Effect of moderate dose of alcohol with evening meal on fibrinolytic factors

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Abstract

***Objectives*—To evaluate the effects of moderate consumption of alcoholic beverages on the fibrinolytic system and to assess whether these effects could help explain the relation between moderate alcohol consumption and reduced coronary heart disease.**

***Design*—Four treatments were allocated in a randomised controlled order on four days over a period of 11 days.**

***Setting*—Metabolic ward of research institute.**

***Subjects*—Eight white healthy middle aged men.**

***Interventions*—Subjects were provided with food for the 11 days. On the four study days mineral water or 40 g of alcohol in the form of beer, wine, or spirits was consumed at dinner early in the evening.**

***Main outcome measures*—Plasminogen activator inhibitor activity, tissue type plasminogen activator antigen, and tissue type plasminogen activator activity one hour before and one, three, five, nine, and 13 hours after dinner with mineral water or alcoholic beverages.**

***Results*—After dinner with alcohol plasminogen activator inhibitor activity rose from 53 (SD 19)% to a maximum of 667 (283%) five hours after dinner ($P<0.001$). Tissue type plasminogen activator antigen levels rose from 5·3 (2·2) μg/l to a maximum of 10·8 (3·8) μg/l nine hours after dinner with alcohol ($P<0.001$). Plasminogen activator activity was reduced in the postprandial period (from 1387 (483) IU/l to 323 (288) IU/l five hours after eating; $P<0.001$) but was higher than normal early the next morning (1516 (809) IU/l after alcohol, 779 (516) IU/l after water; $P=0.04$).**

***Conclusion*—Moderate alcohol consumption with dinner affects plasminogen activator inhibitor activity, plasminogen activator antigen level, and tissue type plasminogen activator activity temporarily. The effects observed in the early morning are consistent with a decrease in risk of coronary heart disease in moderate drinkers.**

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Introduction

Many epidemiological studies have shown that moderate alcohol consumption is associated with a lower risk of coronary heart disease.[1-4] One explanation for this reduced risk is the positive association between alcohol consumption and high density lipoprotein cholesterol concentration. Differences in high density lipoprotein cholesterol may explain up to half of the epidemiological relation.[5] But it remains unclear whether increases in high density lipoprotein cholesterol concentrations are really beneficial, producing reverse cholesterol transport.

In addition to lipoprotein concentrations, which are related to atherosclerosis, haemostatic function is an important determinant of risk of coronary heart disease. In a cohort of 87 526 nurses moderate drinkers had a lower risk of both coronary heart disease and ischaemic stroke but an increased risk of haemorrhagic stroke.[6] Since occlusion of blood vessels occurs in both coronary heart disease and ischaemic stroke, and bleeding occurs in haemorrhagic stroke, effects on haemostatic factors might explain these different effects of moderate consumption of alcohol.

We have previously reported a reduction of platelet aggregation after five weeks of moderate alcohol consumption,[7] but no short term effects on platelet function have been observed.[8] The aim of the present study was to investigate the short term effects of moderate consumption of beer, wine, or spirits on the fibrinolytic system in middle aged men.

Subjects and methods

Eight healthy middle aged men (45-55 years) participated in this study. They were used to moderate alcohol consumption (1-4 glasses a day) and a Western lifestyle and diet and had no family history of alcoholism. Their body mass index was normal (range 22·4-27·2). The men took no drugs and did not smoke. Plasma cholesterol, triglyceride, haemoglobin, and γ-glutamyltransferase concentrations and systolic and diastolic blood pressure were within the normal range (table I). We obtained consent from each subject and the research protocol was approved by the Toxicology and Nutrition Institute's external medical ethics committee.

The study lasted 11 days, from Sunday evening to Wednesday morning, during which the subjects received a standard diet providing 10·7 MJ/day (overall composition: fat 34·5%, carbohydrates 52·7%, and proteins 12·8% of total energy; polyunsaturated to saturated fat ratio 0·46). The 11 days included two experimental periods of two days (four experimental days). During the experimental periods the men stayed in the metabolic ward of the institute. The men arrived in the evening before the experimental period and stayed until the morning after this period. On the non-experimental days the men were allowed to live at home but had to come to the metabolic ward to have dinner and to receive their food for the next 24 hours. The subjects were not allowed to eat or drink anything but the food and drinks supplied.

During the four experimental days the subjects received four different treatments at dinner in the evening: 400 ml of carbonated mineral water (control) or 40 g alcohol in the form of 1000 ml beer (pilsner), 400 ml red wine, or 144 ml spirits (Dutch gin). Two glasses were served as an appetiser one hour before dinner and two were taken during the meal.

The treatments were randomly allocated to the eight subjects according to two Latin squares and were balanced for carryover effects.

Blood samples were taken one hour before dinner

TABLE I—*Characteristics of the eight volunteers*

Characteristic	Mean (SD)	Range
Age (years)	48·2 (3·6)	45-55
Height (m)	1·8 (0·07)	1·68-1·89
Weight (kg)	81·4 (8·0)	70-91
Cholesterol (mmol/l)	5·6 (0·7)	4·5-6·5
Triglycerides (mmol/l)	1·6 (0·6)	1·0-2·7
Haemoglobin (g/l)	157 (9)	148-176
γ-Glutamyltransferase (U/l)	24·8 (14·3)	13-56
Systolic blood pressure (mm Hg)	154·0 (13·0)	140-170
Diastolic blood pressure (mm Hg)	86·2 (9·5)	70-100

and one, three, five, nine, and 13 hours after dinner. Dinner was served at 1800.

ANALYTICAL METHODS

We took blood into ice chilled tubes from the intermedian cubital vein by a venoject system. After centrifugation for 10 min at 1700 *g* and 4°C the plasma was collected, snap frozen, and stored at −80°C until analysis.

To measure activity of plasminogen activator inhibitor and tissue type plasminogen activator we collected blood in CTAD buffer (0·11 M citrate, 15 nM theophylline, 3·7 mM adenosine, and 0·198 mM dipyridamole; Becton Dickinson, Meylon, France); for measuring activity of plasminogen activator blood was collected in Stabilyte tubes (Biopool, Umeå, Sweden).[9] Tissue type plasminogen activator antigen was measured with the Imulyse TM method (Biopool); plasminogen activator inhibitor activity was measured by a titration method with two chain tissue type plasminogen activator according to the method of Verheijen *et al.*[10] Results are expressed relative to pooled plasma; 100% activity corresponds to neutralisation of 7·6 IU/ml of tissue type plasminogen activator. Tissue type plasminogen activator activity was measured after further acidification of the plasma to inactivate plasminogen activator inhibitor-1 by a recently described method.[11] None of these assays is affected by ethanol up to a concentration of 108·5 mmol/l. Blood alcohol concentrations were measured enzymatically by the method of Beutler and Michal.[12]

STATISTICAL METHODS

We used analysis of variance on Genstat statistical software to test the significance of the main effects of alcohol (all beverages combined) as well as the effects of single beverages. The measurements at one hour before dinner, just before ingestion of the first two glasses, were used as a covariable. Variables that showed a skewed distribution were transformed by their logarithms, and the means presented are geometrical means. In all statistical testing performed the null hypothesis was rejected at the 0·05 level of probability.

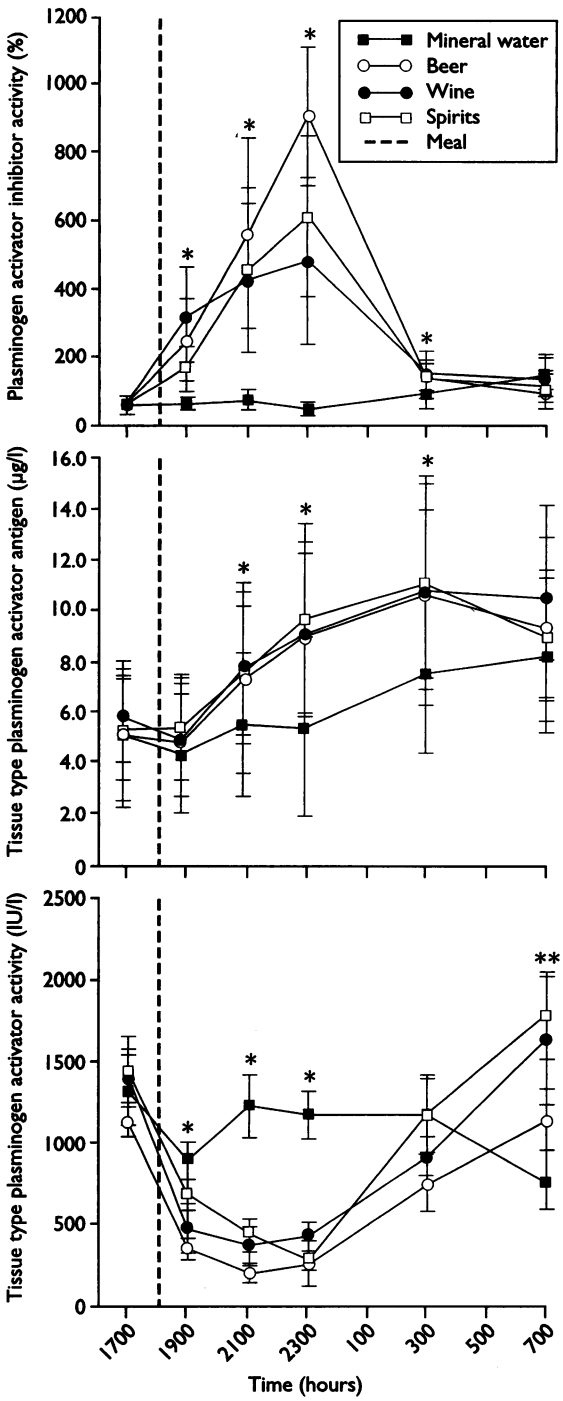
Results

Table II shows the results of the blood alcohol measurements. Subjects always had zero values for blood alcohol concentration when no alcohol had been taken, whereas significant alcohol concentrations were found after ingesting alcohol. In all the volunteers blood alcohol levels at one and three hours after dinner stayed below 10·85 mmol/l (0·5 g/l), the Dutch legal limit for drinking and driving. At one hour after dinner the blood alcohol concentration after drinking spirits was significantly higher than that after consumption of beer or wine ($P=0·038$).

TABLE II—*Mean (SD) blood alcohol concentration (mmol/l) in healthy men one and three hours after a dinner during which beer, wine, spirits, or mineral water was drunk*

	1 hour	3 hours
Beer	6·84 (1·02)	1·95 (0·72)
Wine	6·79 (1·09)	1·98 (0·59)
Spirits	8·25 (1·41)	2·76 (0·98)
Mineral water	0·00 (0·00)	0·00 (0·00)

The figure shows the effects of drinking mineral water, beer, wine, or spirits at dinner on the fibrinolytic system. The consumption of alcoholic beverages at dinner resulted in a sharp increase in plasminogen activator inhibitor activity from 53 (SD 19)% before dinner up to 667 (283)% five hours after dinner.



*Short term effects of drinking alcohol with dinner (at 1800) on plasminogen activator inhibitor activity, tissue type plasminogen activator antigen levels, and plasminogen activator activity. Data are expressed as the mean (SD). *$P<0·001$, **$P<0·05$ between all alcoholic beverages combined versus mineral water.*

Activity of plasminogen activator inhibitor was significantly higher after alcohol than water at one, three, and five hours after dinner ($P<0·001$). Plasminogen activator inhibitor values had returned almost to normal (144 (49)%) at 0300, nine hours after dinner

with alcohol, but remained significantly different from the value after drinking mineral water (101 (47)%; $P<0.001$). By 0700 plasminogen activator inhibitor activity tended to be lower after alcohol than water but this difference was not significant ($P=0.075$).

The mean tissue type plasminogen activator antigen level was 5·3 (2·2) μg/l for all treatments at one hour before dinner. At one hour after dinner no significant differences were observed in antigen levels after mineral water and alcoholic beverages. However, antigen levels significantly increased at three (7·5 (3·0) μg/l), five (9·2 (3·4) μg/l), and nine hours (10·8 (3·8) μg/l) after moderate alcohol consumption compared with the mineral water treatment (5·5 (2·8), 5·4 (3·5), and 7·5 (3·1) μg/l at three, five, and nine hours after dinner; $P<0.001$). The next morning, 13 hours after dinner, antigen levels still tended to be raised (8·2 (3·0) μg/l after mineral water and 9·5 (3·3) μg/l after alcohol; $P=0.068$).

In contrast tissue type plasminogen activator activity fell sharply after dinner with alcohol, from 1327 (483) IU/l before dinner (of all four treatments) to 502 (321) IU/l, 337 (261) IU/l, and 323 (288) IU/l respectively one, three, and five hours after dinner with alcohol. These activities were significantly decreased compared with those after drinking mineral water (891 (329), 1288 (539), and 1175 (399) IU/l at one, three, and five hours after dinner; $P<0.001$). At 0300 tissue type plasminogen activator activity were almost back to control values and by 0700 activity was significantly higher when alcohol had been consumed the evening before (1516 (809) IU/l after alcohol and 779 (516) IU/l after mineral water, representing an average increase of 95% ($P=0.040$)).

We found a range of individual responses to alcohol consumption with respect to tissue type plasminogen activator antigen and plasminogen activator inhibitor activity (data not shown). The responses in tissue type plasminogen activator antigen and plasminogen activator inhibitor activity (areas under the curve) were correlated ($r=0.496$, $P=0.005$), suggesting a coordinated response, most likely from the endothelium.

Tissue type plasminogen activator antigen and plasminogen activator and plasminogen activator inhibitor activity showed a circadian pattern when water was taken with the meal.

Discussion

As the fibrinolytic system has a strong circadian pattern[13,14] it is essential that studies of the system are properly controlled. In addition, the effect of a treatment may depend on the time of the day at which the intervention takes place, and the time of sampling is also important. We therefore decided to study the effects of alcohol taken at dinner early in the evening, which is a usual time of consumption. In most other studies into the short term effects of alcohol on fibrinolysis or platelet function alcohol was given (often in large doses) on an empty stomach, early in the morning. This may be the most practical time but is not the most realistic investigation of the effects of moderate alcohol consumption.[4]

The circadian rhythm in blood fibrinolytic activity,[15-17] has been attributed to changes in specific factors.[18] Both plasminogen activator inhibitor-1 and tissue type plasminogen activator show a circadian, sinusoidal pattern with a slight phase difference, suggesting a circadian behaviour of endothelium.[19]

Our study shows that plasminogen activator inhibitor and tissue type plasminogen activator are strongly influenced by the consumption of moderate amounts of beer, wine, or spirits. We studied healthy people, however, and the results may not be transferable to patients with atherosclerotic disease. The response to alcohol may differ in parts of the endothelium that are affected by atherosclerotic disease. Since the study had a crossover design and all subjects had all four treatments at the same time of the day the observed effects cannot be attributed to differences between individuals or to circadian fluctuations.

A significant increase in tissue type plasminogen activator antigen was observed after consumption of all three alcoholic beverages, so alcohol is probably responsible for the observed effects. Normally, plasminogen activator is continuously secreted by the endothelial cells lining the vessel walls. It acts mainly near the site of release, preventing thrombus formation and dissolving existing blood clots. After its local action, most is eliminated by plasminogen activator inhibitor, which specifically binds to plasminogen activator in the circulation. An increase in local production of plasminogen activator after alcohol with a meal, as indicated by our results, suggests there may be a beneficial effect on local fibrinolysis.

A small amount of the tissue type plasminogen activator remains active in the circulation. Improvements in blood sampling, including low pH to stop the interaction with plasminogen activator inhibitor-1 and additional methods to inactivate plasminogen activator inhibitor-1 during the assay have allowed the activity of circulating tissue type plasminogen activator to be measured.[9,11] Our data show that as a result of the sharp increase in plasminogen activator inhibitor activity, circulating tissue type plasminogen activator activity decreases after alcohol consumption. During the night, however, plasminogen activator inhibitor activity levels returned to control values but tissue type plasminogen activator antigen values remained raised, resulting in increased circulating tissue type plasminogen activator activity early in the morning ($P=0.043$).

The changes we observed in plasminogen activator inhibitor activity, tissue type plasminogen activator antigen, and tissue type plasminogen activator activity may have consequences for thrombus formation and subsequent lysis, processes which play an important part in the pathogenesis of coronary heart disease and ischaemic stroke. The effects of moderate alcohol consumption on the fibrinolytic system may reduce the risk of these diseases in two ways. Firstly, regular intake of low doses of alcohol may induce a local increase of tissue type plasminogen activator activity, which helps prevent blood clot formation and stimulates the dissolution of existing clots. Secondly, the pattern of increased circulating tissue type plasminogen activator activity, particularly in the morning,

Clinical implications

- Moderate alcohol consumption is associated with a lower risk of coronary heart disease
- As well as lipoprotein concentrations haemostatic function is an important determinant of coronary heart disease
- This study shows that moderate alcohol consumption with dinner initially causes a strong increase in plasminogen activator inhibitor activity, and tissue type plasminogen activator antigen levels, which return to normal within 24 hours
- Tissue type plasminogen activator activity was initially strongly reduced up to nine hours after moderate alcohol consumption with dinner but was higher than normal early in the morning
- Moderate alcohol consumption seems to have a beneficial effect on the fibrinolytic system

may have a protective effect at a time that a large proportion of heart attacks normally take place.[20] The effects on the fibrinolytic system were observed at blood alcohol concentrations below the 10·85 mmol/l (0·5 g/l), the Dutch legal limit for drinking and driving. This indicates that even at the low levels of alcohol consumption (5-25 g/day) shown to reduce coronary heart disease risk in epidemiological studies an effect on the fibrinolytic system might be expected. This effect seems to be mediated by the endothelium.

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Early identification of patients at low risk of death after myocardial infarction and potentially suitable for early hospital discharge

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Abstract

***Objectives*—To find (*a*) whether data available shortly after admission for acute myocardial infarction can provide a reliable prognostic indicator of survival at 28 days, and (*b*) whether such an indicator might be used to identify patients at low risk of death and suitable for early discharge.**

***Design*—Retrospective analysis of data collected on patients admitted to a coronary care unit for acute myocardial infarction. A validation sample was selected at random from these patients.**

***Setting*—Coronary care units in Perth, Western Australia.**

***Subjects*—6746 patients aged under 65 and resident in the Perth Statistical Division who during 1984-92 were admitted to a coronary care unit with symptoms of myocardial infarction.**

***Main outcome measures*—Sensitivity and specificity of several models for predicting survival at 28 days after myocardial infarction, and detailed performance characteristics of a particular model.**

***Results*—Patients with a pulse rate of 100 beats/min or less, aged 60 or under, and with symptoms typical of myocardial infarction, no past history of myocardial infarction or diabetes, and no significant Q wave in the admission electrocardiogram had a very high chance of survival at 28 days (99·2%). These patients made up one third of all patients studied.**

***Conclusion*—The prognostic index identifies patients very soon after admission who are at low risk of death and potentially eligible for early discharge from hospital or the coronary care unit. Computing the index does not need complex cardiac investigations.**

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Introduction

Recommendations for hospital stay after myocardial infarction have shortened progressively over the past 30 years. In the 1950s around six weeks of bed rest was recommended, as studies had shown that this was the time required for healing of the myocardial scar.[1] The potential danger of this prolonged bed rest was recognised by Levine and Lown in 1952, when they proposed the "armchair treatment" of coronary thrombosis.[2] They reported that a large proportion of patients could sit in a bedside chair by the third day after infarction without adverse consequences.

Over the subsequent 20 years the duration of hospital care for patients with myocardial infarction decreased steadily. A survey of American physicians by Wenger *et al* in 1973 showed that a hospital stay of three weeks was accepted as normal.[3] From the late 1960s and into the 1970s a series of controlled clinical trials with progressively shorter durations of hospital stay all showed that patients with uncomplicated acute myocardial infarction could be discharged early without adverse effect on mortality or other complications.[4-15] That series of studies set the pattern for practice in the 1980s, and in the United States a hospital stay of seven to 10 days became routine.[16]

In recent years there have been suggestions that an even shorter hospital stay may be feasible for some patients. A randomised trial of early discharge by Topol *et al* showed the feasibility of discharge on the third day after infarction in selected patients.[17] The rate of return to work was marginally better in the early discharge group and the overall care costs of the group were substantially less.

A main difficulty in introducing early discharge after myocardial infarction is the identification of patients