

# Alcohol and Hypertension: Epidemiologic and Experimental Considerations

## The Lipid Research Clinics Program

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**SUMMARY** Most epidemiologic studies suggest that alcohol consumption is associated with increased blood pressure levels and an increased prevalence of hypertension. A review of experimental studies of the blood pressure effects of acute alcohol administration to man and acute and chronic administration to animals does not clearly support the epidemiologic findings, which suggests that other direct or indirect factors besides a simple pharmacologic effect of alcohol may be operative. Several endocrine and renal mechanisms have been postulated, and indirect factors related to both alcohol use and blood pressure pathogenesis cannot be firmly excluded. Preliminary data from the Lipid Research Clinics (LRC) population studies generally show a positive association between alcohol and blood pressure, although women and young men reporting no alcohol use had higher systolic pressures than those reporting low levels of alcohol intake. LRC findings also suggest that the blood pressure elevations associated with use of oral contraceptives appear to be independent of those associated with alcohol. Some preliminary epidemiologic findings and circumstantial evidence suggest that the alcohol-blood pressure relationship may be due in part to the timing of blood pressure measurement during physiologic alcohol withdrawal. Although further verification is needed, this hypothesis implies that the pattern of alcohol consumption and the interval between last use and blood pressure measurement may be as important as the amount of alcohol consumed in explaining the relationship between alcohol and blood pressure.

THE IMPACT of alcohol use on community health has led to considerable research of alcohol's effect on cardiovascular physiology and disease. In this report we review experimental and epidemiologic evidence that links alcohol consumption to blood pressure elevation, with or without chronic hypertension. We also report preliminary findings from the Lipid

Research Clinics (LRC) population studies and suggest some directions for future research. As noted in recent reviews of this topic,<sup>1, 2</sup> the volume of information is enormous and only selected areas can be considered.

### Prior Research in Alcohol and Hypertension Epidemiologic Studies

Observational or nonexperimental studies in community, industrial, clinical and other institutional populations offer substantial evidence of an association between alcohol use and hypertension. Tables 1 and 2 summarize the findings of several studies that explore this association. Most contrasted blood pressure levels with reported alcohol consumption in cross-sectional fashion. Table 1 reviews studies that reported mean blood pressure levels according to alcohol use categories. "Higher" alcohol use was associated with blood pressure elevations of 1.6–10.9 mm Hg. When a dose response was sought, the subjects with

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TABLE 1. *The Relationship of Alcohol Use to Blood Pressure in Representative Epidemiologic Studies*

Subjects	Comparison groups	Blood pressure difference (mm Hg)*		Dose-response relationship
		Systolic	Diastolic	
U.S. civil service workers <sup>3</sup>	Regular ethanol use ≥ 3 days/week vs < 3 days/week	1.9	1.6	No
English executives <sup>4</sup>	≥ 6 drinks/day vs ≤ 2 drinks/day	4.3	3.2	Yes
People's Gas Co. employees <sup>5</sup>	Problem drinkers vs Non-problem drinkers	8.5	4.7	No
Western Electric employees <sup>5</sup>	≥ 5 drinks/day vs < 5 drinks/day	9.7	5.9	Yes
Swedish twin pairs <sup>6</sup>	Twin pairs discordant for alcohol intake	7.1	4.4	Yes
Danish workers <sup>7</sup>	6-10 units/day vs 0 units/day	8.1	4.8	Yes
Prepaid group enrollees <sup>8</sup>	≥ 6 drinks/day	♂ 10.9	4.5	Yes
	0 drinks/day	♀ 5.4	2.1	

\*High-intake group minus low-intake group.

the highest alcohol intake had the highest pressures; systolic pressure increases were nearly always greater than diastolic increases. Most of the studies summarized in table 1 adjusted for differences in age and ponderosity between the high-intake and low-intake groups. These adjustments generally had little effect on the differences in blood pressure levels between the comparison groups. The Framingham cohort<sup>9</sup> showed a mean arterial pressure increase of 7 mm Hg in the heaviest alcohol users compared with all others in the cohort, but no dose-response relationship was found at lower levels of use.

In the studies reviewed in table 2, the association between alcohol and blood pressure was expressed as the relative prevalence of defined hypertension in various usage categories. The prevalence ratios were 1.6-2.4 times greater in the "heavier" or "problem" drinkers compared with various control groups reporting lesser or no alcohol use.

The studies cited in tables 1 and 2 were performed in ambulatory, noninstitutional populations and overwhelmingly support the association between alcohol use and elevated blood pressures. Studies of populations from inpatient units for the management of

TABLE 2. *The Relationship of Alcohol Use to Prevalence of Hypertension in Epidemiologic Studies*

Subjects	Comparison groups	Definition of hypertension (mm Hg)	Prevalence ratio of hypertension (heavy users/light users)
DuPont Company employees <sup>10</sup>	Problem drinkers vs matched non-problem drinkers	BP > 160/95	2.3
Prepaid group enrollees <sup>8</sup>	Heavy drinkers vs nondrinkers	BP ≥ 160/95	2.4 white males 1.8 white females 1.5 black males 1.6 black females
People's Gas Co. employees <sup>5</sup>	Problem drinkers vs non-problem drinkers	BP ≥ 160/95	1.6
Western Electric employees <sup>5</sup>	Heavy drinkers vs non-heavy drinkers	BP ≥ 160/95	1.8
Framingham cohort <sup>11</sup>	Heavy drinkers vs light drinkers	BP > 160/95	2.0

Abbreviation: BP = blood pressure.

alcoholism and alcohol-related diseases are not as consistent. At least four studies have found the prevalence of hypertension no higher in alcohol addicts than among other institutional control subjects.<sup>12-16</sup> Yet, the association between alcohol and blood pressure is supported when less direct approaches are used in clinical populations. Under the assumption that abnormal serum liver function tests (LFTs) were an index of alcohol use, Ramsey<sup>16</sup> found a higher-than-expected prevalence of LFT abnormalities among hypertensives than among normotensives in a clinic setting. Beevers<sup>17</sup> also found a higher prevalence of LFT abnormalities among hypertensives, which suggested a possible role for alcohol. Another epidemiologic approach to the alcohol-blood pressure question has been to relate alcohol use or alcoholism to morbidity and mortality rates from hypertension-related diseases such as stroke or myocardial infarction. Such studies have yielded conflicting results and are not considered here.

Though prior studies generally suggest a positive association between alcohol intake and blood pressure levels, there are many potential methodologic problems in these observational investigations. Most of the studies cited were not designed solely to examine the relationship between alcohol and blood pressure and may not have explored the issues fully. Reported alcohol use may be quite inaccurate. Studies are difficult to compare because of differences in questionnaire design, categories of alcohol use, and definitions of alcohol addicts, problem drinkers and hypertension. Various alcoholic beverages are usually considered together, though their individual effects might vary. Related variables possibly relevant to hypertension, such as salt intake, medication use and exercise, are often unavailable. Problems with intrapersonal blood pressure fluctuation and observer standardization and variation are often not considered. Particularly in the clinical studies, blood pressure recorders may not be blinded to the alcohol-use status of study subjects. The environments in which pressures are recorded may vary; measurements may be taken contiguous to such stressful activities as venipuncture. Further, pressures recorded in the quiet institutional setting with prolonged bed rest may be different from those in the ambulatory setting. Institutional studies may contain many subjects with chronic illness, possibly affecting results. Finally, the pattern of alcohol use in the interval between last use and blood pressure measurement is often unreported.

#### Experimental Studies in Man and Animals

A review of experimental studies relating alcohol use to elevated blood pressures would appear useful, but the physiologic and pharmacologic effects of alcohol are diverse. Alcohol affects many target organs with a role in blood pressure regulation, including the heart, peripheral vasculature, liver, bone marrow and central nervous system.<sup>18</sup> Further, alcohol's effects may depend on whether these organ systems are healthy or diseased. A review of represen-

tative experimental studies addressing the effects of alcohol on blood pressure reveals acute studies in humans and both acute and chronic studies in animals.

There are several experimental studies on the acute effects of alcohol administration on blood pressure in humans.<sup>19-26</sup> The results are inconsistent: Some studies show a relative decrease<sup>19, 21, 22, 24</sup> and others show a relative increase<sup>23, 25</sup> or no change in blood pressure measured before and after alcohol use. Statistically significant blood pressure alterations were observed in only two studies: One showed an increase<sup>23</sup> and the other showed a decrease.<sup>24</sup>

There are several reasons for these inconsistencies. Study subjects vary in age, ethnic group and prior drinking habits. Some have chronic liver or cardiovascular disease or other chronic illness. Alcohol doses differ, as do the rate and route of alcohol administration. Blood pressure measurement intervals vary from minutes to hours. The numbers of subjects are often small, limiting the statistical power of the experiments to detect small alterations in blood pressure. Finally, because study subjects cannot be readily blinded to oral alcohol administration, the impact of psychic factors on blood pressure cannot be excluded. These problems make it impossible to clearly define the true effect of acute alcohol use on blood pressure in man.

Many methodologic problems in interpreting acute human alcohol consumption studies might be obviated in animal experiments. We found four experimental studies in dogs in which alcohol consumption and acute alterations in blood pressure were compared. Alcohol was administered by gastric tube in two studies<sup>27, 28</sup> and intravenously in the other two.<sup>29, 30</sup> Comparisons of mean arterial blood pressures before and after alcohol consumption showed small differences of -1 and 3 mm Hg in dogs fed by gastric tube and larger differences of 7 and 25 mm Hg in those fed intravenously. These discrepant results are unexplained. Obviously, the intragastric experiments more closely resemble human use. Unlike the studies in dogs, human studies in which alcohol was administered intravenously showed no pressure increase.<sup>19-21</sup>

We could find only a few experimental animal studies exploring chronic alcohol consumption and blood pressure. Maines and Aldinger<sup>31</sup> administered 25% ethanol by volume in water ad libitum to rats over a 4-month period. Mean aortic blood pressure decreased. Regan et al.<sup>32</sup> gave an average of 3.1 g of ethanol/kg/day for 9-22 months to seven dogs and found a 5-mm Hg increase in mean aortic blood pressure compared with controls. In another study of 14 dogs by Pachinger et al.,<sup>33</sup> mean aortic blood pressure increased 4 mm Hg after oral consumption of 400 ml of 25% ethanol per day for 14 weeks. In these latter two studies, alcohol was withheld for 1-2 days before blood pressure measurement, possibly indicating that the relative increases seen were a reflection of alcohol withdrawal rather than a direct effect of alcohol.

Findings from the acute and chronic experiments in

animals are difficult to reconcile. There is variation in dose and route of alcohol administration, interspecies variation in pharmacologic response and the presence of barbiturate anesthesia during pressure measurements. Further, the relevance of physiologic responses in animals to those in humans remains problematic.

Even acknowledging the difficulties in evaluating the experimental studies, we feel they do not clearly support the epidemiologic findings. The acute human studies provide scant support of a positive association between alcohol use and blood pressure elevations and the acute animal studies are at best only partially supportive. Finally, the chronic animal studies hint at a possible positive association between alcohol and blood pressure elevation, but blood pressures were measured during the period of alcohol withdrawal.

#### Interpreting the Relationship Between Alcohol and Blood Pressure

In whatever manner the results of experimental alcohol administration are interpreted, the nature of the relationship to blood pressure seen in most epidemiologic studies awaits physiologic explanation. If this relationship is causal, more than one mechanism is probably involved. Alcohol appears to raise blood cortisol levels.<sup>34</sup> A reversible, alcohol-induced Cushing's syndrome with concomitant blood pressure elevation has been described.<sup>35</sup> Alcohol also increases the excretion of urinary catecholamines and their metabolites during experimental administration,<sup>36</sup> possibly leading to elevated blood pressure and arrhythmias.<sup>37</sup> An effect of alcohol on the renin-angiotensin system, possibly related also to vitamin B<sub>6</sub> deficiency, has also been postulated.<sup>38</sup> Plasma vasopressin, renin activity and aldosterone levels have been reported to be increased during and after alcohol administration.<sup>39</sup> Clearly, these various pharmacologic effects of alcohol on blood pressure regulation indicate the need for further study in this area.

Despite these suggested physiologic abnormalities, several authors legitimately contend that the association between alcohol and hypertension in population studies is real but not necessarily causal. Several "confounding" factors have been postulated, including psychosocial stress, exercise, smoking or drug habits, ponderosity and dietary intake of coffee and salt. Klatsky et al.<sup>8</sup> found that adjusting blood pressures for differential ponderosity, smoking habits, coffee consumption and social class did not alter the association between the alcohol and blood pressure. Other factors have not been systematically evaluated. Possibly relevant to this issue is the finding that upon completion of a clinical alcohol withdrawal program, blood pressure levels in nearly all alcoholic hypertensives return to the normal range,<sup>40</sup> suggesting that alcohol-associated hypertension is not necessarily fixed and that the above-mentioned indirect factors, which may presumably still be operative, cannot provide a full explanation.

Alcohol use may be related to blood pressure levels

in other indirect ways. Alcohol-induced liver disease may alter the clearance of blood metabolites involved in pressure regulation. With the accumulating evidence that some types of alcoholism (as opposed to alcohol use) may be familial,<sup>41</sup> it is possible that common or linked genetic factors could be related to both excessive alcohol use and clinical hypertension. One experimental study revealed that blood acetaldehyde levels were higher after alcohol administration in young healthy males with alcoholic parents or siblings than in others without such a family history.<sup>42</sup>

#### The Withdrawal Hypothesis

Several investigators have suggested that the association between alcohol and blood pressure may be related to the temporal sequence of alcohol use and blood pressure measurement. Simply stated, during the period of alcohol withdrawal, the severity of which is probably related to the extent of prior alcohol intake, there is excess central nervous system excitability and adrenergic discharge, which increase blood pressures transiently until withdrawal is complete. Many community studies require an overnight or 12-hour fasting period, during which alcohol withdrawal, albeit subclinical, may be occurring. Similarly, patients may diminish alcohol intake before visiting a clinic or a physician.<sup>1</sup> Thus, blood pressure elevations can be directly related not only to the amount of alcohol consumed, but also to the pattern of consumption and the interval between last alcohol use and blood pressure measurement.

Considering the diverse physiologic effects of alcohol, this hypothesis probably could not explain the entire association, but a volume of circumstantial evidence makes it attractive in our view. As discussed above, the short-term experimental evidence does not clearly suggest that alcohol causes a consistent pharmacologic elevation in blood pressure. Urinary excretion of epinephrine is greater during withdrawal than during alcohol administration,<sup>36</sup> and plasma norepinephrine levels are highest 13-24 hours after alcohol cessation.<sup>43</sup> Epidemiologic studies almost uniformly show greater elevation of systolic than diastolic pressure, consistent with an adrenergic mechanism. The prevalence of hypertension seen on admission to alcohol detoxification programs may decline after a few days of abstinence, even without pharmacologic intervention,<sup>40</sup> which suggests that the hypertensive effects are transient. In the few chronic animal studies that suggest a positive relationship between alcohol and blood pressure, pressures were measured 1-2 days after alcohol cessation. Mendelson and Mello<sup>41</sup> reported that the withdrawal syndrome may occur after a relative decrease in blood alcohol levels, not necessarily requiring their total elimination. This finding further suggests that the pattern of drinking can be as important as the total or average amount consumed. The withdrawal hypothesis has not, to our knowledge, been directly tested experimentally.

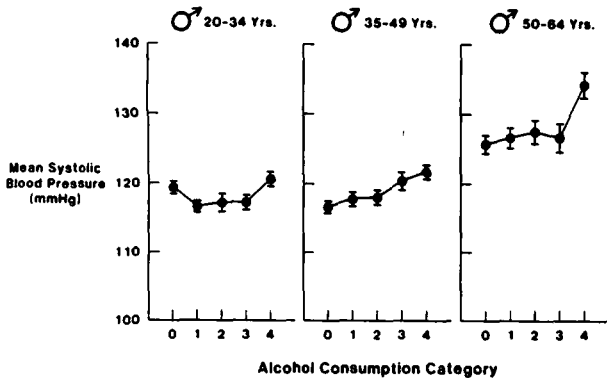


FIGURE 1. Systolic blood pressures in males according to age and alcohol consumption category (0 = none; 1 = < 10 g/day; 2 = 10 to < 20 g/day; 3 = 20 to < 30 g/day; 4 =  $\geq$  30 g/day). Each age/alcohol-use category includes at least 50 subjects. Values are mean  $\pm$  SEM.

### Findings From the LRC Program Population Studies

The LRC population studies include an exploration of the relationship between alcohol use and blood pressure levels as part of a larger study of atherosclerosis risk factors.<sup>44</sup> Blood pressures were measured by trained observers in over 6000 adults from 10 North American study populations using random-zero manometers. Measurements were made in the sitting position in the morning hours after an overnight fast.

We first explored the overall relation of blood pressure to reported alcohol intake. Figures 1 and 2 show preliminary findings of mean systolic blood pressure levels according to reported alcohol consumption in three age strata of white men and women. Subjects reporting current oral contraceptive use were excluded from this analysis. Mean pressures were not adjusted for differences in ponderosity or related variables, which may differ among the alcohol-use categories.

Our findings were generally in keeping with the earlier population studies described in tables 1 and 2:

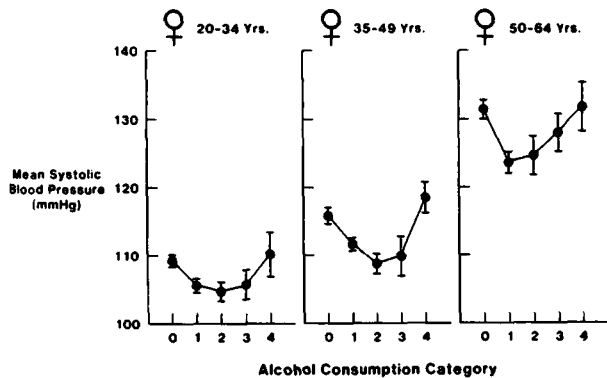


FIGURE 2. Systolic blood pressures in females according to age and alcohol consumption category (see legend to figure 1). Each age/alcohol-use category includes at least 30 subjects. Values are mean  $\pm$  SEM.

Mean systolic blood pressure levels increased with increasing levels of reported alcohol use. However, in all three female age categories (and in the youngest male category), subjects who reported no alcohol consumption had mean levels higher than those reporting minimal or moderate use. This remains unexplained, but has been observed in women in one other population study.<sup>8</sup> One possible explanation is that the category of subjects reporting no alcohol use contains some heavy alcohol users who totally deny such use, a phenomenon that is well documented.<sup>45</sup> The prevalence of other blood pressure correlates, such<sup>2</sup> as obesity, may vary among the alcohol-use categories and provide alternate explanations. Even though the highest systolic pressure levels were observed in those reporting the highest alcohol use, the majority of our female subjects reported low or moderate alcohol use. Thus, overall, women who report alcohol use actually had a lower mean systolic pressure than those who do not report alcohol use. Findings were similar for the association between alcohol use and diastolic pressure in the LRC population (data not shown).

There is considerable evidence that use of oral contraceptives is associated with blood pressure elevation, though the mechanism is unclear.<sup>46, 47</sup> Because oral contraceptives are commonly used, we examined blood pressure levels among white women according to use of both alcohol and oral contraceptives. Figure 3 shows preliminary results for subjects 20-29 years of age. We found no systematic alteration in diastolic pressures associated with use of oral contraceptives, either alone or combined with alcohol, and only findings for systolic pressures are presented. These mean pressures are standardized for differences in ponderosity, cigarette use, and educational attainment among the various study categories. In the absence of reported alcohol use, those taking oral contraceptives had a mean systolic pressure 2.4 mm Hg higher than those not taking them ( $p < 0.001$ ). In the presence of any reported alcohol use, this systolic pressure differential between oral contraceptive users and non-

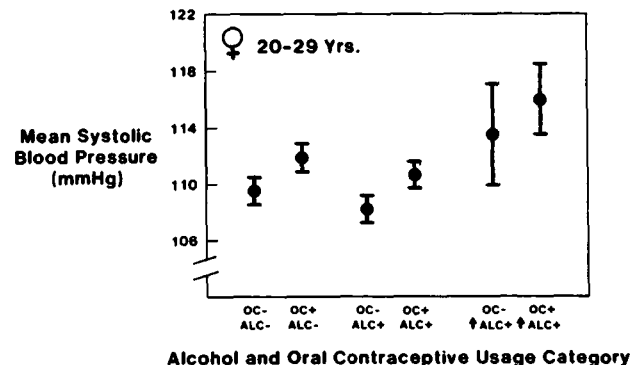


FIGURE 3. Systolic blood pressures in females ages 20-29 years according to alcohol/oral contraceptive (OC) use category. ALC = alcohol; + = reported use; - = reported nonuse;  $\uparrow$ ALC = subjects in highest alcohol-use category ( $\geq$  30 g/day). Values are mean  $\pm$  SEM.

users remained, as it did among those in the highest alcohol consumption category. Thus, it appears that in our populations, use of oral contraceptives exerted an effect on systolic blood pressure independent of that associated with alcohol consumption.

We have also addressed the withdrawal hypothesis using data from the Iowa LRC population study. In the LRC study, personal alcohol use was measured in two ways: estimating average weekly alcohol consumption and a 24-hour dietary recall, which included alcohol intake in that period immediately before the morning of study. From the Iowa LRC analysis file, we identified 47 males in the upper quartile of reported chronic alcohol use who denied such use in the 24 hours before the study and compared them with 61 men, also in the upper quartile, who reported some alcohol use in the previous 24 hours. These two groups had equivalent mean grams per day of overall alcohol use and were similar with respect to mean age and relative weight. The mean systolic and diastolic pressures were 2–3 mm Hg higher in those reporting alcohol use on the day before study, though these findings are not significant at the 5% level (fig. 4). If one assumes, based on experimental evidence, that alcohol does not have a direct and immediate pharmacologic effect on blood pressure, these data at least raise the possibility that subjects taking alcohol on the day before study may be in a state of physiologic withdrawal. Clearly, more experimental verification is needed.

### Conclusions

The relationship between alcohol use and blood pressure is complex at all levels: experimental, clinical and epidemiologic. The positive association seen in community studies is consistent and replicable. Such studies need not be repeated unless new causal hypotheses are generated and tested. However, more clinical research is clearly needed to define the exact nature of blood pressure response to acute alcohol administration and relevant physiologic mechanisms,

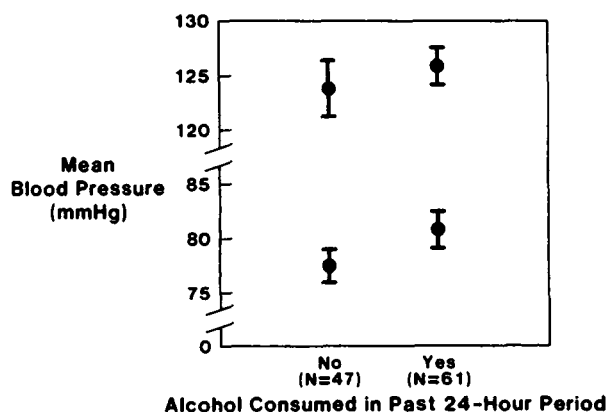


FIGURE 4. Systolic and diastolic blood pressures in males in the upper quartile of alcohol use, according to alcohol consumption in the 24 hours before the study. Values are mean  $\pm$  SEM.

and the studies should be extended for more than the first few hours after the alcohol dose. It should be determined whether the pharmacologic response to alcohol differs according to the presence or absence of cardiovascular disease. Further pathophysiologic study in chronic animal preparations might add considerable insight to the issue.

The withdrawal hypothesis is testable, and if it is at least partly correct, several implications emerge. First, in future studies of alcohol's relationship to blood pressure, drinking patterns and the interval between last alcohol use and pressure determination should be recorded. This could considerably clarify the nature of the relationship as currently understood, and should also be considered for studies relating alcohol use to cardiovascular morbidity and mortality. Second, the clinician evaluating a potentially hypertensive patient should take a detailed history of patterns of alcohol use, particularly in the 48-hour period before the visit, to determine hypertension reversibility and to evaluate the response to therapy. Intercurrent alcohol use may be an important element in evaluating the efficacy of antihypertensive agents in clinical trials. Finally, the hypothesis may have relevance to the investigational relationship of alcohol to other aspects of human physiology, such as lipid metabolism or glucose tolerance. For example, blood lipid and lipoprotein levels may also vary according to the interval since last alcohol use.

It appears that the effect of alcohol on one organ system cannot be evaluated without knowing the health status of and effects upon all the others. Appropriately designed studies could answer some of the questions raised in this presentation.

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