Dose dependent but non-linear effects of alcohol on the left and right ventricle

O A Kajander, M Kupari, P Laippala, V Savolainen, J Pajarinen, A Penttilä, P J Karhunen

Abstract

Objective—To assess how left (LV) and right ventricular (RV) size, wall thickness, and mass depend on daily alcohol consumption. Among alcoholics, most common findings have been LV hypertrophy and mild systolic or diastolic dysfunction, accompanied occasionally by ventricular dilatation resembling dilated cardiomyopathy. Although it is commonly agreed that chronic heavy alcohol use is injurious to the heart, the dose-injury relation remains a matter of dispute.

Design—Prospective series of 700 Finnish men aged 33–70 years who died out of hospital and underwent a medicolegal necropsy.

Methods and results—Data on alcohol use and other risk factors were obtained from the spouse. At necropsy, a transversal slice of the heart was traced on a transparent sheet and analysed later for LV and RV cavity areas and wall thicknesses. Coronary artery stenoses were measured from silicone casts of the arteries. In analyses of all men, daily alcohol dose predicted heart weight ($\beta = 0.17$, $p < 0.001$) and RV cavity area ($\beta = 0.14$, $p = 0.007$) independent of body size, age, coronary artery disease, hypertension, diabetes, and smoking. In the subgroup of men free of significant coronary artery disease, LV area averaged (SEM) 11.0 (1.0) cm² in men drinking < 12 g/day, 7.7 (0.7) cm² in those drinking 72–180 g/day, and 10.0 (0.9) cm² in those drinking > 180 g/day ($p = 0.054$). Very heavy drinking (> 180 g/day) was associated with an increase in RV cavity area ($p = 0.005$).

Conclusions—The effects of alcohol on the heart in middle aged men are dose dependent but partly non-linear. In the absence of coronary artery disease, LV size shows a U shaped reduction with increasing daily alcohol use accompanied by an increase in RV size with very heavy drinking. These findings question the idea of progressive LV dilatation with increasing alcohol consumption among male victims of sudden death.

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Medical School,
University of Tampere
and Tampere
University Hospital,
Tampere, Finland

O A Kajander
P Laippala
P J Karhunen
V Savolainen

Division of Cardiology,
Department of
Medicine, Helsinki
University Central
Hospital, Helsinki,
Finland
M Kupari

Department of
Traumatology,
Helsinki University
Central Hospital,
Helsinki, Finland
J Pajarinen

Department of
Forensic Medicine,
University of Helsinki,
Helsinki, Finland
A Penttilä

Correspondence to:
Dr Kajander
ok53068@uta.fi

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Alcoholic heart muscle disease is characterised by left ventricular (LV) hypertrophy^{1–3} with variable degrees of systolic^{4–6} and diastolic dysfunction.^{7–9} Mostly asymptomatic, it occasionally results in dilated cardiomyopathy with clinical heart failure and may also contribute to the pathogenesis of cardiac arrhythmias and sudden death in heavy drinkers.¹⁰ Precisely how myocardial abnormalities are related to the quantity of habitual daily drinking is not fully established. Although there exist data suggesting that the degree of LV hypertrophy and systolic dysfunction are linearly related to the total lifetime alcohol consumption,^{6–10} other studies have failed to find any clear dose dependency, linear or otherwise, in the effects of heavy alcohol use on the heart.^{1–3–5} All of these studies^{1–3–5–6–11} involved only relatively small numbers of selected alcoholic people and none was able to exclude fully the confounding effect of concomitant coronary artery disease. Further, right ventricular (RV) structure or function was not studied.

The present work was designed to characterise in more detail how alcohol's effects on cardiac anatomy depend on the quantity of habitual consumption. We included two series of consecutive middle aged Finnish men, totaling 700, who had died out of hospital and had undergone a medicolegal necropsy. The LV and RV area, wall thickness, and mass were measured at necropsy and compared with the

history of alcohol use, with adjustment for a number of potential confounders. The daily alcohol doses were calculated from data obtained by a previously validated structured interview of the spouse or close acquaintance.¹² We report here the associations of LV and RV anatomy with the quantity of daily alcohol use for all men and separately for men free of significant coronary artery disease at postmortem angiography. Our findings suggest that alcohol's cardiac effects are dose dependent but in a way that deviates from simple linearity and that may be manifested differently in the right and left ventricle.

Study population and methods

NECROPSY SERIES

This work constitutes part of the Helsinki sudden death study launched in 1981 as a complementary study to the World Health Organization MONICA (monitoring trends and determinants in cardiovascular disease) project^{13–14} with an aim to evaluate the epidemiology and triggers of cardiac out of hospital deaths. To that purpose, two series of medicolegal necropsies were prospectively collected at the Department of Forensic Medicine, University of Helsinki, the first one during 16 months in 1981–1982 and the second during 12 months in 1991–1992. All together 700 (400 plus 300) Finnish men aged 33–70 years were examined. They were consecutive men

Figure 1 Drawing showing the location of the cardiac slice selected for the border tracing and later analyses. The measurements were of the right ventricular cavity area (a), left ventricular cavity area (b), left ventricular anterior wall thickness (c), and left ventricular posterior wall thickness (d).

undergoing necropsy for unexplained out of hospital death, suspected intoxication, accidental death, suicide, or death in connection with medical treatment. The series cover 42% of all deaths of people < 65 years of age in the area of Helsinki city during the study periods. Among the 700 cases, the cause of death was cardiovascular in 290 men (41.4%), other disease in 130 men (18.6%), intoxication in 138 men (19.7%), violence in 134 men (19.1%), and unknown in eight men (1.1%).

The ethics committee of the Department of Forensic Medicine, University of Helsinki approved the study.

COLLECTION OF DATA ON ALCOHOL CONSUMPTION, SMOKING, AND PREVIOUS HEALTH

Lifetime habitual alcohol consumption was evaluated by a structured interview of the deceased's spouse or a close relative or acquaintance. Of all the 700 consecutive cases from the two time periods, a person with detailed enough knowledge on the deceased's lifetime history was reached for interview in 500. The questionnaire incorporated 16 items concerning the intensity, frequency, quantity, and quality of the person's alcohol consumption.¹² Questions were similar to those in AUDIT (the alcohol use disorders identification test)¹⁵ and MAST (Michigan alcoholism

screening test).¹⁶ The responses were used to calculate an estimate of all year average daily alcohol intake as absolute ethanol (g/day). Such an estimate of alcohol consumption could be obtained for 452 men in the present study. However, 17 of them were former heavy drinkers who had recently greatly reduced their drinking. A change that shifted the subject from one consumption class to another was considered major. Thus, we had 435 men with stable drinking habits for our analyses. According to their daily alcohol dose, these men were classified either as teetotallers or light drinkers (< 12 g/day or < 1 drink), moderate drinkers (12–72 g/day or 1–6 drinks), heavy drinkers (72–180 g/day or 6–15 drinks), or very heavy drinkers (> 180 g/day or > 15 drinks).

Questions regarding smoking were also included in the interview. We recorded the average daily cigarette consumption as well as the number of smoking years and whether the deceased was a former smoker. Whether hypertension or diabetes had been diagnosed in the past was also specifically questioned and recorded. In 223 cases, the history of these diseases remained unknown, mostly because the deceased was not known to have visited a doctor.

EXAMINATION AND MEASUREMENTS OF THE HEART AT NECROPSY

The cardiac examinations for research purposes were added to an otherwise complete routine postmortem medicolegal study. The coronary arteries were evaluated first by making a silicone rubber cast of the entire coronary artery tree by a technique detailed elsewhere.¹⁷ Any local narrowing of the lumen of the coronary arteries was measured and determined as a percentage of the adjacent uninvolved lumen. The presence of myocardial infarction was documented by nitroblue tetrazolium staining and confirmed by a histological examination of the myocardium.

After the examination of the coronary arteries, the heart was weighed and the ventricular block was cut into 15 mm transversal slices. The borders of the LV and RV cavities and walls at the equatorial region—the thickest part of the ventricular block—were traced onto a transparent sheet. When clearly separate from the ventricular muscle, the areas covered by trabeculae and papillary muscles were included in the cavity sizes but not in wall thicknesses. Finally, the LV and RV were weighed separately by collecting all of the ventricular muscle pieces dissected free of epicardial fat. The interventricular septum was included in the LV weight. The traced anatomical areas of the ventricular cross sections, as well as the dimensions of the walls, were measured later by computer assisted planimetry (fig 1). The postmortem delay before necropsy was on average 3.6 days (median 3 days) but did not correlate with any of the ventricular dimensions or weights.

Table 1 Characteristics of the men in the necropsy series

	Valid number	Mean (SD) or frequency	Median	Range
Age (years)	700	53.1 (9.6)	54.0	33–70
Height (cm)*	699	175 (7.1)	175	153–195
Weight (kg)*	699	75.3 (16.5)	73	38–145
Body mass index (kg/cm ²)	699	24.6 (4.8)	24.1	13.0–45.3
Body surface area (m ²)†	699	1.90 (0.21)	1.89	1.34–2.73
Alcohol consumption (g/day)	435	95.4 (101.7)	60.5	0.0–510
Smoking (cigarettes/day)	500	17.3 (13.9)	20	0–50
Hypertension	477	107 (22.4%)		
Diabetes	477	113 (23.7%)		
Coronary artery disease at necropsy‡	641			
Not found		399 (62.2%)		
1 vessel disease		109 (17.0%)		
2 vessel disease		71 (11.1%)		
3 vessel disease		62 (9.7%)		
Myocardial infarction at necropsy	700			
Any		183 (26.1%)		
Old		149 (21.3%)		
Recent		85 (12.1%)		

*Measured at necropsy.

†Calculated from height and weight.¹⁸

‡Number of arteries with > 50% stenosis at postmortem angiography.

Table 2 Characteristics of the men with reliable drinking history by categories of daily alcohol consumption

	< 12 g (n=109)	12-72 g (n=105)	72-108 g (n=103)	> 180 g (n=76)	p Value
Age (years)	56.4 (9.9)	53.7 (9.1)	52.7 (9.3)	48.8 (8.7)	< 0.00001
Body mass index (kg/m ²)	25.5 (5.0)	24.8 (4.5)	24.4 (4.6)	24.3 (4.7)	0.29*
Body surface area (m ²)	1.95 (.22)	1.92 (.19)	1.87 (.19)	1.91 (.23)	0.058*
Hypertension	27	25	19	15	0.64
Diabetes	26	29	21	20	0.64
Coronary artery disease†	75	54	39	15	< 0.0001
Smoking (cigarettes/day)	13.5 (13.0)	17.9 (15.2)	18.2 (13.3)	19.2 (14.1)	0.094*

Data are mean (SD) or frequencies. P values are for differences across alcohol consumption groups from analysis of variance and Pearson's χ^2 test.

*For log transformed data.

† > 50% coronary luminal stenosis at postmortem angiography.

STATISTICAL ANALYSIS

Stepwise multiple linear regression analysis was used to study the relations of the postmortem cardiac measurements to the data on alcohol consumption and other potential independent variables (explanatory factors). The results of these analyses are given as standardised regression coefficients (β). Since some relations appeared non-linear, stepwise ordinal polychotomous logistic regression analyses were carried out on cardiac measurements divided into four outcome classes (values 0-3) by the lower and upper quartiles and the median. The analysis is a generalisation of the standard logistic model, but instead of two outcome classes we have now four, which again have an ordinal scale. The results are summarised by odds ratios with 95% confidence intervals, the interpretation of which is analogous to the standard model. In this analysis, when using categorical independent variables, they were classified into four classes and the lowest class was always used as a reference. Finally, in the subgroup of men free of significant coronary artery disease at postmortem angiography, analysis of covariance was used to compare the cardiac measurements across the four alcohol consumption groups. The factors besides alcohol consumption that were included in the multivariate analyses were age, body surface area, smoking (number of

cigarettes/day), and the presence of hypertension and diabetes (both dummy coded variables). The findings at postmortem coronary angiography (number of vessels with > 50% stenosis, 0-3) were used as a confounding factor in analyses of the total study group and to select the subgroup of men free of coronary artery disease for analysis of covariance. The distribution of the confounding explanatory factors across the different alcohol consumption groups was studied using analysis of variance and Pearson's χ^2 test. Variables with grossly asymmetric distribution were square root or log transformed before statistical analyses. The analyses were done with Statistical/Win (Version 5.0, StatSoft, Tulsa, Oklahoma, USA) and SPSS/Win (Version 9.0, SPSS Inc, Chicago, Illinois, USA) on a personal computer or the BMDP Statistical Software (Version 1990, Los Angeles, California, USA) on a SUN/UNIX mainframe.

Results

CHARACTERISTICS OF THE MEN IN THE NECROPSY SERIES

Table 1 summarises the characteristics of the men in the two necropsy series. Of those for whom we had a reliable drinking history, 46% were heavy or very heavy alcohol consumers (> 72 g/day) and only 8% were teetotallers. The median daily consumption was as high as

Table 3 Stepwise multiple linear regression analyses of potential determinants of cardiac measurements at necropsy

	Log BSA	Age	Coronary artery disease*	Hypertension†	Smoking‡	Alcohol use§
Heart weight	0.57	0.26	0.23	0.15	¶	0.17
p Value	< 0.001	< 0.001	< 0.001	< 0.001	¶	< 0.001
Left ventricular weight	0.41	¶	0.26	0.22	¶	¶
p Value	< 0.001		< 0.001	< 0.001		
Cavity area	0.30	0.15	0.19	¶	¶	¶
p Value	< 0.001	0.006	< 0.001			
Anterior wall	¶	¶	¶	0.14	¶	¶
p Value				0.012		
Posterior wall	¶	¶	-0.13	0.13	¶	¶
p Value			0.015	0.019		
Posterior wall to cavity area ratio	0.24	-0.14	-0.19	¶	¶	¶
p Value	< 0.001	0.013	< 0.001			
Right ventricular weight	0.31	0.15	¶	¶	¶	¶
p Value	< 0.001	0.015				
Cavity area	0.23	¶	¶	¶	-0.13	0.14
p Value	< 0.001				0.016	0.007

Data are standardised multiple regression coefficients (β).

*Number of vessels with > 50% stenosis (coded 0-3).

†Dummy variable coded.

‡Log number of cigarettes/day.

§ Square root of daily alcohol consumption (g/day).

¶The factor did not enter the regression model. Diabetes, which did not enter the model for any of the studied dependent variables, is omitted from the table.

BSA, body surface area.

Table 4 Stepwise polychotomous logistic regression analyses of potential determinants of cardiac measurements at necropsy

	BSA*			Age	Coronary disease†			Smoking	Hypertension‡	Alcohol consumption (g/day)§		
	1	2	3		1	2	3			12–72	72–180	> 180
Heart weight	2.0	5.7	28	1.1	1.3	3.9	4.2	¶	2.1	2.4	2.4	3.4
CI	1.1 to 3.7	2.9 to 11	13 to 58	1.0 to 1.1	0.8 to 2.2	1.9 to 7.9	1.3 to 8.3		1.3 to 3.6	1.4 to 4.2	1.4 to 4.3	1.8 to 6.6
p Value	< 0.0001			< 0.0001	< 0.0001				0.003	< 0.001		
LV												
Weight	2.1	4.9	13		1.8	4.7	6.4	¶	2.9	2.4	1.2	2.5
CI	1.0 to 4.4	2.3 to 11	5.6 to 28		0.9 to 3.5	2.0 to 11	2.8 to 15		1.4 to 5.8	1.2 to 4.8	0.6 to 2.4	1.2 to 5.6
p Value	< 0.0001				< 0.0001				0.003	0.013		
Cavity area	1.1	1.4	3.4	1.0	1.1	2.1	2.0	¶	¶	¶		
CI	0.6 to 1.9	0.8 to 2.6	1.8–6.4	1.0 to 1.1	0.6 to 1.8	1.1 to 4.0	1.1 to 3.7					
p Value	< 0.0001			0.012	0.041							
Anterior wall	¶			¶	1.5	1.1	2.0	¶	1.7	¶		
CI					0.9 to 2.6	0.6 to 2.0	1.1 to 3.8		1.0 to 2.7			
p Value					0.088				0.046			
Posterior wall	¶			¶	¶			¶	1.7	¶		
CI									1.0 to 2.8			
p Value									0.033			
Posterior wall to area ratio	1.1	0.8	0.3	0.97	1.0	0.4	0.4	¶	¶	¶		
CI	0.6 to 1.9	0.5 to 1.5	0.2 to 0.6	0.95 to 0.97	0.6 to 1.7	0.2 to 0.8	0.2 to 0.7					
p Value	< 0.001				0.004							
RV												
Weight	1.5	3.3	6.1	1.0	¶			¶	¶	¶		
CI	0.7 to 3.0	1.5 to 7.0	2.8 to 13	1.0 to 1.1								
p Value	< 0.0001			0.032								
Cavity area	1.0	0.8	2.4	¶	¶			0.93	¶	1.2	1.5	2.1
CI	0.6 to 1.9	0.4 to 1.4	1.3 to 4.5					0.88 to 0.98		0.7 to 2.1	0.9 to 2.5	1.2 to 3.7
p Value	< 0.001							0.010		0.065		

Data are odds ratios with 95% confidence intervals (CI). LV, left ventricular; RV, right ventricular.

*Reference class is lowest quartile, p value for improvement among all groups.

†Number of coronary arteries with > 50% luminal stenosis. Reference class is 0 vessels, p value for improvement among all groups.

‡Reference class is “no hypertension”.

§Reference class is “< 12 g/day”, p value for improvement among all groups.

¶ The factor did not enter the regression model. History of diabetes did not enter any model and is omitted from the table.

60.5 g (table 1). The proportions of current and former smokers were 69% and 13%, respectively. Hypertension and diabetes each had a prevalence of a little more than 20% among the men with a reliable history of previous health (table 1). The overall prevalence of significant coronary artery disease at necropsy (at least one vessel with > 50% stenosis) was 38%, and either recent or old myocardial infarction or both were found in 26% of all men (table 1).

Table 2 specifies the characteristics of the men with a reliable drinking history by groups of daily consumption. Importantly, the prevalence of coronary artery disease was much higher among light drinkers (68%) than among moderate (50%), heavy (37%), or very heavy drinkers (20%) ($p < 0.0001$, table 2). The mean age of the men decreased and the intensity of smoking increased gradually from the lowest to the highest daily alcohol consumption (table 2). Hypertension and diabetes, on the other hand, were evenly distributed across the different drinking categories (table 2).

ASSOCIATIONS OF CARDIAC MEASUREMENTS WITH ALCOHOL USE AND WITH OTHER EXPLANATORY FACTORS IN ALL MEN

In stepwise multiple linear regression analyses, alcohol consumption (square root of daily dose) had a significant independent influence on total heart weight and RV cavity area, both of which increased with increasing daily alcohol intake (table 3). These associations were confirmed by the polychotomous logistic regression analyses, which showed in addition a significant influence of alcohol consumption on LV weight (table 4). The analyses were also

done using body mass index instead of body surface area as a confounding factor. The results were essentially similar.

Of the other independent factors, body size was a major determinant of all cardiac measurements aside from wall thickness. Age, severity of coronary artery disease, and history of hypertension each influenced heart weight and some LV measurements (tables 3 and 4). While LV cavity area was related directly to the severity of coronary artery disease, wall thickness was influenced more by the history of hypertension (tables 3 and 4). History of diabetes had no influence on any cardiac measurement by our stepwise analyses. Smoking, too, was of little significance with only a small effect on the RV cavity area (tables 3 and 4).

The whole series

Cases in ANCOVA

Figure 2 Flow chart showing the number of men included in the different analyses.

Table 5 Cardiac measurements in relation to daily alcohol consumption in men free of coronary artery disease and myocardial infarction at necropsy

Measurement	Daily alcohol consumption (g)				p Value*
	< 12	12–72	72–180	> 180	
Number	31–34	44–50	56–59	57	
Heart weight (g)	442 (16)	461 (14)	440 (10)	466 (15)	0.015
Left ventricle					
Weight (g)†	193 (7.3)	207 (8.4)	190 (5.2)	204 (8.7)	0.074
Cavity area (cm ²)	11.0 (1.0)	9.4 (1.0)	7.7 (0.7)	10.0 (0.9)	0.054
Anterior wall (mm)	16 (0.4)	17 (0.5)	17 (0.4)	17 (0.4)	0.10
Posterior wall (mm)	16 (0.5)	17 (0.6)	17 (0.4)	17 (0.4)	0.47
Posterior wall to cavity area ratio (mm/cm ²)	2.0 (0.3)	3.1 (0.5)	5.2 (0.9)	3.7 (0.8)	0.036
Right ventricle					
Weight (g)†	65 (3.3)	67 (2.3)	69 (3.2)	66 (3.4)	0.45
Cavity area (cm ²)	9.8 (0.8)	8.9 (0.7)	8.6 (0.6)	10.8 (0.7)	0.005

The data are mean (SEM).

*p Value from analysis of covariance with log body surface area, age, smoking (log number of cigarettes/day), history of diabetes, and history of hypertension as covariates.

†Number of cases was 21, 34–35, 40, and 36, respectively.

ASSOCIATIONS OF CARDIAC MEASUREMENTS WITH ALCOHOL USE IN MEN FREE OF CORONARY ARTERY DISEASE

Because coronary artery disease had a strongly significant influence on cardiac measurements and was grossly unevenly distributed across the alcohol consumption groups, we also analysed our data separately in men free of coronary artery disease and myocardial infarction at necropsy. The selection of the target group for these analyses is shown in fig 2. The analyses were done with analysis of covariance using

age, log body surface area, smoking (log number of cigarettes/day), history of diabetes, and history of hypertension as covariates. Table 5 and fig 3 show that LV cavity area decreased with increasing consumption of alcohol up to a dose of > 180 g/day ($p = 0.054$ for the overall effect and Scheffé's post hoc $p = 0.007$ for the difference between groups consuming < 12 g/day *v* 72–180 g/day). Alcohol also had an effect on RV cavity area (table 5 and fig 3). This showed a non-significant trend towards a decrease from light to heavy consumption and thereafter an increase from heavy to very heavy consumption ($p = 0.005$ for the overall effect and Scheffé's post hoc $p = 0.005$ for the difference between groups consuming 12–72 g/day *v* > 180 g/day) (table 5 and fig 3). The LV posterior wall to cavity area ratio increased with increasing consumption ($p = 0.036$ for the overall effect and Scheffé's post hoc $p = 0.003$ for the difference between groups consuming < 12 g/day *v* 72–180 g/day) in a pattern that was essentially a mirror image of the relation between LV cavity area and alcohol consumption (table 5 and fig 4). In addition, alcohol had a significant overall effect on total heart weight ($p = 0.015$) (table 5). Since part of alcohol's effects on the heart may be mediated by alcohol related increase of blood pressure, all analyses were repeated without hypertension as a

Figure 3 Left (LV) and right ventricular (RV) cavity areas (mean (SD)) according to daily alcohol consumption in men free of coronary artery disease and myocardial infarction at necropsy. *From analysis of covariance. †Scheffé's post hoc test.

Figure 4 LV posterior wall to cavity area ratio according to daily alcohol consumption in men free of coronary artery disease and myocardial infarction at necropsy. *From analysis of covariance. †Scheffé's post hoc test.

covariate. The statistical associations were essentially unchanged. The analyses were also done using body mass index as a covariate instead of body surface area. The results remained essentially unchanged.

Discussion

Our main finding was a U shaped reduction of LV cavity size with increasing daily alcohol consumption in men free of coronary artery disease. The decrease in LV size with moderate and heavy drinking—a consumption of up to 180 g/day—was accompanied by an increase in the ratio of LV wall thickness to cavity area indicating a trend towards concentric LV remodelling. In all men (with and without coronary artery disease), there was a weak positive linear relation between total heart weight and daily alcohol use but no sign of LV dilatation with even very heavy drinking. The RV cavity size was weakly directly related to daily alcohol use in all men but in the absence of coronary artery disease RV dilatation was found only in men drinking > 180 g/day.

Earlier echocardiographic studies from our country have shown that, compared with teetotallers and occasional drinkers, those with chronic alcoholism have an increased LV wall thickness to diameter ratio and an increased LV mass but no LV dilatation.^{3 9 19} Importantly, these studies included only people from the two opposite extremes of the spectrum of habitual alcohol consumption and may therefore have missed the U shaped relation of LV size with daily drinking (fig 3). Of note, both our necropsy data and the echocardiographic studies indicate that chronic heavy alcohol use can cause concentric LV remodelling and increase LV weight. In the present study, LV weight was altered even in moderate drinkers (12–72 g/day) and there was no progressive increase thereafter with more heavy daily consumption. The association of LV mass with alcohol use has also been shown previously in large scale population studies.²⁰

Impairment of LV diastolic filling is a prominent early functional cardiac abnormality in patients with asymptomatic chronic alcoholism.^{8 9 19 21} Animal studies have shown that chronic alcohol exposure increases the fibrous collagen content of the heart muscle resulting in an impairment of LV filling without cavity dilatation, followed later by systolic dysfunction.²² Although our present data tell little about lifetime cardiac function, the reduction in size and the concentric remodelling of the LV in moderate and heavy drinkers are compatible with lifetime diastolic dysfunction caused by a stiff LV. It is also worth noting that when daily drinking exceeded 180 g (15 drinks), the LV cavity started to increase from its trough values (fig 3), which may be interpreted as a sign of incipient worsening of systolic function.

Our observation of an increase in RV cavity area with increasing alcohol consumption is a novel finding. In fact there exist no previous studies on the effects of alcohol on RV anatomy or function. In men free of coronary artery disease, the enlargement of RV size was seen only

in very heavy drinkers who also showed an increase of LV size from the trough of its U shaped relation to daily alcohol consumption (fig 3). These men may have suffered from alcohol related direct myocardial toxicity that was severe enough to result in RV dilatation and to turn the LV response from cavity reduction to incipient cavity enlargement “normalising” the LV size. It is also possible that an excess of RV afterload caused by passive pulmonary hypertension resulting from alcohol related LV dysfunction may have contributed to RV dilatation. Furthermore, alcohol also may raise pulmonary artery pressure (and RV systolic load) by more direct though as yet unknown mechanisms.^{23–25} RV size and function are important prognostic factors in idiopathic dilated cardiomyopathy.^{26–28} Whether RV measurements have comparable significance in alcoholic heart muscle disease deserves attention in future clinical studies.

A limitation inherent in the design of our study is that the data on alcohol consumption, smoking, and associated diseases were based on an interview of the spouse or a close acquaintance. Further, such people with detailed knowledge of the deceased's lifestyle were not available for a considerable proportion of the cases. However, the questionnaire we used has been validated previously¹² and the daily alcohol doses used in the present study have in our earlier studies shown good correlations with alcoholic liver disease²⁹ and disorders of spermatogenesis.³⁰ Because of this and because we were able to include almost two thirds of all the consecutive cases in our analyses, we feel that biased results are unlikely. Another limitation is that, confirmation of myocardial infarction aside (see Methods), we have as yet no data on myocardial histopathology in relation to alcohol consumption. In addition, since our series included only men, the results may not apply to both sexes and comparable data on women are needed. The strengths of our work are the relatively large number of men studied, the width of the spectrum of alcohol consumption covered, the high prevalence of heavy drinking, and the performance of postmortem coronary angiography helping us take into account the confounding effect of coronary artery disease. The validity of our LV and RV measurements at necropsy is indirectly supported by the significant and medically plausible associations of these measurements with body size, age, coronary artery disease, and hypertension (tables 3 and 4).

Nutritional aspects have been speculated to contribute to the development of alcoholic heart muscle disease. However, apart from the historical toxicity of beer additives, there is little proof of that. Furthermore, several studies have specifically pointed out that the cardiac abnormalities are not dependent on nutritional factors.^{31 32} In the present study, the dose dependency of cardiac findings was independent of body mass index, indicating that obesity or grave malnutrition would not be a major susceptibility factor for alcoholic heart muscle disease among middle aged men who had died suddenly.

In conclusion, the present data suggest that chronic alcohol use influences cardiac anatomy in a dose dependent but non-linear way. If the role of coronary artery disease is excluded, LV size decreases with increasing consumption up to 180 g/day. Concomitantly, the posterior wall to LV cavity area ratio increases suggesting concentric LV remodelling. The LV weight increases even with moderate daily drinking without further change in more heavy drinkers. The RV response is characterised by a trend towards dilatation when alcohol consumption exceeds 180 g/day; lesser quantities of daily drinking appear to have little effect on the RV. Only men were studied, and new studies are needed to discover the mechanisms of the distinctive LV and RV responses to heavy alcohol use. Importantly, our findings disprove the idea of a linear increase in LV size and mass with increasing habitual alcohol consumption.

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