 AM to 3 PM.

Echocardiographic Examinations

A two-dimensionally guided M-mode echocardiogram was obtained as previously described. Six patients with inadequate echocardiographic images were excluded. Thus, echocardiographic examination was performed on eight patients. Three readings of BP were obtained by an automatic BP recorder (Colin 201) at the time of the study, and the lowest value was used for subsequent calculations of hemodynamics. Measurements of the left ventricular internal dimensions (LVID) were made at end diastole and end systole according to the recommendation of the American Society of Echocardiography. Left ventricular volumes were estimated by the cube-function formula from the end-diastolic and end-systolic LVID, and those were used to estimate stroke volume and cardiac output. This method is considered to be appropriate for the study, since the subjects' hearts had neither any asynergy nor valvular regurgitation. Total peripheral resistance (in dyne·s·cm⁻²) was estimated as (mean BP×80)/cardiac output. Mean blood pressure was estimated as diastolic blood pressure+½ systolic–diastolic blood pressure. The LVID changes from end diastole to end systole were calculated as left ventricular fractional shortening. End-systolic meridional wall stress was calculated from echocardiographic dimensions and BP at the time of echocardiography by a catheterization-validated method: end-systolic meridional wall stress=(0.334×LVID×systolic BP)/(PWT×(1+PWT/LVID)), where PWT is posterior wall thickness.

Biochemical Measurements

Urinary sodium was determined by a biochemical analysis system (TBA-80S, Toshiba). Urinary and plasma norepinephrine and epinephrine were assayed by high-performance liquid chromatography and trihydroxyindole fluorometry. Plasma levels of renin activity, aldosterone, cortisol, and insulin were measured by radioimmunoassay.

Statistical Analysis

Data are expressed as mean±1 SD. Comparisons were made by repeated-measures ANOVA: two within, no between factors. The two factors were treatment (control, a single intake and repeated intake of alcohol) and time of day. To further study treatment or time difference effects, we specified a contrast, and mean comparisons were made after data analysis. Linear regression analysis was performed for the evaluation of relationships between the measured variables. ANCOVA was used when the model contained factors and regressors. Analyses were performed using SUPER ANOVA and STAT VIEW II software (Abacus Concepts Inc), and a value of P<.05 was considered statistically significant.

Results

BP and Heart Rate

Circadian patterns of BP for each day are shown in Fig 1. Both systolic and diastolic pressures (SBPs and DBPs), after a single intake of alcohol and after repeated intake for 7 days, were lower for several hours after drinking compared with those of the control phase. However, BPs from midnight to early morning on day 7 were higher than those in the control phase and on day 1.

As shown in Table 2, averaged 24-hour BP in 14 patients after a single intake of alcohol was significantly lower than that of the control phase and after 7 days of repeated intake of alcohol. Averaged 24-hour BP was not different between the control phase and after 7 days of repeated intake.

During the time from 6 PM to midnight, both SBP and DBP on days 1 and 7 were significantly lower than those of the control phase. BP from midnight to 8 AM was not different between the control phase and single intakes; however, it was significantly higher on day 7 than those of the control phase and day 1. BP from 8 AM to 3 PM was not different among the three periods. Mean BP
FIG 1. Graphs of time course of systolic and diastolic blood pressure and pulse rate during the control phase and days 1 and 7 of the alcohol period in 14 hypertensive patients. ○—○ indicates control period; ●—●, day 1; and ■—■, day 7.

changes by single and repeated intakes of alcohol in individual patients are shown in Fig 2.

Pulse rate was higher for several hours after drinking, during which time BPs decreased on both days 1 and 7 compared with the control phase (Fig 1 and Table 2).

Hemodynamic Findings

Cardiac index 1.5 hours after drinking on days 1 and 7 was significantly greater than that of the control phase (Table 3). Total peripheral resistance 1.5 hours after drinking on both days 1 and 7 was significantly lower than that of the control phase. There was a negative relation between left ventricular end-systolic wall stress and fractional shortening in each measurement \(r=0.60\) to \(0.86, P<0.05\). This relation did not change between each period by ANCOVA.

Biochemical Findings

Urinary excretions of sodium, norepinephrine, and epinephrine were not different among the three periods (Table 4). Plasma norepinephrine and epinephrine at 7 PM on day 1 were higher than those at 7 PM of the control phase, and those at 5 PM on day 1 and 8 AM the next morning (Table 5). Cortisol and insulin after alcohol intake at 7 PM on both days 1 and 7 were lower than those of the control phase. Plasma renin activities at 7 PM on days 1 and 7 were higher than those at 5 PM the same day and 8 AM the next.

Relation Between BP Changes and Other Variables

We compared BP changes caused by alcohol intake with study variables in the 14 subjects and identified several significant correlations. BP change was calculated as the difference from baseline BP (control phase) between the same time periods. The change in SBP during the time 6 PM to midnight caused by a single intake of alcohol correlated negatively with baseline 24-hour averaged SBP \(r=-0.894, P<0.01,\) Fig 3. The change in DBP of this time period also correlated with baseline 24-hour averaged DBP \(r=-0.845, P<0.01\). The change in SBP between 6 PM and midnight caused by repeated intake of alcohol on day 7 correlated with plasma levels of norepinephrine at various times of the control phase and days 1 and 7 \(r=-0.594\) to \(-0.793, P<0.05,\) Fig 4). There was also a correlation between the change in SBP between midnight and 8 AM caused by repeated intake of alcohol on day 7 and plasma levels of norepinephrine at various times of the control phase and days 1 and 7 \(r=-0.577\) to \(-0.732, P<0.05\). As for changes of DBP, there were similar relations between SBP and the variables. There were no correlations between BP changes by single or repeated intakes of alcohol in individual patients.

### Table 2. Effect of Alcohol on Averaged Blood Pressure and Pulse Rate by Time of Measurement

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Day 1</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour</td>
<td>137±4/83±2</td>
<td>130±3*/79±1*</td>
<td>136±4*/83±2†</td>
</tr>
<tr>
<td>6 PM to midnight</td>
<td>139±4/83±2</td>
<td>121±2*/73±1*</td>
<td>126±4*/75±2*</td>
</tr>
<tr>
<td>Midnight to 8 AM</td>
<td>131±4/79±2</td>
<td>129±3/77±1</td>
<td>138±4*/83±2*</td>
</tr>
<tr>
<td>8 AM to 3 PM</td>
<td>140±4/86±3</td>
<td>138±4/84±2</td>
<td>141±51/85±2</td>
</tr>
<tr>
<td><strong>Pulse rate, bpm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour</td>
<td>65±2</td>
<td>68±2*</td>
<td>67±2</td>
</tr>
<tr>
<td>6 PM to midnight</td>
<td>66±2</td>
<td>73±3*</td>
<td>72±2*</td>
</tr>
<tr>
<td>Midnight to 8 AM</td>
<td>59±3</td>
<td>63±2*</td>
<td>60±2</td>
</tr>
<tr>
<td>8 AM to 3 PM</td>
<td>69±2</td>
<td>69±2</td>
<td>69±2</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute. Each variable was compared by repeated-measures ANOVA within two factors model (time and day). Mean comparisons were made by the contrast method.

\*P<0.05 vs control; †P<0.05 vs Day 1.
alcohol and plasma levels of renin, aldosterone, insulin, or cortisol.

BP response was examined with respect to alcohol flush. There were four subjects with alcohol flush. BP reduction during the time from 6 PM to midnight on day 1 was greater in those with alcohol flush than in those without (−26.7±5.0 mm Hg versus −14.4±3.1 mm Hg) but was not significant when ANCOVA was done with the baseline BP as covariate. BP reduction at these hours on day 7 was also greater in those with alcohol flush than in those without (−13.6±1.7 versus −5.4±1.8 mm Hg) and was significantly different when ANCOVA was done with plasma norepinephrine at 5 PM of the control phase as covariate. Average 24-hour BP was not significantly different between the control phase and day 7 in either flushers or nonflushers.

**Discussion**

Although prior studies generally suggest a positive relation between alcohol intake and BP levels, there are many methodological problems in these investigations. For example, the pattern of alcohol use in the interval between last use and BP measurement is often unreported. Findings from epidemiological and earlier studies of BP response to alcohol intake,1-8,18,19 coupled with findings in our previous study,20 prompted us to study the effects of repeated intake of alcohol on 24-hour BP, considering periodic sequencing between alcohol intake and BP measurement. In this study, we found that alcohol had two conspicuously different actions on BP between single and repeated intakes of alcohol. Single intake had only depressor action, but repeated intake had both depressor and pressor ac-

**Table 3. Effects of Alcohol on Hemodynamic Variables at 4:30 PM and 6:30 PM Before and After Alcohol Intake**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Day 1</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MBP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:30 PM</td>
<td>114±6</td>
<td>109±5</td>
<td>112±5</td>
</tr>
<tr>
<td>6:30 PM</td>
<td>111±5</td>
<td>96±4†</td>
<td>92±3†</td>
</tr>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:30 PM</td>
<td>60±4</td>
<td>60±3</td>
<td>59±3</td>
</tr>
<tr>
<td>6:30 PM</td>
<td>64±3</td>
<td>70±5*†</td>
<td>71±4*†</td>
</tr>
<tr>
<td><strong>Cardiac index, L · min⁻¹ · m⁻²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:30 PM</td>
<td>2.9±0.2</td>
<td>2.9±0.2</td>
<td>3.0±0.2</td>
</tr>
<tr>
<td>6:30 PM</td>
<td>3.1±0.2</td>
<td>3.4±0.2*†</td>
<td>3.4±0.2*†</td>
</tr>
<tr>
<td><strong>TPR, dyne · s · cm⁻⁵</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:30 PM</td>
<td>1809±115</td>
<td>1783±158</td>
<td>1790±154</td>
</tr>
<tr>
<td>6:30 PM</td>
<td>1658±95</td>
<td>1313±72*†</td>
<td>1249±65*†</td>
</tr>
</tbody>
</table>

MBP indicates mean blood pressure; bpm, beats per minute; and TPR, total peripheral resistance. Each variable was compared by repeated-measures ANOVA within two factors model (time and day). Mean comparisons were made by the contrast method. *P<.05 vs control; †P<.05 vs 4:30 PM.
TABLE 4. Urinary Excretion of Sodium, Norepinephrine, and Epinephrine on Control Day and Days 1 and 7 of Alcohol Phase

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Day 1</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNaV, mEq/d</td>
<td>177 ± 23</td>
<td>180 ± 28</td>
<td>178 ± 24</td>
</tr>
<tr>
<td>Norepinephrine, μg/d</td>
<td>81.0 ± 8.8</td>
<td>92.2 ± 5.8</td>
<td>85.4 ± 7.4</td>
</tr>
<tr>
<td>Epinephrine, μg/d</td>
<td>8.4 ± 0.9</td>
<td>7.9 ± 1.2</td>
<td>7.9 ± 0.9</td>
</tr>
</tbody>
</table>

UNaV indicates urinary sodium excretion. There were no differences between treatments in each variable by repeated-measures ANOVA.

Depressor Action of Alcohol

A single intake of alcohol decreased BP for several hours after alcohol intake, and 24-hour BPs were lower than that of the control phase in habitual drinkers with essential hypertension. These findings are consistent with our previous studies and those reported by Howes and Reid. There was also a depressor action in repeated intakes of alcohol for several hours after alcohol ingestion as well as in single intakes. However, the depressor response found in repeated intakes was somewhat attenuated compared with single intakes. The degree of BP reduction by single intakes correlated with the baseline BP, that is, the higher the baseline BP, the greater the BP reduction.

The depressor action mechanism of repeated alcohol intake is considered a direct vasodilation, because total

TABLE 5. Changes in Neurohormonal Variables in Plasma at 5 PM and 7 PM Before and After Alcohol Intake and at 8 AM Before Breakfast the Next Morning

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Day 1</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>373 ± 49</td>
<td>339 ± 51*</td>
<td>361 ± 37</td>
</tr>
<tr>
<td>5 PM</td>
<td>344 ± 56</td>
<td>449 ± 62‡</td>
<td>435 ± 51</td>
</tr>
<tr>
<td>7 PM</td>
<td>299 ± 36‡‡</td>
<td>280 ± 46§§</td>
<td>312 ± 40§</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>24 ± 6</td>
<td>63 ± 31†‡</td>
<td>44 ± 19</td>
</tr>
<tr>
<td>5 PM</td>
<td>25 ± 4</td>
<td>22 ± 7§</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>7 PM</td>
<td>24 ± 4</td>
<td>63 ± 31†‡</td>
<td>44 ± 19</td>
</tr>
<tr>
<td>Cortisol, mg/mL</td>
<td>6.2 ± 0.6</td>
<td>5.5 ± 0.6</td>
<td>5.6 ± 0.4</td>
</tr>
<tr>
<td>5 PM</td>
<td>6.4 ± 1.0</td>
<td>3.8 ± 1.6*</td>
<td>3.8 ± 0.6*</td>
</tr>
<tr>
<td>7 PM</td>
<td>11.1 ± 0.6‡‡</td>
<td>10.0 ± 0.9$</td>
<td>11.0 ± 0.7$</td>
</tr>
<tr>
<td>8 AM</td>
<td>7.8 ± 0.7</td>
<td>9.0 ± 1.0</td>
<td>8.1 ± 0.8</td>
</tr>
<tr>
<td>Insulin, mU/mL</td>
<td>73.6 ± 11.4‡</td>
<td>47.8 ± 6.9‡‡</td>
<td>45.1 ± 3.3‡‡</td>
</tr>
<tr>
<td>5 PM</td>
<td>6.5 ± 0.7$</td>
<td>5.2 ± 0.5$</td>
<td>5.7 ± 0.7$</td>
</tr>
<tr>
<td>7 PM</td>
<td>1.2 ± 0.4</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>8 AM</td>
<td>1.4 ± 0.3</td>
<td>2.2 ± 0.7‡‡</td>
<td>1.6 ± 0.5‡‡</td>
</tr>
<tr>
<td>PRA ng/mL per hour</td>
<td>1.1 ± 0.9</td>
<td>1.4 ± 0.3§</td>
<td>1.1 ± 0.2§</td>
</tr>
<tr>
<td>5 PM</td>
<td>5.7 ± 0.7</td>
<td>6.3 ± 1.4</td>
<td>4.3 ± 0.6†</td>
</tr>
<tr>
<td>7 PM</td>
<td>4.6 ± 0.6</td>
<td>3.3 ± 0.5‡</td>
<td>3.6 ± 0.5</td>
</tr>
<tr>
<td>8 AM</td>
<td>7.0 ± 0.9$</td>
<td>6.2 ± 0.8§</td>
<td>5.9 ± 0.8§</td>
</tr>
</tbody>
</table>

PRA indicates plasma renin activity. Each variable was compared by repeated-measures ANOVA within two factors model (time and day). Mean comparisons were made by the contrast method.

*P < .05 vs control; †P < .05 vs day 1; ‡P < .05 vs 5 PM; §P < .05 vs 7 PM.
Pressor Action of Alcohol

Repeated intake of alcohol for 7 days increased BP for several hours after 6 hours since the last drink. This indicates that a double condition is needed for alcohol to start an increase of BP: first, continuous drink for several days or more and second, timed BP measurement since the last drink. The importance of the rise in BP after repeated intake of alcohol is best appreciated when comparisons are made with earlier studies.

Puddey et al.29,30 studied the effects of withdrawal and resumption of alcohol on BP in treated hypertensive and normotensive subjects. BP measurement times were not recorded, and the fall and rise in BP occurred within 2 to 3 weeks after reduction of alcohol intake or resumption of normal drinking habits. Potter and Beevers31 reported that it took at least 48 hours for BP to start to increase after alcohol consumption was re-started. Maheswaran et al.31 have suggested that the effect of alcohol on BP appears to be predominantly due to alcohol consumed in the few days immediately preceding BP measurement, with alcohol consumption before those few days exerting little effect on BP. Results of these and our studies indicate that pressor effects of alcohol appear after at least a few days of repeated intake.

For alcohol to raise BP several hours after the last drink, a second condition was needed. Howes and Reid32 also studied the effects of moderate consumption of alcohol for several days on BP, relating it to sympathetic activity in normotensive volunteers. Alcohol was taken between 5 PM and midnight and supine BPs were measured several times from 9:30 AM to 4 PM. They found a mean 3.0 mm Hg rise of daytime SBP and 3.1 mm Hg in DBP; however, BPs for several hours after alcohol intake were not measured. Wallace et al.33 compared men with chronic alcohol use who were denied alcohol use in the 24 hours before the study with men who drank alcohol within the 24 hours. The mean SBP and DBP were 2 to 3 mm Hg higher than in those with reported alcohol use on the day before the study. They also showed that alcohol consumed in the 24 hours before the study was more strongly associated with elevated BP than alcohol consumed in the week before the study excluding the previous 24 hours.34 These studies suggest that drinking patterns and intervals between the last alcohol use and pressure measurements are important.

Experimentally, chronic alcohol intake was not always associated with an increase of BP. Rather, hypotensive and antihypertensive actions were seen in spontaneously hypertensive rats and normotensive rats.35 However, Crandall et al.36 succeeded in making Sprague-Dawley rats hypertensive with twice-daily intermittent drinks of ethanol. They found normotensive BP at peak blood alcohol levels; however, they found a hypertensive response 24 hours after the final drink. These experiments also suggest that critical time intervals since the “last drink” are needed for alcohol to raise BP.

There are several possible explanations for BP increases caused by alcohol.37 These include a direct action on the central nervous system by an interference of central inhibitory pathways controlling the vasomotor center, increased sympathetic activity, alcohol-induced Cushing's syndrome, activation of the renin-angiotensin

peripheral resistance decreased along with a reduction of BP as is found in single intakes of alcohol. In the present study, increased cardiac output associated with the decrease of BP after ethanol is in line with previous work showing decreased peripheral resistance20,27 and vasodilation.20 After 7 days of repeated intake, there was no change in cardiac contractility assessed by the relation between fractional shortening and end-systolic wall stress. Therefore, the depressor action of alcohol was not attributable to the negative inotropic action of alcohol.

There is a possibility that depressor action is a limited finding in Orientals who exhibit flushing. Kupari et al.27 compared the responses of BP to low doses of acute alcohol intake between Finnish and Japanese who were normotensive. In the five Japanese subjects, postdrinking facial flush was associated with elevated blood acetaldehyde, marked BP reduction, and tachycardia. Although other Japanese and Finnish without facial flush had no detectable acetaldehyde in the blood and fewer hemodynamic changes, alterations were similar in direction. Our subjects all had drinking habits and hypertension; no subjects developed hangover symptoms. BP reduction after alcohol intake was greater in the subjects with alcohol flush than in those without. However, BP reduction after alcohol on days 1 and 7 was significant even in the subjects without flushing.

FIG 4. Scatterplots. Top, A negative relation between plasma norepinephrine concentration at 5 PM (1700 hours) of control phase and change in systolic blood pressure on day 7 (r = -0.621, P < 0.05). Bottom, A negative relation between plasma norepinephrine concentration at 5 PM (1700 hours) of control phase and change in systolic blood pressure on day 7 (r = -0.672, P < 0.05).
system, volume expansion as a result of excessive corticosteroid and mineralocorticoid production, increase of calcium in the vascular smooth muscle cells, magnesium deficiency, ingestion of excessive amounts of salt, psychosocial factors, caloric content, and withdrawal from alcohol.

From our data, increase of BP is not related to plasma renin activity or plasma levels of aldosterone, cortisol, insulin, or increased intake of salt. Instead, plasma levels of norepinephrine and epinephrine in various conditions independently and negatively correlated with the increase of BP. According to pulse rate estimated by BP recorder, sympathetic activation seems unlikely, because pulse rates did not increase as much as BPs in the early morning hours of our study. Even though the time of blood sampling at 8 AM was almost the tail period when the pressor action of alcohol was seen, plasma levels of norepinephrine and epinephrine at 8 AM on day 7 did not increase compared with those of the control phase. Urinary excretion of norepinephrine and epinephrine was comparable between the control phase and day 7. Therefore, sympathetic overactivity is considered not to be involved in the genesis of BP increase in repeated intake, as is found in alcohol withdrawal syndrome.

Negative correlation between baseline plasma levels of norepinephrine and an increase of BP by alcohol is hard to explain. One possible explanation is that the vascular reactivity to norepinephrine may be sensitized, hence, a subtle increase of norepinephrine may be sensitive enough to raise BP.

Experimentally, Altura and Altura described studies in rats in which chronic alcohol consumption appears to convert the acute vasodilator effect of ethanol into a constrictor response, and they suggest that the effects of circulating neurohumoral vasoconstrictor substances are potentiated by an alcohol-induced accumulation of calcium in vascular smooth muscle cells. Criscione et al studied the effect of ethanol infusion on vasoconstrictor response to norepinephrine in isolated rat mesenteric artery. They found that alcohol has a dual effect on the vascular system. An infusion of ethanol caused concentration-related inhibition of norepinephrine-induced vasoconstriction. Interestingly, however, 1 hour after the end of the infusion, the vasoconstricting effects of norepinephrine were potentiated. This seems analogous to the biphasic action of repeated intake of alcohol, depressor response followed by pressor response, in this study. They also suggest that the potentiation of vasoconstrictor response by norepinephrine might be due to the suppression of endothelium-dependent relaxation by ethanol.

Therefore, our and other studies indicate that alcohol withdrawal plays an important role, but not a straightforward action, in the pressor effect of alcohol. However, there also may be other “slow pressor” mechanisms, since the 24-hour blood pressure pattern on day 7 of the alcohol phase seemed to be elevated in parallel compared with that on day 1 in our study.

Effects of Alcohol on 24-Hour BP

In the present study, repeated alcohol intake for 1 week did not change average 24-hour BP, although it raised BP in the early morning and lowered it in the evening hours. Our results suggest that the hypertensive effect of alcohol has been overestimated, since earlier studies depended on casual BP measurement.

The amount of daily alcohol consumption was 1 mL/kg in our study. This dose has been shown to elevate SBP by 5 to 6 mm Hg in epidemiological studies. It should be mentioned that we observed a similar increase in early morning BP on day 7 of the alcohol phase. The failure of alcohol to raise 24-hour BP might be attributed to the relatively short intervention period. However, we often experience that alcohol acutely lowers BP in habitual drinkers who have been consuming alcohol for many years. In our recent randomized crossover study, average 24-hour BP was similar between the 1-month alcohol period and the control period in hypertensive patients.

The effect of alcohol on 24-hour BP may not be the same among various ethnic groups. It is possible that profound acute hypotension may offset the chronic pressor effect of alcohol in subjects with alcohol flush. However, average 24-hour BP at the end of the alcohol phase did not change in either flushers or nonflushers in this study. The results of our study also might be influenced by various factors such as hospitalization, prior discontinuation of alcohol, and antihypertensive medication. We measured BP five times a day (from 6 AM to 9 PM) throughout the control phase, alcohol phase, and recovery phase (3 days) as a branch of the present study. Since average BPs at the end of each period were similar, these factors do not appear to modify the time course of BP.

Circadian variation of BP is known to be modified by physical and mental activities. A major feature of the 24-hour BP profile is a substantial lowering of BP during sleep. Individual profiles, however, can diverge widely, with some patients showing greater nocturnal fall of blood pressure compared with daytime (dippers) and others showing negligible changes (nondippers). Our findings in this study suggest that BP circadian patterns, especially sleep BP, are influenced by alcohol intake. Moreover, the rise in morning BP can also be increased. In evaluation of circadian patterns of BP, therefore, it is important to know whether the subjects drank and the time they drank.

Although alcohol intake was thought to elevate BP, epidemiological studies have shown that alcohol has protective effects against coronary artery disease. Increased high-density lipoprotein cholesterol level, decreased platelet aggregation, and possible effects on other clotting factors could account for the reduced risk of coronary artery disease among drinkers. Criqui and Langer showed that an alcohol-induced increase in BP had a noxious effect on coronary heart disease, although such effect was small compared with the protection offered by favorable changes in lipoproteins. Since our results do not support a pressor effect of alcohol for 24 hours, the deleterious effects of alcohol-induced hypertension may be less than expected. However, regular alcohol intake appears to augment not only the morning BP rise but also the nocturnal hypotension. This changing pattern of circadian blood pressure may influence the onset of cardiovascular diseases.

We conclude that chronic alcohol intake has both depressor and pressor effects depending on the time interval since the last drink and that the chronic effects of alcohol on BP may be overestimated when based on
casual BP measurements alone. It is important to ascertain how many hours it has been since the last drink when BP is measured.

References


Biphasic effects of repeated alcohol intake on 24-hour blood pressure in hypertensive patients.

H Abe, Y Kawano, S Kojima, T Ashida, M Kuramochi, H Matsuoka and T Omae

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