# Relation between alcohol intake, myocardial enzyme activity, and myocardial function in dilated cardiomyopathy

## Evidence for the concept of alcohol induced heart muscle disease

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SUMMARY   Detailed drinking histories were taken in 38 patients in whom dilated cardiomyopathy was diagnosed by cardiac catheterisation and left ventricular biopsy. On the basis of the drinking history twenty patients were classified as being in an abstinent or light drinking group and eighteen patients as being in a heavy drinking group (daily alcohol intake in excess of 80 g or cumulative lifetime intake exceeding 250 kg). Activities of myocardial creatine kinase, lactate dehydrogenase, α hydroxybutyric dehydrogenase, malic dehydrogenase, and aspartate aminotransferase were all higher in the heavy drinkers and myocardial enzyme activity correlated with cumulative lifetime alcohol intake, maximum daily intake, and recent daily intake. Activities of creatine kinase, α hydroxybutyric dehydrogenase, and malic dehydrogenase correlated with ejection fraction, irrespective of the alcohol intake of the patient. These findings were not altered by exclusion of patients with hypertension.

The results indicate that among patients with dilated cardiomyopathy there is a group characterised by a high alcohol intake and raised myocardial tissue enzymes which supports the concept of alcoholic heart muscle disease as a distinct entity.

Although the association between excessive alcohol consumption and congestive (dilated) cardiomyopathy has long been known,[1][2] a causal relation remains controversial.[3] There are no studies that relate quantitative alcohol intake to myocardial damage, as there are for alcoholic liver disease.[4][5] Indeed the clinical diagnosis of alcoholic heart muscle disease merely reflects the coexistence of global myocardial dysfunction in a heavy drinker in whom no other cause for myocardial disease has been found.

The development of endomyocardial biopsy has enabled histological assessment of the myocardium during life, but there are no specific histological features for alcoholic heart muscle disease.[6] More recently, measurement of myocardial enzyme activity by microassay of biopsy specimens has been introduced.[7][8] Wide differences in activities of several myocardial tissue enzymes were found among patients with dilated heart disease who were both haemodynamically and histologically indistinguishable.[8] Preliminary data suggested that enzyme activities were highest in those patients diagnosed as having alcoholic heart muscle disease.[9]

The purpose of the present study was to assess the alcohol intake in a group of patients with dilated cardiomyopathy and to relate alcohol intake to myocardial enzyme activities and to myocardial function in order to establish objective evidence in support of the concept of alcohol induced heart muscle disease.

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## Patients and methods

Seventy nine patients underwent myocardial biopsy over a period of 28 months; 41 had dilated cardiomyopathy. The other patients were diagnosed as having a specific heart muscle disease, including acute or healed myocarditis, ischaemic heart disease (with >50% stenosis of two or more vessels), or hypertrophic cardiomyopathy. Thirty eight of the 41 patients with dilated cardiomyopathy were investigated; the other three were not available for interview. No patient had any clinical evidence of abnormal nutrition and thiamine deficiency was excluded. We studied 36 men (aged 29–62 years (mean (SD) 49·5 (9·3)) and two women (aged 31 and 49 years). Twenty nine were white, three were Asian, and six were West Indian. Diastolic blood pressure was recorded at the fifth phase of the Korotkoff sounds.

ASSESSMENT OF ALCOHOL INTAKE
Patients were interviewed by one of two clinicians (ADW or JBS) who used a standardised interview schedule, which has previously been described and validated in a study of alcoholic cirrhosis,[10] to ascertain lifetime alcohol consumption. The evolution of the patient's drinking habits was elicited by reference to key events such as school-leaving and changes in employment. With these as anchor points, questions were asked about the average weekly intake of alcohol, pattern of drinking, and the type of beverage taken during successive periods of a patient's life up to the time of presentation with heart disease. From this information various measures of alcohol intake were considered: (a) duration of drinking when daily alcohol intake exceeded 40 g and 80 g, (b) the corresponding mean daily intake during these periods, (c) the corresponding cumulative alcohol intake, (d) cumulative lifetime alcohol consumption, (e) maximum daily alcohol intake that was maintained for a period of at least a year, and (f) mean daily alcohol intake in the three months before investigation.

Six consecutive patients in the present study were interviewed on a subsequent occasion by the second observer independently to validate the technique in this group of patients. The intraclass correlation coefficients for the comparisons of cumulative lifetime consumption, duration of drinking >40 g alcohol/day, and corresponding cumulative intake for the two observers were 0·91, 0·89, and 0·80 respectively.

CARDIAC CATHETERISATION AND MYOCARDIAL BIOPSY
All patients underwent routine diagnostic catheter-

isation including selective coronary arteriography and left ventriculography. The left ventriculograms were obtained in the right anterior oblique projection at 30°. The systolic and diastolic frames were traced so that the left ventricular ejection fraction could be measured with a Summographic digitising table linked to a Commodore computer. The ejection fraction was calculated by application of Simpson's rule.[11] Coronary arteriography showed that in 30 patients all coronary vessels were free of important narrowing (patency >50%); in eight patients there was stenosis (>50%) of one vessel only, but in none was there occlusion of the vessel.

Endomyocardial biopsy samples of the left ventricle were obtained with the King's endomyocardial bioptome and the Cordis long sheath introducer system. An average of four tissue samples were taken from each patient. At least two biopsy specimens were examined by routine light and electron microscopy as previously described.[6] In 24 patients there was sufficient material for enzyme measurement and this was immediately frozen in liquid nitrogen and stored at −70°C.

MYOCARDIAL TISSUE ENZYME MICROASSAY
Biopsy samples of approximately 2–5 mg were weighed and homogenised in 0·25 mol/l ice cold sucrose. The following enzymes were assayed spectrophotometrically[9] at 25°C under conditions of optimum pH and substrate concentration: creatine kinase, lactate dehydrogenase, α hydroxybutyric dehydrogenase, malic dehydrogenase, and aspartate aminotransferase. Protein was assayed by the method of Lowry et al,[12] and enzyme activities are expressed as mU/mg of tissue protein; 1 mU corresponds to the hydrolysis of 1 μmol of substrate/min.

OTHER LABORATORY INVESTIGATIONS
Routine haematological and biochemical tests, including liver function tests and serum γ glutamyltransferase measurements were performed on the day of admission.

DATA STORAGE AND STATISTICAL PROCEDURES
Data were stored and analysed in a CDC 6600 computer by means of the program suite Statistical Package for the Social Sciences.[13] The distribution of variables was assessed by calculating the skewness (g3) and kurtosis (g4) and the Kolmogorov-Smirnov statistic Z; skewed data were transformed to log 10. Statistical significance was assessed by the $\chi^2$ test (with Yates's correction where necessary) and Student's t test. Multiple regression analysis was performed with values for myocardial enzyme activity as the dependent variables; independent variables were
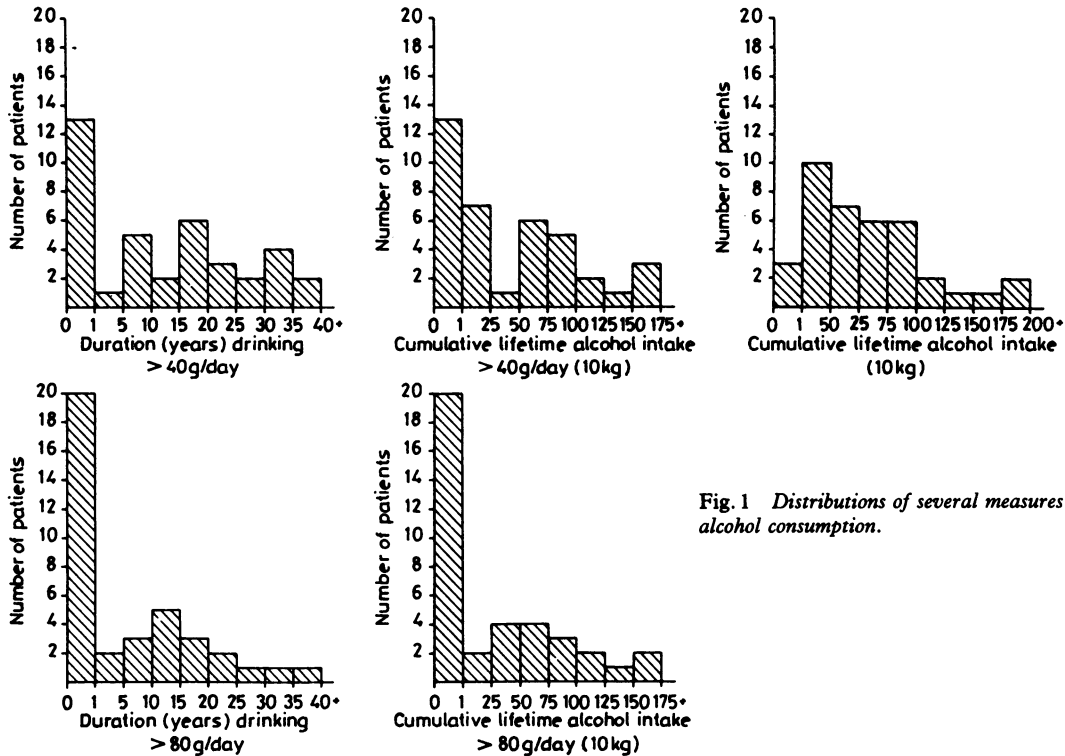
Fig. 1 *Distributions of several measures of alcohol consumption.*

entered in a stepwise fashion according to the F value for entry into the regression equation.

## Results

### DISTRIBUTION OF ALCOHOL CONSUMPTION

Figure 1 shows the distribution of several measures of alcohol consumption in the 38 patients. Three (8%) patients were teetotal. The distribution of cumulative lifetime intake was skewed (g3 = 1·9) but it was unimodal. Thirteen (34%) patients had never drunk more than 40 g alcohol/day and in another seven (18%) patients the daily intake had never exceeded 80 g. When cumulative alcohol intake was calculated for periods when drinking exceeded these threshold amounts, a discontinuous distribution was apparent (z = 0·94 and 1·46 respectively).

While two of the three Asian patients had a cumulative lifetime intake <250 kg all six of the West Indian patients had a lifetime alcohol intake >250 kg.

### RELATION OF MYOCARDIAL TISSUE ENZYME ACTIVITY TO ALCOHOL INTAKE

There were significant correlations between myo-

cardial enzyme activities and cumulative lifetime alcohol consumption, maximum daily intake, and recent daily intake (Table 1 and Fig. 2). Correlation analysis was not performed for the other measures of alcohol intake because of the discontinuities in their distributions. Tissue enzyme activities, except for aspartate aminotransferase, were significantly higher in the heavy drinking group compared with the abstaining or lightly drinking group (Table 2). There was no significant difference in ejection fraction between these two groups.

### RELATION BETWEEN MYOCARDIAL ENZYME ACTIVITIES, MYOCARDIAL FUNCTION, AND BLOOD PRESSURE

The mean (SD) ejection fraction was 42·6 (16·2) and 12 (32%) patients had an ejection fraction of <30%, indicating severely impaired myocardial function. There was a correlation between certain myocardial enzyme activities and myocardial impairment as measured by the ejection fraction. The strongest relations were for creatine kinase (r = 0·58, p < 0·01), α hydroxybutyric dehydrogenase (r = 0·52, p < 0·01), and malic dehydrogenase (r = 0·44, p < 0·05).

Thirteen patients (34%) had a history of hypertension or were hypertensive (blood pressure > 160/95 mm Hg) on admission. When these patients were excluded, the correlation between myocardial enzyme activities and alcohol intake remained significant. Although enzyme activities tended to be higher in hypertensive heavy drinkers than in normotensive heavy drinkers, the differences did not reach statistical significance.

RESULTS OF MULTIPLE REGRESSION ANALYSIS
A multiple regression analysis was performed (Table 3) to assess the relations between cumulative alcohol intake, myocardial function (ejection fraction), blood pressure, and myocardial tissue enzyme activities. This confirmed the relation between cumulative alcohol intake and myocardial enzyme activities and showed that ejection fraction was related to the activities of creatine kinase and α hydroxybutyric dehydrogenase independently of alcohol consumption. Neither systolic nor diastolic blood pressure had a significant independent association with tissue enzyme activities.

ALCOHOL INTAKE AND HAEMATOLOGICAL AND BIOCHEMICAL MARKERS OF ALCOHOL CONSUMPTION
There were weak correlations between cumulative lifetime alcohol intake, maximum daily intake, and recent alcohol intake and mean corpuscular volume ($r = 0.32$, $p < 0.05$, $r = 0.29$, $p < 0.05$, $r = 0.32$, $p < 0.05$ respectively). There was no significant correlation between alcohol intake and serum aspartate transaminase, alkaline phosphatase, or γ glutamyltransferase activities.
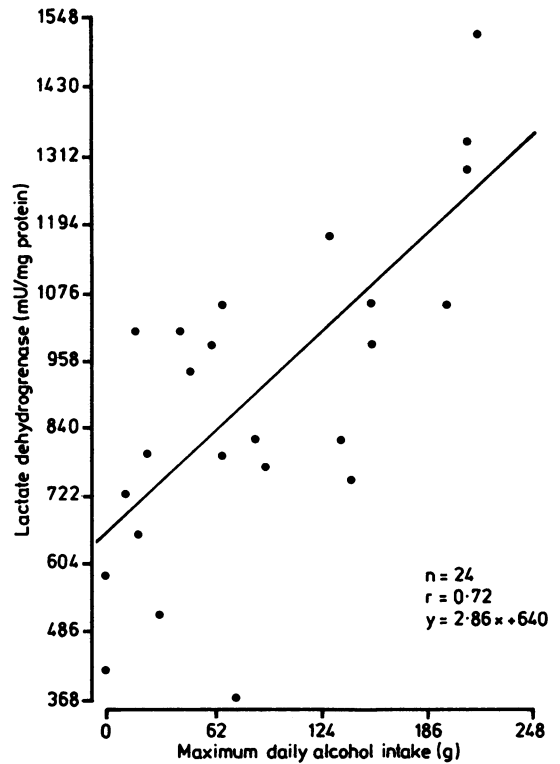


Fig. 2 *Relation between myocardial tissue lactate dehydrogenase activity and maximum daily alcohol intake.*

Table 1 *Results of correlation analysis of myocardial enzyme activities with alcohol intake*

| | Cumulative lifetime alcohol intake | | Maximum daily alcohol intake | | Recent daily alcohol intake | |
|---|---|---|---|---|---|---|
| | r | p | r | p | r | p |
| Creatine kinase | 0·56 | <0·01 | 0·52 | <0·01 | 0·35 | <0·05 |
| α hydroxybutyric dehydrogenase | 0·59 | <0·001 | 0·61 | <0·001 | 0·49 | <0·01 |
| Lactate dehydrogenase | 0·68 | <0·001 | 0·72 | <0·001 | 0·60 | <0·001 |
| Malic dehydrogenase | 0·53 | <0·01 | 0·56 | <0·01 | 0·50 | <0·01 |
| Aspartate aminotransferase | 0·19 | NS | 0·28 | <0·10 | 0·26 | NS |

Table 2 *Comparison of myocardial enzyme activities (mean (SE)) in abstinent or lightly drinking patients and in heavily drinking patients*

| | Abstinent or light drinkers (cumulative intake* < 250 kg) (n = 13) | Heavy drinkers (cumulative intake* > 250 kg) (n = 11) | p |
|---|---|---|---|
| Creatine kinase (mU/mg protein) | 1674 (129) | 2719 (226) | <0·001 |
| α hydroxybutyric dehydrogenase | 568 (39) | 828 (57) | <0·001 |
| Lactate dehydrogenase | 730 (57) | 1109 (69) | <0·001 |
| Malic dehydrogenase | 2089 (185) | 2976 (185) | <0·005 |
| Aspartate aminotransferase | 510 (63) | 661 (61) | <0·10 |

*When daily alcohol consumption exceeded 40 g/day.

Table 3 *Results of multiple regression analysis of the relation between cumulative alcohol intake, ejection fraction, and blood pressure and myocardial enzyme activities*

| Enzyme | | F | p | Multiple r |
|---|---|---|---|---|
| Creatine kinase | Cumulative alcohol intake (log 10) | 4·59 | <0·05 | 0·69 |
| | Ejection fraction | 9·54 | <0·01 | 0·58 |
| | Diastolic blood pressure | 2·21 | NS | 0·73 |
| α hydroxybutyric dehydrogenase | Cumulative alcohol intake (log 10) | 8·09 | <0·01 | 0·54 |
| | Ejection fraction | 5·86 | <0·05 | 0·68 |
| | Diastolic blood pressure | 1·53 | NS | 0·71 |
| Lactate dehydrogenase | Cumulative alcohol intake (log 10) | 14·47 | <0·02 | 0·65 |
| | Ejection fraction | 2·03 | NS | 0·69 |
| | Diastolic blood pressure | 2·03 | NS | 0·73 |
| Malic dehydrogenase | Cumulative alcohol intake (log 10) | 6·90 | <0·02 | 0·51 |
| | Ejection fraction | 3·35 | NS | 0·61 |
| | Diastolic blood pressure | 2·04 | NS | 0·66 |
| Aspartate aminotransferase | Cumulative alcohol intake (log 10) | 6·42 | <0·02 | 0·49 |
| | Ejection fraction | 1·89 | NS | 0·55 |
| | Diastolic blood pressure | 1·78 | NS | 0·61 |

## Discussion

There is no clinical or histopathological difference between alcoholic heart muscle disease and dilated cardiomyopathy,[6 14] and indeed there are some who do not accept the former as a distinct entity.[15] In the present study patients with dilated heart muscle disease seemed to consist of two groups defined by their alcohol intake. The bimodal distribution of alcohol intake contrasts with the findings of surveys of alcohol consumption in the general population which show that alcohol intake has a unimodal distribution, with only 4% of males drinking more than 80 g/day.[16 17] It is likely that the abstinent and lightly drinking patients represent the general population in terms of drinking ≤80 g alcohol/day; higher consumption is implicated in other forms of alcohol induced tissue damage such as cirrhosis of the liver.[4] The possibility that some light drinkers are especially sensitive to the cardiotoxic effect of alcohol cannot, however, be excluded.

Unlike patients with alcoholic cirrhosis drawn from the same geographical area who drink more spirits (J B Saunders, A D Wodak, R Williams, unpublished observations) the heavy drinkers in our study were predominantly (83%) beer drinkers. The reason for this is unknown. Excess consumption of beer, because of its high carbohydrate content, may precipitate beriberi in patients with incipient thiamine deficiency, but none of our patients were thiamine deficient. Cobalt contaminated beer was implicated in the development of heart muscle disease in Canada several years ago, but this problem has now been eliminated.[18] In previous studies alcoholic heart muscle disease was reported to be confined to men,[1 2] and in the present study all the heavy drinkers were men. Again this contrasts with our experience of alcoholic liver disease, to which women are more susceptible.[10 19] No hormonal or

other genetically determined factors predisposing to alcoholic heart muscle disease have been identified.[20] We found that as in alcoholic liver disease a pattern of continuous drinking rather than episodic drinking seems to be associated with alcoholic heart muscle disease. This may simply reflect the fact that a pattern of unremitting drinking is more likely to result in a higher cumulative alcohol intake than periodic drinking.

It has been suggested that dilated heart muscle disease may be caused by previous hypertension in subjects who have become normotensive after the development of impaired myocardial function (decapitated hypertension). The known association of alcohol use and hypertension may thus be a mechanism for the development of alcoholic heart muscle disease. The results of this study in which the correlations between myocardial enzyme activity and alcohol intake were unaffected by blood pressure do not support the notion of decapitated hypertension as the mechanism for development of alcoholic heart muscle disease.

The increases in myocardial enzyme activities in the heavy drinkers could be adaptive and may reflect chronic exposure to alcohol. Although alcohol can undergo esterification with fatty acid in the myocardium[21] there is no evidence for appreciable myocardial metabolism of alcohol. In theory patients with alcoholic heart muscle disease may have always had abnormal tissue enzymes concerned with glycolysis and respiration and exposure to alcohol may have precipitated myocardial damage. This seems unlikely in the face of the close correlation between enzyme activity and exposure to alcohol.

Alternatively the enzyme changes may be secondary to myocardial tissue damage caused by an unrelated mechanism. Acute exposure to alcohol increases the concentration of several cardiac enzymes, including malic dehydrogenase, in the

coronary venous effluent[22] and this may imply a direct cytotoxic action of ethanol. On this basis, however, it is difficult to explain how myocardial enzyme activities increase in response to chronic alcohol exposure.

The threshold dose of alcohol intake for heart muscle damage cannot be determined directly from studies such as the present one. The risk of developing cirrhosis at various levels of alcohol intake has been determined in epidemiological studies by comparison of the alcohol intake of patients with established cirrhosis with that of healthy age and sex matched patients drawn at random from the same geographical area. For alcoholic heart muscle disease, however, this would be a formidable undertaking in view of the comparative rarity of the condition and the fact that invasive investigation is necessary for a firm diagnosis of specific heart muscle diseases to be made.

Laboratory tests such as mean corpuscular volume, serum aspartate aminotransferase, and $\gamma$ glutamyltransferase have been shown in several studies to be useful markers of excessive alcohol consumption. In the present study, however, although there was a correlation between mean corpuscular volume and alcohol intake it was not of practical use as a diagnostic marker and activities of serum enzymes were similar in the lightly drinking and heavily drinking groups. The best way to discriminate between these two groups seems to be a detailed lifetime drinking history. Serum activities of specific myocardial enzymes such as creatine kinase MB isoenzyme may prove to be a useful diagnostic tool, though so far this approach has proved to be disappointing.[23] Myocardial biopsy and measurement of tissue enzyme activity provide useful supportive evidence in favour of an alcoholic aetiology in patients with dilated heart muscle disease.

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