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Prospective studies of moderate alcohol consumption and the risk of coronary disease and stroke in men and women

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Abstract

The association between self-reported alcohol intake and coronary disease and stroke was studied prospectively among 87 526 female nurses and 49 999 male health professionals. During 334 382 person-years of follow-up among women, 200 cases of coronary disease and 120 cases of stroke were documented, and in 72 290 person-years of follow-up among men, 350 cases of coronary disease and 60 cases of stroke were documented. After adjusting for coronary risk factors, including diet, increasing alcohol intake was inversely related to coronary disease incidence among women and men ($P < 0.01$ for trend).

Compared to nondrinkers, women who consumed 5 to 14 g of alcohol per day had a relative risk of coronary disease of 0.6 (95% confidence interval (CI) 0.4–0.9); for 15 to 24 g per day the relative risk was 0.6 (0.3–1.1); and for 25 g or more per day the relative risk was 0.4 (0.2–0.8). Compared to nondrinkers, men drinking 15.1 to 30 g of alcohol per day had a relative risk of coronary disease of 0.7 (0.5–1.0); for 30.1 to 50 g the relative risk was 0.6 (0.4–0.9); and for more than 50 g per day the relative risk was 0.4 (0.2–0.8).

A similar reduction in risk among drinkers was also found for ischemic stroke among women. The relative risk of ischemic stroke was 0.3 (0.1–0.7) among women drinking 5 to 14 g of alcohol per day. With only 31 ischemic strokes among men, the

This review is based largely upon two previously published papers:
– Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. New England Journal of Medicine 1988;319: 267-273
– Rimm EB, Giovanucci EL, Colditz GA, Ascherio A, Rosner B, Willett WC, Stampfer MJ. A prospective study of alcohol consumption and the risk of coronary disease in men. Lancet 1991;338: 464-468.

confidence intervals around the risk estimates are wide. For men drinking 5 to 30 g of alcohol per day compared to nondrinkers the relative risk was 1.5 (0.5–4.0). A positive association was found between alcohol consumption and subarachnoid hemorrhagic stroke among women. After two years of follow-up, the number of men diagnosed with subarachnoid hemorrhage was too small for a complete analysis.

These data strongly support the hypothesis that moderate alcohol consumption is inversely associated with coronary disease among women and men. The inverse association was evident between alcohol and ischemic stroke for women, but the risk estimates were unstable among men. However, the risk of hemorrhagic stroke was increased among women drinkers.

Introduction

In most studies among women and men, moderate alcohol consumption is inversely associated with risk of coronary disease (40). Although women generally consume less alcohol than men, the inverse relationship between alcohol and coronary disease is consistent across moderate levels of consumption among both women and men (43, 52). Despite the consistency of the findings, some argue that the association may be due, at least in part, to an excess risk in the comparison group of nondrinkers which may include heavy drinkers who deny their alcohol intake or individuals who have stopped drinking because of illness (9, 51). We therefore examined prospectively the relation of alcohol consumption to risk of coronary disease among women and men without pre-existing cancer and cardiovascular conditions, controlling for diet and other risk factors. The association between alcohol consumption and stroke is more controversial with reports of both increased and decreased risks among moderate drinkers (18). We examined the association between alcohol and total stroke among both women and men. Among women, we further investigated the relationship between alcohol and type of stroke.

Methods

Nurses' Health Study

The Nurses' Health Study began in 1976, when 121 700 female registered nurses living in 11 US states completed a mailed questionnaire that included items about their medical history and risk factors for coronary heart disease (6) and cancer (67). Follow-up questionnaires are mailed every two years to update information on potential risk factors and to identify newly diagnosed cases. In 1980, a semiquantitative food-frequency questionnaire was added, which included questions on the consumption of alcoholic beverages. The women were 34–59 years of age in 1980.

Health Professionals Follow-up Study

The Health Professionals Follow-up Study is a prospective investigation of dietary etiologies of heart disease and cancer among 51 529 men aged 40 to 75. The population consists of dentists (57.6%), veterinarians (19.6%), pharmacists (8.1%), optometrists (7.3%), osteopathic physicians (4.3%), and podiatrists (3.1%). The study began in 1986 when health professionals completed a detailed food-frequency questionnaire and provided information about medical history, heart disease risk factors and dietary changes during the past ten years. Follow-up questionnaires were sent in 1988 to learn of newly diagnosed coronary disease and stroke. Further detailed information of the Health Professionals Follow-Up Study can be found elsewhere (20, 43).

Dietary assessment

The semiquantitative food-frequency questionnaire used in the Nurses' Health Study listed 61 food items, each specifying a commonly used portion size. The subjects were asked to report the average frequency of consumption of each item during the previous year. In addition, for each item we asked whether consumption had greatly increased or greatly decreased during the previous ten years. We computed the average daily intake of nutrients by multiplying the frequency of the consumption of each food item by the nutrient content in the specified portion size, summed over the food items for each nutrient. Beer (360-ml can or bottle), wine (120-ml glass), and liquor (one standard drink) were included as separate items. Total alcohol intake was the sum of values for all three beverages; beer was assumed to contain 13.2 g of alcohol, wine 10.8 g, and liquor 15.1 g (3). The reproducibility and validity of this questionnaire have been documented elsewhere (8, 57, 65, 66) with particular attention to alcohol intake (15).

In 1988, the men completed a 131-item semiquantitative food-frequency questionnaire which included questions about average consumption of beer, white wine, red wine, and liquor during the past year. The format of the questionnaire and the calculation of total daily alcohol consumption were identical to those used in the Nurses' Health Study.

We assessed the validity of the food-frequency questionnaire in a random sample of women ($n = 173$) and men ($n = 136$) living in the Boston area who had completed a dietary questionnaire as part of the 1980 follow-up cycle in the Nurses' Health Study or the 1986 baseline questionnaire for the Health Professionals Follow-up Study. A second food-frequency questionnaire was completed approximately one year later (15, 42, 66). We compared alcohol intake as measured by the first and second dietary questionnaires with alcohol intake from 28 days of diet records for the women and 14 days of diet records for the men. The diet records were evenly spaced between the two administrations of the dietary questionnaire (15). The average daily intake of alcohol as measured by the diet records and by the first and second food-frequency questionnaires did not differ appreciably among the women or the men.

Spearman correlations between alcohol calculated from the dietary questionnaire and from the diet records were 0.86 for the women and 0.83 for the men using the first questionnaire for comparison, and 0.90 for the women and 0.86 for the men using the second questionnaire, which was directed to the year during which the diet records were kept (15). Alcohol intake calculated from either food-frequency questionnaire was significantly correlated with serum HDL-cholesterol levels for both the women and men (15).

Population for analysis

A total of 98 462 nurses returned the diet questionnaire in 1980. We excluded women with 10 or more blank food items (4%) or unrealistic total food scores (2.7%). To identify a healthy population at baseline, we excluded subjects with a history of cancer (except nonmelanoma skin cancer), angina, myocardial infarction (MI), or stroke, which left 87 526 subjects for this analysis. Of the eligible participants, 85 881 (98.1%) completed one or both questionnaires or responded to a telephone interview in 1982.

Men were excluded (n = 1530) who reported average daily energy intakes less than 3.4 and greater than 17.6 MJ or who returned dietary questionnaires with more than 70 blank food items. In addition, we excluded 5940 men who reported a diagnosis of cancer (except nonmelanoma skin cancer), MI, angina, stroke, coronary artery bypass graft (CABG), or coronary angioplasty on the baseline questionnaire. The remaining 44 059 men were followed for disease incidence in the subsequent two years.

After repeated mailings to nonrespondents of the 1988 questionnaire, including the use of certified mail (44), we received questionnaires from 96% of the remaining eligible participants. The 1693 nonresponding participants were assumed to be alive after searching the National Death Index.

Case ascertainment

Follow-up questionnaires were mailed to all participants in the Nurses' Health Study in 1982 and 1984 to identify incident cases of MI and stroke. Participants who reported such a diagnosis were requested to grant permission for examination of their medical records.

In the Health Professionals Follow-Up Study, fatal coronary disease, nonfatal MI, CABG, or percutaneous transluminal coronary angioplasty (PTCA) occurring between the return of the baseline 1986 questionnaire and January 31, 1988 were considered endpoints. Similar procedures were used to document self-reported MI from the 1988 questionnaire.

For both populations, MI was confirmed if it met WHO criteria (45): symptoms plus either typical electrocardiographic changes or elevation of cardiac enzymes. An MI was classified as probable if the medical records could not be obtained, but the

participant required hospitalization and the diagnosis was corroborated by supplementary mailed correspondence or telephone interview.

We requested medical records from a sample of men reporting a CABG or PTCA. Because 98 of the 102 (96%) self-reported events were confirmed by medical records, we considered self-report of all other CABGs or PTCAs as coronary disease endpoints.

Strokes were confirmed by medical records if characterized by a typical neurologic deficit, sudden or rapid in onset, lasting at least 24 hours and attributable to a cerebrovascular event. Subdural hematomas were excluded, as were strokes caused by infection or neoplasia. Strokes were subclassified, according to criteria of the National Survey of Stroke, as due to ischemia (embolism or thrombosis), subarachnoid hemorrhage, intracerebral hemorrhage, or unknown cause (62). Strokes were considered probable if they required hospitalization, and were corroborated by additional information provided by letter or interview if records could not be obtained.

Most deaths were reported by next-of-kin, work associates, or postal authorities. After each questionnaire cycle, we search the National Death Index for nonrespondents; we estimate that over 98% of deaths are identified (54). In suspected cases of cardiovascular death, we request permission to review the medical records. A death was designated as due to coronary heart disease if it was the result of a confirmed fatal myocardial infarction. If coronary disease was listed as the underlying cause on the death certificate, without another plausible cause, and the subject was known to have had coronary heart disease, the endpoint also was considered confirmed. In no case did we rely solely on the cause stated on the death certificate to confirm a death as due to coronary disease. Sudden death was defined as death occurring within an hour of the onset of symptoms when no previous serious illness was reported and no other plausible cause of death (other than coronary disease) was reported. Because a large proportion of sudden deaths in men are from coronary events, sudden deaths were included in the fatal infarction category; however, primary analyses were repeated excluding sudden deaths. Sudden death can often occur in the absence of coronary disease in women; therefore, we excluded eight cases of sudden death among women.

Fatal strokes were confirmed by medical records or were considered probable if no records were obtainable, including strokes for which only the cause listed on the death certificate was known.

We included endpoints that occurred after the return of the 1980 questionnaire but before June 1, 1984 for women, and after the baseline questionnaire but before February 1, 1988 for men. All medical records were reviewed by physicians who had no knowledge of any of the reported exposure variables.

Statistical analysis

Each participant contributed person-months of follow-up beginning on the date of return of the baseline questionnaire until a confirmed cardiovascular event, death, or

the end of the follow-up period (from June 1, 1980 to May 31, 1984 in the women, and after the month of return of the 1986 questionnaire to January 31, 1988 in the men). Relative risk estimates were calculated as the incidence rate of coronary artery disease in different categories of alcohol intake as compared to the incidence rate among nondrinkers (unless otherwise noted). Relative risk estimates were first calculated by adjusting for age (five-year categories) and smoking (never, past, or current: < 15, 15–24, and > 24 cigarettes/day) using the Mantel-Haenszel summary estimator (48). The Mantel extension test (36) was calculated to test for a linear trend with increasing alcohol intake. Multiple logistic regression analysis was used to simultaneously control for other potential risk factors of coronary disease.

Table 1. Prevalence of risk factors and consumption of selected nutrients, according to level of alcohol intake among 87 526 women in the Nuses' Health Study. (Adapted with permission from New England Journal of Medicine 1988;319: 267-273.)

Risk factor/nutrient	Prevalence of risk factors (%)					
Alcohol consumption category (g/day)	0	< 1.5	1.5-4.9	5.0-14.9	15.0-24.9	≥25
Size of category (%)	32.1	12.8	20.8	20.1	7.0	7.3
Percentage with potential risk factor[1]						
High cholesterol	6.0	5.1	5.2	4.7	4.7	5.7
Myocardial infarction in parent ≤60 yr	14.0	14.4	14.9	14.6	14.1	14.4
Current hormone use (postmenopausal women)	18.1	20.4	20.7	20.4	20.0	21.0
Hypertension	17.1	15.9	14.7	13.9	15.3	18.0
Diabetes	3.7	2.2	1.5	1.1	1.1	1.3
Current smoking	22.5	27.0	27.3	31.4	38.1	48.7
Past smoking	20.2	26.1	29.8	34.0	34.3	32.1
Body mass index[2] ≥29	20.0	16.3	12.7	8.3	7.1	8.1
Percentage in overall highest quintile						
Total fat	21.3	17.8	19.3	18.8	19.5	19.7
Saturated fat	21.2	18.1	19.3	19.0	20.0	20.3
Monounsaturated fat	21.6	18.2	19.3	18.7	19.7	20.0
Polyunsaturated fat	22.3	19.1	20.1	19.1	20.0	18.4
Cholesterol	21.4	19.0	19.0	18.9	21.0	20.7
Dietary fiber	21.0	21.0	21.1	20.0	18.0	16.2

[1] Adjusted for five-year categories by the directed method, with rates among nondrinkers used as the standard.
[2] Quetelet's index, body weight in kg divided by height in m squared (kg/m^2).

Table 2. Baseline characteristics[1], according to alcohol consumption, among 44 059 male health professionals free from cardiovascular disease and cancer in 1986. (Adapted with permission from Lancet 1991;338: 464-468.)

	Average alcohol consumption (g/day)							
	0	0.1-2.0	2.1-5.0	5.1-10.0	10.1-15.0	15.1-30.0	30.1-50.0	>50.0
n	10302	4328	6330	6256	5220	6267	3834	1522
% of population	23.4	9.8	14.4	14.2	11.8	14.2	8.7	3.5
Mean age	53.4	53.0	52.0	52.4	53.1	53.4	54.7	54.9
Mean body mass index (kg/m^2)	25.2	25.1	25.1	24.9	24.9	24.9	25.0	25.3
Percentage of men with self-reported cardiovascular diagnoses								
Hypertension	20.1	18.8	18.4	19.3	18.0	20.9	24.3	27.4
High cholesterol	10.0	10.4	10.9	10.3	10.8	10.1	10.8	12.3
Diabetes	4.4	2.8	2.2	1.9	1.7	1.5	1.5	2.5
Gout	4.4	4.0	4.5	4.0	4.3	4.6	6.2	8.0
Percentage of men with potential risk factor								
Current smoker	6.9	8.1	7.4	8.6	8.7	10.7	19.0	23.2
Past smoker	29.4	34.0	37.7	41.2	45.6	50.3	52.0	52.4
Myocardial infarction in parent ≥60 yr	28.2	30.8	31.1	30.0	29.1	29.0	31.0	30.4

[1] Age-adjusted using direct standardization to the cohort of 44 059 men free from cardiovascular disease and cancer.

Results

Among the participants eligible for analysis, 32.1% of the women and 23.4% of the men reported consuming alcoholic beverages 'never or less than once per month', and 14.6% of the women and 26.4% of the men drank more than 15 g of alcohol (more than one drink per day). Baseline characteristics and potential risk factors according to level of alcohol intake are shown in Tables 1 and 2. The prevalence of hypertension was similar among abstainers and light drinkers, but higher among the heaviest drinkers. Current smoking was highly associated with levels of alcohol consumption. Likewise, a higher percentage of the past smokers were heavier drinkers.

During the 334 382 person-years of follow-up for women, 164 nonfatal infarctions (133 confirmed and 31 probable) and 36 confirmed deaths due to coronary disease occurred among women. There were 86 nonfatal strokes (71 confirmed and 15 probable) and 34 fatal strokes (18 confirmed and 16 probable). Of the 120 strokes, 66 were due to cerebral infarction, 28 to subarachnoid hemorrhage, and 12 to intracerebral hemorrhage; 14 were unclassified. Probable and confirmed

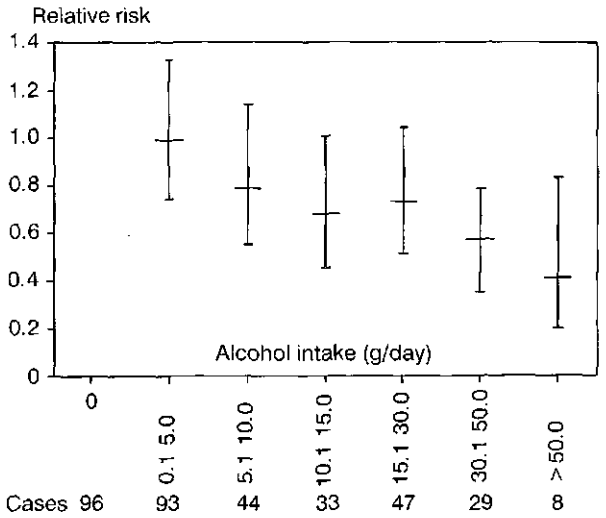

Fig. 1. Relative risk of severe coronary disease, Health Professionals Follow-up Study. $P < 0.001$ for trend. (Derived with permission from data previously published in Lancet 1991;338: 464-468.)

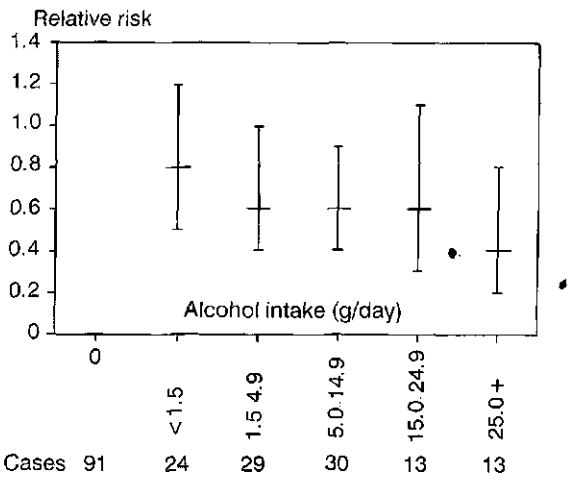

Fig. 2. Relative risk of severe coronary disease, Nurses' Health Study. $P < 0.01$ for trend. (Derived with permission from data previously published in New England Journal of Medicine 1988;319: 267-273.)

cases of both stroke and coronary disease had similar patterns of risk factors; therefore, probable cases were merged with the confirmed cases for most analyses.

After 72 290 person-years of follow-up for men, 164 nonfatal MIs (136 definite and 28 probable), 50 coronary disease deaths (including 12 sudden deaths) and 136

CABG or PTCA procedures occurred among men. There were 60 fatal strokes, 31 of which were ischemic.

The multivariate relative risks of coronary disease by category of alcohol intake are presented graphically in Figs. 1 and 2. Controlling for family history of infarction, smoking status (never, past, or current: <15, 15-24, and >25 cigarettes/day), hypertension, diabetes, high cholesterol, age, obesity, exercise, cholesterol intake, saturated fat intake, polyunsaturated fat intake, menopausal status, and hormone use (among women), time period (among women), and profession (among men), the risk of severe coronary disease at each level of alcohol consumption was lower than among nondrinkers. There was about a 40% reduction of risk among women drinking 1.5 g of alcohol per day (1 drink per week) up to 24.9 g per day (2 drinks per day). A further reduction of risk was found among women drinking more than 25 g of alcohol per day (RR = 0.4, 0.2–0.8). Among men, a similar decline in risk was found at increasing levels of alcohol consumption. Compared to nondrinkers, the relative risks of any coronary artery disease event were 0.74 (0.56–0.97) for men drinking an average of 5.1 to 30.0 g of alcohol per day, and 0.53 (0.35–0.79) for more than 30 g of alcohol per day. The relative risks of coronary disease also did not differ appreciably after excluding participants (2.7% of the women and 5.0% of the men) who left an alcoholic beverage category blank. Results did not change substantially either when participants with probable MI or non-specific sudden death (men only) were omitted from analyses.

In further analyses, we explored the possibility that the reference category of nondrinkers may be a combination of participants with previous alcohol problems or pre-existing disease. After excluding 2822 women and 5693 men who did not drink at baseline and who reported a substantial reduction in their drinking over the pervious 10 years, the relative risks of coronary disease remained unchanged. Because of the large number of cases among men, we could further exclude participants with conditions potentially related to coronary disease. Specifically, we excluded an additional 16 242 men who had, at baseline, reported gout, diabetes, high cholesterol, high triglycerides, hypertension, paroxysmal atrial tachycardia, heart rhythm disturbances, or other heart disturbances. Although only 142 total cases remained, we still found a significant inverse association between alcohol consumption and coronary artery disease incidence (chi for trend –2.29, $P = 0.02$) (Fig. 3). For example, the multivariate relative risk of coronary disease was 0.61 (0.3–1.2) among men drinking more than 30 g of alcohol per day compared with nondrinkers.

We also separately examined the association between alcohol from beer, wine, or liquor and coronary artery disease. Increasing consumption of alcohol from each beverage type was inversely related to risk of total coronary artery disease among both women and men. The benefit was strongest among women who consumed wine and men who consumed liquor. The relative risk of coronary disease for women drinking 5 or more g per day of alcohol from wine was 0.4 (0.2–0.8) compared to nondrinkers. Men who consumed an average of 5 to 30 g of alcohol from liquor had a relative risk of 0.7 (0.6–0.9) compared to nondrinkers. After using a logistic model

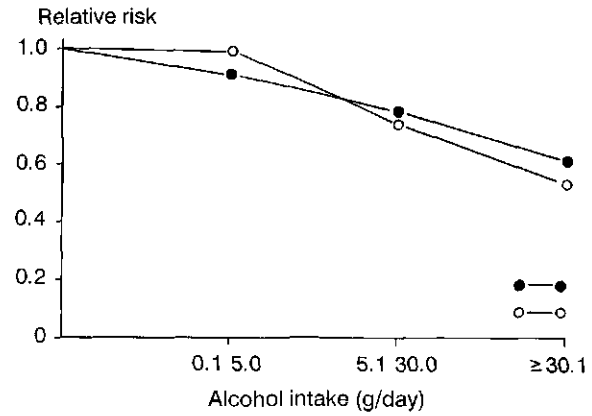

Fig. 3. Alcohol and coronary artery disease in the Health Professionals Follow-up Study. o, total cohort; +, no pre-existing Dx. (Adapted with permission from Lancet 1991;338: 464-468.)

to simultaneously control for alcohol from each source, the associations between alcohol (continuous variables) from beer, wine, or liquor with risk of coronary artery disease were not statistically different from each other.

The findings concerning fatal and nonfatal stroke were similar within the category of the type of stroke and were therefore merged. Among women we observed a

Table 3. Relative risk of ischemic stroke, subarachnoid hemorrhagic stroke, and total stroke among women according to alcohol intake, after simultaneous adjustment for potential risk factors in a proportional hazards model.[1] (Adapted with permission from New England Journal of Medicine 1988;319: 267-273.)

Alcohol consumption (g/day)	Ischemic stroke		Subarachnoid hemorrage	
	cases	RR (95% CI)	cases	RR (95% CI)
0	33	1.0 (referent)	3	1.0 (referent)
≤1.5	9	0.7 (0.4–1.6)	3	2.4 (0.5–12.1)
1.5–4.9	8	0.4 (0.2–0.9)	6	2.9 (0.7–11.5)
5.0–14.9	6	0.3 (0.1–0.7)	9	3.7 (1.0–13.8)
≥15	10	0.5 (0.2–1.1)	7	2.6 (0.7–10.3)

[1]The potential risk factors included in the model were a parental history of infarction before the age of 60 (yes or no), menopausal status and hormone use (premenopausal; postmenopausal with current hormone use; or postmenopausal without current hormone use), period (1980 through 1982, or 1982 through 1984), smoking status (currently (three levels of tobacco use), formerly, or never), hypertension (yes or no), high cholesterol (yes or no), age (five categories), obesity (highest quintile vs. other), exercise (highest two quintiles vs. other), cholesterol intake (highest two quintiles vs. other), intake of saturated fat (highest two quintiles vs. other), and intake of polyunsaturated fat (highest two quintiles vs. other).

Table 4. Relative risks of ischemic stroke and total stroke among men according to alcohol intake, after simultaneous adjustment for potential risk factors in a proportional hazards model.[1]

Alcohol consumption (g/day)	Ischemic stroke		Total stroke	
	cases	RR (95% CI)	cases	RR (95% CI)
0	6	1.0 (referent)	15	1.0 (referent)
≤5.0	5	0.9 (0.3–3.0)	11	0.8 (0.4–1.8)
5.1–30.0	13	1.5 (0.5–4.0)	21	1.0 (0.5–2.0)
>30	7	1.9 (0.5–6.6)	13	1.6 (0.7–3.7)

[1] The potential risk factors included in the model were familial history of myocardial infarction (before the age of 60, at the age of 60 or older), current smoking status (three categories), age, body mass index, profession, self-reported diabetes, hypertension or high cholesterol, quintiles of dietary intake of cholesterol, fiber, saturated fat, monounsaturated fat, polyunsaturated fat, and energy.

moderate inverse association between alcohol intake and the risk of stroke, except perhaps for the highest level of consumption (Table 3). Among men, the inverse association was not as pronounced among the moderate drinkers. With only 60 total strokes among men, the risk of total stroke in all alcohol consumption levels was not significantly different from rates of stroke among nondrinkers (Table 4).

The risk of stroke among women was highly dependent on the type of stroke. Each level of alcohol consumption was associated with a decreased risk of subsequent ischemic stroke. The multivariate relative risk for an intake of 5 to 14.9 g per day was 0.3 (0.1–0.7). However, the risk of subarachnoid hemorrhage was elevated for each category of alcohol use. Women consuming 5 to 14.9 g per day had a relative risk of 3.7 (1.0–13.8) compared to nondrinkers. The other categories of stroke had too few cases for separate analysis. The risk of ischemic stroke among men was similar to the risk of total stroke. With only 4 subarachnoid hemorrhages and 27 other or unknown classifications of stroke, separate analyses were not performed.

Discussion

Our results, from two large prospective studies among both women and men, provide strong evidence supporting the hypothesis that alcohol intake is inversely associated with coronary artery disease in women and men and ischemic stroke in women. However, women who consumed moderate amounts of alcohol had an increased risk of hemorrhagic stroke. The association between alcohol and stroke in men did not have a distinctive pattern, but a suggestion of increased risk was found at high levels of consumption.

In both studies, exposure information was collected before outcome events occurred, avoiding population recall bias. The dietary questionnaire reliably measures alcohol intake for both women and men (8, 15, 57). Because we achieved a

98.1% follow-up rate in women and a 96% follow-up rate in men eligible for this analysis, our results are probably not biased by participants lost to follow-up.

A possible limitation of the analyses is the relatively short follow-up period between alcohol reporting and incident coronary artery disease; however, this short interval reduces the possibility of misclassification of alcohol due to changes of intake during follow-up.

The knowledge of pre-existing disease at the baseline assessment of alcohol intake could bias the measure of effect between alcohol and coronary artery disease if an individual had reduced alcohol consumption due to perceived disease status. Similar biases may occur if heavy drinkers report little or no alcohol consumption. Although this possibility cannot be excluded entirely, several lines of evidence suggest that such effects are unlikely. Women and men with the highest alcohol intake had the lowest risk of coronary disease, and their relative risk was about half that of participants who consumed small amounts. The level of alcohol intake in the cohort was generally moderate; more than 98% of the women drinkers reported consuming 45 g per day or less and 96.5% of the men consumed 50 g per day or less. Also, heavy drinkers tend not to participate as volunteers in surveys (1) and would be even less likely to complete detailed repeat questionnaires, as did the subjects included in this analysis. Excluding participants who did not respond to any questionnaire item regarding alcoholic beverages had no effect on the findings. Also, excluding those who did not currently drink but who reported a substantial decline in drinking during the past 10 years had no effect.

Furthermore, we found a significant reduction in coronary disease risk among women drinking 25 g or more per day and men drinking 30 g or more per day, when we used light drinkers, rather than abstainers, as the reference group (43, 52). Finally, to illustrate that pre-existing medical conditions did not bias our conclusions, we found a significant inverse risk of heart disease with increasing alcohol consumption among a separate subset of 27 717 men with no baseline cardiovascular disease or related conditions (diabetes, hypertension, etc.) (Fig. 3).

Shaper (51) has argued that the reference group of alcohol abstainers or low consumers may contain a diverse group of subjects who have migrated from higher to lower alcohol consumption levels because of pre-existing disease. After removing 23.8% of the men from the British Regional Heart Study (50) who recall being diagnosed with cardiovascular or 'cardiovascular-related' conditions, the authors reported no association between alcohol consumption and cardiovascular mortality, controlling for age, social class, and cigarette smoking. However, there were few nondrinkers in this subgroup of healthy men, and only 6 cases of fatal coronary disease occurred among them. Moreover, after controlling for highly correlated variables, including social class and smoking (49), reduced variability in alcohol intake would suggest wide confidence intervals around their relative risk estimates. Wannamethee and Shaper recommend using men who drink less than 15 drinks per week as a reference group (63). This reference group would include levels of alcohol consumption for which we have found a substantial reduction in risk.

The results are internally consistent, with similar findings concerning fatal and nonfatal coronary disease. Adjustment for confounding factors yielded expected results: adjustment for cigarette use tended to strengthen the apparent protective effect of alcohol. A family history of heart disease, current smoking, and a large body mass index, are all strong predictors of cardiovascular events. Adjustment for self-reported diabetes tended to attenuate the observed relative risks (probably because diabetics are often urged to avoid drinking, but possibly in part because drinking is inversely associated with the risk of the development of diabetes (55)). Perhaps the positive association between alcohol intake and the risk of hypertension (68) was balanced by a tendency of subjects with known hypertension to avoid alcohol.

The inverse association between alcohol and heart disease is consistently found in most studies of women and men (24, 40), and the few previous studies in women. Briefly, inverse associations have been found in most case-control and cohort studies between moderate alcohol consumption and coronary disease. In a case-control study of women under the age of 50, Rosenberg et al. (46) found that current drinkers had a relative risk of 0.7 (0.5–1.0). Results have been reported for three prospective studies in women in which a nested case-control design was used. Petitti et al. (41) found that among subjects 18 to 54 years old, those who drank alcohol (any amount) had a lower risk of myocardial infarction than those who did not (RR 0.3, 0.1–0.6). Ross et al. (47) observed in a retirement community that drinkers had a lower risk of death due to ischemic heart disease than did living controls (RR 0.4; $P < 0.01$) or dead controls (RR 0.9). Klatsky et al. found that women who had two drinks or fewer per day had a relative risk of myocardial infarction of 0.8, as compared with nondrinkers with similar risk factors (31).

Results from two other prospective cohort studies of alcohol and coronary heart disease risk in women have been reported. In the Framingham Study, moderate drinkers (10 to 30 g per day) had a relative risk of 0.6 (0.3–1.1) for all forms of coronary disease, including angina, as compared with women who consumed less than 10 g of alcohol per day; there was no adjustment for confounding (56). A later analysis of Framingham data (17) also showed an inverse association between alcohol intake and all forms of coronary disease. Because lipid profile, a likely biologic mechanism for the effects of alcohol, was controlled for as a potential confounder, the degree of protection was probably underestimated. In the Busselton Study (11), women who drank alcohol (any amount) had a (nonsignificantly) lower death rate for coronary disease than did nondrinkers, but there were only 19 cases of coronary disease among drinkers.

A thorough survey of the association between alcohol and coronary disease among men has been published previously (40). Most reports compare current drinkers to current nondrinkers. However, Klatsky et al. (29) report a relative risk of 0.5 for coronary disease hospitalization among women and men who consumed 1–5 drinks per day as compared to life-long nondrinkers. Jackson et al. (26) also used life-long nondrinkers for reference in a New Zealand case-control study. The authors report a relative risk of 0.6 for nonfatal MI among men drinking 5–15 drinks per week. Using life-long nondrinkers as the reference category alleviates

misclassification of alcohol intake associated with recent reduction due to illness. However, lifetime abstainers may represent an unusual sample of people uncharacteristic of the general population (37). Boffetta and Garfinkel (5) reported reduced mortality from coronary disease among all women and men enrolled in the American Cancer Society Prospective Study. After excluding 32.8% of the cohort with poor health or chronic disease, the inverse association persisted between alcohol and coronary disease death.

Few studies have controlled for dietary intake, leaving open the potential for confounding between alcohol, diet, and coronary disease. In populations where intakes of fat, cholesterol, and dietary fiber vary by alcohol consumption level (7, 28, 59), diet may distort the relationship between alcohol and coronary artery disease. Using dietary data from 18 countries, Hegsted and Ausman (22) found that the best multiple regression model for predicting coronary heart disease mortality included dietary variables for saturated fat, polyunsaturated fat, and alcohol. Because alcohol drinkers tend to consume diets higher in fat and lower in dietary fiber (Tables 1 and 2), controlling for concurrent diet strengthened associations between alcohol and coronary disease.

One of the proposed mechanisms by which alcohol reduces coronary artery disease is through raising high density lipoprotein (HDL) levels (40). Alcohol raises the concentrations of both apoproteins A-I and A-II (14, 58), which are associated with HDL particles. Although alcohol was originally thought only to increase HDL-3 subfractions (21), positive correlations between both HDL-2 and HDL-3 subfractions have been reported (61). Moreover, both HDL-2 and HDL-3 subfractions are associated with a reduced risk of coronary artery disease (4, 16, 23, 39), with a recent report from the Physicians' Health Study showing the inverse association between HDL subfractions was strongest for HDL-3 (53).

Although an effect on HDL might explain much of the benefit (10), alcohol has other potentially important effects. It is associated with an increase in the prostacyclin/thromboxane ratio (32, 60), and a decrease in platelet aggregability (27, 64), and it interacts with aspirin to prolong bleeding time (12). Alcohol also increases the release of plasminogen activator (33) and lowers the level of fibrinogen, a potent risk factor for coronary heart disease (38).

Among men, heavy drinking is associated with stroke (18), but the effects of moderate intake are unclear. For women, the existing data are sparse and refer mainly to the association of both ischemic (25) and hemorrhagic stroke (35) with preceding alcohol intoxication. Our findings among women of an increased risk of subarachnoid hemorrhage among moderate drinkers is consistent with findings in men in a prospective study, the Honolulu Heart Program (13), in which drinkers had two to three times the risk of nondrinkers. Similar to our results among men, that study found no evidence of a protective effect of alcohol against ischemic stroke.

Some of the mechanisms that mediate the apparent protective effect of alcohol for coronary heart disease and ischemic stroke could increase the risk of subarachnoid hemorrhage, in particular the effects on platelets and clotting. Also,

alcohol can increase the risk of hypertension (30, 68), and in animals even moderate amounts can cause spasm in the cerebral vasculature (2).

Obviously, heavy drinking is harmful, but the risks and benefits of moderate intake are not simple to weigh. For example, among women, subarachnoid hemorrhage was less than half as common as ischemic stroke but caused four times the number of deaths due to stroke (21 vs. 5). Moreover, most women who do not smoke or who do not have the classic risk factors for coronary disease are at very low risk of myocardial infarction. Further complicating this issue is the finding that moderate alcohol intake is associated with an increased risk of breast cancer (67) (with 5 to 14 g per day, the relative risk was 1.3 (1.1-1.7)), and a possible increase in the risk of colon and rectal cancer (34), in addition to oral cancers (19).

Our findings provide additional evidence to support the hypothesis that moderate alcohol consumption reduces the risk of coronary artery disease. The inverse association for alcohol was not an artifact due to pre-existing disease or differences in dietary habits. The magnitude and consistency of the results, the lack of obvious biases, the biologic plausibility, and the internal consistency of the results, lead us to believe that the inverse associations we observed between alcohol and coronary disease are likely to be causal.

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Alcohol consumption and coronary heart disease risk in the Seven Countries Study

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Abstract

The Seven Countries Study is a cross-cultural study in which relations between alcohol consumption and coronary heart disease (CHD) mortality were studied at the cohort and at the individual level. Between 1958 and 1964, 16 cohorts consisting of 12 763 men aged 40–59 were examined in seven countries. These men were followed for 25 years with respect to mortality. Average alcohol consumption of the 16 cohorts at baseline was inversely related to 25-year mortality from CHD. This association disappeared when confounders such as saturated fat intake were taken into account. In the 2255 men aged 65–84 examined after 25 years of follow-up in Finland, Italy and the Netherlands relations between alcohol consumption and CHD risk factors were studied. There was a strong postive association between HDL cholesterol and alcohol consumption and a weak one between systolic blood pressure and alcohol consumption. Alcohol consumption was unrelated to total cholesterol and body mass index (BMI, in kg/m^2). In Italy, a culture characterized by a high alcohol intake, a J-shaped relation between alcohol consumption and CHD mortality was observed. The inverse relation for low consumption levels was not significant after adjustment for cardiovascular disease (CVD) status. It can be concluded on the basis of the results of the Seven Countries Study that alcohol should not be promoted as a measure to prevent CHD.

Introduction

In 1979, St. Leger and co-workers reported a strong inverse relation between per capita alcohol consumption (especially wine) and mortality from CHD in 18 countries (8). Their analysis was based on routinely available mortality data and per capita alcohol and food consumption data. A drawback of these data is that they do not provide information about the real intake because no allowance is made for offal and waste. Also the per capita alcohol and food consumption data can not be broken down by age and gender. Consequently, age- and gender-specific data are not

available for analysis in relation to CHD mortality. Therefore, results are needed of a cross-cultural study using high-quality alcohol consumption and mortality data. These data were collected in the Seven Countries Study. The data collected in this study provide the possibility to analyse the relation between alcohol consumption and CHD risk both at the cohort and at the individual level.

Ecological analysis of the Seven Countries Study data

At the end of the 1950s, the Seven Countries Study was designed to investigate relations between diet and CVD (2–4). Sixteen cohorts were selected in seven countries: Finland, Greece, Italy, Japan, Netherlands, USA and Yugoslavia. In total, 12 763 men aged 40–59 were examined between 1958 and 1964. Information about their alcohol consumption pattern was collected by the dietary record method in subsamples of the study populations (6). Mortality data of the study populations are complete now for the subsequent 25 years. This provides the possibility to relate the alcohol consumption data collected at baseline to the 25-year mortality data from CHD.

Large differences were observed in alcohol consumption patterns between the 16 cohorts (6). Very low levels of alcohol consumption were observed in Finland and the Netherlands. In contrast, high levels of consumption were found in Italy and Dalmatia (Yugoslavia). The logarithm of alcohol consumption was inversely related to 25-year mortality from CHD. The logarithm of alcohol consumption was also significantly associated with saturated fat intake. Saturated fat intake was the strongest determinant of CHD mortality. Multivariate analysis showed that only saturated fat, and not alcohol consumption, was important in explaining cross-cultural differences in CHD mortality.

Studies among elderly people in Finland, Italy and the Netherlands

In the Finnish, Italian and Dutch cohorts of the Seven Countries Study 25-year follow-up surveys were carried out. The 2255 men who participated in these surveys were 65–84 years of age. In these surveys information was collected about alcohol consumption and the major risk factors for CHD.

Alcohol consumption was significantly associated with serum total and HDL-cholesterol (7). Average total and HDL-cholesterol levels were 10 mg/dl higher in men who consumed 30 g alcohol or more per day than those of non-drinkers. The association between alcohol consumption and total cholesterol disappeared after multivariate analysis taking age, BMI, coffee consumption and cigarette smoking into account. The relation between alcohol consumption and HDL-cholesterol remained strongly significant after adjustment for the other determinants.

Systolic blood pressure levels were 3 mmHg higher in men who consumed more than 30 g alcohol per day than in non-drinkers. This association was not statistically significant. After adjustment for age, BMI, coffee consumption and cigarette

smoking this association became borderline significant ($P = 0.10$). Alcohol consumption was unrelated to Quetelet index.

Alcohol consumption and coronary heart disease mortality in the Italian cohorts of the Seven Countries Study

Many cohort studies have observed an inverse relation between alcohol consumption and CHD mortality. Most of these studies were carried out in cultures characterized by a relatively low alcohol intake. It has been suggested that this association could be confounded by health status. The percentage of people who suffer from diseases could be larger among non-drinkers than among moderate alcohol users. Another confounder could be fish consumption. In the Zutphen Study alcohol consumption was positively associated with fish consumption (5). There are therefore doubts as to whether the association between alcohol and CHD is causal.

It is also of interest to study the association between alcohol consumption and CHD in a culture characterized by a high alcohol intake. Middle-aged men in Crevalcore and Montegiorgio, two Italian cohorts of the Seven Countries Study, have an average alcohol intake of 86.9 g per day (1). The average alcohol intake in the highest quintile of these cohorts was 165 g per day, accounting for 37% of total energy intake. These cohorts provided the possibility to study the relation between alcohol consumption and CHD mortality over a broad range of intake. In these cohorts a J-shaped relation was found between alcohol intake and 20-year mortality from CHD. The inverse relation for low consumption levels was no longer significant when all men with cardiovascular manifestations were excluded.

Conclusion

Cross-culturally, alcohol consumption is inversely related with CHD mortality. This association disappears however when saturated fat intake is included in the model. In cultures with a relatively low alcohol intake an inverse relation is observed between alcohol intake and CHD mortality. It is however possible that this association is confounded by other factors such as health status and fish consumption. In a culture with a high alcohol intake a J-shaped relation was observed between alcohol intake and CHD mortality. The inverse relation at low levels of alcohol intake was not significant after adjustment for CVD status. The results of the Seven Countries Study suggest that alcohol consumption should not be promoted as a measure to prevent CHD.

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Alcohol and blood pressure

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Abstract

Since 1915, many studies have addressed the putative role of alcohol use in blood pressure elevation. The discussion, however, is still unsettled. While there is general agreement on the view that heavy alcohol use, i.e. 6 or more glasses per day, is associated with an increased prevalence and incidence of hypertension, doubt remains on the chronic effects on blood pressure of a more moderate alcohol intake. Some studies even indicate that blood pressure is elevated in those not drinking alchol as compared to consumption levels of 1 to 3 glasses per day. There are several problems in interpreting findings in observational studies of alcohol and blood pressure. The most important limitation is the difficulty to assess alcohol intake reliably. Also, alcohol intake is connected with various other aspects of life-style that may relate to blood pressure level. Biochemical markers do not provide an adequate substitute for a questionnaire or for history data on alcohol use, although associations between various liver enzymes and blood pressure have been reported. From several short-term intervention studies, most of which were non-randomized or uncontrolled, it appears that a restriction of alcohol use may reduce blood pressure in hypertensive subjects. Moreover, moderation of alcohol use may be useful in a multifactorial approach to the non-pharmacological treatment of primary hypertension. Several mechanisms have been proposed to explain the short- and long-term effects of alcohol on blood pressure, including the renin-angiotensin system, cortisol, sodium and water retention as well as certain metabolic effects. Interestingly, withdrawal from alcohol prior to blood pressure measurement, and the concomitant sympathetic arousal, may be an additional explanation for the apparent relation between hevay alcohol use and elevated blood pressure in some studies. From a public health point of view, the estimates on the contribution of alcohol use to hypertension vary from 5% to 30%. The lower estimate is probably more realistic than the higher one although alcohol use is fairly common in Westernized societies. From the available data it appears that modest alcohol use is unlikely to have a major

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impact on blood pressure and may even have some cardioprotective effects through other mechanisms. Yet, in hypertensive subjects, moderation of alcohol use may be considered as an element in the primary management of elevated blood pressure.

Abbreviations
ALAT, alanine aminotransferase; ASAT, asparatate aminotransferase; GGT, gamma-glutamyltransferase; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; HDL,high-density lipoprotein; MCV, mean corpuscular volume.

Introduction

In 1915, Camille Lian wrote a paper entitled 'L'alcoolisme, cause d'hypertension arterielle' in which he proposed that heavy alcohol use is one of the main causes of hypertension (1). Lian's statement was based on the observation that more subjects with a high alcohol intake suffered from hypertension than those with a low alcohol intake. In his study he discriminated four drinking categories; 'sober' (light alcohol use: 1.0 l of wine per day); 'moyens buveurs' (moderate alcohol use: 1.0–1.5 l of wine per day); 'grands buveurs' (heavy alcohol use: 2.0–2.5 l of wine per day and use of spirits); 'très grands buveurs' (very heavy alcohol use: 3.0 l of wine per day and use of spirits).

More than 60 years later, the relationship between alcohol and blood pressure was studied by Klatsky et al. (3). They confirmed the findings of Lian but were also able to define and study a category of moderate alcohol intake, a category virtually lacking from the previous data from France. Subsequently, many studies have been published addressing the putative association between the use of alcoholic beverages and hypertension.

In this review we will first discuss the most important observational and experimental investigations into alcohol intake and blood pressure and the possible mechanisms involved. Next, methodological aspects that may complicate the interpretation and conduct of studies of both the effects of alcohol on blood pressure and the consumption of alcohol in general will be considered. Finally, we will offer our conclusions as to the alcohol-blood pressure association and the mechanisms that play a role in this relationship.

Findings in observational studies

Most indications of a positive relationship between alcohol intake and (high) blood pressure come from observational studies of various populations across the world. The aim of such studies was to investigate the difference in prevalence and incidence of hypertension between groups with a high and low alcohol intake and to find trends in average blood pressure with respect to alcohol consumption (1–26). The first type of question has been addressed in studies across and within populations. With regard

Table 1. Examples of differences in prevalence of hypertension between groups with high and low alcohol consumption.

Authors	Ref.	Definition of hypertension (mmHg)[1]	P1/P2[2]
Lian	1	?	4.0
Klatsky et al.	3	160 and (or) 95	1.5–2.4
Arkwright et al.	4	140 (systolic)	4.0
D'Alonzo et al.	5	160 and (or) 95	2.3
Dyer et al.	6	160 and (or) 95	1.8
Kannel et al.	7	160 and (or) 95	2.0
Mathews	65	>120 (average pressure)	2.7

[1] Systolic and diastolic pressure respectively.
[2] Ratio, among hypertensive patients, between those with a high alcohol consumption (P1) and those with a low level of consumption (P2).

to between-population comparisons, the recently completed INTERSALT study, although designed to provide definitive data on the association between dietary salt intake and blood pressure, has provided clear evidence in support of the view that high alcohol use in a defined population is related to the prevalence of hypertension (26).

In studies conducted within populations the prevalence of hypertension for the group with a high alcohol intake was typically found to be 1.5 to 2.5 times higher than that for a control group (Table 1).

To achieve a better quantification of alcohol consumption and to make it easier to identify individuals with a high alcohol intake, two studies were carried out at Glasgow. One study focused on disturbed liver function in patients in a clinic for hypertension, and the other one on subjects with a diastolic blood pressure over 105 mmHg as assessed in a population study (32, 33). In both population groups, higher frequencies of abnormal serum aspartate aminotransferase (ASAT; or glutamic-oxaloacetic transaminase, GOT) and serum alanine aminotransferase (ALAT; or glutamic-pyruvic transaminase, GPT) levels, in particular, were found among hypertensives than among normotensive subjects. Although not specific for (alcoholic) liver dysfunction, this finding suggests that liver damage is more common in the hypertensive group.

The γ-glutamyltransferase (GGT) level is believed to be a better indicator of alcohol consumption, especially when combined with oral or written information on drinking habits (34, 35). In a Scandinavian study of middle-aged men, an elevated GGT level was found in 38.8% of a group with high blood pressure (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥105 mmHg) versus 18.5% of the normotensives. After 24 months of treatment of high blood pressure, without advice on alcohol consumption, the blood pressures were significantly lower in the group with normal than the group with elevated GGT levels.

In a number of epidemiological studies, the relationship between alcohol use and blood pressure was investigated by the simultaneous assessment in large groups of

blood pressure and alcohol consumption. Despite the large differences in methods and criteria among these studies, there was in general a positive relationship between blood pressure and alcohol consumption (Table 2). The association appears to be most pronounced for systolic blood pressure; in some cases the diastolic blood pressure did not exhibit any correlation with alcohol consumption (4, 7, 17). In these studies statistical adjustments were made for differences in age, weight (14, 19, 37), smoking habits (4, 18, 19), pulse (6, 19) and serum cholesterol level (6). It is important to note that a positive correlation between alcohol consumption and blood pressure has been found especially among those with a higher than average alcohol intake. The findings for moderate and light alcohol consumption are less clear-cut (Fig. 1). Some have described a 'threshold phenomenon': mean blood pressure was only elevated if alcohol intake exceeded 3 glasses per day (3, 6). Others report a J-shaped relationship between alcohol and blood pressure, moderate alcohol drinkers having a lower blood pressure than teetotalers (1, 3, 14). For women this J-shaped alcohol intake-blood pressure curve is even more pronounced than for men. Many studies do not focus on light to moderate alcohol consumption, due to limited data on this part of the distribution curve for alcohol use. Yet, a continuous increase in

Table 2. Examples of differences in blood pressure between subjects with the highest and those with the lowest blood pressure.

Authors	Ref.	Gender	Description of category with highest alcohol consumption	Difference in systolic blood pressure (mmHg)	Difference in diastolic blood pressure (mmHg)
Klatsky et al.	3	f	≥6 glasses/day (1 glass = 12 g alcohol)	10.9	4.5
		m	same definition	5.4	2.1
Arkwright et al.	4	m	>350 ml alcohol/week	5.1	
Dyer et al.	6	m	'problem drinkers'	4.7	
		m	≥5 glasses/day (1 glass = 21 g alcohol)	9.7	5.9
Myrhed	8	m + f	'high alcohol group' (>10 000 g alcohol/year)	9.6	6.7
Cooke et al.	12	f	>21 units/week (1 unit = 10 g alcohol)	5.0	3.8
		m	same definition	7.7	4.7
Gyntelberg et al.	13	m	6–10 units/day ('unit' not defined)	8.1	4.8
Hartburg et al.	14	f	'heavy' (≥395 g/week)	2.0	5.5
		m	'heavy' (≥450 g/week)	5.8	3.8
Gordon et al.	18	f	≥2270 g/month	8.4	
		m	same definition	7.3	
Hofman et al.	19	m	daily alcohol consumption	2.2	2.7
		f	same definition	0.7	1.3
Pincherle et al.	37	m	≥6 glasses/day (1 glass = 10–15 ml alcohol)	4.3	3.2

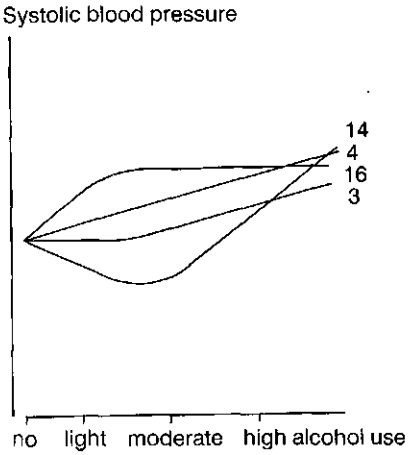

Fig. 1. Various relationships between alcohol use and blood pressure as described in the literature. Numbers refer to References.

blood pressure with increasing alcohol consumption for the range from total abstainers to heavy drinkers has been described in some, but not all, studies (4, 10–12). A factor that can play a role in these inconsistent findings is inadequate information on low or no alcohol consumption so that the group of total abstainers may be 'contaminated' with subjects who do not admit to have a high alcohol consumption. This could cause an inverse relationship at the beginning of the curve although the general view is that this phenomenon, if present, does not completely account for the absence of an association among light to moderate alcohol users.

Very few reports of prospective studies provide data on the association between regular alcohol use and the incidence of hypertension. In the Western Electric Study the increase in blood pressure of initially normotensive subjects was greater in persons consuming six or more drinks per day than in those consuming less. Recently, however, results from the Nurses' Health Study have been published (27). From a cohort of 58 000 American nurses free of diagnosed hypertension, 3275 reported an initial diagnosis of elevated blood pressure during a four-year follow-up period. As compared to non-drinkers, women drinking 20–34 g of alcohol per day had a ca. 1.4-fold increased risk of occurrence of hypertension during follow-up. In those drinking 35 g or more the relative risk was 1.9.

In several studies the question has been addressed whether certain characteristics of the participants modified the association between alcohol use and blood pressure. So far, the association shows no consistently different patterns across genders or between different races. It has been proposed that an effect of alcohol on blood pressure is more pronounced with increasing age, as in the recent analysis of data from the Kayser Permanente study (23). This was not confirmed in some other

studies including the prospective Nurses' Health Study. In the latter study alcohol from spirits and beer showed a stronger association with incidence of hypertension than alcohol from wine. Similarly, in a Norwegian study, wine appeared to be least hypertensive (21). Yet, it should be noted that a certain beverage preference may be an indicator of a life-style that may have an effect on blood pressure through other mechanisms. These and other confounding factors will be discussed in some more detail below.

Data from experimental studies, i.e. randomized trials, on the effects of alcohol use on blood pressure are sparse (28). Potter et al. studied the short-term effects of alcohol on blood pressure and pulse rate in normotensive subjects five hours after the use of alcohol-containing or alcohol-free beer in a double-blind randomized trial (29). Both systolic and diastolic blood pressure rose after alcohol consumption; maximum responses occurred at peak alcohol concentrations and were significantly higher than those seen after placebo treatment. Puddey et al. studied the long-term effects of alcohol reduction in 46 healthy male drinkers with an average pre-trial alcohol intake of 360 g/week (30). The trial aimed at a reduction to 20% of usual intake by drinking low-alcohol beer for six weeks. After adjustment for changes in weight during the study, reduction of alcohol showed an independent effect on diastolic blood pressure with an average fall of 3.1 mmHg for a decrease in alcohol consumption of 70 ml/week.

Mechanisms

Any hypertensive effect of alcohol should eventually be explained by its influence on cardiac output and/or the peripheral vascular resistance as these two haemodynamic characteristics determine arterial blood pressure. Such an influence can occur in a number of ways. An increase in sympathetic nervous system activity, as indicated by elevated concentrations of circulating catecholamines, or an activation of the renin-angiotensin system could raise peripheral resistance. A similar effect could be expected from increases in circulating vasopressin and aldosterone or an elevation of plasma cortisol level. Alcohol could raise cardiac output and the cardiac index (cardiac output per m^2 body surface) by direct or indirect effects on the heart or by enlargement of the circulating volume due to water and salt retention. Finally, it can be assumed that some of the metabolic consequences of alcohol intake will have a hypertensive effect. Several of the above-mentioned factors were investigated and will be discussed briefly here. Comparison of 30 men who had an average alcohol intake of 408 ml/week with a group of men who did not drink alcohol at all revealed that the systolic and diastolic blood pressures were higher in the former group but that there were no differences in plasma concentrations of adrenaline, noradrenaline, active renin, angiotensin II or cortisol (39). In addition, a number of standard stimuli used to measure the sympathetic reaction to physiological stress did not reveal differences between the two groups. This was partially confirmed in another

investigation, although the plasma renin concentrations were twice as high in a group with high alcohol intake than in a group with a low intake (40, 41).

The findings are different after acute ingestion of a quantity of alcohol. Fourteen male students with an average alcohol consumption were studied (42). The reaction to an oral alcohol dose of 0.5 ml/kg body weight was found to be an elevation of adrenaline, noradrenaline and, to a lesser extent, cortisol levels. In addition, the blood glucose level increased, probably as a result of the hepatic glycolytic effect of adrenaline. There was a brief increase in systolic blood pressure and in pulse frequency. The diastolic blood pressure exhibited a decrease after about 40 min. The findings suggest an increase in cardiac minute volume followed by a decrease in peripheral resistance. This can be explained by the increase in circulating adrenaline, possibly in combination with a direct peripheral vasodilative effect of the alcohol. In fact, various reactions of blood pressure to an acute alcohol load have been described, varying from an increase (47) to a decrease (48) or no effect at all (49, 50). One explanation could be that alcohol can have a 'slow pressor' effect on blood pressure which sometimes does not develop until 24 hours after consumption (51).

Haemodynamic changes after acute alcohol intake have also been investigated. To this end minute cardiac output and other ventricular functions were assessed by invasive (dye dilution (50)) as well as non-invasive (echocardiography (52)) methods. In both cases an increase in minute cardiac output and pulse frequency was established; in addition, echocardiography also demonstrated a decrease in stroke volume and peripheral resistance (–15%). Acute intake of alcohol appeared to affect each of the parameters of ventricular function (pulse frequency, preload, afterload) but there was no measurable effect on myocardial function. In contrast, such an effect is found in case of cardiomypathy in chronic heavy alcohol use. However, so-called 'alcoholic cardiomyopathy' is a syndrome comprising at least two histologically different cardiomyopathies, and the question arises whether hypertension also plays a role in pathogenesis (53).

Alcohol use or alcohol withdrawal?

The association between alcohol and blood pressure found in non-experimental studies could partly result from a restriction of alcohol use just before blood pressure measurement. In addition, it is well known that people slow down their alcohol intake in the period just before they visit their physician. Alcohol withdrawal in individuals with a high alcohol intake causes both overactivity of the central nervous system and an increase in sympathetic activity, which is expressed biochemically as an increase in serum catecholamine concentration. In addition, hypercortisolism can develop (54). Both factors may well explain an increase in blood pressure, particularly systolic blood pressure. In two investigations, the blood pressure of patients participating in a detoxification programme was correlated with the severity of the withdrawal symptoms (55, 56). Withdrawal symptoms occur not only as a result of the acute discontinuation of alcohol consumption but also after a less

pronounced decrease in serum alcohol level (57). It is certainly possible that even the consumption of a few glasses of alcohol per day will cause (subclinical) withdrawal symptoms. Although it is not yet clear how these findings affect the observed relationship, it is important to take this possibility into account.

Interpretation of the data

Methodological problems complicate the interpretation of data collected, especially those of non-experimental epidemiological studies. As a rule, alcohol intake in these studies is estimated on the basis of oral or written information provided by the subject himself, which is not always reliable. It has been reported that 50% of the patients of a clinic for hepatic diseases denied alcohol consumption although alcohol could be demonstrated in their urine (58). It is not inconceivable that this means that the group of abstainers might include a number of heavy drinkers who deny alcohol consumption. This could explain the conflicting data concerning the onset of the blood pressure-alcohol curve (see above). In general, the result of these irregularities in data is a weakening of the observed relationship. There are some other reporting-related phenomena that may be operative in some studies (31). A general, non-differential, underreporting of alcohol use results in a systematic underestimation of the actual levels of alcohol use at which effects can be expected.

A number of biochemical determinations are recommended to obtain more insight into alcohol consumption: GGT, GOT, GPT, mean corpuscular volume (MCV) and high-denisty lipoprotein (HDL)-cholesterol (34). However, none of these biochemical parameters appears to be sufficiently sensitive or specific to serve as a biomarker that may replace or substantiate interview or questionnaire data.

Interpretation of the correlation between blood pressure and alcohol consumption is influenced not only by quantification and potential misclassification of alcohol intake but also by various confounding factors which can be associated with both blood pressure and alcohol intake and therefore might explain any eventual correlation. This applies, in particular, for age, sex and body weight; in most investigations results are corrected for these factors. Several other variables have, however, often not been included in the analysis because the relevant information was not available or assessment was too difficult. This applies, for example, to electrolyte intake, notably sodium, potassium and magnesium, medication and physical activity. As it has also repeatedly been found that drinkers smoke more cigarettes (18, 37, 40), it is conceivable that alcohol consumption is related to a life-style that could have an independent effect on blood pressure (59). In addition, a general poor nutritional condition could play a role, especially for heavy drinkers. In this respect stimulation of the renin-angiotensin system by vitamin B deficiency could be considered (44). Chronic alcohol consumption can also cause hypomagnesaemia (53) while a deficient intake of magnesium can be related to (essential) hypertension (60). The same applies for potassium.

Self-selection could cause the observed relationship due to the differences between individuals who choose to drink and those who prefer not to drink. The reverse also applies: specific personality characteristics of hypertensive individuals could give rise to the consumption of alcohol (61). Finally, it is possible that genetic factors give rise to either an elevated blood pressure or (excessive) alcohol consumption, but such an effect remains speculative as there is still quite some discussion on the genetic basis and mechanisms of both high blood pressure and excessive alcohol use. The above-mentioned problems are less important in experimental studies; however, the question then arises of the extent to which the acutely induced effects of alcohol can be extrapolated to the situation of chronic alcohol consumption. Another aspect that plays a role in both types of investigation is the fact that the researcher is never truly 'blind' as far as alcohol consumption or the acute alcohol load is concerned, which could influence his findings. The importance of double-blind studies is obvious, but the execution of such studies is exceedingly difficult.

Conclusions

In limited alcohol use, up to 2 to 4 glasses per day, blood pressure levels hardly show an independent association with the amount of alcohol consumed. When intake of alcohol is high, however, there is a clear, albeit not very strong, relationship between blood pressure and the number of drinks taken per day. Similarly, and not surprisingly, in moderate to heavy alcohol users the incidence of hypertension appears to be increased. The pathogenetic mechanisms of such a relationship are as yet not sufficiently clear. Further investigations are required to determine the importance of differential misclassification of heavy alcohol consumers and the blood pressure effects of alcohol withdrawal in explaining some of the findings in non-experimental studies. These studies may shed more light on the shape of the curve relating low levels of alcohol consumption to blood pressure. In several studies, blood pressure levels in fact appeared to be lowest in moderate alcohol users.

The fact that in the Western world alcohol consumption is common (53) suggests that it is probable that the high prevalence of hypertension in effluent societies is attributable at least in part to the consumption of alcoholic beverages. The degree to which alcohol contributes to the hypertension problem, however, is not easy to determine. The suggestion, by Mathews (65), that about 30% of the cases of hypertension can be attributed to alcohol consumption would seem unlikely and a realistic estimate would probably be closer to 5 to 10%. Nevertheless, the physician treating a patient with high blood pressure should try to obtain the most reliable impression possible of the patient's alcohol consumption habits. A decrease of excessive consumption of alcohol can then be part of the therapeutic management.

From the medical point of view, various standpoints on the consumption of alcohol have been defended in the course of time (66). Although limited use of alcohol appears not to induce an elevation of blood pressure and some data suggest

that blood pressure may actually even drop slightly, there is little basis to stimulate alcohol use as a preventive measure against high blood pressure or cardiovascular disease (67). Moreover, from the perspective of population measures to prevent heavy alcohol use it seems prudent to try to shift the overall distribution of alcohol consumption to the left, whereas any promotion of moderate alcohol use for its potential cardioprotective properties is likely to result in the reverse. On the other hand, there are insufficient arguments to add moderate alcohol consumption to the list of factors responsible for the current epidemic of high blood pressure and its cardiovascular sequelae.

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Alcohol consumption: Protection against coronary disease and risks to health

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Abstract

Prospective cardiovascular surveys in Trinidad (West Indies) and London (UK) provide further evidence for alcohol's protective action against CHD and suggest mechanisms for this effect. In the Trinidad survey of 1386 men aged 35–69, ex-drinkers had higher prevalence rates of cardio-respiratory disorders, liver disease and alcohol dependence than abstemious men, indicating that drinkers tended to relinquish the habit with deteriorating health. Relative risk of death from all causes in typical drinkers was 66% of that for abstemious men, partly because, unlike in the alcoholic men, their drinking habit did not carry an increased risk of injury or disorders such as liver disease and hypertension, and partly because drinking was associated with a reduced risk of CHD. Thus, after exclusion of ex-drinkers and allowance for other risk factors including HDL and total serum cholesterol, men reporting 5–14 drinks in the week before entry had only 46% of the risk of CHD of abstemious men. The London (Northwick Park) Study found that alcohol intake was inversely related to plasma fibrinogen concentration, positively associated with plasma fibrinolytic activity, and inversely related to platelet aggregability.

Alcohol may afford protection against coronary thrombosis by effects on haemostatic and fibrinolytic pathways, as well as through changes in plasma lipoproteins.

Introduction

Many prospective surveys have described either a linear and inverse relation (23, 29) or a U- or J-shaped association (2, 3, 8, 12) between alcohol consumption and the risk of coronary heart disease (CHD). The interpretation of these findings to mean that a moderate alcohol intake confers some protection against CHD has aroused contention (22, 24). In the British Regional Heart Study (23) the inverse association was apparent only in men who already had cardiovascular disease (CVD) or CVD-related disease diagnosed before entry. This observation led to the suggestion that

the associations described had arisen not because alcohol was protective in moderation, but because drinkers tended to relinquish the habit with deteriorating cardiovascular health. On the other hand, in several studies in which changes in drinking pattern before baseline had been recorded, the risk of CHD was found to be higher in lifelong abstainers than in moderate drinkers (7, 26, 29). Shaper has argued that deficiencies in studies to date have included a lack of documentation of the burden of chronic disease by category of alcohol consumption in men entering prospective surveys, a failure to separate the lifelong teetotaller from the ex-drinker, and failure to exclude from the statistical analysis not only men with CHD at entry, but also those with other conditions which the data suggest act as a discouragement to further drinking (22, 24). These questions have been addressed in a ten-year survey undertaken in Trinidad, West Indies, in which drinking habits, previous drinking habits and health status were recorded at recruitment. Some insights into possible mechanisms for the putative association have been suggested by the Northwick Park Heart Study. This contribution considers the evidence provided by these two epidemiological studies.

The St. James Survey, Trinidad

The survey population

The forebears of the surveyed community came mainly from West Africa and India. Smaller numbers were of Chinese, European and Semitic origins, while even fewer were Amerindian. The social disorganization created among these peoples by colonial immigration policies has taken many years to correct, and even today have not been rectified fully. However, common nationality, language, law, education and forms of employment have led to considerable cohesion in what nevertheless remains a pluralistic urban society. There has been considerable miscegenation, particularly between African and European. Even within the home, tastes in diet and other habits are shared to a large extent, and no trait is confined to one group.

Trinidad and Tobago experienced rapid socio-economic development between 1966 and 1980, when the gross national product increased by more than eightfold (21). These advancements brought improvements in health such that when the survey began, the average life expectancy of men aged 40–60 years was only 2 years less than in England and Wales (16). Morbidity and mortality nowadays resemble those in temperate climes, and cardiovascular disease is the leading cause of death over 44 years of age (5, 16). The St. James Survey was conducted in this setting between 1977 and 1986. All residents aged 35 to 69 years in a geographically defined area of the capital, Port-of-Spain, were identified by household census. Each subject was then given an appointment for a home visit between 06.00 and 08.00, and a second for examination at the survey office.

Baseline assessment

A questionnaire was used to record ethnic origin (based upon the ancestry of grandparents), medical history, and cigarette and alcohol consumption. Blood pressure was recorded with a random-zero sphygmomanometer and a resting electrocardiogram (ECG) was taken and coded by Minnesota criteria (20). A blood sample was drawn before breakfast for serum lipoprotein lipid and blood glucose concentrations as described elsewhere (17, 19). One physician conducted all examinations, noting hepatomegaly and seeking confirmation of diseases of the cardiovascular system, eye disease, mental disorders and alcohol dependence from the participant's physician when suspected.

The alcohol questionnaire

This commenced with 'How many drinks of beer, wine and spirits have you had in the past 7 days?' Subjects were encouraged to recall each day to reach a best estimate. (Beer is sold in 280 ml bottles, 4.2% alcohol by volume. Rum and whisky are 43% alcohol. Thus, as elsewhere, one drink was equivalent to approximately 10 g of absolute alcohol.)

The second question asked whether the respondent usually drank. A negative response was coded when the reply was 'No' or 'Not any more'. Past and present drinking problems were then detected with the CAGE questionnaire (3) (slightly modified to suit local dialect):

1. 'Has your drinking habit ever reached the point where you felt you should cut it down?'
2. 'Have you ever felt bad, ashamed or guilty about your drinking habit?'
3. 'Have you ever found yourself becoming annoyed or irritated by anybody criticizing your drinking habit?'
4. 'Have you ever taken a drink first thing in the morning to steady your nerves, or get rid of a hangover?'

The answers to this questionnaire were used to place each respondent into one of four categories:

1. Abstemious: did not usually drink and responded negatively to all four questions on problem drinking. Some will have been totally abstinent.
2. Ex-drinker: did not usually drink but responded positively to at least one of the questions on problem drinking. These men were not necessarily totally abstinent.
3. Alcoholic: usually drank and answered at least three questions on problem drinking positively.
4. Typical: usually drank but did not qualify as alcoholic. Some admitted to drinking problems nevertheless.

Prospective surveillance

Each participant was visited at least once yearly. Any who gave a history suggestive of CHD was recalled for diagnostic evaluation and, when required, referral for care. Those who went abroad were sent a questionnaire annually and were re-examined during return visits. All survivors were offered a repeat ECG after five years.

The medical records were abstracted for all hospital admissions, and deaths were traced through families, hospital records, registers of death and obituary notices. The underlying cause of morbidity or mortality was established by independent review of the assembled documentation by two physicians, without reference to baseline status, with a third as arbiter when needed. All injuries, diseases and causes of death were coded according to the International Classification of Diseases (9th revision) (11). Events in which CHD was considered to be the underlying cause were coded by presentation as ischaemic heart disease (410–414), dysrhythmias (427), heart failure (428), myocardial degeneration (429.1), sudden death (798.1–2), or a new major Q-wave (11) in V5 of the 5-year ECG.

Baseline drinking and disease patterns

Of the 1386 men in the area without mental handicap, 1342 (97%) answered the alcohol questions (one of whom refused to answer the CAGE questions). Their distribution by drinking category (%) was as shown in Table 1.

Overall, as many as 40% of these men answered positively to at least one of the questions on problem drinking (504 (38%) had felt a need to cut down on drinking, 248 (18%) had felt ashamed or guilty, 196 (15%) had experienced annoyance over criticism, and 167 (12%) had taken alcohol first thing in the morning). Positive responses to 3 or 4 questions on problem drinking were given by as many as 191 (14%) of men, some of whom were ex-drinkers. Table 1 shows a distinct tendency for 'usual drinkers' (typical and alcoholic) to decline in frequency and for the abstemious and ex-drinker patterns to increase at older ages.

Table 1. Survey population by drinking category.

Drinking category	Number (%) within age group (years)		
	35–54	55+	all ages
Abstemious	136 (18.3)[1]	164 (27.5)	300 (22.4)
Typical	469 (63.0)	311 (52.2)	780 (58.2)
Alcoholic	87 (11.7)	56 (9.4)	143 (10.7)
Ex-drinker	53 (7.1)	65 (10.9)	118 (8.8)
Total	745 (100)	596 (100)	1341 (100)

[1] In parenthesis: % of total.

Table 2. Drinks in previous week by age group.

Number of drinks	Number (%) within age group (years)				
	35–44	45–54	55–64	65+	all ages
0	82 (24)[1]	132 (34)	164 (40)	91 (50)	475 (35)
1-4	71 (20)	66 (17)	94 (23)	33 (18)	264 (20)
5-14	85 (23)	95 (25)	77 (19)	35 (19)	292 (22)
15-59	94 (26)	76 (20)	71 (17)	21 (12)	262 (20)
60+	24 (7)	15 (4)	8 (2)	2 (1)	49 (4)
Total	362 (100)	384 (100)	414 (100)	182 (100)	1342 (100)

[1] In parenthesis: % of total.

Table 2 gives the number of drinks reportedly consumed in the previous week by each age group.

The proportions of men reporting no alcoholic drinks in the previous week increased steadily with increasing age group, whereas the proportions taking 15–59 or 60 or more drinks in the same period showed a gradual decline. Of the men aged 35-44 years 7% reported taking at least 60 drinks in the previous week, whereas the respective figure in those over 64 years was only 1%. These figures accorded with the distribution of drinking categories by age group. None in the abstemious and ex-drinker categories (i.e. those who stated that they did not usually drink) had had any alcohol in the previous week. Among typical drinkers, 6% reported no drinks, 32% reported 1–4 drinks, 33% reported 5–14 drinks, 26% reported 15–59 drinks, and 3% reported 60 or more drinks in the previous week. In the alcoholic category 20% had taken 60 or more drinks in this period.

Baseline disease rates

In Table 3 the frequencies (%) of certain symptoms and physician-diagnosed diseases reported by men in the abstemious and ex-drinker categories are shown by age group:

In both age groups, ex-drinkers reported higher frequencies of prolonged chest pain, exertional dyspnoea, diseases of the heart and arteries, liver disease and physician-diagnosed alcohol dependence than abstemious men. Younger ex-drinkers gave a history of gastro-intestinal disorders more commonly than abstemious men, while the older ex-drinkers reported exertional chest pain, diabetes mellitus and cataract more often than the abstemious group. None of the signs, symptoms and disease diagnoses sought was found to be significantly more frequent in abstemious men than in ex-drinkers. These results suggested that drinkers tended to give up drinking when they developed cardio-respiratory symptoms, gastro-intestinal disorders and perhaps deteriorating vision, or when a diagnosis was made of cardiac disease, hepatic disease, or alcohol dependence.

Table 3. Baseline disease patterns.

Symptom/disease	Frequency (%) in age group (years)			
	35–54		55+	
	abstemious $n = 136$	ex-drinker $n = 53$	abstemious $n = 164$	ex-drinker $n = 65$
Exertional chest pain	3.0	0	6.7	12.3
Prolonged chest pain	2.2	9.5	6.1	9.7
Exertional dyspnoea on level ground	2.9	9.4	5.0	9.4
Diseases of the heart and arteries	4.4	7.5	12.2	18.5
Hypertension	18.3	18.9	31.8	38.4
Diabetes	8.0	7.6	18.3	24.4
Liver disease	0.7	5.7	0	7.7
Alcohol dependence	0	7.5	0	13.8
Cataract	0	0	2.4	7.7
Other 'serious' disease, mainly gastro-intestinal	3.7	11.3	5.0	3.2

Morbidity and mortality during follow-up

During the study, 9.1% of alcoholics had a serious accident, injury or poisoning, as compared with 5.1% of ex-drinkers, 2.2% of typical drinkers and 2.7% of abstemious men (age-adjusted rates). The all-causes mortality by drinking category is presented in Table 4.

Abstemious men and ex-drinkers had a similar mortality rate, whereas in typical drinkers the overall death rate was only 66% of that experienced by the abstemious group. Although mortality was highest among alcoholics, the difference with that of the abstemious group was not statistically significant. When this analysis was repeated according to the number of drinks reported in the previous week, with those taking no alcohol as the referent group, men consuming 5–14 drinks had the lowest relative risk (0.58), and those taking 60 or more drinks the highest (1.95), but these group differences in all-causes mortality were not statistically significant.

Table 4. All-causes mortality by drinking category.

Drinking category	Deaths[1]	Deaths per 1000 person-yrs[1]	Relative risk (95% confidence interval)
Abstemious	61	25.3	1 (by definition)
Ex-drinker	27	21.8	1.10 (0.69–1.73)
Typical	89	16.2	0.66 (0.48–0.92)
Alcoholic	35	34.9	1.38 (0.91–2.11)

[1] Adjusted for age and ethnic group.

Table 5. Coronary heart disease incidence according to recent alcohol consumption.

Drinks in previous week	CHD events	Event rate per 1000 person-years[1]	Relative risk (95% confidence interval)
0	21	12.2	1 (by definition)
1–4	12	10.1	0.83 (0.4–1.7)
5–14	9	5.6	0.46 (0.2–1.0)
15–59	7	3.8	0.31 (0.1–0.8)
60+	0	0	

[1] Adjusted for age, ethnic group, smoking habit, systolic blood pressure and serum cholesterol concentration.

Cardiovascular morbidity and mortality

The analysis so far has suggested that drinking habits changed with age, and that men tended to give up drinking as their health deteriorated. These factors clearly needed to be controlled for in any analysis of alcohol intake in relation to cardiovascular disorders. Furthermore, drinking habits and disease patterns also differed between ethnic groups, as reported elsewhere (16–19), and therefore ethnicity must also be taken into account in communities such as that in Trinidad. Allowance for effects of age, ethnic group and other risk factors on cardiovascular mortality was made by appropriate statistical adjustment in log-linear regression. Change in drinking habit owing to illness prior to entry was taken into account by excluding all ex-drinkers and all men with CHD or diabetes mellitus at baseline from the further analysis. Table 5 presents the numbers of CHD events, event rate and relative risk of an event according to the number of drinks reported in the previous week in the 928 men eligible for inclusion in this analysis.

After adjustment for other risk factors, a distinct linear trend to decreasing risk of CHD with increasing alcohol intake was apparent (χ^2_1, 11.5, $P < 0.001$). Men who reported 5–14 drinks in the previous week had less than half the risk of CHD of men who took no alcohol in that period.

When this analysis was repeated to include adjustment for HDL cholesterol concentration in addition to the 5 variates shown, relative risk estimates remained essentially unchanged. Of the men reporting 5–14 drinks in the previous 7 days, 88% were typical drinkers.

The Northwick Park Heart Study - mechanisms of protection

The St. James Study suggested that alcohol affords protection against CHD through additional mechanisms other than plasma lipoprotein lipid concentrations. Data from the Northwick Park Heart Study raise the possibility that alcohol might have beneficial effects on plasma fibrinogen concentration, fibrinolytic activity and platelet aggregability, thereby reducing the risk of an occlusive coronary thrombosis. In this

British cardiovascular survey, 3500 men and women were recruited between 1972 and 1978 from a number of occupational groups. The primary objective was to seek associations between haemostatic factors and individual risk of CHD.

Of 7 factors measured at baseline, factor VII coagulant activity and plasma fibrinogen concentration emerged as powerful predictors of CHD (14). Other groups have yet to report definitely on factor VII as a predictor of risk, but several other epidemiological studies have confirmed the positive relation between fibrinogen concentration and risk of CHD (6, 27, 28, 30). In cross-sectional data from the Northwick Park Heart Study, plasma fibrinogen concentration was on average about 5% lower in current drinkers than in non-drinkers, both in smokers and non-smokers, and appeared to decrease linearly with increasing intake in both sexes (13). This association between alcohol intake and fibrinogen concentration has been reported by others (9, 31).

In the Northwick Park Heart Study, fibrinolytic activity as measured by a dilute blood clot lysis time method was weakly but significantly associated with risk of CHD in middle-aged men, those with the highest activity levels having a relatively low risk (14). Alcohol consumption was positively associated with fibrinolytic activity in both sexes, though only the relation in men was statistically significant (13). Finally, platelet dose-response aggregometry was introduced during the course of the Northwick Park Heart Study. Platelet responsiveness to adenosine diphosphate and adrenaline were both inversely related to alcohol consumption, implying a decreasing aggregability with increasing intake (15). Although an epidemiological association between platelet responsiveness in vitro and risk of CHD has yet to be established prospectively, there are good reasons to believe that the readiness of platelets to aggregate in vivo may be an important determinant of thrombus formation.

Risks and benefits

Alcohol consumption is well known to increase the risk of all types of injury, particularly fatal accidents, in both a recreational and occupational setting. This association was well illustrated in the St. James Study, in which 9.1% of the alcoholic group suffered a miscellany of serious injuries and poisonings during follow-up, as compared with 5.1% of the ex-drinkers, 2.7% of the abstemious group and 2.2% of typical drinkers.

The vulnerability of the alcoholic was also demonstrated by the basal distributions of symptoms, signs and physician-diagnosed diseases. For example, liver disease had been diagnosed in 10.1% of the alcoholic group and 6.6% of ex-drinkers, but in only 0.4% of the abstemious group and 0.1% of the typical drinkers. Hypertension had been noted in 33.7% of the alcoholic men, 27.6% of ex-drinkers, 24.3% of the abstemious men and 22.7% of the typical drinkers. Disabling breathlessness was complained of by 11.9% of alcoholics, 9.4% of ex-drinkers, 3.9% of abstemious men and 3.1% of typical drinkers. These contrasts suggested that alcohol consumption is not injurious to health until dependence overrides its use merely for social purposes.

The problem, of course, is to recognize those at risk of dependence. Here a simple instrument such as the CAGE questionnaire may prove of value.

The typical drinker had a significantly lower all-causes mortality than abstemious men. This appeared to be due in part to an absence of any excess of injury, poisonings, liver disease and hypertension, and in part to a low risk of cardiovascular disease. On the other hand, mortality in the alcoholic was raised owing to an increased risk of death from a multiplicity of causes which more than offset any protective role of alcohol against CHD.

The danger of dependence, combined with the dose-response nature of the relation between acute intake and motor-vehicle accidents for example (1, 10), makes alcohol an unsuitable cardioprotective drug. Nevertheless, these problems should not deter further research into the mechanisms whereby alcohol protects against CHD.

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Alcohol and fibrinolysis

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Abstract

Epidemiological studies have shown an inverse relation between moderate alcohol use and the incidence of coronary heart disease. Potential mechanisms explaining that relation may be found in the haemostatic processes. One possible candidate is the fibrinolytic system which, as the natural anticoagulant system in the body, may be reinforced by moderate alcohol consumption. Such an effect might protect against thrombo-embolic complications.

From epidemiological and experimental studies into the effects of alcohol consumption it can be concluded that the long-term effects of alcohol consumption on fibrinolytic variables are moderate. The short-term or acute effects, however, are marked and involve two- to ten-fold changes in blood levels of some components.

A recent study has shown that alcohol induces significant short-term increases in levels of the tissue-type plasminogen activator (t-PA). The data further support the notion that this increase is mainly effective with moderate alcohol consumption.

It is postulated that this increased fibrinolysis potential can contribute to a reduction of the risk for thrombo-embolic disease in two ways.

1) The increase of t-PA, which lasts for 10–15 hours, can counteract new thrombotic events and enhance the removal of old clots locally in the vessels where t-PA is released by the endothelium.
2) The t-PA increase reaches a peak in systemic activity in the early morning following an evening of moderate alcohol consumption. This peak coincides with the period of highest risk for myocardial infarction. It can be postulated that in moderate alcohol consumers the morning peak in frequency of infarctions is blunted, thus possibly explaining the lower risk in this group.

Abbreviations
dDAVP, desamino-D-arginine vasopression; LP(a), lipoprotein (a); PA, plasminogen activator; PAI-1, plasminogen activator inhibitor-1; t-PA, tissue-type plasminogen activator; u-PA, urokinase-type plasminogen activator.

Introduction

In epidemiological studies an inverse relationship between moderate alcohol use and the incidence of coronary heart diseases has been found (reviewed in 44, 51, 56) which has been confirmed very recently (24). In view of the importance of thrombo-embolic mechanisms in coronary heart disease potential mechanisms explaining this relationship might be found in the haemostatic processes.

In epidemiological and experimental studies several effects of alcoholic beverages on the natural anticoagulant system of fibrinolysis have been reported, which will be summarized in this paper. These effects will be interpreted retrospectively on the basis of recent data and recent insights into the mechanisms of fibrinolysis. In addition, some unpublished data from recent studies will be included.

Fibrinolysis

As a natural consequence of coagulation and local fibrin formation, the fibrinolytic system becomes activated and eventually generates the proteolytic enzyme plasmin which degrades the fibrin matrix of a clot or thrombus (see Fig. 1) (30, 31). These processes usually occur locally at the site of injury, and the fibrinolytic process is, to a large extent, regulated by local molecular mechanisms involving binding to, and assembly on, the fibrin structure. Also, acute local supply of factors from platelets and the endothelium plays an important role, while other factors are supplied by the blood. As can be seen in Fig. 1, the local supply mentioned mainly involves tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1).

Baseline situation

In epidemiological and long-term experimental studies, the condition in baseline blood samples (taken at rest, usually in the morning) has been recorded, reflecting the resting state or potential of the fibrinolytic system in the circulating blood. The fibrinolytic potential in such samples has frequently been evaluated by using a functional analysis of the overall potency of the blood system in clot lysis methods where the whole blood (or a fraction) is clotted and lysis is quantified. In such methods the changes observed can be due to changes in various factors of the whole fibrinolytic cascade (see Fig. 1). In more recent years specific functional and immunological methods for practically all fibrinolytic components have become available. The major cell types supplying these factors to blood are hepatocytes (e.g. factor XII system, plasminogen, α_2-antiplasmin, fibrinogen, histidine-rich glycoprotein, possibly PAI-1), endothelium (t-PA and possibly PAI-1) and possibly smooth muscle cells (PAI-1).

In the study of baseline blood, important local supply mechanisms that only happen during coagulation activation are not evaluated. Such effects can be

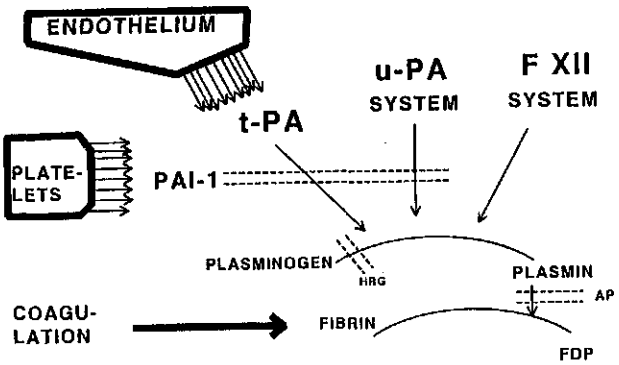

Fig. 1. Schematic representation of the fibrinolytic pathway. Fibrinolysis is the degradation of fibrin into soluble fibrin degradation products (FDPs). This degradation is achieved by plasmin formed from its precursor when needed by three different routes involving plasminogen activators. Abbreviations: u-PA, urokinase-type plasminogen activator; t-PA, tissue-type plasminogen activator; F XII, factor XII; HRG, histidine-rich glycoprotein; AP, α_2-antiplasmin. The scheme indicates specifically the acute local supply of the factor t-PA from endothelium and the factor PAI-1 from platelets accumulating during coagulation. PAI-1 is an inhibitor capable of inhibiting both t-PA and u-PA.

evaluated, for instance, for t-PA to a certain extent by experimental stimulation through dDAVP infusion, exercise and venous occlusion.

In recent years, another approach has gained momentum and other methods have become available (32). This approach concerns the evaluation of specific degradation or activation products which mark the action or turn-over in the process. Such turn-over happens continuously at a very low level and its condition and changes can be recorded. Examples of products for evaluation are fibrin degradation products (FDPs) and plasmin-α_2-antiplasmin complexes.

Adaptation/acute effects

Two important features of the fibrinolytic system which complicate evaluation are the occurrence of a sinusoidal diurnal fluctuation in appearance in blood of t-PA and PAI-1 and the possibility of rapid adaptation of synthesis and clearance of some of the fibrinolytic components.

For the circadian rhythm, analysis of a single blood sample should at least be standardized with respect to time of sampling. For factors with a circadian rhythm this carries the risk of missing changes (33). Only an evaluation of 2–3 samples sampled on well chosen times is adequate.

The rapid adaptation of the system should either be avoided or deliberately included in the approach, in a standardized way. Rather strict rules for sampling of blood have been formulated for the study of a baseline condition (34). Recent observations indicate that there can be residual effects of alcohol intake the evening before, which are especially evident in middle-aged volunteers. This has led to a more strict rule that alcohol consumption is to be avoided at least 24 h before

sampling (34). It is possible that, depending upon instructions to participants, epidemiological studies are affected by carry-over effects of the participants' evening habits, particularly with regard to alcohol consumption.

In evaluating fibrinolysis in relation to alcohol consumption we have strictly divided the studies into epidemiological and long-term experimental studies involving analysis of 'base-line' blood samples on the one hand and a category of studies on acute effects on the other. A similar division has also proved to be valuable in the past for the effects of smoking: the acute and chronic effects on blood fibrinolytic activity were found to be opposite (1, 2).

Recent improvements in laboratory methods

It has only recently been fully appreciated how the coexistence in the circulating blood of the active enzyme t-PA and its active specific inhibitor PAI-1 (usually present in excess) influences existing pre-analytical technology and assay methods and what an ideal methodology should be.

It is theoretically obvious that the interaction of these components continues to manifest itself in vitro and reduces the recovery of active t-PA. To be able to identify the situation in the circulating blood, the situation needs to be 'frozen' immediately on sampling. The problem not only concerns specific assays for t-PA activity; because t-PA activity determines largely the spontaneous fibrinolytic activity of blood and blood fractions, it holds for all such methods. The necessity to stabilize t-PA can be calculated from kinetic data which have indicated that, in normal individuals, levels of both components are such that t-PA activity is halved (also in vitro) in 5–10 minutes. PAI-1 levels can be increased temporarily 10- to 1000-fold (circadian rhythm, trauma), and already with a 10-fold increase the time to reduce t-PA activity by 50% is ca. 30 s (31). Sampling at about pH 6.0 is one way of stopping the interaction of t-PA and PAI-1, and the above calculation could be confirmed experimentally (49, 62). It is now clear that special blood sampling procedures are required for t-PA activity and blood fibrinolytic activity measurements and that any use of normal, usually frozen, plasma should be abandoned. In practice, pre-analytical variation was controlled by rigorous standardization of blood handling and, in retrospect, the dilute blood clot lysis method requiring rapid handling and early dilution provided the best situation for maintenance of t-PA activity and for standardization of losses.

Another misfortune (retrospectively) concerned the fact that PAI-1 was recovered in euglobulin fractions (29). Earlier, it was generally believed that this fraction is poor in fibrinolysis inhibitors and hence a proper matrix for recovering t-PA and measuring its activity appropriately. We found that eventually only about 3% of the original t-PA activity was measured when euglobulin fractions were used. Accordingly, normal blood levels of t-PA activity currently reported are around 1 IU/ml, compared with previously reported normal values of ca. 0.05 IU/ml.

The latest achievement in methodology concerns the inactivation of PAI-1 activity at a pH of around 3 and dilution of the sample which allows for appropriate recovery

of plasma t-PA activity (39, 62). This new methodology in sampling and assay has been used only very recently in clinical studies and in an unpublished study which is reviewed below.

Epidemiological studies

Until recently, few epidemiological studies have included fibrinolytic variables in the laboratory test battery. It can be expected that ongoing studies will soon report further data, but at present only inconclusive data on fibrinogen concentrations and limited data on blood fibrinolytic activity and some specific plasma factors of fibrinolysis are available.

Fibrinogen

After one report had suggested a relation between alcohol consumption and fibrinogen concentrations in blood, also a substantial number of reports showing no association appeared. Thus, in 1979, Meade et al. (41) reported a study among 1601 men and 707 women aged 18–64 in North-West London in which a negative association between fibrinogen concentration and alcohol consumption was found. This association was confirmed in 1983 by Yarnell et al. (63) in a study among 670 men from the general population (aged 30–69) of Caerphilly, South Wales. However, the latter group found this association only when fibrinogen was determined chemically, not with a clotting rate assay. The association was further detailed in 1988 by Rogers et al. (50) in a sub-sample of 665 men of the Caerphilly study; fibrinogen was correlated both with data from a 7-day weighed dietary inventory ($P < 0.01$) and with data from the complete cohort of 2512 completing a questionnaire ($P < 0.001$). A non-significant trend was reported in 1991 by Iso et al. in 150 Japanese and Caucasians (23), while in 1983 Bain (4), in a sub-set of 237 men and 149 women of a study on volunteers from the staff of the Prince Charles Hospital, Brisbane, Australia, and of a large London insurance firm found the association only in women. No association between alcohol consumption and fibrinogen was observed in 1988 by Boniton-Kopp et al. (7) in 251 apparently healthy men aged 40–50 in Paris; in 1985 by Balleisen et al. (6) in 2880 men and 1306 women in the Münster Arteriosclerosis Study; in 1991 by Møller & Kristensen (43) in a cohort of 439 men in the Glostrup Population Studies; in 1982 by Baker et al. (5) in 265–281 men (aged 45–64) drawn randomly from the practices of 16 general practitioners in the Speedwell study, with two methods of fibrinogen determination; in 1987 by Hamsten et al. (18) in 85 families with a proband with early myocardial infarction and 85 families randomly selected from the general Swedish population.

A variety of causes may underly these differences in observations: the effect is not large (23, 50, 63) and can be obscured by various other aspects. Such aspects may be differences in accuracy of recording the alcohol consumption, the average level of

alcohol consumption in a population, the type of beverage (80% beer in the study of Meade et al. (41)) and interaction of alcohol with other demographic and life-style characteristics such as smoking and dietary habits (6). The assay of fibrinogen may also be of significance as suggested by the discrepancy between methods in the Caerphilly study (63). Hamsten et al. (18) observed in the Swedish population that 51% of the variance of the plasma fibrinogen levels was accounted for by genetic heritability and concluded that there was a limited role for environmental influences.

Plasminogen

In a small cross-sectional study among 15 smokers and 15 non-smokers, all healthy males between 30 and 40 years of age, reported in detail previously (2), we observed in both groups a positive association between alcohol consumption and plasminogen concentration ($P < 0.05$ and $P < 0.02$, respectively) (Fig. 2). Alcohol consumption was generally moderate, not exceeding 1–2 consumptions a day on a regular basis, and weekend drinking.

In a later experimental study in 12 apparently healthy young men (21–29 years), we observed a small dose-dependent increase of 4 and 6.5% ($P = 0.01$) in plasminogen concentration after consumption of 2 or 4 glasses of wine a day for 5 weeks (48). The values rose with increasing dose, but only the differences between abstaining and drinking were significant.

Recently, it was discovered that the LDL-like particle, lipoprotein (a), harbours an apoprotein with strong homology with plasminogen. Elevated plasma levels of this component had been identified as a risk marker for atherosclerotic coronary disease

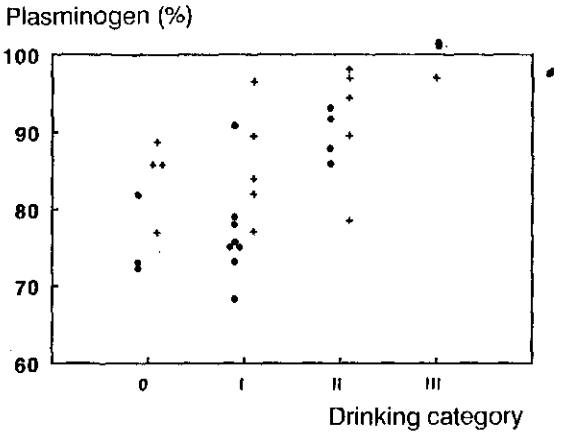

Fig. 2. Relation between plasma plasminogen concentration and drinking habits in healthy males aged 30–40. Plasminogen is expressed as percentage of a pooled plasma; drinking category: 0, no alcohol; I, irregular, small amount per week; II, 1–3 drinks a day, weekend; III, 1–2 drinks a day + weekends. · non-smokers; + smokers. After: Allen et al. (2).

Table 1. Lipoprotein (a) concentrations in Inuit classified into categories with different level of habitual alcohol consumption. After: Johanson et al (25).

Alcohol category[1]	Number of individuals	LP(a), mean ± SD (mg/dl)
1	15	8.7 ± 11.1
2	85	9.2 ± 10.4
3	33	8.0 ± 6.5

[1] 1, less than 1 consumption a day; 2, 1–2 consumptions; 3, more than 2 consumptions a day; $P = 0.595$.

(54). A potential mechanism explaining the risk of high LP(a) might concern competition with plasminogen and inhibition of its action (37). In addition, it is possible that PAI-1 expression in endothelial cells is increased by LP(a) (14).

The observation that LP(a) levels increased rapidly after ethanol withdrawal in alcoholics raises the possibility that ethanol intake is one of the few factors that affect the quite stable, genetically determined plasma LP(a) concentrations (27). Further investigations are required. In a recent study in 133 Inuit living in Greenland, no relation with habitual alcohol consumption was observed (see Table 1). Thus, in this population (25) there was no support for the above hypothesis.

Blood fibrinolytic activity

Until now only one report about blood fibrinolytic activity and alcohol consumption is known. Meade et al. (41) reported a positive association between fibrinolytic activity as measured by a dilute blood clot lysis technique and alcohol consumption. This association only concerned the 1601 men in the study and was not significant in the 707 women (9, 41), who had a lower average consumption (40).

These epidemiological data are hard to confirm because it is unlikely that further data on the dilute blood clot lysis time method will become available: this method is no longer in general use and is technically and logistically demanding, requiring fresh blood to be studied immediately. It can be expected that data on specific fibrinolysis factors possibly involved in the change of the blood fibrinolytic activity will become available. The dilute blood clot lysis method is sensitive to variation in various factors of fibrinolysis, including fibrinogen and plasminogen, but it is unlikely that the small differences in fibrinogen and plasminogen induced by alcohol (ca. 5%) fully explain the observed changes reported by Meade et al. (41). Other factors with a large impact on the dilute blood clot lysis test such as, notably, α_2-antiplasmin, plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (t-PA) might be candidates.

Reported data indicate that α_2-antiplasmin is not likely to be involved. Boniton-Kopp et al. (7) noted a slight negative trend (not statistically significant), if any effect at all, between alcohol consumption and α_2-antiplasmin. Mettinger (42) found no

significant relation with α_2-antiplasmin and alcohol consumption in 119 subjects with minor ischaemic cerebral lesions living in a district of Stockholm.

Data on PAI-1 are limited and provide at the very most a suggestion of alcohol dependence. Mettinger (42) found no relationship in the Stockholm population mentioned, and in a recent study among sedentary male workers recruited at the Free University of Amsterdam (aged 25–40) no correlation between PAI activity (after logarithmic transformation) and alcohol consumption was found ($r = 0.0756$, $n = 57$, $P = 0.576$). The average alcohol consumption was 1.43 ± 1.48 (SD) glasses per day. The consumption recorded by questionnaire correlated with the consumption recorded on two occasions by a three-day diet diary method ($r = 0.509$–0.767, $P < 0.0001$). The relationship between alcohol consumption and PAI activity is shown in Fig. 3.

A trend becomes apparent only when regular drinkers (more than one glass a week) are studied separately ($r = 0.2615$, $n = 47$, $P = 0.076$), while comparison with the non-drinkers (below one glass/week) shows significance ($P = 0.038$). This suggestion of a relation is possibly supported by data from Tran-Thang et al. (53) who found elevated PAI-1 and normal t-PA values in alcoholics without signs of liver damage.

It can be concluded that the effects of alcohol on PAI-1 are not likely to contribute to an increased blood fibrinolytic activity, but may at the most exert an opposite trend in inhibiting lysis.

One of the remaining candidates is t-PA, which is expressed relatively well in the dilute blood clot lysis time assay. There is an acute increase in t-PA antigen upon alcohol consumption (see below), which effect might stabilize with regular alcohol

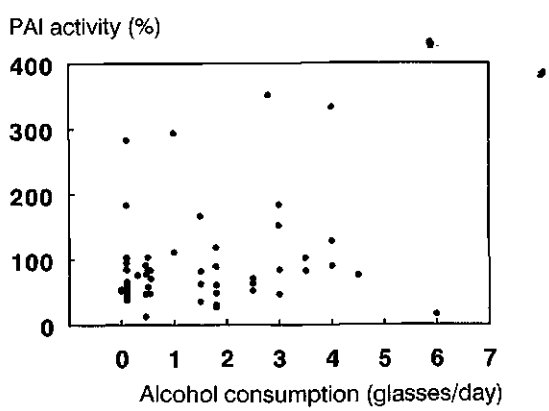

Fig. 3. Relation between alcohol consumption and PAI activity. PAI activity was recorded in morning blood samples (09.00–11.00) and expressed as a percentage relative to a pooled plasma standard (290385) determined to neutralize 7.6 IU/ml of t-PA activity (60). Alcohol consumption is expressed as the average number of glasses of alcoholic beverages per day over the past three months. Subjects were recruited from the pool of male workers at the Free University of Amsterdam aged 25–40 and had not been involved in sport or fitness training during the preceding half year (17).

consumption. With the new method for t-PA activity assessment mentioned above its possible chronic elevation can be verified in the future.

Experimental studies

Long-term effects

In a large, randomized, controlled trial, Burr et al. (8) studied in a single cross-over design the effects of 4 weeks of alcohol consumption as compared to 4 weeks of total abstinence in 48 men and 52 women aged 19–60. Alcohol consumption was not standardized and varied from less than two drinks a week to more than 20 per week (mean intake 18.4 g alcohol per day). The type of alcoholic beverage was left to choice. At the end of each experimental period a fasting blood sample was taken. No significant effect of alcohol consumption on fibrinogen was observed.

Pikaar et al. (48) confirmed the absence of an effect on fibrinogen in a study comprising four different standardized amounts of red wine during a five-week experimental period in 12 male volunteers between 21 and 29 years of age. The treatments consisted of 0, 2 and 4 glasses of red wine per day. The effect of 'binge drinking' was also studied over a period of five weeks in which 14 glasses of red wine were consumed each weekend. Plasminogen levels were found to increase moderately; only the differences (4–6.5%) between abstinence and drinking were significant. t-PA activity in euglobulin fractions of plasma showed a large and dose-dependent decrease. Additional analysis revealed an increase in PAI-1 activity (35), which might cause the reduction of euglobulin t-PA activity in view of the large impact of PAI-1 on evaluation of this variable with previous methods (see above).

It appears that a long-term increase in PAI-1 requires alcohol to be consumed over a prolonged period. Thus, a single episode of four days of wine consumption (58) was insufficient to cause an effect. Another question is how regular alcohol consumption needs to be to bring about an effect. Apparently, binge drinking on three days a week was insufficient to cause an effect that lasted until the time of sampling on the next Wednesday/Thursday (48). It would be interesting to see what degree of irregularity (abstinence for one day a week, two days a week, ...?) would prevent a long-term effect on PAI-1 in case of moderate alcohol consumption.

Acute effects: A very acute effect by non-alcoholic factors?

In 1960, Fearnley et al. (16) observed by chance an unusual prolonged blood clot lysis time after consumption of one glass of beer. Subsequently, an acute effect was delineated with a peak effect 2–3 hours after the consumption of beer, wine or cider confirmed by others (3, 45). Notably, the (very acute) effect was not present after consumption of gin, whisky or pure alcohol, which has been confirmed by others (3, 12, 16, 45). These data suggested that a non-alcoholic component is responsible. Consequently, Nilsson et al. (45) and, later, Anderson et al. (3) observed in vitro a

Table 2. Inhibition of plasmin activity on fibrin plates (unpublished data).

Addition to plasmin	Lysed zone of fibrin plate after 18 h (mm)	
	in saline	in gelatin buffer
1:1 with saline	14.2	15.2
1:1 with 12% ethanol	14.2	15.7
1:1 with wine	0	0
1:20 with wine	9.5	14.2

Plasmin (purchased from KabiVitrum AB, Stockholm) was diluted to a concentration of 0.4 CU/ml in either 0.15 M NaCl or gelatin buffer (0.05 M sodium diethyl barbiturate, 0.10 M NaCl, 0.25% (w/v) gelatin (microbiological grade, Merck), 2.7 mM EDTA adjusted to pH 7.8 with HCl). The solution was mixed 1:1 with either saline, 12% ethanol in saline, wine dialysed against saline pH 7.35, or wine diluted in saline. Pre-incubation: 15 min at 37 °C. 30 µl drops were spotted in triplicate onto bovine plasminogen-free fibrin plates (20) (093; Organon Teknika, Boxtel, Netherlands) and lysed zones were measured after 18 h incubation at 37 °C.

fibrinolysis-inhibiting effect of the beverages mentioned and identified a pectin substance (45) and polyphenols (46) as inhibitory substances whereas ethanol was found not to be inhibitory.

In vitro studies showed inhibition of the polyphenols (46) and wine components to be directed at plasmin (see Table 2) and to be more pronounced for t-PA-induced plasmin formation than for u-PA-induced plasmin formation (45, 46).

If we compare the inhibition of the non-alcoholic factors in vitro with the observed inhibition in vivo, it appears, however unlikely, that the pectin and polyphenol components penetrate in sufficient amounts into the blood to exert as strong an effect as observed after drinking the beverages. For example, Nilsson et al. (45) observed an average decrease in activity on fibrin plates from 7.5 mm to 3.0 mm (average effects presented in Table 1 of ref. 45) which is stronger than our inhibitory effect in vitro with 5% wine in a protein-rich milieu (gelatin buffer). Effects in vitro on purified enzymes reported by Nilsson are stronger but might be related to a lower content of other proteins in the in vitro milieu. Furthermore, Anderson et al. (3) noted in in vitro clot lysis experiments that there was hardly any further effect at dilution below 1% cider. The 60–80% inhibition by the strongest polyphenols is found around 5 µg/ml (46) which requires for Bulmer's 'Woodpeckers' cider, with a content of procyanidin polymers of 64 µg/ml, an unrealistically high absorption to obtain the reported 60–80% inhibition with consumption of 750 ml after 2 hours in blood (3).

The delineation of a very acute effect was in fact only based on studies of the time profile in a small number of individuals by Fearnley et al. (16) and Nilsson et al. (45). In retrospect, it can be concluded that a more prolonged effect was over-looked. This was because these researchers did not include a control group which is essential in view of the diurnal variation in blood fibrinolysis discovered in roughly the same time

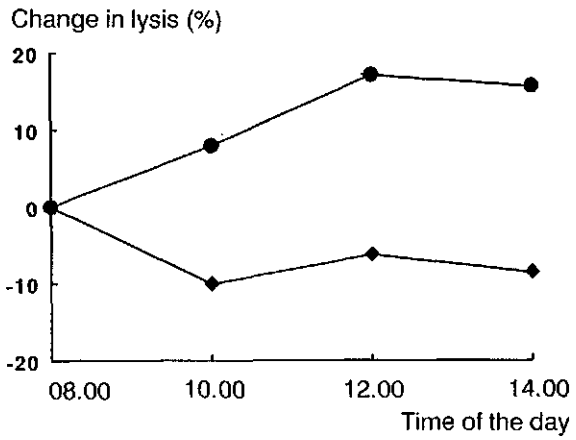

Fig. 4. Relationship between acute fibrinolytic activity changes and alcohol consumption. The percentage change from the starting point at 08.00 was calculated for 10 volunteers in two groups. The average of each group derived from Fig. 1 in Walter et al.'s paper is plotted. Dots: group with breakfast at 07.00, low-fat dinner at 11.30, total energy intakely 3.4 MJ; diamonds: group with same breakfast and dinner and 1000 ml beer between 07.45 and 08.15. After: Walter et al. (61).

period (15). They considered the effect to be ended when the fibrinolytic activity 'returned to pre-treatment levels' not taking into account the diurnal increase that can be expected.

The effect of diurnal variation was already properly considered in 1979 by Walter et al. (61). The effect of beer on fibrinolytic activity clearly follows a slower pattern (Fig. 4, adapted from Walter's study); the decrease in fibrinolytic activity (when compared with a control session with a clear diurnal change) clearly extends beyond the 2–3 hour period.

On the other hand, the fact that the effect of ethanol per se on blood fibrinolytic activity was slower misled the investigators and was initially also overlooked. Hillbom et al. (21, 22) first reported in 1982 a decrease of euglobulin lysis on fibrin plates upon consumption of 1.5 g/kg ethanol in fruit juice. The effect, documented for 12 healthy male volunteers aged 22–30, was apparent after 3 hours and was evaluated using data from a control session. In 1987, Olsen & Østerud (47) confirmed and established the effect, further showing a dose-dependent effect on whole-blood clot lysis time. Ethanol in fruit juice was consumed over a prolonged period of 3 hours at rather high dosages, reaching a level of ca. 10 and 22 mM in blood. Four hours after the start of drinking, clot lysis was already significantly retarded and remained so for the highest dose after 14 hours, whereas a control session showed no effects.

In a recent series of studies jointly performed by TNO Nutrition and Food Research and the Gaubius Laboratory, IVVO-TNO, we have identified the involvement of PAI-1 in the reduction of blood fibrinolytic activity and also showed

that t-PA antigen levels could increase. Both effects could be obtained with gin as well as with wine and beer. The effects appeared to be more pronounced with older volunteers. We also observed that beer and wine gave a more rapid onset of effects than gin, which might further add to the understanding of the historical development of studies on the time profile of acute effects summarized above.

In one of the studies (57) we confirmed rapid effects of a combination of red port and wine. Two age groups of volunteers (20–30 and 45–55 years of age), each consisting of eight healthy men, were studied. All subjects received an aperitif (red port, 10 g of alcohol) half an hour before dinner and two glasses of red wine (20 gram of alcohol in total) during dinner. The results were compared with a similar session with the same volumes of mineral water on another day. These moderate amounts of alcohol resulted in a strong decrease in euglobulin t-PA activity (results dominated by PAI-1; see section Fibrinolysis) in the middle-aged group (–70%, $P < 0.001$) and in a smaller decrease in the young men (–29%, $P = 0.037$) one hour after dinner. PAI activity levels increased significantly in the middle-aged men (+60%, $P = 0.010$), whereas the increase in young men (+34%) was not significant ($P = 0.144$).

In a subsequent study (59), we confirmed the more extended time profile and observed that a period of one hour is too short for full effects on euglobulin t-PA activity, PAI activity and PAI-1 antigen. Six hours after a dinner with 2 glasses of red wine, a strong effect was seen with a 95% ($P < 0.001$) reduction in t-PA activity, and a 230% ($P < 0.001$) increase of PAI activity. We also observed an increase in t-PA antigen, but no effects on variables of u-PA were noted (59), although an effect on u-PA with other beverages might exist (52). It should be noted that in the above study the volunteers also consumed, one hour before the time point mentioned, two glasses of Hollands gin in combination with a snack, which complicates the interpretation of the effects and time profile.

Therefore, in a very recent study we analysed in eight healthy middle-aged men (aged 45–55) with multiple time points (1, 3, 5, 9, 13 hours) after 40 g alcohol contained in various alcoholic beverages taken during the evening meal the time profile of PAI activity, t-PA antigen and PAI-1 antigen. We observed a peak in the increases at 5 hours in all variables relative to the control experiment with mineral water. We used in the study 1000 ml beer, 400 ml red wine or 144 ml Hollands gin and observed the increases for all drinks (unpublished). In a parallel study (unpublished) in collaboration with the Centre for Human Drug Research (Leiden University) we also observed, during continuous infusion of ethanol in healthy young volunteers, an increase in PAI activity peaking after 5 hours.

There was a difference in the speed at which the PAI-1 and t-PA peak returned to normal. PAI-1 showed a much faster decline and t-PA antigen was still elevated the next morning. This was further substantiated with an assay of t-PA activity in acidified blood (62) which showed a significant increase in the morning in t-PA activity compared with the control session with mineral water.

Mechanisms

The fibrinolytic factors involved in effects of alcohol and discussed above are produced in the body by several cell types. They include endothelial cells (t-PA and PAI-1), hepatocytes (fibrinogen, plasminogen, PAI-1) and possibly smooth muscle cells (PAI-1).

Direct effects

Recently, Klöcking et al. (28) reported a direct effect of ethanol on t-PA release in the isolated perfused pig ear. The effect was significant starting at rather high dosages of 50 mM ethanol. Such effects on the well-known very acute release of t-PA (time scale of minutes) differ among species (13): in our experiments t-PA antigen only increased on a time scale of hours. It seems unlikely, therefore, that this very acute t-PA release mechanism contributes directly to the observed increases in t-PA antigen.

Information on the direct effects of ethanol on the cells mentioned in culture is scanty. Laug (38) reported the effects of ethanol on the production of PA activity by bovine endothelial cells cultured in serum-free medium. After 18 h incubation alcohol increased PA in medium and cell lysates of endothelial cells from various origins. The effect was dose-dependent and started to be significant at higher levels of 0.2% (v/v) ethanol and to be robust at 0.5% (v/v). The type of PA was not identified and might be, in this case of cultured bovine endothelial cells, u-PA.

Some preliminary data on human endothelial cells and the human hepatoma cell

Table 3. Effects of ethanol on cell cultures.

Cell type	Component	Level in conditioned medium with 0.1% (v/v) ethanol (% of control without alcohol)	
HUVEC	t-PA antigen	24 h culture:	103 ± 11% (n = 11)
HUVEC	PAI activity	6 h culture:	96 ± 14% (n = 11)
		24 h culture:	105 ± 11% (n = 11)
Hep G2	PAI activity	6 h culture:	101 ± 9% (n = 7)
		24 h culture:	99 ± 16% (n = 7)

Confluent HUVEC (human umbilical venous endothelial cells) cultures were used at second or third passage, and re-fed the day before the experiment with M199 medium, supplemented with 10% human serum, 20 mM HEPES, 100 IU/ml penicillin and 100 µg/ml streptomycin. Confluent Hep G2 cells as for HUVEC, with DMEM, supplemented with 10% heat-inactivated foetal bovine serum, 100 IU/ml penicillin and 100 µg/ml streptomycin. Conditioned medium was obtained by incubating cells in 5 cm^2 dishes with 1 ml of incubation medium either or not containing ethanol. t-PA antigen was measured using the Imulyse TM5 t-PA kit from Biopool AB, Umeå, Sweden; PAI activity was assayed with the method of Verheijen et al. (60).

line Hep G2, with low ethanol levels and an assay of the specific components t-PA and PAI-1, are summarized in Table 3. No effects on t-PA and PAI release were apparent. Similarly, we did not observe effects on production of plasminogen and fibrinogen by Hep G2 cells with low levels of ethanol (0.07% v/v). Such studies should be carried out more systematically and also include higher ethanol concentrations which in other studies have clearly shown to affect cellular metabolism (11).

Attention has also been given to the metabolites of ethanol, acetaldehyde and acetate. For human endothelial cells (HUVEC) we observed that acetaldehyde is toxic to cells at concentrations as low as 0.01% (cell death after 6 hours). This compares well to the experience with bovine endothelial cells reported by Laug (38) indicating that acetaldehyde is rather toxic to endothelial cells. For Hep G2 toxicity is apparent at 0.1% acetaldehyde or above after 24 hours. At low concentrations of acetaldehyde no effect on bovine endothelial cells has been found (38). For acetate, some effect on t-PA and PAI-activity in the medium of HUVEC has been reported at the relatively high concentration of 5 mM. At 8 hours PAI-1 activity had increased to 117% and at 24 hours to 127% of the controls; t-PA antigen at 24 hours had increased to 123% (36).

Indirect effects

For the induction of t-PA and PAI-1 synthesis numerous substances are known. Ethanol might be involved in generating one of these factors. No data are available to identify any intermediate factor for the induction of t-PA and PAI-1 synthesis. It can be mentioned that various effects of alcohol have been reported that might be considered to have a role. They include the generation of kinin (19), of endothelin-1 (26), and effects on growth hormone release (10, 55).

Concluding remarks and perspectives

Long-term effects of alcohol consumption on fibrinolytic variables, as observed in epidemiological and experimental studies, are of minor magnitude, especially when compared with robust effects observed acutely (peak at 5 hours) after alcohol consumption. Long-term effects concern factors produced by hepatocytes such as fibrinogen (inconsistent decrease) and plasminogen (slight increase). The impact of the small changes in blood levels of these factors for fibrinolysis is considered to be very moderate.

Long-term effects are documented for PAI-1 (its source can be multiple, including endothelium, but cannot be deduced from blood measurements), but not yet in full detail for endothelial t-PA, notably for its free fraction. For PAI-1 the regularity of alcohol consumption seems to be relevant for a stable long-term effect of increase. Recognition of this aspect indicates that for an adequate description of

effects moderate alcohol consumption should be defined more exactly with regard to regularity of daily consumption rather than in terms of average consumption.

Only one epidemiological study has documented increased blood fibrinolytic activity in moderate alcohol consumers. It is not clear yet how this relates to observations of increased PAI-1 in long-term experimental studies. It could be due to a simultaneous increase in t-PA and, notably, free t-PA (not yet studied by a specific assay). It should also be noted that it remains possible that in epidemiological studies the rather long-lasting acute effects contribute to the situation in the blood sample studied because of the alcohol consumed by the participants in the late afternoon or early evening. We recorded in this respect a late effect of increased t-PA activity, after alcohol consumption 'the early evening before', expressed in the morning after the increase of PAI-1 had ceased.

Acute effects involve both t-PA and PAI-1, with a robust peak in blood levels approximately 5 hours after alcohol consumption. The time profile, especially a rapid onset of reduced fibrinolytic activity with wine and beer compared with gin and ethanol, suggests non-alcoholic factors to be involved in the stimulation of PAI-1 appearance in blood. The direct inhibitory effect of non-alcoholic factors on fibrinolytic activity is not likely to be significant. The induction of inhibitory activity (PAI-1) seems to be enhanced at higher age and to be dose-dependent.

The data on t-PA and PAI-1 responses suggest that both factors differ in timing of effect. With moderate consumption the increase of PAI-1 induced by early-evening consumption has ceased the next morning, while heavier drinking still shows persistence of inhibition. The t-PA response is characterized by a slower reverting pattern and can, in the case of moderate drinking, result in significantly elevated t-PA activity in the early morning. This suggests that an early-morning t-PA increase counteracts the early-morning risk of acute myocardial infarction (and also stroke) and may be the basis for the observed lower risk for myocardial infarction among moderate alcohol users.

The increase in t-PA during the high PAI-1 peak in the earlier phase after drinking might also exert beneficial effects locally in the vascular tree. The local versus systemic situation is represented schematically in Fig. 5. The locally produced

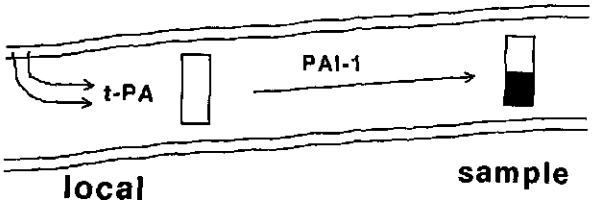

Fig. 5. Cartoon of a blood vessel indicating differences in the status of locally released t-PA (free/active) and t-PA recovered in a sample obtained by venapuncture. The coexistence of t-PA and PAI-1 results in inactivation of 50% of the t-PA (dark part of the bar) in case of normal PAI-1 in about 360 seconds and with 10-fold elevated PAI-1 in about 36 s. (See text.)

t-PA is active and reacts only later with PAI-1. At the site of release, the alcohol thus creates an increased t-PA activity. Only gradually the PAI-1 diminishes t-PA activity, the more rapidly when PAI-1 is elevated as in the case of alcohol consumption. At the site of sampling in a larger vein the majority of t-PA derives from the circulation and a minor part is contributed locally by the endothelium in this vessel (an unfavourable wall/fluid ratio). When we sample arbitrarily at an average time of 5 min after release, t-PA activity is – normally, but especially with increased PAI-1 – strongly reduced in this sampled blood. Comparing the normal situation with the situation after alcohol intake, when PAI-1 has increased 5–10-fold and t-PA 2-fold, it can be seen from Fig. 5 that the assessment of the situation in the sampled blood is not representative of the local situation. Locally, increased t-PA activity can be a dominating feature of alcohol responses.

These considerations of the results in view of the fibrinolytic mechanisms result in two postulates with regard to mechanisms that might contribute to a reduced risk of myocardial infarction upon moderate alcohol use.

1. *Local t-PA increase.* The every-day locally increased t-PA upon daily moderate alcohol consumption might contribute to the prevention of formation or to the dissolution of mural and other fibrin deposits in patients at risk, such as with unstable angina pectoris. The t-PA release might also be beneficial at more distant locations when PAI-1 is not greatly elevated, allowing t-PA to disseminate. This latter situation might exist when drinking is moderate. For experimental verification of the effectiveness of the mechanism in patients with increased fibrin deposits, such as patients with unstable angina pectoris, it may be possible to measure effects brought about by a single drinking session by 24-h monitoring of fibrin degradation products compared to a control session.
2. *Early-morning increase in systemic t-PA activity.* The increase in early-morning t-PA activity in the whole circulation might contribute specifically to a lowered risk of myocardial infarction. It may be possible to verify this by registering the 24-hour frequencies of myocardial infarction (and also stroke) in patients in relation to alcohol consumption. It is postulated that the early-morning peak in frequency of myocardial infarction is blunted in moderate alcohol consumers.

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Effects of alcohol on blood lipids and platelet function

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Abstract

Even before it was shown that moderate drinkers had a lower risk of coronary heart disease (CHD) it was already known that the level of alcohol consumption is related to high-density lipoprotein (HDL) cholesterol. As this was an observation made in epidemiological studies, not proving a causal relationship, there was a need for carefully controlled experimental studies. From experimental studies, performed at TNO Nutrition and Food Research and by others, a causal relationship between alcohol consumption and level of HDL-cholesterol clearly emerges. This is a strong indication that an alcohol-induced increase in HDL-cholesterol at least contributes to the protective effects of drinking in moderation. Current research is aimed at elucidating the mechanism underlying the HDL-cholesterol increase.

Studies into the effects of alcohol on platelet function are dominated by studies into the acute effects of an excessive amount of alcohol. In a study at TNO Nutrition and Food Research, in which the acute effects of moderate drinking were studied, no effect on platelet function could be observed. Until now only one carefully controlled study into the long-term effects (5 weeks) of moderate alcohol consumption on platelet function has been reported. This study, also performed by TNO, shows a significant decrease in aggregability of the platelets when 2 or 4 glasses of red wine are taken per day. The existence of this long-term effect of alcohol is confirmed in an epidemiological study showing an inverse association between alcohol consumption and platelet aggregation on a population level. In the studies mentioned, platelet function is measured in vitro. Future research in this area will be aimed at measuring in-vivo platelet function.

Introduction

In epidemiological studies moderate drinkers are often found to have a reduced risk of coronary heart disease (CHD) (reviews in 9, 17). This has led to a lively debate on the causality of the association. In epidemiological studies there is always a possibility left that the observed relationship between alcohol and CHD is not really caused by

alcohol but, rather, by other life-style factors closely related to alcohol consumption. Most studies are controlled for a number of these factors such as age, social class and smoking. Other disturbing factors or confounders, however, such as physical activity, stress, dietary habits and many other social and psychological factors are much more difficult to control for.

Another way to prove whether the relationship between moderate alcohol consumption and the reduced risk of CHD is a causal one is to do experimental research aimed at explaining how alcohol can protect against CHD. If it can be shown in carefully controlled clinical studies with human volunteers that moderate alcohol consumption influences important risk indicators of CHD, this would be the best direct proof of a relationship.

In the past seven years a number of these experimental studies have been performed at TNO Nutrition and Food Research. At present, the main three areas of interest are effects of alcohol on blood lipids, platelet function and the fibrinolytic system. These are all possible mechanisms which, if influenced by moderate alcohol consumption, may explain a reduced risk of CHD. The results of our research into the effects of alcohol on the fibrinolytic system are described in detail elsewhere in this volume. This paper will be confined to the effects of alcohol on blood lipids and platelet function.

Blood lipids

Even before it was shown in the early 1980s that moderate drinkers have a reduced risk of CHD, it was already known that alcohol consumption was associated with an increase in high-density lipoprotein (HDL) cholesterol. That this association is independent of the type of alcoholic beverage consumed has been shown in the Tromsø Heart Study (1). For beer, wine and spirits a dose-dependent increase in HDL-cholesterol was observed with increasing alcohol consumption. In many other epidemiological studies, such as the Seven Countries Study (see Kromhout & Bloemberg's paper elsewhere in this volume (6)) and the Nurses' Health Study and the Health Professionals Follow-Up Study (see Rimm & Stampfer's paper in this volume (11)) a similar relationship has consistently been shown. Higher HDL-cholesterol levels are associated with a lower risk of CHD, so these observations perfectly fit in with the reduced risk of moderate drinkers. The initial excitement evoked by this explanation, however, was soon tempered when it was found that it is mainly the HDL_3 subfraction of HDL-cholesterol that is associated with alcohol consumption, whereas most studies showed the HDL_2 subfraction to have the strongest association with a lower risk of CHD. More recent studies (12–14), on the other hand, show that HDL_3-C is also strongly related to CHD risk reduction and also that alcohol consumption is not only related to HDL_3, but also to HDL_2 (4, 7).

These studies into the relationship between alcohol consumption and HDL-cholesterol level, like the studies showing that moderate drinkers have a lower risk of CHD, are epidemiological studies showing a relationship between people with

different drinking habits. These studies still have the problem that confounding factors might cause the relationship instead of alcohol per se.

In most experimental studies, instead of looking at differences between individuals with different drinking habits, differences within the same individual are being studied. What happens if an individual, after a period of abstinence, starts drinking moderately? What is the effect on risk factors for CHD? In the first TNO study into this subject matter (10), the effects of moderate drinking for a period of 5 weeks were investigated. Subjects were 12 healthy young men aged 20–30. They all received 4 different treatments in a randomized order: no alcohol, 2 glasses a day, 4 glasses a day, and binge drinking. Binge drinking implies that they had only alcohol in the weekend (4 glasses on Friday, 5 on Saturday and 5 on Sunday). The total amount of alcohol consumed by the binge drinkers (14 glasses per week) equalled that for the low consumption group.

Table 1 presents the results of the measurement of blood lipids in this study. No significant effects were observed for total cholesterol and triglycerides. HDL_3-C, however, increased significantly with increasing alcohol consumption. HDL_2-C, on the other hand, only tended to increase.

After this study, we performed an even longer-term study of 20 weeks (18), in which the significant increase in HDL_3-C was confirmed (Fig. 1). HDL_2-C again tended to be higher upon the treatment with alcohol, but the difference did not reach significance. Total HDL-cholesterol also increased significantly.

A large number of studies, all of different design, have been devoted to the relation between alcohol use and HDL-cholesterol. They vary in type of alcoholic beverage used, amount of alcohol consumed or length of the study which varied between 2 and 20 weeks. With the exception of one study lasting only 2 weeks, all groups have found that alcohol increases HDL-cholesterol or apolipoprotein A1, which is the main apolipoprotein of the HDL particle.

The increase in HDL-cholesterol after a few weeks of moderate levels of alcohol is therefore well established. Although this is a strong indication that an alcohol-induced increase in HDL-cholesterol at least contributes to the protective effect of drinking in moderation, a possibility remains that this is not the case. The question is what is the mechanism that causes HDL to rise. This increase can be the result of:

Table 1. Mean values of blood lipids in response to red wine consumption.

	0 glasses	2 glasses	Binge	4 glasses
Total cholesterol (mmol/l)	3.72	3.74	3.72	3.75
Triglycerides (mmol/l)	0.80	0.78	0.76	0.76
HDL_3-cholesterol (mmol/l)	0.78^{a}	0.82^{ab}	0.82^{ab}	0.84^{b}
HDL_2-cholesterol (mmol/l)	0.39	0.40	0.39	0.42

Values sharing a superscript do not differ significantly at $P < 0.05$.

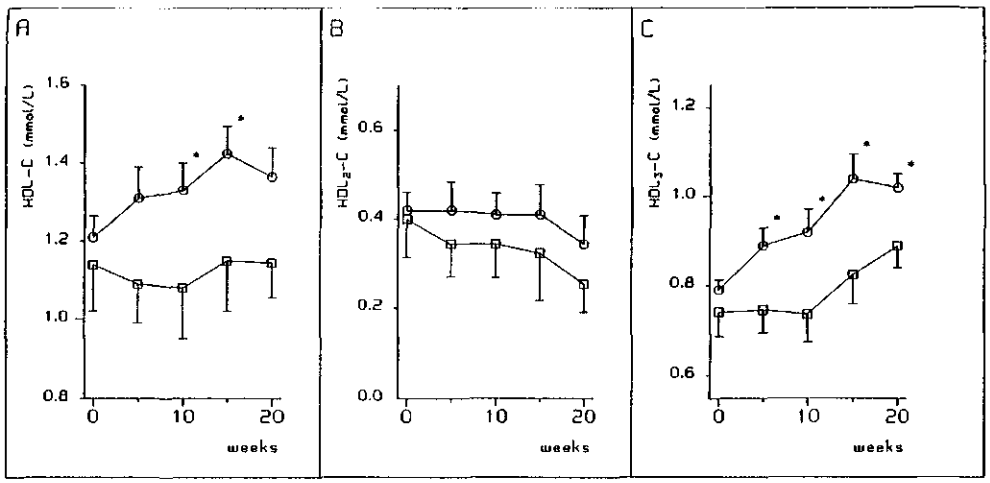

Fig. 1. Effects of moderate alcohol consumption on total HDL-cholesterol (A) and the HDL-cholesterol subfractions HDL_2-C (B) and HDL_3-C (C). The bars indicate the standard error of the mean (SEM). Asterisks indicate a significant difference ($P < 0.05$) between the experimental group (circles) and the control group (squares).

– induction of synthesis of nascent HDL in the liver;
– an increase in the rate of very low-density lipoprotein (VLDL) catabolism, resulting in an increase of mature HDL;
– a decrease in the catabolism of HDL, due to a reduction in clearance of HDL by the liver.

If alcohol increases HDL-cholesterol through this latter mechanism, this would mean that cholesterol accumulates in the body and the risk of CHD would be increased instead of decreased. To rule out this possibility, more information is needed on the mechanism through which alcohol increases HDL-cholesterol.

All studies discussed so far covered a comparatively long experimental period, just like most other studies into the effects of diet on blood lipids. Another important characteristic of these studies is that measurements take place early in the morning, before breakfast, after an overnight fast. In more recent TNO experiments, however, the acute effects of moderate alcohol consumption in combination with a meal on blood lipids were measured when the alcohol is still present in the circulation (19). Table 2 presents some of the results of that study.

In this study, besides young men (aged 20–30), we included middle-aged men, who at an age between 45 and 55 were well in the risk age for CHD. There was no change in total cholesterol, a significant increase in HDL-cholesterol, resulting from an increase in – predominantly – HDL_2-C. Also a significant increase in apolipoprotein A_2 and in triglycerides was found after alcohol consumption. The fact that a moderate dose of alcohol acutely influences these blood lipid parameters

Table 2. Mean values for lipid variables of young and middle-aged men one hour after the consumption of 30 g of alcohol or mineral water.

	Mineral water	Alcohol	*P*
Total cholesterol (mmol/l)	5.394	5.468	0.387
HDL-cholesterol (mmol/l)	1.167	1.301	0.002
HDL_2-cholesterol (mmol/l)	0.396	0.457	0.066
HDL_3-cholesterol (mmol/l)	0.718	0.735	0.544
Apolipoprotein A_1 (g/l)	138.7	145.9	0.150
Apolipoprotein A_2 (g/l)	37.5	40.2	0.024
Apolipoprotein B (g/l)	73.3	78.8	0.064
Triglycerides (mmol/l)	1.845	2.127	0.044

opens the possibility that the increase in HDL-cholesterol induced by moderate alcohol consumption seen in the long-term studies, originates from these acute effects of alcohol.

In the most recent TNO study 8 healthy middle-aged men received 4 different treatments: no alcohol or 40 g of alcohol in the form of beer, wine or spirits, all in combination with a dinner early in the evening (J. Veenstra et al., manuscript in preparation). More blood samples than in the previous studies were taken after alcohol consumption. In this study again a major effect on triglyceride levels was observed (Fig. 2).

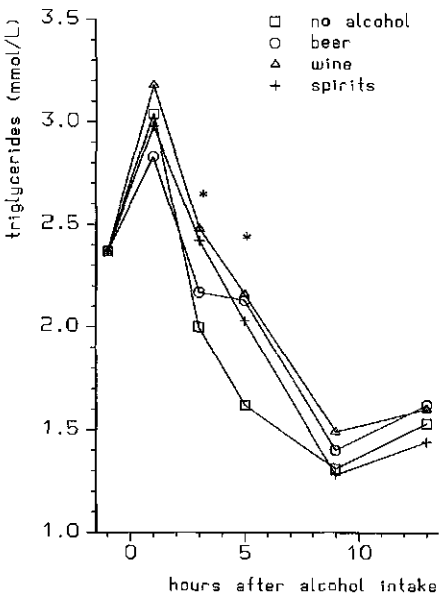

Fig. 2. Effects of beer, wine and spirits (40 g alcohol) on postprandial triglyceride levels. An asterisk indicates a significant difference between alcohol-treated subjects and controls ($P < 0.05$).

Fig. 2 clearly shows that alcohol slows down the decrease in triglycerides that normally takes place after a meal. Normally the liver uses fatty acids as its main fuel, but when alcohol is present in the circulation, alcohol is metabolized in the liver and provides much of the energy needed by the liver, leaving the fat circulating for a longer period of time. This probably also contributes to the increase in HDL-cholesterol.

We cannot yet draw definite conclusions as to whether the increase in HDL-cholesterol is beneficial. This may depend on the level of alcohol consumption (see Välimäki's paper elsewhere in this volume (16)).

Platelet function

In epidemiological studies it has been shown that controlling for differences in HDL-cholesterol may explain up to 50% of the reduced risk of CHD (2). This means that the protective effect of alcohol is partly independent of the HDL mechanism and therefore should be attributed to other mechanisms such as the effects of alcohol on the fibrinolytic system and on platelet function. These latter two mechanisms have received much less attention.

That blood platelets play an important role in CHD is shown by the fact that in most cases of myocardial infarction a coronary artery is blocked by a clot primarily consisting of platelets (3). When somewhere the blood vessel wall is ruptured – which, in the case of CHD, is mostly the result of atherosclerosis – the platelets passing by are activated by substances that are released from the damaged tissue. The platelets aggregate, and a blood clot is formed, which in the end may block the whole blood vessel, thus causing an infarction.

Platelet function is normally measured in the laboratory by isolating platelets from the blood in platelet-rich plasma, and subsequently activating these platelets by adding – mostly non-physiological – stimuli. This in vitro test of platelet function is called the platelet aggregation test. What is actually measured by the instrument that measures platelet aggregation, is the change in light transmission through the test tube when the platelets in the platelet-rich plasma start forming larger clots.

Studies into the effects of alcohol on platelet function are dominated by studies into the acute effects. Most of them are not very much concerned with the hypothesis of a reduced risk for CHD in moderate drinkers. In 10 out of the 14 acute studies published so far, the volunteers consumed 5 glasses or more. In quite a number of studies they drunk 10, 12 or even more glasses. Obviously, these studies cannot have been very well controlled. Moreover, the results are contradictory.

In one of the acute studies in which the effects of moderate levels of alcohol consumption were investigated, a decrease in platelet function was found, and in three other studies there was no clear effect. One of these latter studies is a study performed recently in our Institute (20). Eight healthy middle-aged men were housed in the metabolic ward of our Institute in four experimental periods of three days each. This metabolic ward is a small hotel with 12 rooms where the subjects live

during the experiments. There is also a large living room where they can watch television, play games or read a book. Since many life-style factors such as diet, physical activity and stress may have an effect on platelet function it is important to do studies in this area under strictly controlled conditions. Most of the studies mentioned above were less strictly controlled. In a more controlled study design there is less disturbance of platelet function by other factors, and therefore there is a better chance of finding an effect if there is one, and less chance of finding an effect if there is no effect at all. The four different treatments in this particular experiment were the combinations of 'alcohol or no alcohol' and 'diet rich in polyunsaturated fatty acids or rich in saturated fatty acids'. Of course, they all received the treatments in a randomized order. In the first two days of the experimental period no alcohol was given in any of the treatments. On the third day of the treatment with alcohol, two glasses of red wine were consumed during the dinner and two glasses of Hollands gin were consumed later in the evening together with a snack. This is not an uncommon pattern of alcohol consumption in the Netherlands, especially on weekend days. During the treatments without alcohol, the same volumes of mineral water were consumed.

Finally, blood samples were drawn four times: before dinner, one hour after dinner, one hour after the snack, and the next morning before breakfast. At none of these moments a significant effect of alcohol on platelet aggregation could be observed.

So, there is probably no acute effect of a moderate dose of alcohol on platelet aggregation. There has been only one long-term study, performed by our Institute, in which the effects of moderate alcohol consumption were studied (10). Four different treatments were given for five weeks to 12 healthy young men. (In that same study the effects of five weeks of moderate alcohol consumption on blood lipids were investigated; see above.) The treatments were: no alcohol, 2 glasses per day, 4 glasses per day, and binge drinking. In this study moderate alcohol consumption for 5 weeks significantly reduced platelet aggregation by up to 36%. Unfortunately, up to now no experimental studies have been published that confirm this result. There is one epidemiological study in which platelet aggregation was measured, namely the Northwick Park Heart Study (see Miller's paper elsewhere in this volume (8)). In that study an inverse relationship between alcohol consumption and platelet aggregation was found. The results of these two studies, one showing that 5 weeks of moderate alcohol consumption reduces platelet aggregation, the other showing that platelet aggregation is higher in people who drink less, indirectly confirm one another.

As mentioned before, platelet aggregation is measured in vitro, in a test tube in the laboratory, by adding non-physiological stimuli to the platelets. In vivo, in the living human being, platelet aggregation fortunately is constantly inhibited and takes place only at a very low level. If this was not the case and large blood clots were constantly formed, we would run a much greater risk of a heart attack or an ischaemic stroke. This means that in measuring platelet aggregation something is measured that probably, even under extreme conditions, never takes place in the

human body. We may therefore well detect a decreased or increased tendency of the platelets to aggregate, but we can never be sure that this effect also takes place in vivo. Therefore, although the studies mentioned above indicate that moderate alcohol consumption may reduce the risk of CHD through this mechanism, definite conclusions cannot be drawn yet.

A number of techniques have recently been developed that can give an indication of the level of in vivo platelet activation. During their activation, platelets release proteins. Specific assays have been developed for the measurement of two of these, i.e. β-thromboglobulin and platelet factor 4. High levels of these proteins in the circulation indicate an increased in vivo platelet aggregation. However, it is very difficult to take a blood sample without some platelet activation taking place when the blood flows into the tube. Currently, special blood sampling tubes are being developed which reduce this ex vivo activation of the platelets. Until now, no studies into the long-term effects of moderate alcohol consumption on these in vivo indicators of platelet aggregation have been reported.

Another new technique is the measurement of activated platelets in the circulation. When platelets are activated they not only release proteins, but also display a different protein pattern on their surface. Recently, a number of specific monoclonal antibodies have been developed that can recognize activated platelets. With an instrument called a flow cytometer, it is possible to determine the percentage of activated platelets in a blood sample, which is a direct measure of the level of platelet aggregation in vivo. A reduction in the amount of in vivo platelet activation caused by moderate alcohol consumption would clearly be an indicator of reduced risk of CHD. Measuring such a decrease, however, is not easy: in vivo platelet aggregation already takes place at a very low level, and measuring a further decrease may be difficult.

Another way of showing a decrease in the in vivo tendency of platelet aggregation is to measure an increase in the activity of those systems that prevent blood clot formation. One such system, the fibrinolytic system, is clearly influenced even by moderate intakes of alcohol (see Kluft et al.'s paper elsewehere in this volume (5)). Another mechanism that prevents spontaneous in vivo platelet activation is the constant production by the endothelial cells of the blood vessels of a substance called prostacyclin. Prostacyclin is a metabolite of the polyunsaturated fatty acid arachidonic acid. Platelets also produce an arachidonic acid metabolite called thromboxane, which is the physiological counterpart of prostacyclin. A few years ago it was shown that taking aspirin every other day reduces the risk of CHD, probably by changing the balance between prostacyclin and thromboxane in favour of the platelet inhibitor prostacyclin (15). No studies into the long-term effects of moderate alcohol consumption on the thromboxane/prostacylin ratio have been published to date. Therefore, also in this area there are still a number of questions to be answered.

In summary, many epidemiological studies have shown that moderate drinkers have a reduced risk of CHD. This does not necessarily mean, however, that there is a causal relationship between alcohol and CHD. On the other hand, in experimental studies,

moderate consumption of alcohol influences the fibrinolytic system, increases HDL-cholesterol and reduces in vitro platelet aggregation. Although there are still a number of questions to be answered, the results of these experimental studies strongly indicate that moderate alcohol consumption directly influences the risk of CHD.

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Effects of different doses of alcohol on serum lipoproteins

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Abstract

The effects of alcohol intake on serum lipids and lipoproteins depend on the dose and mode of alcohol intake, individual susceptibility, and dietary factors. Therefore the changes of lipoprotein pattern are different among moderate and heavy drinkers. Moderate intake of alcohol increases the concentrations of apolipoprotein (apo) A-I, apo A-II, and the high-density lipoprotein subfraction (HDL_3) in serum, the increase of HDL_2 being less pronounced. The concentration of lipoprotein (Lp) A-I particles, which contain only apo A-I and are considered to be the antiatherogenic part of HDL, increases. The concentrations of total and very low-density lipoprotein (VLDL) triglyceride and low-density lipoprotein (LDL) cholesterol either remain unchanged or increase slightly. In chronic alcoholics with normal liver function the lipoprotein pattern is characterized by a normal or subnormal VLDL triglyceride level, a low LDL cholesterol level, and increased levels of HDL_2 cholesterol, apo A-I and apo A-II, as well as low lipoprotein (a) (Lp(a)). Thus, the most favourable lipoprotein pattern is produced by doses of alcohol which otherwise are detrimental to health. However, also the changes in serum lipoproteins associated with moderate intake may provide some protection against atherosclerosis. According to the present knowledge, the effects of alcohol are practically identical for both sexes. The targets of alcohol action are diverse, including enhanced production of VLDL, nascent HDL, apo A-I and apo A-II in the liver as well as induction of lipoprotein lipase activity. There is also evidence that alcohol may enhance the catabolism of LDL.

Introduction

Moderate alcohol intake reduces the degree of coronary atherosclerosis and the risk of myocardial infarction (34). This association has been mostly ascribed to the beneficial effects of alcohol on serum lipoproteins, which are complex structures of triglycerides, cholesterol, phospholipids, and protein (apoproteins) (Table 1). Increased risk of atherosclerosis is associated with an elevation of serum low-density lipoprotein (LDL) cholesterol and serum very low-density lipoprotein (VLDL) triglyceride whereas increased concentrations of high-density lipoprotein (HDL)

Table 1. Composition of serum lipoproteins.

Lipoprotein	Contribution (%)				Apoproteins
	TG	chol.	PL	prot.	
Chylomicrons	85–95	2–5	3–8	1–2	B-48, E, A-I, A-IV, C
VLDL	55–65	18–20	12–18	5–10	B-100, E, C
IDL	25–40	30–50	16–24	12–16	B-100, E, C
LDL	8–12	40–58	20–25	20–24	B-100
HDL_2	6–10	20–25	25–30	40–45	A-I, A-II, C, E
HDL_3	4–8	14–18	18–25	60–65	A-I, A-II, C, E, D

TG, triglyceride; chol., cholesterol; PL, phospholipids; prot., protein; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

cholesterol protect against atherosclerosis. Antiatherogenic properties of HDL may be accounted for by the capacity of HDL to mediate the reverse transfer of cholesterol from tissues to the liver. Alcohol intake may affect all of these lipid factors, but major interest has been in its ability to increase the serum HDL cholesterol concentration (4, 8, 15). From this point of view the question which one of the two HDL subfractions (Table 1) – more antiatherogenic HDL_2 or less effective HDL_3 (2, 23) – is influenced by alcohol has been of potential relevance. Circumstantial evidence indicates that the ability of high serum levels of apoproteins A-I (apo A-I) and A-II (apo A-II) to provide protection against coronary heart disease may be even stronger than that of HDL cholesterol per se (5). Consequently, the question arises how alcohol influences these major protein constituents of HDL (6, 11, 20, 22). Recently, interest has been focused also on lipoprotein (a) (Lp(a)), which seems to be a strong independent risk factor for ischaemic heart disease (26). Lp(a) is formed when the apolipoprotein (a) in serum is attached to apoprotein B of LDL particles (24).

The effects of alcohol on lipid metabolism are both dose- and time-dependent (37). In the following the influence of chronic alcohol abuse, acute heavy drinking and habitual moderate intake of alcohol will be dealt with separately. The most relevant studies have been carried out in men, but scarce data available on women is briefly discussed, too. Finally, an effort is made to address possible mechanisms behind the lipid alterations.

Lipoprotein pattern and effect of alcohol withdrawal in chronic alcoholic men

To determine the characteristics of the lipoprotein pattern in chronic alcoholics and to define the mechanisms of the observed changes we have conducted several studies over the past few years (27, 32, 36). In alcoholic men with normal liver morphology

and function the lipoprotein pattern was characterized by normal or subnormal total and VLDL triglyceride, low LDL cholesterol, and increased levels of HDL cholesterol (54% higher than those of control men). Similar data have been reported in several other studies (4, 8, 15). During alcohol withdrawal the HDL cholesterol concentration decreased significantly already within two days of abstinence and returned to normal in one week (36). The LDL cholesterol level increased slightly but did not reach the normal range within two weeks (32).

Immediately following the drinking period the mass concentrations (the sum of triglyceride, cholesterol, phospholipids and protein) of both HDL_2 and HDL_3 were clearly higher in alcoholic men than in non-alcoholic controls (Fig. 1). The mean HDL_2 levels were increased by 60% and those of HDL_3 by 20% over the respective control values. Consequently, the rise in total HDL cholesterol in the alcoholic men was predominantly the result of that of HDL_2 cholesterol. These findings are consistent with the results of Ekman et al. (10) and Avogaro et al. (1). Apo A-I and apo A-II concentrations in the two HDL subfractions decreased after ethanol withdrawal.

It is well established that plasma total HDL and HDL_2 are regulated by the activities of two lipolytic enzymes, lipoprotein lipase (LPL) and hepatic lipase, the former increasing the production and the latter the degradation of HDL_2 (30). Immediately after the drinking period the mean LPL activity in post-heparin plasma was 80% higher in alcoholic men than in non-alcoholic male controls (32). On the basis of this finding we postulated that the elevation of HDL_2 was due to the alcohol-induced increase of LPL. The enzyme activity dropped significantly after only 2 days of abstinence and reached the normal range after one week of alcohol withdrawal (36). Also hepatic lipase activity increased significantly in alcoholic men immediately

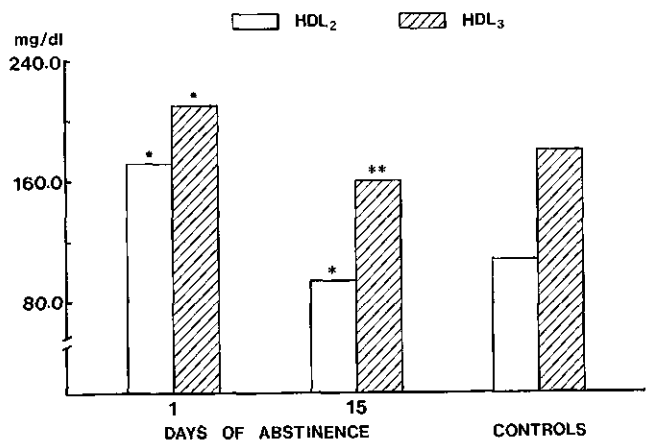

Fig. 1. Concentrations of HDL_2 and HDL_3 masses calculated as the sums of triglyceride, cholesterol, phospholipid and protein contents in HDL subfractions. The results are means of 10 male alcoholics before and after abstinence for 15 days. The data are compared with values in non-alcoholic male controls matched for age and relative body weight ($n = 42$).

after drinking, but the change was less marked than that of LPL activity (32). The activity fell during abstinence, albeit more slowly than LPL, reaching the normal range after one week of abstinence (36).

So far only two studies have addressed Lp(a) levels in chronic alcoholics. In one study (21) alcohol consumers had markedly reduced Lp(a) levels. In another study Lp(a) showed a continuous increase over four consecutive days after the beginning of abstinence (16).

Effect of heavy acute alcohol intake on serum lipoproteins

To monitor the sequence of alcohol-induced changes in serum lipoproteins, we conducted a study (33) in which alcohol (5.5 g/kg of body weight) was served over 3 days to 10 non-alcoholic male volunteers. Drinking started at dinner time on Friday and continued until Sunday evening. The alcohol was served with meals and as after-dinner drinks. The amount of alcohol exceeded moderation (160 g per day), but the degree of alcohol intoxication as estimated by blood alcohol levels and clinical signs was moderate. The mode of alcohol intake represents habits in societies where occasional drinking is more common than the regular daily intake of moderate amounts of alcohol.

Alcohol intake was followed by a progressive increase in fasting VLDL triglyceride concentrations (Fig. 2). LDL and HDL triglyceride concentrations paralleled the increase of VLDL. Similar responses were found for VLDL, LDL and HDL phospholipids. However, VLDL cholesterol did not change until the third morning. The LDL and HDL cholesterol concentrations remained unaffected during the period of alcohol consumption.

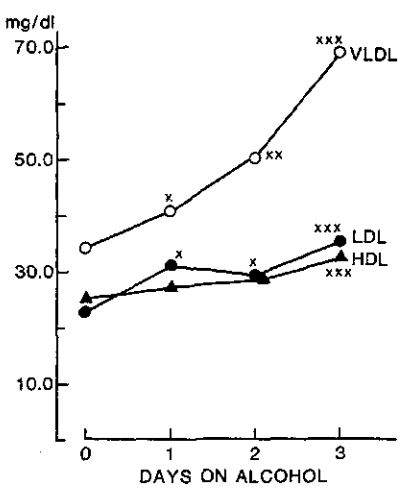

Fig. 2. Responses of triglyceride concentrations in VLDL, LDL and HDL to short-term alcohol intake (5.5 g/kg) served over 3 days. The results are means of 10 non-alcoholic healthy volunteers.

Although the level of total HDL cholesterol remained constant, the HDL subfractions showed definite changes over the 3 days of alcohol intake. The mass concentration of HDL_2 increased progressively, whereas the HDL_3 concentration remained unchanged (33). The response of HDL_2 was the result of a rise in its phospholipid, triglyceride and apo A-I and apo A-II contents, whereas the HDL_2 cholesterol levels did not change. The mean for LPL activity in adipose tissue increased 2.6-fold over the drinking period (33). These data also pointed out that the elevation of the HDL_2 level bis related to the induction of LPL.

Habitual moderate intake of alcohol and serum lipoproteins

There is an apparent heterogeneity in the reported responses of VLDL, HDL and HDL subfractions to moderate alcohol intake. These differences may be accounted for by variable doses of alcohol and the length of the experimental period. VLDL triglyceride levels have been reported either to increase, to remain unchanged or to decrease (see 31). In one study moderate intake of alcohol (less than 40 g per day) was associated with rises in HDL_3, apo A-I and apo A-II (13). Thus, the impact of moderate alcohol intake on HDL subfractions seems to differ from that of heavy drinking. To resolve this difference we conducted a study (37) in which alcohol-induced changes in serum lipoproteins were related to time and dose. Ten non-alcoholic male volunteers consumed either 30 or 60 g alcohol per day over 3-week periods, preceded and separated by an abstinence period of 3 weeks. The levels of total and VLDL triglyceride remained unchanged on the smaller dose and increased only slightly on the higher dose. LDL was affected only by the dose of 60 g per day which increased the total LDL mass by 10%. This change was accounted for by increments in the LDL triglyceride, cholesterol, phospholipid and protein concentrations.

The alcohol dose of 30 g per day caused no changes in HDL_2 concentration (Fig. 3). However, the total mass of HDL_3 increased by 10 %, due to elevations of HDL_3 triglyceride, cholesterol, phospholipids and proteins (Fig. 4). On the higher dose of alcohol the concentration of total HDL_2 increased by 16% and that of HDL_2 cholesterol by 18% (Fig. 3). Moreover, the concentration of the total HDL_3 rose progressively throughout the drinking period, exceeding the baseline by 25% at the end of the study (Fig. 4). (Note that the increment of HDL_3 cholesterol was 15%.) These results are in keeping with the studies of Haskell et al. (13) and Camargo et al. (6) and suggest that moderate alcohol use is most consistently associated with a rise in HDL_3 level.

It is also obvious from our studies that the serum levels of apo A-I and A-II were increased slightly by the daily dose of 30 g alcohol and markedly by the 60 g dose (Fig. 5). The peak concentration of apo A-I exceeded the preceding baseline value by 22% after one week of drinking. The serum concentration of apo A-II displayed a progressive rise during the drinking period and was 35% higher at the end of the period than before (Fig. 5). These data are consistent with earlier reports (6, 11, 20,

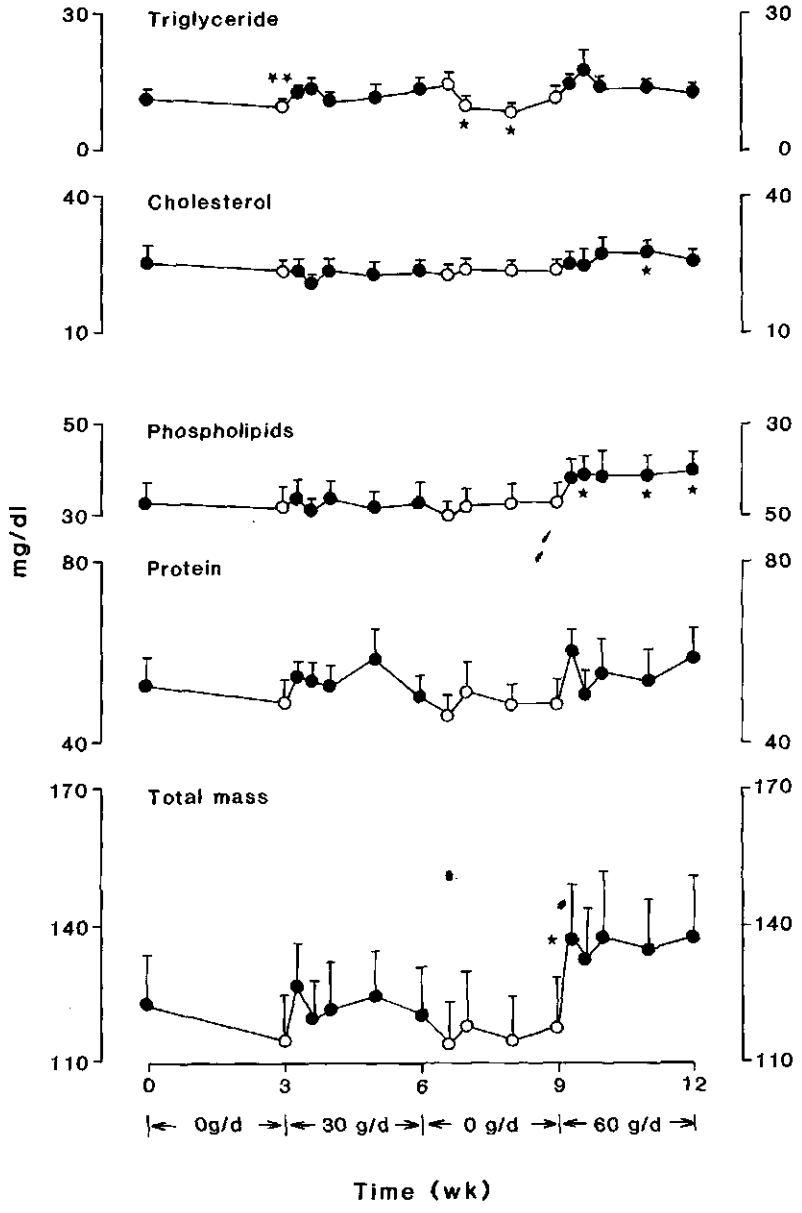

Fig. 3. The concentrations (mg/dl) of triglyceride, cholesterol, phospholipids and proteins as well as their sum (total mass) in HDL_2. The results are means + SEM for 10 non-alcoholic healthy volunteers who first abstained totally from alcohol for 3 weeks. Thereafter the subjects were given 30 g ethanol per day for 3 weeks. Another 3-week period of abstention preceded the second drinking period when the men were served 60 g per day of ethanol. Open circles denote sober values and closed circles drinking values. $^{*}P < 0.05$; $^{**}P < 0.01$ for differences from the preceding sober or drinking value.

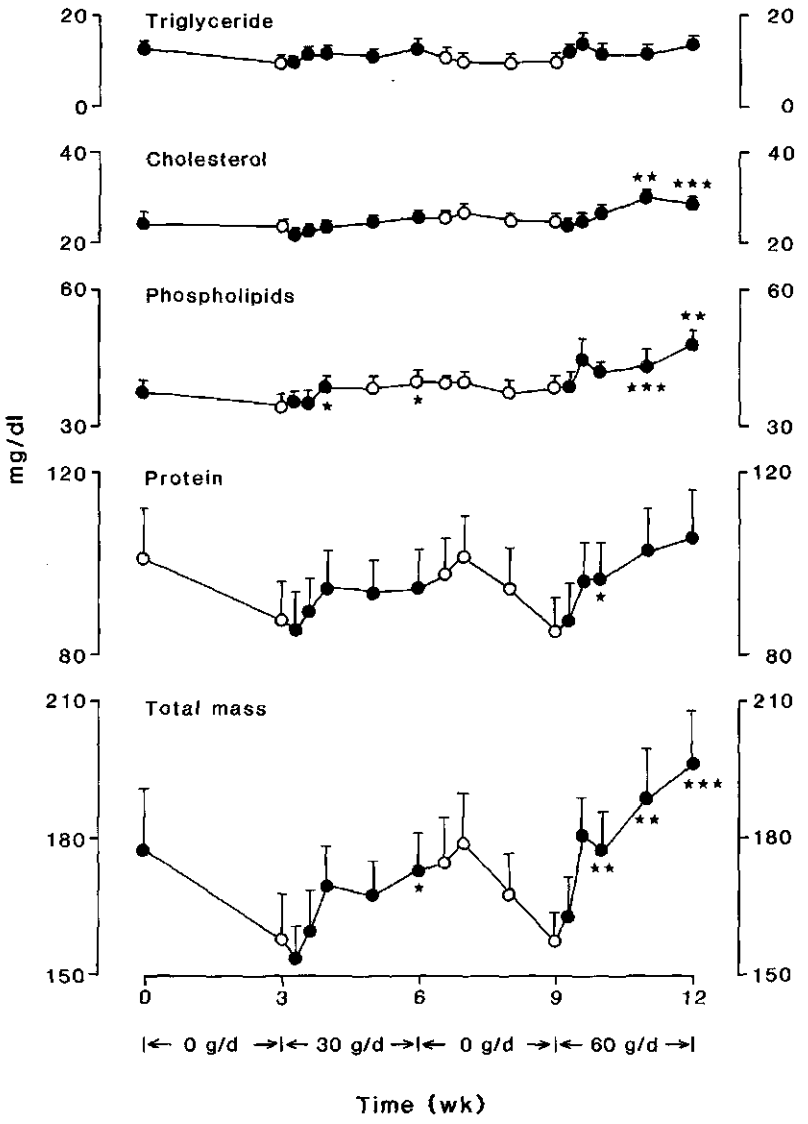

Fig. 4. The concentrations (mg/dl) of triglyceride, cholesterol, phospholipids and proteins as well as their sum (total mass) in HDL_3. For the study design, see the legend to Fig. 3. Open circles denote sober values and closed circles drinking values. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ for differences from the preceding sober value.

22). Neither of the doses of alcohol had an effect on post-heparin plasma LPL and hepatic lipase activities.

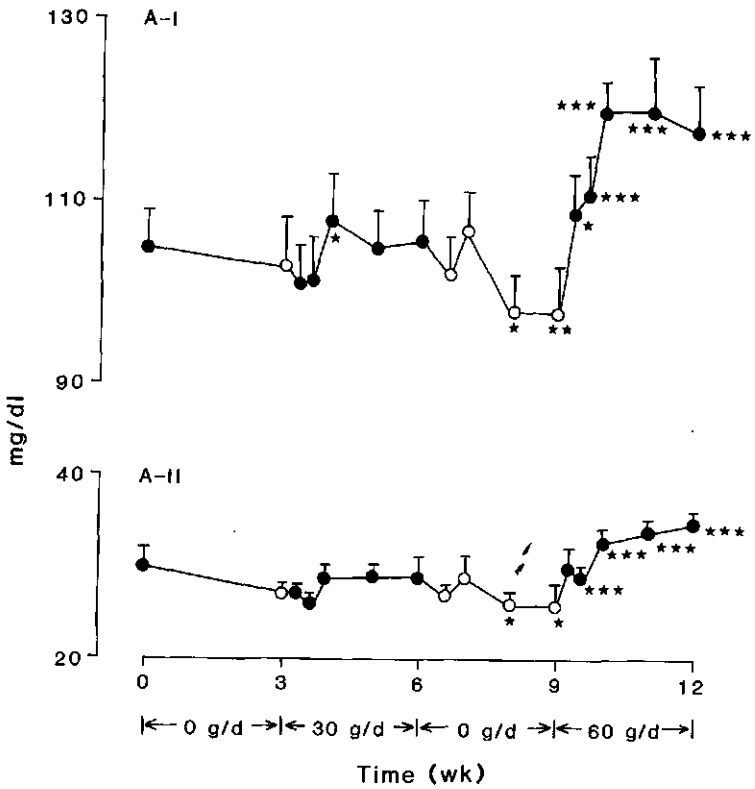

Fig. 5. The concentrations (mg/dl) of apoprotein A-I and A-II in whole serum. For the study design see the legend to Fig. 3. Closed circles denote sober values and closed circles drinking values. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$ for differences from the last preceding sober or drinking value.

It is well recognized that HDL contains at least two types of apo A-I-containing lipoprotein particles which might have different metabolic functions and clinical significance (7). One species contains as main protein components both apo A-I and A-II (Lp A-I:A-II) while in the other (Lp A-I) apo A-II is absent (7). Lp A-I particles reside within both the HDL_2 and HDL_3 density ranges although the majority is distributed within the HDL_2 density (18). Recently, data from patients with angiographically defined coronary artery disease suggested that Lp A-I might represent the anti-atherogenic fraction of HDL (25). The anti-atherogenic potential of Lp A-I particles may reside in their putative role in reverse cholesterol transport (3). In a recent study (35) we addressed the question how moderate alcohol intake affects apoprotein A-I-containing lipoproteins in serum. Ten healthy male volunteers were given 60 g ethanol per day over a period of three weeks. The drinking period was preceded and followed by an abstinence period of three weeks. Ethanol intake caused an increase in the serum levels of both Lp A-I and Lp A-I:A-II, the former

explaining one third of the total rise of apo A-I. Thus, the increment of the anti-atherogenic Lp A-I by ethanol may be one beneficial effect with respect to coronary heart disease.

In the same study we also followed the changes in serum Lp(a) levels. The Lp(a) concentration decreased by 33% during the first week of ethanol intake but returned to the baseline level before the end of drinking. It is possible that the initial fall reflected only continuation of the effect of the preceding abstention period since a falling tendency was visible already before alcohol intake. If this interpretation is valid, then moderate ethanol intake seems to increase Lp(a).

Effects of alcohol on serum lipoproteins in women

Also in middle-aged women moderate alcohol consumption decreases the risks of coronary heart disease and ischaemic stroke by 40 to 70% (29). By analogy to men, these beneficial effects of alcohol might be ascribed to the elevation of serum HDL cholesterol, but such data on alcohol-consuming women are sparse (4, 9, 12, 14). That HDL_3 is affected by moderate alcohol intake also in women is supported by the only study available (9). As to the apoproteins A, of the two studies available apo A-I was increased in one (12) and apo A-II in the other (14).

Recently we have followed the gradual changes of serum lipids and lipoproteins as well as of lipase activities during withdrawal of alcohol in women with chronic alcoholism (Välimäki et al., unpublished data). In alcoholic women the mean HDL cholesterol level was 48% higher than in female controls, which level decreased by 27% and 34% during 1 and 2 weeks of abstention, respectively. The rise in HDL cholesterol was totally accounted for by an increment in HDL_2 cholesterol. Immediately after the drinking period the serum concentration of apo A-I was slightly elevated in alcoholic women and decreased by 23% during one week of abstention to a level even lower than that in non-alcoholic women. The apo A-II concentration increased by 40% in the patients at the start of alcohol withdrawal and had totally normalized one week later. Both post-heparin plasma LPL and hepatic lipase activities fell during withdrawal. During alcohol withdrawal the Lp(a) concentration increased in 11 of 12 alcoholic women.

Possible mechanisms behind the changes in serum lipoproteins

It is apparent that no single pathophysiological mechanism can explain all alcohol-induced changes in serum lipoproteins (Fig. 6). Even short-term intake of alcohol (exceeding 60 g/day) stimulates the synthesis of VLDL particles in the liver and increases the level of total and VLDL triglyceride in serum. Consequent lipolysis of VLDL particles by lipoprotein lipase leads to the formation of intermediate-density lipoprotein (IDL), and ultimately LDL, and is associated with a concomitant transfer of released surface material to HDL when HDL_2 particles are formed. Since the induction of LPL activity by alcohol is dose-dependent, this explains why the HDL_2

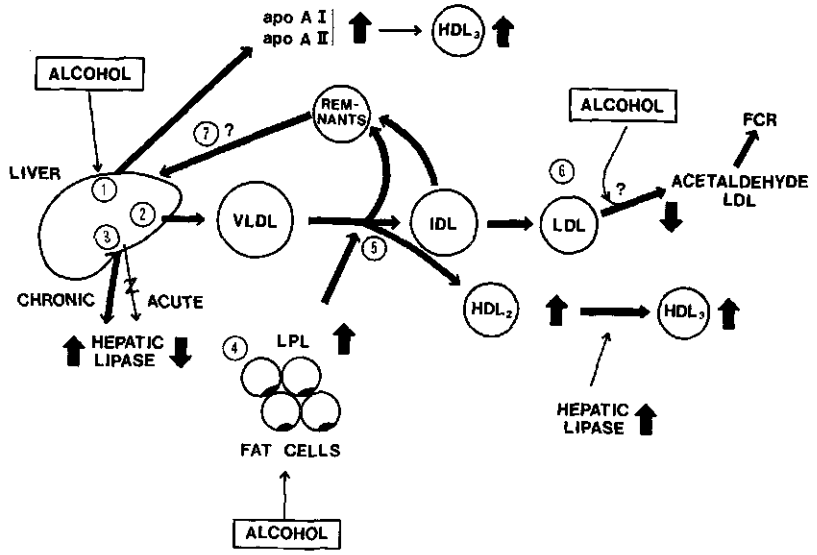

Fig. 6. Effects of alcohol on lipoprotein metabolism in man. The encircled numbers address the targets of alcohol action.

level is elevated in chronic alcoholics and during acute heavy drinking but is not consistently increased by habitual moderate intake. In addition, concomitant induction of hepatic lipase activity by chronic alcohol intake counteracts the effect of high LPL on the HDL_2 level by favouring the formation of HDL_3.

In heavy drinkers, the enhanced lipolysis of VLDL due to the induction of LPL exceeds and/or compensates the increase in hepatic synthesis of VLDL and the final result is subnormal or normal serum levels of VLDL (27). However, increased transport through VLDL-LDL cascade should lead to an elevation of LDL levels in circulation if LDL catabolism remains constant. Therefore, low or subnormal LDL cholesterol levels in chronic alcoholics indicate that alcohol may have direct effects on LDL metabolism. This paradox may be explained if an increased proportion of VLDL is removed without conversion to LDL. Another possible explanation is that LDL can be modified by alcohol in vivo. Indeed, Kesäniemi et al. (17) have pointed out that the fractional removal rate of acetaldehyde-modified LDL is faster than that of native LDL.

Since alcohol is a microsomal enzyme inducer in the liver, the action of habitual moderate intake on HDL_3 could be attributed to increased production of nascent HDL particles and their subsequent conversion to HDL_3. A positive correlation between the hepatic cytochrome P-450 and apo A-I levels has been described in alcohol consumers (19). Therefore, the induction of microsomal enzymes could enhance the synthesis of apoproteins A-I and A-II or the processing of their precursors in the liver.

Finally, one alternative for the elevation of HDL cholesterol and the reduction of LDL cholesterol in alcoholics may be the suppression of cholesteryl ester transfer

activity (28). The physiological function of cholesterol ester transfer protein is to facilitate the transfer of cholesteryl esters from HDL to other lipoproteins, mainly to VLDL and LDL. Reduced transfer activity impairs interparticle exchange of core lipids (cholesteryl esters) from HDL particles, and consequently the cholesterol concentration increases in HDL and decreases in LDL. These different pathogenetic sequences are not mutually exclusive but can occur in concert.

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CHAPTER 10

Effects of alcohol on the cardiovascular system

J. Veenstra

Most of the early publications on the effects of alcohol on the cardiovascular system emphasize the detrimental effects of alcohol abuse on the heart, causing such diseases as cardiomyopathy and cardiac beriberi. Since the late 1970s, however, an overwhelming majority of epidemiological studies indicate that, although excessive alcohol consumption is associated with increased risk of cardiovascular diseases, moderate alcohol consumption is associated with a reduced risk as compared to non-drinkers, especially of coronary heart disease. These epidemiological studies have initiated a vast number of epidemiological as well as experimental studies into the possible mechanism of this protective effect. In this chapter the effects of both moderate and excessive alcohol consumption will be reviewed.

10.1. Blood lipids and lipoproteins

In epidemiological studies the levels of blood lipids and lipoproteins are clearly associated with the risk of cardiovascular diseases (CVD) of which the most common form is coronary heart disease (CHD). The levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol and apolipoprotein-B (Apo-B) are found to be positively associated with atherosclerosis and CHD, whereas the levels of high-density lipoprotein (HDL)-cholesterol and the apolipoproteins Apo-A1 and Apo-A2 show negative associations. Successive experimental studies have shown that several dietary factors may influence blood lipid and lipoprotein concentrations and consequently probably also influence the risk of CVD.

A large number of epidemiological studies (3, 5, 16, 19, 21, 28, 33, 34, 44, 53, 54, 61, 75, 83, 103, 104, 108, 112, 134, 135, 185, 196, 209–211) all over the world have consistently shown a positive association between alcohol consumption and HDL-cholesterol levels. Fig. 10.1 shows some results of the Tromsø Heart Study (28). Significant positive associations were found for all three types of alcoholic beverage. Even low alcohol consumption was associated with increased HDL-cholesterol levels. HDL, in which Apo-A1 and Apo-A2 are the major proteins, is considered to be an essential factor in the body's defence against accumulation of cholesterol in tissues, in a process called 'reverse cholesterol transport'. The initial excitement evoked by this apparent explanation for the observed lower risk of CHD in moderate alcohol consumers was tempered when it was found that it was mainly

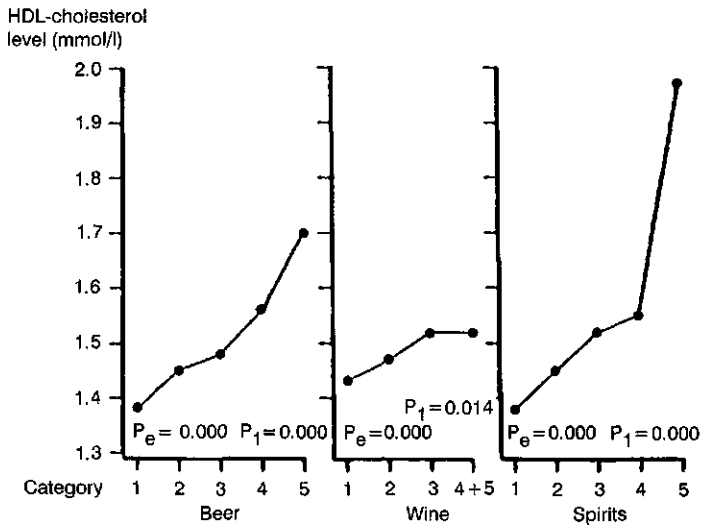

Fig. 10.1. Relationship between HDL-cholesterol and alcohol consumption. P_e, *P* value for test of equal group means: P_1, *P* value for test of similar trend. Values adjusted for time since the last meal.

the HDL3 subfraction of HDL-cholesterol that was associated with alcohol consumption, whereas it was the HDL2 subfraction that showed the strongest association with CHD (151). In more recent studies, however, it was found that HDL3-cholesterol was also associated with lower risk of CHD (180, 188). In addition, Miller et al. (150), in the first large-scale study (4860 men) on the effects of alcohol consumption on HDL-cholesterol subfraction levels, found comparable positive associations for HDL2- and HDL3-cholesterol.

In a relatively small number of epidemiological studies attention has been paid to the relationship between alcohol consumption and the apolipoprotein concentrations. The levels of Apo-A1 and Apo-A2 may be even better predictors of a low CHD risk than HDL-cholesterol. Phillips et al. (161) have found a positive association between alcohol use and Apo-A1 in a group of 289 Californian men and women, but have not measured Apo-A2. Haffner et al. (86) and Williams et al. (211) report positive correlations for both Apo-A1 and Apo-A2 in smaller groups (77 men and 50 men and women, respectively).

The relationships between alcohol consumption and HDL-cholesterol and the apolipoproteins A1 and A2, observed in epidemiological studies, have been confirmed in a number of experimental studies. The experimental studies, however, varied widely in study design with respect to the length of the experimental period, the beverage type used, the amount of alcohol consumed and the variables measured. Table 10.1 gives an overview of the variation in study design.

In most of the long-term studies (22, 30, 39, 42, 45, 69, 90–92, 146, 162, 197) a rise in HDL- or HDL-cholesterol was observed within a few weeks. In only two

Table 10.1. Survey of studies into the effects of alcohol consumption on blood lipids and lipoproteins.

Alcohol dose (g/day)	Type of beverage	Duration of study (weeks)	Reference
28	beer	3	90
39	white wine	6	197
31 (average)	optional	6	92
31	red wine	5	42
18.4 (average)	optional	4	30
24	beer	6	146
23 or 46	red wine	5	162
75	alcohol or beer	5	22
75	red wine	5	39
90	diluted alcohol	4	45
34 or 53	wodka	2	73
12.6	beer	8	152
40	beer	6	69
12.5 or 25	beer	3	91

studies (73, 152) no effects were found. In one of these studies (73), however, the experimental period was rather short, and in the other one (152) the dose of alcohol was very low. In the latter study, despite the absence of an effect on HDL, a significant increase in Apo-A1 was observed after consumption of only one glass of beer (12.6 g of alcohol) per day for 8 weeks.

In the long-term studies blood lipids have been examined in the fasting state, usually after an overnight fast. In a few studies (66, 74, 204) the acute effects of alcohol on blood lipids in the postprandial state have been investigated. Goldberg et al. (74) and Franceschini et al. (66) have studied the effects of a single dose of 120 ml whisky (40 g alcohol), using comparable experimental designs. The alcohol was drunk at 09.00 after a 14-hour fast. In the study of Franceschini et al. whisky was consumed mixed with a fluid meal of 100 g mayonnaise and 25 g bread. In both studies it was assumed that the alcohol had been fully metabolized after 4 hours, and measurements were performed 4, 6, 8, 10 and 12 hours after consumption. Goldberg et al. found significantly higher levels of HDL-cholesterol after alcohol consumption as compared to the control treatment. In addition, a 67% decrease was observed for activity of hepatic lipase, an important enzyme in the reverse cholesterol transport. By contrast, Franceschini et al. found a lower HDL-cholesterol level after consumption of alcohol, mayonnaise and bread relative to the treatment without alcohol.

Only one study has been reported (204) in which the effects of alcohol on blood lipids were studied shortly after consumption, when the alcohol is still in the circulation. In that study, Veenstra et al. tried to approximate reality as closely as possible in a carefully controlled experiment. Sixteen male volunteers (8 aged 20–30 and 8 aged 45–55) consumed 30 g of alcohol as port and wine during a normal evening dinner. For comparison, they drank similar amounts of mineral water instead

on another day. One hour after dinner, when the blood alcohol levels reached a maximum (mean 0.175 g/L, SD 0.055), significantly higher levels of HDL-cholesterol, Apo-A2 and triglycerides were found for the alcohol treatment than for the mineral water treatment. The HDL-cholesterol-enhancing effect was more prominent in the middle-aged men and was most evident for the HDL2-cholesterol fraction.

In a number of studies (23, 47, 48, 50, 109, 195, 200) HDL-cholesterol levels have been studied in alcoholics during a period of abstention. Most alcoholics have increased HDL-cholesterol levels, which rapidly decline as soon as alcohol consumption is stopped. The changes upon abstention in alcoholics are mainly found in the HDL2 subfraction, whereas most epidemiological studies suggest a relationship between alcohol and the HDL3 subfraction. This controversy prompted Välimäki et al. (56) to compare the effects of moderate (30 g/day) and heavy (60 g/day) alcohol consumption. The consumption levels differed in their effect on the HDL-subfraction. Heavy alcohol consumption increased HDL2 levels within two days and gradually increased HDL3 levels later on, whereas moderate alcohol consumption affected HDL3 levels only.

The epidemiological and experimental studies mentioned above clearly show a relationship between alcohol consumption and levels of blood lipids which is the most frequently cited explanation for a beneficial effect of moderate alcohol consumption on risk of CHD. However, whether these changes are beneficial indeed depends strongly on the exact mechanism causing the increase in HDL-cholesterol, which may be indicative of an increased reverse cholesterol transport, but could just as well be due to a decreased clearance of HDL-cholesterol. More detailed studies into the precise mechanism are needed. In this respect, the possibility that the observed changes originate from acute effects of alcohol on blood lipids as observed by Veenstra et al. as well as the differences between moderate and heavy alcohol consumption observed by Välimäki et al. deserve further attention.

10.2. Haemostasis

Haemostasis is the balance between the formation of blood clots, in which blood platelets (thrombocytes) are involved, and fibrinolysis, the dissolution of such clots. In most cases of myocardial infarction a coronary artery is blocked by a clot primarily consisting of thrombocytes (51). In normal physiological conditions clotting of thrombocytes, called platelet aggregation, most probably takes place constantly to some extent. The fibrinolytic system, on the other hand, plays a part in continually dissolving the newly formed clots. An effect of alcohol on this complex and delicate haemostatic balance would, of course, also have an effect on the risk of CVD.

Measurement of platelet aggregation is complicated and labour-intensive; So far, only one epidemiological study has been devoted to the relationship between alcohol consumption and platelet aggregation. Meade et al. (148) found an inverse association in a population of 685 British men and 273 British women (Northwick

Park Heart Study). In the same study Meade et al. (147) found the level of alcohol consumption to be associated with a decreased plasma fibrinogen level and an increased fibrinolytic activity. These latter results were confirmed in several other studies (13, 27, 174, 217). However, no correlation between alcohol consumption and fibrinogen was observed by Balleisen et al. (14) in 2880 men and 1306 women in the Munster Arteriosclerosis Study.

The experimental studies into the effects of alcohol consumption on platelet aggregation and other platelet function tests (52, 55, 60, 63, 71, 95, 96, 99, 113, 131, 136, 149, 154, 162, 206) are characterized by a large diversity in experimental design (Table 10.2).

First, the amount of alcohol consumed varied widely between 15 g and ad libitum consumption. In six studies, the amount of alcohol consumed in a single binge was 100 g or more (1 drink contains approximately 10 g). Furthermore, the studies varied considerably in type of alcoholic beverage. In almost all studies the alcohol was consumed on an empty stomach, mostly in the morning. The results are conflicting: no effects (55, 71, 99, 154, 206) inhibitory effects (60, 63, 149) as well as stimulating effects (95, 96) on platelet aggregation have been observed. The data on thromboxane production are also conflicting, with some studies showing an increase (95, 96) and other ones showing no effect (71, 99, 154), whereas one study showed a decrease (149) in platelet thromboxane production. Consequently, no definite conclusions can be drawn from the experimental studies. In the only study reported on the longer-term effects of moderate alcohol consumption on platelet

Table 10.2. Survey of studies into the effects of alcohol use on platelet function.

Alcohol dose[1] (g)	Term	Number of volunteers	Platelet function[2]	Year of publication	Reference
Ad libitum	acute	20	0	1981	55
50	acute	12	0	1982	52
120	acute	12	–	1982	113
120	acute	8	–	1982	131
64	acute	7	–	1983	149
51	acute	10	–	1984	60
32	acute	6	–	1984	136
100	acute	15	–	1984	63
32	acute	4	0	1984	71
120	acute	8	+	1985	96
120	acute	10	+	1985	95
88	acute	12	0	1987	99
20	acute	6	0	1987	154
23 and 46	5 weeks	12	–	1987	162
40	acute	8	0	1990	206

[1] The alcohol dose, irrespective of the volunteer's body weight, has been converted for a hypothetical 80-kg subject for comparison sake.
[2] Platelet function: + increased; 0 no effect; – decreased.

aggregation (162), a decrease in platelet aggregation was observed in agreement with the epidemiological findings of Meade et al. (148). In the only study published on the acute effects (206), in which the alcohol was consumed at a customary time of the day and under habitual conditions (during dinner instead of early in the morning and on an empty stomach) no acute effects of alcohol on platelet aggregation could be found.

Table 10.3. Survey of studies into the acute effects of alcohol on fibrinolysis.

Parameter	Amount of alcohol	Type of beverage	Effect[1]	Year of publ.	Reference
Blood clot lysis time	20–40 g	beer/cider/ white wine	+	1960	62
Blood clot lysis time	20–40 g	gin/whisky/ alcohol	0	1960	62
Fibrinolytic acticity	25–100 g	beer/wine	–	1961	155
Fibrinolytic activity	25–100 g	alcohol	0	1961	155
Euglobulin lysis time	90 g	cider	+	1983	4
Fibrinolytic activity	1.5 g/kg	alcohol	–	1983	97, 98
Euglobulin lysis time	1.5 g/kg	alcohol	+	1983	97, 98
Fibrin degr. products	1.5 g/kg	alcohol	0	1983	97, 98
Factor VIII: C activity	1.5 g/kg	alcohol	+	1983	97, 98
Factor VIII: antigen	1.5 g/kg	alcohol	+	1983	97, 98
Factor VIII: R cofactor	1.5 g/kg	alcohol	+	1983	97, 98
Antithrombin III	1.5 g/kg	alcohol	0	1983	97, 98
Factor VIII	0.8 g/kg	whisky	0	1984	59
Fibrin degr. products	0.8 g/kg	whisky	0	1984	59
Plasminogen	0.8 g/kg	whisky	0	1984	59
Fibrinogen	0.8 g/kg	whisky	0	1984	59
Fibrinolytic activity	0.8 g/kg	whisky	0	1984	59
Euglobulin lysis time	0.8 g/kg	whisky	0	1984	59
Antithrombin III	0.8 g/kg	whisky	0	1984	59
Blood clot lysis time	0.5–1.0 g/l	ethanol	+	1987	156
Euglobulin lysis time	24–47 g	shochu/ sake/beer	–	1988	193
Fibrin degr. products	24–47 g	shochu/ sake/beer	0	1988	193
Fibrinolytic activity	24–47 g	shochu/ sake/beer	+	1988	193
t-PA activity	30 g	red wine/port	–	1990	203
PAI activity	30 g	red wine/port	+	1990	203
PAI activity	40 g	red wine/gin	+	1990	202
PAI antigen	40 g	red wine/gin	0	1990	202
t-PA activity	40 g	red wine/gin	–	1990	202
t-PA antigen	40 g	red wine/gin	+	1990	202
Total UK-PA antigen	40 g	red wine/gin	0	1990	202
Pro-UK-PA antigen	40 g	red wine/gin	0	1990	202
UK-PA inhibitor complex	40 g	red wine/gin	0	1990	202

[1] Effect: + increased; 0 no effect; – decreased.

Besides platelet aggregation, Pikaar et al. investigated in the same study (162) the long-term effects of moderate alcohol consumption on a number of fibrinolytic factors. No effects on fibrinogen could be observed after 5 weeks of moderate alcohol consumption (23 or 46 g/day) or after 5 weeks of binge drinking (14 glasses of wine per week consumed on the three weekend days). The levels of plasminogen and tissue-plasminogen activator (t-PA) activity, however, appeared to be clearly affected by wine consumption. Plasminogen levels moderately increased with an increasing dose of wine. The t-PA activity, on the other hand, showed a large and dose-dependent decrease. There was no effect on bleeding time. In additional analyses (128), the levels of plasminogen activator inhibitor 1 (PAI-1) were measured, and significantly higher levels were observed after 5 weeks of moderate alcohol consumption than in the control treatment. Since high PAI-1 levels inhibit fibrinolytic activity these results are in contrast with the epidemiological findings of Meade et al. (148).

In a number of studies (4, 59, 62, 97, 98, 155, 156, 193, 202, 203) over a period of 30 years, the acute effects of alcohol on fibrinolytic parameters have been investigated (Table 10.3).

In the earlier studies, overall fibrinolytic activity of plasma or whole blood was measured in global assays. These measurements are very aspecific because fibrinolytic activity is influenced by many variables and the results obtained hence strongly depend on the experimental conditions used. This probably explains some of the contradictions shown in Table 10.3. In recent years, however, new analytical techniques have made possible the measurement of more specific fibrinolytic factors. A strong and consistent decrease in t-PA activity and an increase in PAI activity have been observed in two studies (202, 203), in agreement with the long-term study of Pikaar et al. (162). The levels of t-PA antigen, on the other hand, increased whereas no effects on the urokinase-plasminogen activator (UK-PA) system could be observed.

In conclusion, the results of studies on alcohol and fibrinolysis are contradictory. Alcohol consumption is epidemiologically associated with increased fibrinolytic activity, whereas decreases in fibrinolytic activity and t-PA activity and increases in PAI activity and t-PA antigen have been observed in experimental studies. Further research is needed to explain this contradiction and to investigate the mechanisms and consequences of these effects of alcohol. Some recent epidemiological studies suggest a relationship between lipid metabolism and fibrinolysis. This possible relationship also needs further attention.

10.3. Blood pressure

There is strong epidemiological evidence that regular use of large quantities of alcohol is related to higher blood pressure and a greater prevalence of hypertension (10, 12, 31, 41, 43, 56, 58, 65, 70, 77, 85, 88, 89, 116, 123, 138, 153, 159, 163, 190, 198, 207, 213), even after correction for confounding factors such as obesity

and excessive salt intake. In the Kaiser Permanente study, the prevalence of hypertension was twice as high among people who had 6 or more drinks per day as among people who had 2 or less drinks per day (123). It seems prudent for health practitioners to advice hypertensive patients who are used to take three or more drinks a day to reduce their alcohol use. Potter & Beevers (166) and Malhotra et al. (143) have reported significant favourable responses to a reduction of alcohol intake within a few days (4 and 5 days, respectively). Puddy et al. (169), in a study among 44 hypertensive men with an average alcohol consumption of 6 to 7 glasses per day, demonstrated a significant reduction in blood pressure after a switch from regular beer (5% v/v alcohol) to low-alcohol beer (0.9% v/v alcohol). In the study of Puddy et al. not only blood pressure, but also body weight fell significantly in the period of low-alcohol beer consumption. This body weight reduction has undoubtedly contributed to a lowering of blood pressure. Unfortunately, no studies among hypertensives have been conducted yet in which the independent effect of alcohol, i.e. the energy from alcohol versus non-alcohol energy, has been investigated.

There is much less consensus with regard to the effects of moderate alcohol consumption. Some studies have found a continuous increase in blood pressure from abstainers to heavy alcohol users (10, 31, 41, 198). Other studies (43, 123, 213) have established a threshold above which alcohol was found to be positively associated with blood pressure. In still other studies (85, 88, 89, 116) a J-shaped relationship between alcohol consumption and blood pressure was found.

In an epidemiological study, Periti et al. (159) classified 1190 Italian men and women into two groups. In one group the people were asked to abstain for 3 days from alcohol before their blood pressure was measured, the others continued their normal alcohol consumption habits until the day of blood pressure measurement. In the men, but not the women, of the latter group, systolic blood pressure increased significantly with increasing alcohol use, regardless of age, body weight, smoking or coffee consumption. The systolic blood pressure increased by 4.6 mmHg per 100 g of alcohol per day. No significant relationship between alcohol consumption and diastolic blood pressure could be observed. In the group that was asked to abstain from alcohol for 3 days, no relation between alcohol consumption and blood pressure was found. These results are consistent with earlier findings showing an association of increased blood pressure with excessive alcohol consumption and also indicate that this increase disappears after a few days of abstention.

The effects of a single dose of alcohol have been investigated in a number of studies (105, 106, 168, 191, J Veenstra & E. te Wierik, in preparation). Potter et al. (168) have studied the effect of a single dose of alcohol on blood pressure in 16 young male students. Blood pressure was measured over a 5-hour period after the ingestion of either 600 ml non-alcoholic beer or 600 ml non-alcoholic beer spiked with alcohol (0.75 g per kg body weight). All volunteers were subjected to both treatments in a cross-over design. The period between the treatments was at least one week. The blood pressure course roughly paralleled the blood alcohol level: after a rapid increase by ca. 7 mmHg within one hour, blood pressure gradually decreased. Similar acute effects have been observed by Ireland et al. (105, 106).

In a recent study by J. Veenstra & E. te Wierik (in preparation) the effects of a moderate dose of beer, wine and spirits (40 g alcohol) and mineral water were studied in a randomized cross-over design. The drinks were consumed during a normal evening dinner, the volunteers being 8 healthy middle-aged men aged 45–55 years. In contrast to the studies mentioned above, a lower blood pressure was observed after alcohol consumption as compared to the mineral water treatment. There were no significant differences among the alcoholic beverages, albeit the effect was not as strong for beer as for wine or spirits, possibly due to the larger volume of the beer. The contradiction with the earlier studies can possibly be explained by the lower alcohol dose, the combination with a meal, the age of the volunteers or the time of the day. In the study of Veenstra & te Wierik the aim was to study the effects of alcohol under conditions mimicking normal life as closely as possible. Therefore, normal alcoholic beverages were used in combination with a normal but standardized evening dinner in a non-laboratory environment.

The acute studies mentioned so far have the drawback that the treatments are not isocaloric, i.e. the caloric value of the alcohol is not compensated for in the control treatment. This energy effect was taken into account in a study by Stott et al. (191). In that study, the design of which was comparable with that of Potter et al., an isocaloric amount of glucose was added to the non-alcoholic drink. In agreement with the results of Potter et al., a slight increase of blood pressure was observed one hour after alcohol ingestion, followed by a decrease. However, a similar increase and subsequent decrease in blood pressure was observed after the consumption of the glucose-enriched non-alcoholic drink. From this study it was concluded that the increase of blood pressure after the consumption of a single moderate dose of alcohol does not differ from the increase after the ingestion of an isocaloric amount of glucose.

Kelbaek et al. (117, 118) recently studied the effect of a single alcohol dose (0.9 g per kg body weight) on the heart function of 20 male CHD and cardiopathy patients. Ten controls with a similar clinical picture received an equal amount of an isocaloric non-alcoholic drink. A slight but significant decrease (–6%) of the systemic arterial blood pressure was found after alcohol ingestion. Alcohol was found to have no effect on central venous pressure, pulmonary artery pressure, cardiac output, stroke volume or global peripheral resistance. Kelbaek et al. concluded that ingestion of a moderate dose of alcohol by CHD patients is unlikely to evoke disease symptoms.

In some studies (101, 105, 167, 170) an increase in plasma adrenaline and noradrenaline after alcohol consumption has been connected with a rise in blood pressure. In the carefully controlled study of Stott et al., however, no effects of alcohol consumption on plasma catecholamine levels were observed. An alternative explanation for the relation between alcohol consumption and blood pressure is that alcohol induces changes in electrolyte excretion (36). J Veenstra & E. te Wierik (in preparation) observed large changes in mineral excretion in the urine and a strong diuretic effect of alcohol, which could possibly explain the acute decrease of blood pressure observed in their study. Finally, the results of a study by Finch et al. (64) suggest that an increase in peripheral blood flow and subsequently in skin

temperature may be responsible for a decrease in blood pressure after a moderate dose of alcohol.

10.4. Atherosclerosis

In several studies the relationship between level of alcohol consumption and degree of atherosclerosis has been investigated. The degree of atherosclerosis has been established by autopsy (72, 100, 139) or in vivo by means of arteriography (15, 17, 18, 20, 67, 82, 87, 158, 183).

As early as 1904, it was concluded from an autopsy study that atherosclerosis is uncommon in alcoholics. However, judging by present standards, this study was poorly designed, lacking controls. Later, in 1965, Hirst et al. (100) observed no differences in degree of occlusion between non-cirrhotic alcoholics and controls. In cirrhotic alcoholics, however, he found fewer occlusions, which made him conclude that cirrhosis may have a protective effect against atherosclerosis, possibly by a change in oestrogen metabolism or blood coagulation. Some studies have confirmed this association between cirrhosis and atherosclerosis, others did not find any effect (11, 72).

In a few studies among non-alcoholics the extent of occlusion of coronary arteries in CHD cases has been related to the level of alcohol consumption (17, 18, 67, 82, 158). Barboriak et al. (17) have studied the effects of smoking and of alcohol consumption on coronary artery occlusion in a group of 2989 men. Fig. 10.2 summarizes the results of that study. Smoking was found to have a dose-dependent

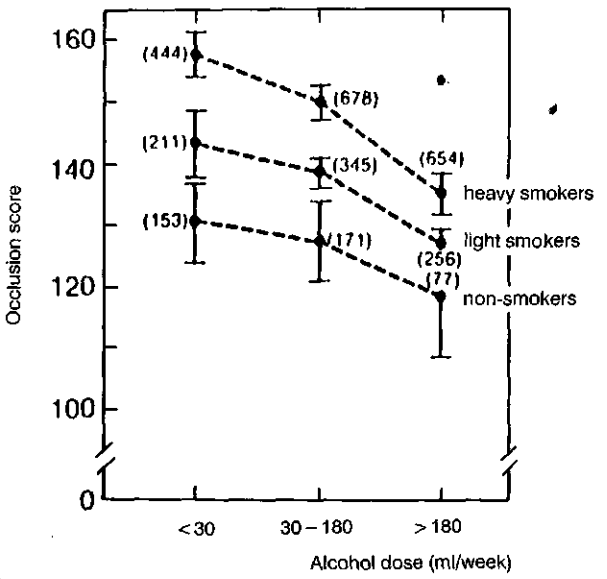

Fig. 10.2. Interrelationships between the extent of coronary occlusion, alcohol intake and smoking (17). Number of patients in parenthesis. Vertical bars: SEM.

occlusive effect, whereas the effect of alcohol was associated with lower occlusion scores in non-smokers, light smokers as well as heavy smokers.

Within the same study framework Gruchow et al. (82) investigated the effect of alcohol consumption patterns by classifying the subjects into non-drinkers, occasional drinkers, regular drinkers adhering to a more or less fixed dose, and regular drinkers varying the amounts consumed. Regular users of moderate doses of alcohol were found to be at significantly lower risk of occlusion of coronary arteries. Irregular drinkers were at higher risk irrespective of the level of alcohol consumption.

In a very recent study by Handa et al. (87), the relation between alcohol consumption and severity of coronary atherosclerosis was examined in 212 men undergoing coronary angiography. In addition, a blood sample was taken to measure blood lipids. The men were categorized as follows: non-drinkers, light drinkers (1–100 ml alcohol weekly), moderate drinkers (101–300 ml weekly) and heavy drinkers (> 300 ml weekly). HDL-cholesterol levels increased and total cholesterol levels decreased with increasing alcohol consumption. After adjustment for age, smoking, hypertension, HDL-cholesterol, total cholesterol and triglycerides the relative risk of coronary stenosis for moderate drinkers was only 0.29 (95% confidence interval 0.13–0.63). The relative risk of light and of heavy drinkers did not differ significantly from that of non-drinkers. Also the severity of coronary atherosclerosis was significantly less in the moderate drinkers category (about 8–24 glasses weekly).

Fried et al. (67) studied in a group of 31 men with coronary arteries of normal diameter the effects of smoking and of alcohol consumption on the diameter of three main coronary arteries. Smoking and alcohol use appeared to affect these diameters highly significantly and independently. Smoking was found to have a vasoconstrictive effect, whereas alcohol consumption promoted vasodilatation.

In contrast with the studies mentioned above, two earlier studies, an autopsy study by Gent et al. (72) and an arteriographic study by Sirtori et al. (183), have reported a positive correlation, i.e. an increase in alcohol consumption associated with a larger number or more extensive atherosclerotic lesions.

10.5. Coronary heart disease and mortality

The relationship between level of alcohol consumption and risk of CHD has been investigated in many epidemiological studies. In ecological studies the per capita alcohol consumption in various countries has been correlated with the mortality rate for CHD (29, 93, 119, 137, 181, 184, 208). St. Leger et al. (184), for example, compared these values for 18 countries and found a clear inverse relation between average alcohol consumption and CHD. The observed effect of alcohol was not attributable to differences in known CHD risk factors such as smoking, cholesterol intake, fat intake or total energy intake. The strongest association was observed for wine consumption and CHD (Fig. 10.3).

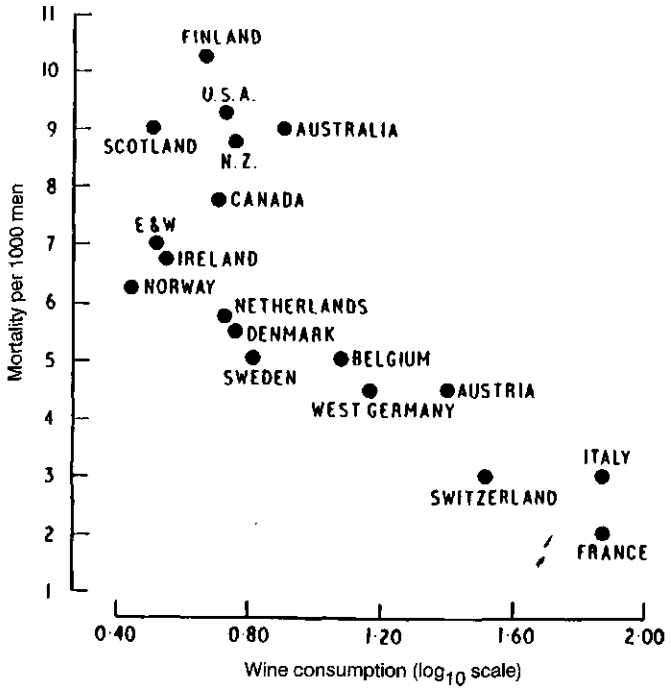

Fig. 10.3. Relationship between CHD mortality rate in men aged 55–64 and wine consumption (143).

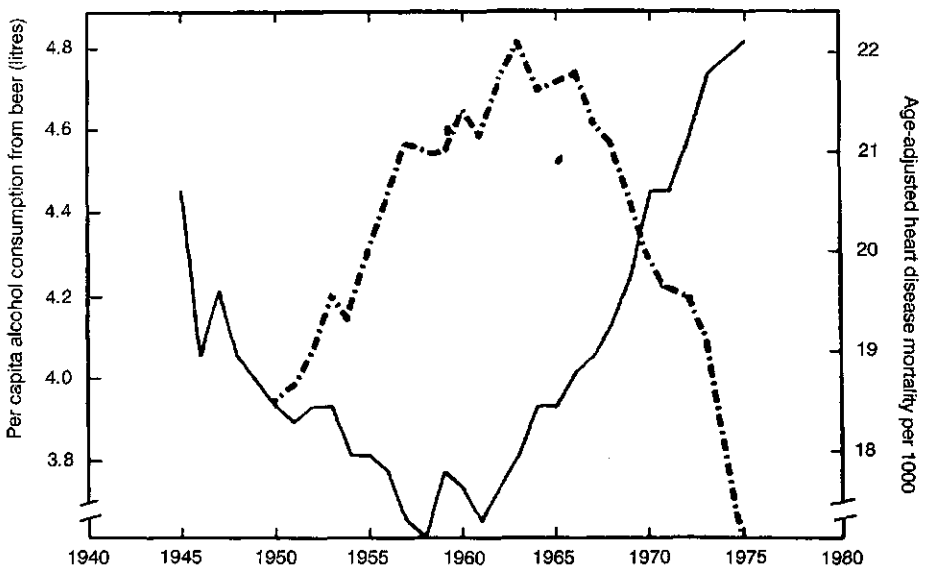

Fig. 10.4. Relationship between changes in adult per capita intake of alcohol in beer (solid line, 1945–1975) and changes in total age-adjusted heart disease death rates in the USA (broken line, 1950–1975) (137).

Comparable results have been reported by others (29, 93, 119, 137, 181, 208). Schmidt & Popham (181) and Werth (208) also reported significant negative correlations between total consumption of alcohol, wine and spirits and CHD mortality in the 50 states of the USA. LaPorte et al. (137) have also paid attention to trends in alcohol use and CHD incidence rates between 1945 and 1975 and found significant correlations between these, the strongest for beer. Taking into account a 5-year lag period, the correlation coefficient between beer consumption and CHD mortality was –0.943 (Fig. 10.4).

Ecological studies are no real proof of a favourable effect of alcohol consumption on CHD development. The results just indicate a relationship on a population level, and differences between countries with regard to culture and living and working conditions are not taken into account. A second drawback of these studies is that the alcohol consumption data are derived from alcohol sales data, uncorrected for home production, for sales to visitors from abroad or for consumption abroad. Finally, the hypothetical U-shaped curve between alcohol consumption and CHD poses an insurmountable problem for ecological studies since the use of sales statistics does not differentiate between non-drinkers, moderate drinkers and heavy drinkers.

In several case-control studies the alcohol consumption of CHD patients has been compared with a control group (94, 115, 126, 160, 171, 175, 177, 189). The results of these studies fairly consistently point at an inverse relation between moderate alcohol consumption and CHD for both men and women. Only Kaufman et al. (115) found no effect of moderate alcohol consumption.

Hennekens et al. (94) classified their study population into three categories, with an average daily alcohol consumption of 0, 0–3.5 and >3.5 glasses respectively. The relative risk was found to be significantly lower for moderate drinkers than for non-drinkers (relative risk (RR) = 0.4). The relative risk for drinkers of more than 3.5 glasses per day, on the other hand, was not significantly different from that of non-drinkers (RR = 0.7). In contrast, Klatsky et al. (126) found the relative risk to decrease with increasing consumption level, with relative risks of 1.0, 0.7 and 0.4 for categories with a daily alcohol consumption of <3, 3–5 and >5 glasses respectively.

Case-control studies, just as ecological studies, have a number of drawbacks. Probably the most serious one is that alcohol consumption is asked about after the disease has been diagnosed. This may result in specific underreporting of alcohol consumption by the patients. Moreover, the patients may have gradually reduced their alcohol use in the preclinical phase of the disease.

The strongest support for a protective effect of moderate alcohol consumption on CHD risk comes from cohort studies. In cohort studies, also called prospective or longitudinal studies, large populations are classified into categories varying in alcohol consumption level. After a number of years the association between alcohol consumption and CHD incidence is studied. In a remarkably large number of these studies performed in various parts of the world, a reduced risk of CHD in moderate drinkers has been found (7–9, 25, 26, 32, 38, 46, 57, 68, 76, 78, 79, 81, 114, 120, 122, 124, 129, 130, 133, 145, 179, 182, 186, 192, 214–216). In two studies – one in Ireland (81), another in California (32) – no effects of alcohol use were found. A

recent study in Finland showed, in contrast to all other studies, a positive association between consumption of alcohol, in particular of spirits, and CHD incidence (192).

It is also from cohort studies in particular that the idea of a U-shaped curve has arisen, i.e. moderate drinkers would be at lower risk of CHD than both teetotallers and heavy drinkers. Dyer et al. (57), in 1980, were the first to suggest such a U-shaped curve on the basis of a study in which they followed 1899 employees of the Western Electric Company from 1957 to 1974. A decrease in CHD incidence was found with increasing alcohol consumption up to a daily dose of 5 glasses. At higher doses CHD incidence was found to increase again. However these results lost their significance after correction for smoking habits, serum cholesterol and blood pressure. In 1981, the existence of a U-shaped relationship was confirmed in two independent studies, one by Klatsky et al. (124), the other by Marmot et al. (145). Later support came from a study of Friedman & Kimball (68) among 5209 men and women in Framingham during a 24-year follow-up period.

Although the vast majority of all studies have reported a decreased incidence of CHD among moderate drinkers as compared to non-drinkers, not all studies have found a U-shaped relationship. There is, however, no doubt that heavy alcohol consumption, besides increasing other health risks, damages the cardiovascular system (see also Sections 10.3 and 10.6–10.8). Possibly alcoholics and excessive alcohol users are less likely to be included in the cohort studies. This is, for example, the case in the Nurses Health Cohort Study by Stampfer et al. (186), in which the alcohol consumption of the cohort was relatively low.

A serious drawback of many cohort studies is that the category of non-drinkers considered in these studies may comprise former heavy drinkers as well as people who have given up alcohol on medical advice owing to, for example, heart complaints. This potential bias has recently been studied by Shaper et al. (182) in a cohort of 7735 men living in 24 different towns in England, Scotland and Wales. They found a U-shaped relationship between alcohol consumption and total mortality and an inverse relationship between alcohol consumption and cardiovascular disease mortality, in fair agreement with the results of earlier studies. At the start of the follow-up study, when the average age of the subjects was 50 years, 24.2% of the subjects already had heart complaints. The associations between alcohol use and total mortality and between alcohol use and CVD mortality were also studied for both sub-cohorts separately (men suffering from and men free from heart disorders). In the category initially free from heart disorders a U-shaped or inverse relationship could no longer be found. Shaper et al. concluded that the U-shaped curve could largely be explained from the fact that people suffering from CVD disorders tend to reduce or even give up alcohol consumption so that the curvature cannot be attributed to any favourable effects of moderate alcohol use. An alternative explanation, however, could be that by excluding 24.2% from the cohort, those people are removed that are most susceptable to CVD and therefore could benefit most from a potential protective effect of moderate alcohol consumption. The Lancet paper of Shaper et al. (182) has evoked a lively discussion in that journal as to whether moderate alcohol use protects against CHD (7–9).

In a number of studies the non-drinkers group has been clearly defined. In the Honolulu Heart Study (216), in which the non-drinkers were classified into lifelong teetotallers and former drinkers, a higher CHD incidence as compared to drinkers was found for both categories. This finding is supported by the results of a case-control study among 513 cases and 918 controls (175) and other studies (122, 129, 130). In the Honolulu Heart Study (184) and in a study by Klatsky et al. (122) no significant differences in CHD risk were found between lifelong teetotallers and former drinkers. Finally, Stampfer et al. (186), in a cohort of as many as 87 526 nurses, has recently searched for any changes in drinking habits over the past ten years. Subjects who had given up drinking on medical advice could be excluded from the study this way. The CHD risk for the non-drinkers group was found to be up to 2.5 times as high as for the drinkers categories.

Interestingly, Stampfer et al., in the Nurses Health Cohort Study, also describe a decreased risk of ischaemic stroke in light and moderate alcohol consumers, which indicates a possible common physiological mechanism. The risk of haemorrhagic stroke, on the other hand, showed a dose-dependent increase with increasing alcohol consumption. These results were recently confirmed for both men and women in a cohort study by Klatsky et al. (121) comprising over 100 000 people. The increased risk of haemorrhagic stroke could partly be explained by the effects of alcohol on blood pressure.

An important question with respect to the proposed beneficial effects of moderate alcohol consumption on risk of CHD is whether total mortality rates are also favourably influenced. Obviously, it is important to show that, when the risk of CHD in moderate drinkers decreases, the risk of other death causes does not simultaneously increase. Large-scale epidemiological studies, such as the Chicago Western Electric Company Study (57), the Honululu Heart Study (25), the London Civil Servant Study (145), the Kaiser Permanente Study (124), the Framingham Study (78) and – very recently – the large American Cancer Society Prospective Study (26), however, have shown that not only CHD risks are lower in moderate alcohol consumers, but that there is also a U- or J-shaped relationship between alcohol consumption and risk of total mortality.

Finally, the effects of alcohol consumption on blood lipids, haemostasis, blood pressure and atherosclerosis (see sections 10.1–10.4) all have been put forward to explain the observed beneficial effects of moderate alcohol consumption in epidemiological studies. An alternative explanation, however, might be that moderate alcohol consumption is associated with a healthier life-style. In a few studies the relationship between level of alcohol consumption and dietary patterns has been investigated (49, 84, 107, 110, 205). With respect to the intake levels for various nutrients the results are not very consistent and may vary due to cultural differences in dietary habits between the populations studied. It was fairly consistently shown, however, that total energy intake increases with increasing alcohol consumption. In other words, the energy consumed in the form of alcohol is not compensated for by omitting calories from other dietary sources. Furthermore, it was shown that alcohol consumption, even in moderate amounts, is strongly

associated with smoking, which is in agreement with findings in many other epidemiological studies (125, 144, 187). These findings do not provide an alternative explanation for the observed decreased risk of CHD in moderate drinkers. Therefore, the physiological mechanisms described in sections 10.1–10.4 still form the most likely explanation.

10.6. Angina pectoris

According to Orlando et al. (157), angina pectoris (pain in the chest during exercise, caused by ischaemia of the coronary arteries), occurs more frequently after alcohol consumption. In earlier studies alcohol was proved either to have no effect (40) or to attenuate angina pectoris (178). Hrubec et al. (102) found a statistical relationship between angina pectoris and the number of times individuals are intoxicated, but found no clear relation with the quantity of alcohol consumed weekly.

Takizawa et al. (194) concluded that alcohol consumption may provoke attacks of variant angina, a type of angina pectoris which may occur spontaneously in rest.

In view of the conflicting evidence no definite relationship between alcohol consumption and angina pectoris, either positive or negative, can be said to exist.

10.7. Cardiomyopathy

A single large dose of alcohol has a deleterious effect on cardiac performance such as myocardial contractility and depression of the left ventricular function. Van Zwieten (218) reported consumption of 80 g alcohol in 2 hours to be associated with this phenomenon. Regan et al. (172) reported this change to occur at a blood alcohol level of 0.75 g/l. Others mention with regard to this syndrome blood alcohol levels of 0.1 to 2.85 g/l (1, 35). The consumption of a single large dose of alcohol may also cause arrhythmia of the heart muscle such as atrial fibrillation (132, 140). In a study by Lowenstein et al. (140), 35% of the cases admitted to the hospital with new-onset atrial fibrillation could be linked with excessive alcohol consumption. In a large prospective study by Cohen et al. (37) it was shown that arrhythmia in general was 2.3 times more common in heavy drinkers (more than 6 glasses per day) than in light drinkers (less than 1 glass per day). The so-called 'holiday heart syndrome', which is characterized by arrhythmia, is also associated with acute excessive alcohol consumption (80, 111).

Alcoholism may cause myocardial injury (173, 218). This effect of excessive alcohol consumption is not specific for the heart muscle, but may affect other muscles as well (see Chapter 11). Recently, Urbano-Marquez et al. (199) showed strong correlations between the total lifetime amount of alcohol consumed and the performance of both skeletal and cardiac muscle, in a group of severe alcoholics. There is now sufficient evidence (see Table 10.4) to support the causal role of alcohol and/or acetaldehyde in injury of the heart muscle (cardiomyopathy) in

Table 10.4. Evidence in support of the syndrome called 'alcoholic cardiomyopathy' (from 127).

1.	Association of drinking and heart muscle disease noted by numerous authorities.
2.	High proportion of chronic users of large amounts of alcohol among patients with congestive cardiomyopathy.
3.	Cases that show convincing evidence of heart muscle dysfunction in relation to episodic drinking.
4.	Acute impairment of heart muscle contractility due to alcohol in man and animals.
5.	Acute rhythm disturbances related to alcohol in man ('holiday heart syndrome').
6.	Impaired heart function in alcoholics without acute alcohol load.
7.	Heart muscle metabolic dysfunction in animals related to acute alcohol load.
8.	Alcohol-produced heart muscle cellular abnormalities in animals.
9.	Autopsy evidence of heart muscle damage in alcoholics without a history of clinical heart disease.
10.	Well-documented acute and chronic skeletal muscle syndromes owing to alcohol.

alcoholics (127, 172, 218), also in the absence of the nutritional deficiencies often observed in alcoholics (176, 199).

Among the possible causes mentioned are: changes in ion permeability of muscle cells (164), inhibition of protein synthesis, inhibition of actin and myosin binding in the heart muscle (6), and mitochondrial abnormalities (1).

Cardiomyopathy may also be caused by intoxication due to trace elements, cobalt in particular (1). Alexander (2) found myocardial injury in 27 heavy drinkers who used to drink one particular brand of beer to which 1–1.5 mg/l cobalt had been added to stabilize the froth.

Alcohol abuse must have continued over a long period of time in order to cause severe heart muscle injury. Wink (212) mentioned an alcohol limit of 250 g/day over 10 years as the borderline above which definite cardiac risk will occur. A limit of 10 years of excessive alcohol intake is also indicated elsewhere (1, 6). Damage to other organs in the body is usually observed prior to cardiomyopathy (6, 218).

10.8. Cardiac beriberi

Beriberi is a nutritional disorder caused by deficiency of thiamin (vitamin B-1). The disease has been widespread in poor communities in East Asia, with rice as the staple food and an otherwise very poor diet. However, in rich countries thiamin deficiency may also occur in people whose main source of energy is alcohol. Thiamin deficiency may lead to the Wernicke-Korsakoff syndrome (see Chapter 9) in some alcoholics, or cause cardiac failure with generalized oedema, pulmonary congestion and breathing difficulties in others (28, 142, 165). These diseases can occur together in one patient, but this is uncommon. There is no explanation as to why in some patients the heart is affected by the thiamin deficiency and in others the brain. In beriberi among alcoholics lactacidosis is regularly observed (141), which is not the case for beriberi in non-alcoholics. In its early stages the disease can also be treated with thiamin, but recovery of severe cases is slow and often incomplete (127). Supplementation with

thiamin is a very successful and cost-effective way of preventing the disease. Doctors and social workers should therefore pay attention to the alcoholic's diet and be aware of the risks of thiamin deficiency.

10.9. Final considerations

In this chapter the effect of alcohol on the cardiovascular system is described. Excessive alcohol use has obviously detrimental effects on the vascular system, by increasing blood pressure, and on the heart muscle itself. Moderate alcohol use, on the other hand, has been shown to have a protective effect on CHD. The exact mechanism of this effect is not yet fully known, but a number of plausible mechanisms have been put forward. These results underline the sense of prudent drinking limits. On the one hand, they should not be used to promote alcohol consumption among non-drinkers. It should be realized that the lower risk of CHD is mainly observed in population studies and is not necessarily applicable to each single individual. On the other hand, these results may be used to persuade excessive drinkers to moderate their alcohol use.

Summary

Consumption of alcohol has an influence on several processes that play an important role in the development of diseases of the cardiovascular system.

- Alcohol consumption is positively correlated with HDL-cholesterol in epidemiological studies. In experimental studies alcohol increases the HDL-cholesterol level within some weeks.
- Studies on the acute effects of alcohol on platelet aggregation have revealed conflicting results. Epidemiological and long-term experimental evidence shows that alcohol consumption probably reduces platelet aggregation.
- Alcohol consumption, even at moderate doses, strongly affects the components of the fibrinolytic system, acutely and in the long term. PAI activity and the level of t-PA antigen is increased, whereas the level of t-PA activity is strongly decreased.
- Excessive alcohol consumption is clearly associated with an increased blood pressure. The effects of moderate alcohol use are less evident. Some epidemiological studies have shown a continual dose-dependent increase, other ones have shown an increase above a certain level, and in some studies a U-shaped relationship between alcohol and blood pressure has been found.
- Studies among hypertensive excessive alcohol consumers have clearly shown a marked reduction in blood pressure within days after reducing alcohol intake.
- A number of studies have shown that moderate alcohol use is associated with lower scores for occlusion of the coronary arteries. In these studies, the drinking pattern was shown to be an important factor. Binge drinking was associated with a higher risk.

The relationship between alcohol consumption and cardiovascular diseases has been the subject of a large number of studies.

- In a number of ecological studies an inverse relationship between alcohol use and the incidence of CHD has been found.
- A protective effect of moderate alcohol consumption against the development of CHD has been confirmed in many patient-control and cohort studies. Total mortality was also shown to decrease among moderate drinkers as compared to non-drinkers.
- Since excessive alcohol use is associated with an increased risk of CHD, the relationship between alcohol consumption and CHD is said to be U-shaped.
- Moderate alcohol use has been found to be associated with a lower incidence of ischaemic stroke. The risk of haemorrhagic stroke, on the other hand, increases with alcohol consumption.
- In a number of studies moderate alcohol consumption was found not to be associated with a healthier life style as far as dietary patterns and smoking habits are concerned.
- Long-term as well as acute excessive alcohol consumption has been shown to increase the risk of cardiac arrhythmia.
- Long-term excessive alcohol consumption can cause cardiomyopathy, even in the absence of nutritional deficiencies. In alcoholics, the total lifelong consumption of alcohol has been shown to be inversely correlated with both cardiac performance and skeletal muscle strength.
- In alcoholics, thiamin deficiency may result in cardiac beriberi, which in an early stage can be prevented easily and cost-effectively by thiamin supplementation.

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