Coronary Artery Disease Modifies Left Ventricular Remodelling due to Heavy Alcohol Consumption

Olli A. Kajander, Markku Kupari, Pekka Laippala, Antti Penttilä, and Pekka J. Karhunen

Background: Coronary artery disease (CAD) and excessive alcohol use can both damage the myocardium. Their combined effect on the heart muscle has not been characterized. We set out to assess whether the presence of CAD modifies the effects of chronic alcohol consumption on the left ventricular (LV) structure in middle-aged men.

Methods: A postmortem examination was performed on 700 Finnish men (age range, 33–70 years) who experienced a sudden, nonhospital death. A coronary arteriography and measurement of the LV wall thickness, cavity area, and ratio by planimetry of transversal ventricular slices were done at the autopsy. The men were grouped by the most severe coronary artery diameter stenosis (<30%, 30–60%, >60%) and by daily alcohol dose (<12 g, 12–72 g, 72–180 g, >180 g) estimated by a structured interview of their lifetime partner.

Results: Analysis by ANCOVA, adjusted for age, body size, smoking, hypertension, and diabetes, showed a statistically significant interaction between the effects of coronary artery stenosis and daily alcohol dose on the LV cavity area ($p = 0.037$) and on the LV wall thickness/cavity area ratio ($p = 0.018$). In the group with <30% stenosis, the LV wall thickness/cavity area ratio (mean ± SEM) increased from 1.6 ± 0.2 mm/cm² in men drinking <12 g/day to 6.2 ± 1.4 mm/cm² in men drinking 72–180 g/day ($p = 0.021$). A similar trend was seen in men with 30–60% coronary stenosis ($p = 0.32$). By contrast, in men with >60% coronary stenosis, the LV wall thickness/cavity area ratio decreased with increasing daily alcohol use from 2.2 ± 0.3 to 1.4 ± 0.1 mm/cm² ($p = 0.27$).

Conclusions: CAD modulates the effects of alcohol on the heart muscle. Heavy drinking results in concentric LV remodelling in men with no or only mild coronary artery stenoses whereas an opposite trend is seen in men with severe coronary artery obstructions. The mechanism of the interaction remains unknown.

Key Words: Ventricles, Alcohol, Remodelling, Coronary disease, Sudden Death.

Although regular alcohol consumption may offer some protection against the development of coronary artery disease (CAD) (Doll et al., 1994; Hart et al., 1999; Rimm et al., 1991), chronic alcoholism and CAD are not mutually exclusive conditions. Because CAD can damage the myocardium and heavy alcohol use also has harmful effects on left ventricular (LV) structure (Askanas et al., 1980; Kupari et al., 1991; Mathews et al., 1981) and function (Ahmed et al., 1980; Kino et al., 1981; Kupari et al., 1990; Silberbauer et al., 1988; Spodick et al., 1972; Urbano-Marquez et al., 1989), it is logical to question their combined effect on the heart muscle. Studies on the acute effects of alcohol in the presence of CAD suggest an exaggeration of exercise-related myocardial ischemia (Orlando et al., 1976; Rossinen et al., 1996) and an impairment or no change in LV function (Gould et al., 1972; Kelbaek et al., 1988). Furthermore, chronic moderate or heavy alcohol use has recently been reported to increase the risk of cardiac events in the presence of clinically established CAD, as opposed to its effects in the absence of CAD (Shaper and Wannamethee, 2000). No earlier report has, however, described the combined effect of chronic alcohol use and CAD on the heart muscle.

Chronic alcoholics who are asymptomatic for any cardiac disease frequently have an increased LV wall thickness/diameter ratio at echocardiography, with or without increased LV mass, suggesting that concentric LV remodelling or hypertrophy is an early response to heavy drinking (Kupari and Koskinen, 1992; Kupari et al., 1990, 1991). In the present work, we studied by autopsy the relationship of cardiac anatomy to habitual lifetime alcohol consumption in a series of 700 men who died suddenly out of hospital. In addition to the assessment of LV anatomy, our study in-
cluded detailed examination of the coronary arteries by postmortem angiography. Daily alcohol doses were obtained by a previously validated structured interview of the deceased’s lifetime partner (Karhunen and Penttilä, 1990). The present report compares the relation of LV anatomy to daily alcohol dose across groups of men with different severities of coronary artery obstructions. We focused on the LV wall thickness/cavity area ratio in particular to see if alcohol-related concentric LV remodelling is influenced by coexistent CAD.

**STUDY POPULATION AND METHODS**

**The Autopsy Series**

The study consisted of two series of medicolegal autopsies collected during two time periods, 12 months in 1981–1982 and 16 months in 1991–1992, at the Department of Forensic Medicine, University of Helsinki, Finland. A total of 700 (400 + 300) consecutive men were included in the series by using male sex and age between 33–70 years as inclusion criteria. Autopsies were performed in cases of out-of-hospital deaths for previously healthy men or if deaths were due to suspected intoxication, accidental death, suicide, or death in connection with medical treatment. The series covered 42% of all deaths of individuals < 65 years old in the Helsinki city area during the study periods. Cause of death was cardiovascular in 290 men (41.4%), other disease in 131 men (18.7%), intoxication in 138 men (19.7%), other violent cause in 134 men (19.1%), and unknown in 7 men (1.0%).

The Ethics Committee of the Department of Forensic Medicine, University of Helsinki approved the study.

**Alcohol Consumption and Other Cardiovascular Risk Factor Data**

To evaluate the deceased’s lifetime alcohol consumption, a structured interview of the subject’s spouse or a close relative or acquaintance was conducted. The questionnaire incorporated 14 items concerning intensity, frequency, quantity, and quality of the individual's alcohol consumption (Karhunen and Penttilä, 1990, see appendix for the alcohol questionnaire). Using this raw data, all-year average daily alcohol intake as absolute ethanol (grams/day) was estimated. Of the 700 consecutive autopsy cases, a person with sufficiently detailed knowledge of the deceased’s lifetime history was reached in 500 (71.4%) cases. Among these, calculation of daily alcohol dose could be performed in 452 cases, whereas in the remaining 48 cases the data were considered incomplete. Of these 452 cases, 17 were excluded because the subjects were previous heavy drinkers who had recently reduced their drinking markedly. Thus, we ultimately had a total of 435 men with known stable drinking habits for our analyses. According to their daily alcohol use, these men were classified as 97 non-drinkers or light drinkers (<12 g/day = <1 drink), moderate drinkers (12–72 g/day = 1–6 drinks), heavy drinkers (72–180 g/day = 6–15 drinks) or very heavy drinkers (>180 g/day = >15 drinks).

History of lifetime tobacco smoking was recorded as cigarettes/day and how long the deceased had smoked and whether he was an ex-smoker. History of hypertension and diabetes were specifically questioned in the interview. In 223 cases, no reliable history of hypertension or diabetes was obtained, mostly because the deceased had never visited a doctor for these reasons.

**Examination and Measurements of the Heart at the Autopsy**

After a complete routine postmortem medicolegal study, a silicone rubber cast of the whole coronary tree was made by a technique described elsewhere (Weisman et al., 1999). The percent obstruction of the arterial lumen diameter relative to the nearest proximal uninvolved segment was measured for all local coronary artery narrowings from the cast model. According to the most severe coronary artery obstruction, the men were classified into groups of no or mild stenosis (< 30% obstruction), mild-to-moderate stenosis (30–60% obstruction), and severe stenosis (> 60% obstruction).

To assess the cardiac anatomy in detail, the heart was weighed and the ventricular block was cut transversally into 15-mm thick slices. The borders of the cavities and walls at the equatorial ventricular region were traced onto a transparent sheet and analyzed later by computer-assisted planimetry for left and right ventricular cavity areas and wall thicknesses. The LV, including the interventricular septum, and the right ventricular free wall were finally weighed separately. In the present work, we focused on the LV measurements. The postmortem delay after autopsy, which was, on average, 3.6 days (median 3 days), did not correlate with any of the ventricular dimensions.

**Statistical Analysis**

ANOVA and χ² test were used to compare the characteristics of the men across the four different alcohol consumption groups. The effects on the LV measurements of the daily alcohol dose and the severity of CAD, as well as their interaction, were assessed with 2-way ANCOVA. Confounding factors such as body surface area, age, smoking (log cigarettes/day), and presence of lifetime hypertension and diabetes (binary dummy variables) were incorporated as covariates in ANCOVA. Variables with grossly asymmetric distribution were square root or log-transformed before the analyses. Two-tailed p values < 0.05 were considered statistically significant. Statistica/Win (Version 5.0, StatSoft Inc., Tulsa, OK) was used to compute the analyses on a personal computer.

**RESULTS**

**Characteristics of the Autopsy Series**

Of the men with reliable drinking histories, nearly one half (46%) were heavy or very heavy drinkers (>72 g/day) and only 8% were teetotalers (<12 g/day). The proportion of current smokers was 69% whereas 13% were ex-smokers. Table 1 lists selected characteristics of the men by the groups of daily alcohol use. It is noteworthy that men having drunk heavily or very heavily were younger and heavier smokers and had less severe CAD than the men with the least daily alcohol consumption. The prevalence of hypertension or diabetes did not differ across the alcohol consumption groups (Table 1).

There was no statistical significance between the men who were excluded due to lack of data on alcohol use (n = 265) and the men included (n = 435) with respect to age, severity of CAD, or any of the LV measurements at autopsy (data not shown). Body area, however, differed between the two groups, averaging 1.87 ± 0.21 m² (mean ± SEM) in the cases that were excluded versus 1.92 ± 0.21 m² in the included cases (p = 0.003).

**Association of the LV Measurements With Alcohol Use and CAD Severity**

Table 2 shows the data on LV anatomy by groups of daily alcohol consumption and severity of CAD. In 2-way ANCOVA adjusted for effects of age, body surface area, smoking, diabetes, and hypertension, CAD severity had a statistically significant overall effect on the LV cavity area (p = 0.030) and the posterior wall/cavity area ratio (p = 0.014) but not on either anterior or posterior wall thickness or LV
However, there were statistically significant interactions between the effects of alcohol dose and CAD severity on the LV posterior wall/cavity area ratio (Fig. 1) and the LV cavity area (p = 0.037) (Fig. 2), which suggests that the influence of alcohol was dependent on the severity of coronary artery stenosis. Further analyses showed that in the group with no or only mild CAD (men with <30% maximal coronary artery stenosis) the LV posterior wall/cavity area ratio increased with increasing daily alcohol use and was statistically significantly higher in men who drank 72–180 g/day compared with those who drank <12 g/day (p = 0.021) (Table 2, Fig. 1). The difference mainly reflected a smaller LV cavity area in men with higher daily alcohol consumption (p = 0.021) (Fig. 2). Directionally similar but statistically nonsignificant trends in the LV measurements were seen in men with 30–60% maximal coronary artery stenosis (Table 2). By contrast, in the group with severe coronary artery obstructions (>60% maximal diameter stenosis), increasing daily alcohol use was associated with a trend toward a smaller LV posterior wall/cavity area ratio and a larger LV cavity area (Table 2, Fig. 1). Because some of alcohol’s effects may be mediated by hypertension, the statistical analyses were repeated without history of hypertension as a covariate. The statistical associations remained essentially the same.

CAD was alternatively classified by the number of vessels with >50% stenosis (coded from 0 to 3). The interactions between the effects on LV measurements from daily alcohol use and CAD severity classified in this way did not reach statistical significance (p = 0.10–0.15). One reason may have been that heavy drinking was rarely combined with multivessel CAD reducing considerably the size of some of the subgroups in 2-way ANCOVA (data not shown).

**DISCUSSION**

The present data indicate that the influence of chronic alcohol consumption on LV anatomy in middle-aged men is dependent not only on the daily alcohol dose but also on the presence and severity of CAD. In individuals with no CAD or at most <30% coronary artery diameter stenosis, larger daily doses of alcohol were accompanied by concentric LV remodelling, whereas an opposite though statistically nonsignificant trend (eccentric remodelling, i.e., an increase in LV cavity size without change in LV weight) was

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**Table 1. Characteristics of the Men With Reliable Drinking History by Categories of Daily Alcohol Consumption**

<table>
<thead>
<tr>
<th>Most severe stenosis</th>
<th>Daily alcohol dose</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12 g</td>
<td>12–72 g</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.4 (9.9)</td>
<td>53.7 (9.1)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.95 (22)</td>
<td>1.92 (19)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27/109</td>
<td>25/105</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26/109</td>
<td>29/105</td>
</tr>
<tr>
<td>Most severe stenosis</td>
<td>&lt;30%</td>
<td>15/109</td>
</tr>
<tr>
<td></td>
<td>30–60%</td>
<td>34/109</td>
</tr>
<tr>
<td></td>
<td>&gt;60%</td>
<td>60/109</td>
</tr>
<tr>
<td>Smoking (cigarettes/day)</td>
<td>13.5 (13.0)</td>
<td>17.9 (15.2)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or frequencies. p values are for differences across alcohol consumption groups from ANOVA or χ² test.

* For log transformed data.

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**Table 2. Left Ventricular Measurements at Autopsy by Daily Alcohol Consumption and Most Severe Coronary Artery Stenosis**

<table>
<thead>
<tr>
<th>Most severe stenosis</th>
<th>Left ventricular measurement</th>
<th>Daily alcohol dose</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;12 g</td>
<td>12–72 g</td>
</tr>
<tr>
<td>Posterior wall/cavity area ratio (mm²)</td>
<td>1.6 ± .2</td>
<td>2.7 ± .4</td>
<td>6.2 ± 1.4*</td>
</tr>
<tr>
<td>Cavity area (cm²)</td>
<td>12.4 ± 1.4</td>
<td>9.9 ± 1.6</td>
<td>7.2 ± .9†</td>
</tr>
<tr>
<td>Anterior wall (mm)</td>
<td>15.9 ± .6</td>
<td>16.6 ± .6</td>
<td>17.2 ± .6</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>16.6 ± 1.0</td>
<td>16.5 ± .7</td>
<td>16.8 ± .5</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>197 ± 16.5</td>
<td>216 ± 15.0</td>
<td>196 ± 7.8</td>
</tr>
<tr>
<td>Cavity area (cm²)</td>
<td>12.1 ± 1.0</td>
<td>9.5 ± 1.0</td>
<td>9.0 ± .8</td>
</tr>
<tr>
<td>Anterior wall (mm)</td>
<td>16.4 ± .7</td>
<td>17.2 ± .5</td>
<td>16.8 ± .4</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>16.0 ± .5</td>
<td>17.2 ± .8</td>
<td>16.7 ± .6</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>196 ± 9.9</td>
<td>206 ± 9.5</td>
<td>186 ± 7.9</td>
</tr>
<tr>
<td>Posterior wall/cavity area ratio (mm²)</td>
<td>2.2 ± .3</td>
<td>2.2 ± .5</td>
<td>1.4 ± .1</td>
</tr>
<tr>
<td>Cavity area (cm²)</td>
<td>12.2 ± .8</td>
<td>12.2 ± .8</td>
<td>13.4 ± 1.2</td>
</tr>
<tr>
<td>Anterior wall (mm)</td>
<td>17.7 ± .5</td>
<td>16.8 ± .6</td>
<td>16.9 ± .7</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>16.6 ± .4</td>
<td>17.0 ± .6</td>
<td>15.5 ± .5</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>236 ± 10.7</td>
<td>240 ± 9.0</td>
<td>217 ± 14.3</td>
</tr>
</tbody>
</table>

Data are mean ± SEM. p values are from ANCOVA adjusted for age, body size, smoking, hypertension, and diabetes.

* p = 0.021, <12 g/day vs. 72–180 g/day, Scheffe’s post hoc test; † p = 0.021, <12 g/day vs. 72–180 g/day, Scheffe’s post hoc test.
consistent finding along with Doppler echocardiographic signs of impaired LV relaxation (Kupari et al., 1990, 1991). Our present data that show increased LV wall thickness/cavity area ratio with heavy drinking in men with no or only mild coronary artery obstructions agree with our earlier results and support the idea of LV concentric remodelling being a typical structural manifestation of alcoholic heart muscle disease. Although based on the present data, it is not possible to evaluate the lifetime cardiac function of the men studied; the LV concentric remodelling among heavy drinkers without significant CAD is compatible with lifetime diastolic dysfunction due to a stiff left ventricle. Why heavy drinking combined with severe CAD should result in reduced LV wall thickness/cavity area ratio rather than in concentric remodelling remains unknown. It is noteworthy, however, that alcohol can exaggerate exercise-related myocardial ischemia in patients with CAD (Orlando et al., 1976; Rossinen et al., 1996). More ischemia certainly means a greater potential for myocardial damage with LV wall thinning and cavity enlargement.

The adverse prognostic effects of LV hypertrophy are well known (Haider et al., 1998; Kannel, 1991; Krumholz et al., 1995) but there are data which suggest that even the mere concentric LV remodelling, without hypertrophy, may increase the risk of acute cardiovascular events (Verdecchia et al., 1995). Like heavy drinking, hypertension and old age are also commonly associated with concentric LV remodelling (Ganau et al., 1995; Verdecchia et al., 1995). Whether alcohol-related concentric LV remodelling could contribute to the risk of arrhythmias and sudden death in alcoholics is unknown at the present time. The finding that concentric remodelling is associated with increased QT dispersion in hypertensive patients (Bugra et al., 1998) suggests that some vulnerability to re-entry ventricular arrhythmias may ensue.

In the present study, the period of time from death to autopsy did not determine any of the cardiac measurements in multivariate analyses (data not shown). The postmortem volumes of the ventricles have earlier been shown to depend on the stage of rigor mortis and the use of formalin fixation (Sairanen, 1985). Because our series of hearts was studied without fixation and during a relatively short period of time after death, the postmortem changes can be considered random. Even after the potential additional variation from the postmortem changes, the standard errors of the measurements are reasonably small (see Table 2). The validity of our cardiac measurements is also supported indirectly by statistically significant and medically plausible associations between body size, age, CAD, and hypertension and these measurements (data not shown).

A limitation of our study is that the data on alcohol consumption and cardiovascular risk factors were indirect and based on an interview of the deceased’s lifetime partner. However, we emphasize that the questionnaire we used has been validated previously (Karhunen and Penttila, 1990) and that there simply is no alternative method suit-
able for postmortem studies like the present one. Furthermore, our earlier analyses of these very same men have shown good correlations of the estimated daily alcohol dose with alcoholic liver injury (Savolainen et al., 1993) and with disorders of spermatogenesis (Pajarinen et al., 1997). The strengths of the present study include the relatively large size of the population studied, the width of the spectrum of alcohol use covered, the high prevalence of heavy drinking, and the availability of detailed data on coronary artery stenoses.

In conclusion, our data suggest that the severity of CAD modulates alcohol-related LV remodeling in middle-aged men. Heavy daily alcohol use was associated with concentric LV remodelling in men with no or only very mild CAD whereas men with at least one severe coronary artery stenosis showed a trend toward eccentric remodelling with heavy drinking. The mechanism of the interaction between alcohol consumption and CAD severity remains unknown.

**ACKNOWLEDGMENT**

The authors thank Kaisa H. Lalu, MD, Kimmo K. Liesto, MD, and Antti Männikkö, MD, from the Department of Forensic Medicine, Helsinki, Finland, for participation in the collection of the autopsy series. Assistant Seppo Tynelä from the same department and Synnöve Staff, MD, from Medical School, University of Tampere, Finland, are acknowledged for assistance with the planimetric measurements.

**APPENDIX**

Interview questions concerning alcohol consumption data:

1. Did the subject use alcohol during his lifetime?
   1 no (move to question 17)
   2 yes
   3 yes, discontinued
   4 other data
   9 no data

2. For how long did he use alcohol regularly?

3. Has he changed his drinking habits during the past decade?
   0 no change
   1 continuous increase
   2 sudden increase
   3 sudden decrease
   4 decrease—increase
   5 increase—decrease
   6 other data
   7 no data

Periods. If there are distinct periods in drinking habits, use either column I or II for the different drinking periods, respectively.

4. When did he usually drink alcohol?
   I II
   — — only on festive occasions
   — — on weekends (Fri-Sat-Sun)
   — — mainly on weekends, occasionally during the week
   — — daily
   — — other data

5. Did the subject have drinking bouts?
   0 no
   1 yes, during period I

2 yes, during period II

3 on the average, how many drinking bouts per month?

4 other data

6. Reasons and dates for possible alterations in the drinking habits.
   0 no change
   1 death of a close relative
   2 retirement
   3 illness, which?
   4 domestic disagreements (also divorce or separation)
   5 changes in working environs
   6 criminal act and its consequences
   7 financial alterations
   8 no obvious explanation
   9 other data

7. How often and how much did the subject consume spirits?
   I II
   — — did not drink during the last year
   — — daily consumption
   — — three times a week or more often
   — — twice a week
   — — once a week
   — — twice a month
   — — once a month
   — — less seldom than once a month
   — — daily drinking bouts
   — — other data

The average consumed amount of spirits per one drinking occasion:

1 one bottle or more (10–12 drinks)

2 5–8 drinks (slightly more than half a bottle)
3 3–4 drinks (1.5 dl)
4 1–2 drinks (4–8 cl)
9 other data

8. How often and how much did the subject consume wines?

I II
— — did not drink during the last year
— — daily consumption
— — three times a week or more often
— — twice a week
— — once a week
— — twice a month
— — once a month
— — less seldom than once a month
— — daily drinking bouts
— — other data

The average consumed amount of wines per one drinking occasion:
1 one bottle or more
2 more than half a bottle
3 less than half a bottle
4 one glass of wine
9 other data

9. How often and how much did the subject consume beer or long drinks?

I II
— — did not drink during the last year
— — daily consumption
— — three times a week or more often
— — twice a week
— — once a week
— — twice a month
— — once a month
— — less seldom than once a month
— — daily drinking bouts
— — other data

The average consumed amount of spirits per one drinking occasion:
1 more than 8 bottles
2 5–8 bottles
3 2–4 bottles
4 1 bottle
9 other data

12. How often was the subject drunk?

I II
0 0 never
1 1 daily
2 2 three times a week or more
3 3 twice a week
4 4 once a week
5 5 twice a month
6 6 once a month
7 7 less seldom than once a month

13. In your opinion, what was the degree of intoxication?

I II
1 1 pass-out
2 2 rather high (clearly drunk)
3 3 moderate
4 4 mild, or not drunk

14. Was the subject ever arrested because of ethanol intoxication?

15. Was the subject ever treated for alcoholism?

16. Your estimation of the overall consumption habits of the subject (interview and information from police protocols):

<table>
<thead>
<tr>
<th>Relatives view</th>
<th>Interviewers view</th>
</tr>
</thead>
<tbody>
<tr>
<td>I II</td>
<td>I II</td>
</tr>
<tr>
<td>0 0 abstainer</td>
<td>0 0</td>
</tr>
<tr>
<td>1 1 mild to moderate</td>
<td>1 1</td>
</tr>
<tr>
<td>2 2 excessive consumption</td>
<td>2 2</td>
</tr>
<tr>
<td>3 3 alcoholic</td>
<td>3 3</td>
</tr>
<tr>
<td>4 4 chronic alcoholic</td>
<td>4 4</td>
</tr>
<tr>
<td>5 5 unable to estimate</td>
<td>5 5</td>
</tr>
<tr>
<td>9 9 no data</td>
<td>9 9</td>
</tr>
</tbody>
</table>

REFERENCES


