Lipoproteins and Blood Pressure as Biological Pathways for Effect of Moderate Alcohol Consumption on Coronary Heart Disease

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Background. Several epidemiological studies have shown light-to-moderate alcohol consumption to have a net protective effect on the incidence of coronary heart disease (CHD).

Methods and Results. Major components of this effect, both positive and negative, may be explored using models that include both alcohol and variables expected to mediate the observed alcohol effect. Such modeling in a cohort of men of Japanese descent followed in the Honolulu Heart Program indicates that about half of the observed protection against CHD afforded by moderate alcohol consumption is mediated by an increase in high density lipoprotein cholesterol. An additional 18% of this protection is attributable to a decrease in low density lipoprotein cholesterol, but it is counterbalanced by a 17% increase in risk due to increased systolic blood pressure. The explanation for the residual 50% benefit attributable to alcohol is unknown but may include interference with thrombosis. The results in this population replicate those in the Lipid Research Clinics cohort studied earlier with the same analytic technique.

Conclusions. The consistency of these findings across populations, along with the demonstration of reasonable biological pathways for this effect of alcohol, provides strong support for the hypothesis that light-to-moderate alcohol intake is protective against heart disease in men. (Circulation 1992;85:910–915)

KEY WORDS • alcohol • blood pressure • cholesterol • coronary heart disease • lipids

Several studies have shown a protective association between light or moderate alcohol use and coronary heart disease (CHD) mortality.1–7 Blackwelder et al.,1 in 1980, looked at 8-year age-adjusted mortality by cause and level of alcohol intake in the Honolulu Heart Program (HHP). They observed an inverse linear relation between alcohol use and CHD at the four levels of alcohol intake analyzed. The highest level of alcohol use tested in that analysis was 31+ ml/day. A further analysis of this same data by Kagan et al.,2 using five rather than four categories of alcohol intake and with an upper limit of 40+ ml/day, showed an inverse linear association between alcohol and incident CHD defined in three different ways. By contrast, the relation between alcohol and all-cause mortality was U-shaped, with moderate drinkers faring better than either nondrinkers or heavy drinkers.

The associations between alcohol and variables related to CHD were explored in the Cooperative Lipo-

protein Phenotyping Study8 that included men from the HHP. A positive linear relation was demonstrated between alcohol and high density lipoprotein (HDL) cholesterol, whereas an inverse linear relation was shown for alcohol and low density lipoprotein (LDL) cholesterol. These effects were demonstrated despite relatively modest levels of alcohol consumption (generally less than 20 oz/wk).

Possible physiological mechanisms for the effect of alcohol on CHD have been explored in analyses of the Lipid Research Clinics (LRC) population. These data suggested that the beneficial effect of alcohol on CHD was in part mediated by HDL cholesterol,6 and that a noxious component of alcohol’s effect was mediated by systolic blood pressure (SBP).5,8 A recent report by Shaper et al.9 claimed that the U-shaped relation between alcohol and total mortality in the British Regional Heart Study reflected selective cessation of drinking in men ill with CHD, although this effect appears unlikely to explain the consistent results in other studies.10–15 In addition, if the U-shaped curve were purely an artifact of selective migration, multivariate analyses would not suggest biological pathways for alcohol’s effect, as occurred in the LRC study. To see if the previous findings in the LRC cohort could be replicated in an entirely different population and to better understand the biological pathways through which alcohol affects CHD, we analyzed the effects of alcohol on CHD in men studied in the HHP and the extent to which any effect appeared to be mediated by HDL cholesterol, LDL cholesterol, and SBP.
Methods

The HHP is a longitudinal study of heart disease and related factors in a defined population. Begun in 1965, the HHP initially enrolled 8,006 men of Japanese descent who were born between the years of 1900 and 1919 and resided on the island of Oahu in 1965. The methods used to identify the cohort and response rates have been described in detail elsewhere. The initial examination (HHP visit 1) took place between 1965 and 1968. A second examination (HHP visit 2), 2 years after the first, was conducted between 1967 and 1970 and included 95% of these subjects.

The Lipoprotein Study was established during the period 1970–1972 (lipoprotein visit 1). This population, which participated in the Cooperative Lipoprotein Phenotyping Project, consisted of a 30% probability sample of visit 2 participants plus men with serum cholesterol or nonfasting triglyceride levels above the 90th percentile and men who had experienced either a stroke, myocardial infarction (MI), acute coronary insufficiency, or angina pectoris by the time of this examination. The Lipoprotein Study subgroup included 2,780 men who met these criteria.

Men selected for examination because of cardiovascular disease or elevated lipids were excluded from the present analysis, leaving only those subjects in the 30% random sample (n=1,859). An additional 91 men were excluded for cancer at baseline. The population evaluated therefore consists of 1,768 men randomly selected from the entire HHP cohort, from whom lipoprotein studies were obtained between 1970 and 1972, and who did not have evidence of hyperlipidemia, CHD, cancer, or stroke at that time.

Survivors in the Lipoprotein Study subgroup were reexamined in 1975–1978 (lipoprotein visit 2) and 1980–82 (lipoprotein visit 3). Data on incident nonfatal disease were obtained at these follow-up examinations. In addition to these repeat examinations, the HHP maintains a comprehensive community surveillance system to obtain data on study end points for all participants. This case ascertainment system has been described in detail elsewhere.

The end point for the present analysis was definite CHD. This included fatal CHD and incident nonfatal MI determined by specific examination-based criteria. Baseline data used in this analysis were from lipoprotein visit 1 (1970–1972). Blood pressure was recorded as the mean of three readings—two by a nurse and one by a physician. Alcohol was recorded as consumption per week of specific beverages. These data were converted to ounces of ethanol using standard tables (US Department of Agriculture handbook 819). For convenience, these amounts are presented as milliliters per day of ethanol. Cigarette consumption was recorded as cigarettes per day. HDL and LDL cholesterol values were measured according to the standards set by the National Heart, Lung, and Blood Institute for the Cooperative Lipoprotein Phenotyping Study.

Survival analysis was done using the proportional hazards general linear model procedure and related programs in the SAS software series. Linear models were used because the relation between CHD and alcohol in this population has been significantly inverse and linear at each stage of follow-up reported to date. To assess how blood pressure, LDL cholesterol, and HDL cholesterol might relate to alcohol in the biological pathways affecting CHD, Cox proportional hazards models were obtained first for alcohol with age and cigarettes as covariates, then with the sequential addition of each of the other risk factors. SBP was used as the measure of blood pressure in these models. If SBP, LDL cholesterol, or HDL cholesterol were in the biological pathways through which alcohol affected CHD, the risk associated with alcohol in the model would be expected to change as these factors were added. This would occur because that part of CHD risk mediated by one of these factors would become associated with the added factor rather than with alcohol. For example, if all the alcohol-associated decrease in CHD resulted from increased HDL cholesterol, when HDL cholesterol was added to the model, HDL cholesterol would be associated with reduced risk, and the coefficient for alcohol would be zero.

Results

Definite CHD events occurred in 124 of the 1,768 subjects. There were 75 nonfatal MIs and 49 deaths (36 definite CHD deaths and 13 sudden deaths presumed to be acute coronary events). Mean values for age, cigarettes, alcohol, SBP, LDL cholesterol, and HDL cholesterol are presented in Table 1.

The basic proportional hazards model consisted of age, cigarettes, and alcohol. A measure of obesity (such as body mass index) was not included as obesity and was not an independent predictor of CHD in this subgroup.

In this base model, the β coefficient for alcohol was -0.0099 (p=0.04) per milliliter per day. Table 2 displays the results of the sequential addition of the other factors. With the addition of SBP, the coefficient for alcohol becomes more negative (β=-0.0116, p=0.02). Adding LDL cholesterol to this model brings the coefficient for alcohol back to -0.0095 (p=0.05), approximately the original level. Finally, adding HDL cholesterol moves the coefficient for alcohol considerably further toward zero and sharply reduced its statistical significance (β=-0.0052, p=0.30). In this model, the coefficients for SBP and LDL cholesterol were positive, and the coefficient for HDL cholesterol was negative. All three covariates remained statistically significant (p≤0.01 or better).

Figure 1 shows graphically the change in the coefficient for alcohol with the sequential addition of the other variables in the proportional hazards model. In the base model, alcohol has a moderate negative association with CHD (left bar). Adding SBP (second bar) removes the adverse impact of this factor from alcohol in the model, making alcohol appear more protective. In the third bar, adding LDL cholesterol (which is de-
creased with alcohol use in this population) makes alcohol look less protective, as the benefit associated with LDL cholesterol lowering is removed from alcohol in the model and attributed directly to LDL cholesterol. The effects of SBP and LDL cholesterol in the middle two bars are of nearly equal magnitude but in opposite directions. Finally, in the right bar, the role of HDL cholesterol in the inverse alcohol association with CHD is clearly seen as nearly half of the negative (protective) effect modeled for alcohol and the statistical significance of alcohol’s benefit were eliminated when HDL cholesterol was included in the model, indicating this benefit is due to HDL cholesterol.

### Discussion

In the base model, the negative β coefficient for alcohol indicates that overall alcohol provides some protection versus CHD. This effect, however, is the sum of multiple components: some of which may be protective (e.g., increased HDL cholesterol and decreased LDL cholesterol) and some of which may increase CHD risk (e.g., SBP).

In the regression models, a variable in the biological pathway that accounts for a positive association between alcohol and CHD will make alcohol’s effect appear more negative (protective). Conversely, a variable that accounts for a negative association will make alcohol appear more positive (less protective).

It is well known (from previous analyses in the HHPP and elsewhere), that alcohol is associated with increased blood pressure. This effect is greater in heavy drinkers. A strong positive correlation between blood pressure and CHD is also well documented. Given these facts, we might hypothesize that one effect of alcohol is to promote CHD by increasing blood pressure. If this were true, the coefficient for alcohol should change in the direction suggesting greater protection (i.e., it should become more negative) when SBP is added to the model, because the effect of SBP associated with alcohol is then attributed to SBP and no longer associated with alcohol. This is exactly what happens. The addition of SBP caused the coefficient for alcohol to change from -0.0099 to -0.0116, a 17% increase in apparent benefit. A similar result has previously been published using data from the LRC study.

Alcohol is associated with lower LDL cholesterol in this and other cohorts, and a strong positive association between LDL cholesterol and CHD is well known. These facts lead to the hypothesis that alcohol-mediated decreases in LDL cholesterol should decrease CHD risk. The addition of LDL cholesterol to the model should make alcohol appear less protective as this effect is attributed to LDL cholesterol instead of alcohol. This effect was also observed as the addition of LDL cholesterol changed the alcohol coefficient by about 18% in the positive direction (from -0.0116 to -0.0095).

Alcohol is also known to increase HDL cholesterol in this and in other populations, and higher HDL cholesterol is associated with decreased CHD risk. Adding HDL cholesterol to the model (and attributing the decrease in CHD to HDL cholesterol instead of alcohol) should therefore make the alcohol coefficient less protective (less negative). The addition of HDL cholesterol caused substantial positive movement in the alcohol coefficient from -0.0095 to -0.0052, a change of 45%. In addition to this change in magnitude, adding HDL cholesterol to the model caused the coefficient for alcohol to lose statistical significance, further reinforcing the suggestion that HDL cholesterol accounts for much of the decrease in CHD associated with alcohol.

These effects closely mirror the results in the previously reported analysis based on men followed in the LRC study. Table 3 shows comparable alcohol data from these two studies. In the LRC study, morbidity was not evaluated, and there was an insufficient number of CHD deaths for analysis, so the end point was cardiovascular disease mortality. As can be seen from the table, despite somewhat different end points, the rela-
tive risks for 20 ml/day of alcohol were similar in these two populations (0.83 in the HHP and 0.80 in the LRC). After the addition of HDL cholesterol to the model for each cohort, the new relative risks for alcohol were again similar (0.90 and 0.91), neither of which remained statistically significant. These results demonstrate the consistency of the probable biological pathways for alcohol's effect in two completely different populations. The two studies were inconsistent only in that a small LDL cholesterol pathway was apparent in the HHP cohort but not in the LRC men. This result was expected because alcohol was associated with lower LDL cholesterol in the HHP population but not in the LRC cohort. Alcoholic myopathy was associated with increased HDL cholesterol in both cohorts.

Until recently, it was believed that the alcohol-associated increase in HDL cholesterol was limited to the HDL subfraction and that HDL, not HDL, was protective against CHD. Newer data, however, suggest this may not be so; HDL may be increased by alcohol, and HDL may be protective against CHD. In addition, alcohol intake is associated with increased levels of apolipoproteins A-I and A-II, which are correlated with HDL cholesterol and reduced CHD.

This analysis was designed to explore possible biological pathways for the inverse association between alcohol and CHD. Accordingly, we did not consider CHD mortality as an independent end point because this would represent only the most severe subset of disease and might not adequately represent the biological mechanisms underlying CHD. For incident CHD, there is consistent evidence in Honolulu and elsewhere of an inverse linear relation with alcohol. Thus, linear modeling is the appropriate statistical method with which to explore intervening factors within this relation. CHD mortality in heavy drinkers may be due to mechanisms both similar to and different from CHD in those who consume less alcohol. Specifically, alcoholic cardiomyopathy and congestive heart failure related to liver disease may confound the reverse J-shaped association seen in some studies for alcohol versus CHD mortality. For similar reasons, the association between alcohol and all-cause mortality is usually U-shaped. Thus, neither CHD mortality or all-cause mortality endpoints were considered independently in the present analysis, as their relation to alcohol and the biology mediating it would reinforce mechanisms not relevant to the association between all CHD and alcohol.

A report describing a U-shaped association between alcohol consumption and all-cause mortality in British men suggested that the decreased mortality associated with alcohol could be explained by reduced drinking in men with preexisting disease. An accompanying editorial endorsed this viewpoint. In a report based on 6-year follow-up in the HHP, Yano et al found that exdrinkers had higher CHD rates than never-drinkers and that never-drinkers had rates higher than current drinkers. A recent prospective study in Trinidadian men addressed this question by assessing alcohol-related problems before baseline as well as alcohol consumption during the week before the baseline examination. After excluding all subjects with prevalent cardiovascular disease at baseline and all current non-drinkers with a past drinking history, alcohol was shown to have a linear protective effect against CHD according to quantity consumed in the range of one to 59 drinks of alcohol per week. Klatsky et al further addressed this point by showing that exdrinkers and life-long abstainers have similar relative risks for CHD after adjustment for other CHD risk factors. Our study also provides strong evidence against cessation of drinking among persons with disease as the explanation for this phenomenon because we have demonstrated these effects after excluding subjects with disease at baseline. In the LRC study, subjects with disease at baseline were similarly excluded. In addition, the biological explanations suggested by our results provide further evidence that these are effects of alcohol and not an artifact of differential drinking habits occasioned by the diagnosis of disease. These conclusions are consistent with the findings of other investigators.

Misclassification bias must be considered when analyzing data using a factor such as alcohol, the use of which may carry some social stigma. If alcohol intake were underreported, the effect of alcohol would be underrepresented in the model. Unless men with certain lipid levels or certain blood pressure levels systematically misrepresented their alcohol intake, any misclassification would tend to weaken the results of our analysis. If any bias is present, the findings we report probably represent a lower level of effect than may be true biologically.

These results have been demonstrated in a cohort of men of Japanese ancestry. Although caution is always in
order when generalizing results from one specific population to other groups, the degree to which these findings confirm results obtained from an entirely different cohort of diverse ethnicity seen in LRC study reinforces the validity of these conclusions.

In summary, these models indicate that alcohol’s slight beneficial effect in decreasing LDL cholesterol is essentially canceled by alcohol’s noxious effect in increasing SBP. After accounting for these factors that neutralize each other, increased HDL cholesterol accounts for about half of alcohol’s protection against CHD; the other half remains to be explained. Factors influencing hemostasis are likely candidates and deserve further study.44-46

This effect of alcohol has been demonstrated only for CHD and not for other categories of cardiovascular disease or for total mortality. The present analysis should not be construed as endorsing heavy alcohol consumption for longevity. Evidence from this cohort has consistently shown increased all-cause mortality in heavier drinkers. Instead, our goal was to evaluate potential pathways for this observed protective association between alcohol and CHD in moderate drinkers using epidemiological data. We conclude that increased HDL cholesterol accounts for a substantial proportion of this effect.

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