Influence of increased adrenergic activity and magnesium depletion on cardiac rhythm in alcohol withdrawal

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Abstract
Objective—To investigate the prevalence of arrhythmias in alcoholic men during detoxification and its relation to neuroendocrine activation and electrolyte disturbances.
Design—Consecutive case-control study.
Setting—Primary and secondary care, detoxification ward.
Patients and controls—19 otherwise healthy alcoholic men (DSM-III-R) with withdrawal symptoms necessitating detoxification in hospital. 19 age matched, healthy non-alcoholic men as controls for Holter recordings.
Interventions—Treatment with chlormethiazole; additional treatment with carbamazepine in patients with previous seizures.
Main outcome measures—Computer based analyses of mean heart rate and arrhythmias from 24 hour Holter recordings, 24 hour urinary excretion of adrenaline and noradrenaline, magnesium retention measured by means of intravenous loading test, and serum concentrations of electrolytes.
Results—The 24 hour mean heart rate was higher in the alcoholic men (97.4 beats/minute, 95% confidence interval (CI) 91.2 to 103.6) than in the controls (69.6 beats/minute, 95% CI 65.4 to 73.8, P < 0.001). However, there was no difference in diurnal heart rate variation. The prevalence of premature supraventricular depolarisations was lower in the alcoholic men (P < 0.05). Neither atrial fibrillation nor malignant ventricular arrhythmias occurred. The sinus tachycardia in the alcoholic men correlated with the concomitant urinary excretion of catecholamines (P < 0.05). The mean serum magnesium concentration was 0.78 mmol/l (95% CI 0.73 to 0.83) in the alcoholic men and 0.83 mmol/l (95% CI 0.81 to 0.85) in a reference population of 55 men aged 40. Magnesium depletion (defined as magnesium retention >30%) was detected in 10 alcoholic men (53%). Three alcoholic men had serum potassium concentrations ≤3.5 mmol/l on admission.
Conclusion—Increased adrenergic activity, magnesium depletion, and hypokalaemia are often seen after heavy drinking, but in alcoholic men without clinical heart disease these changes were not accompanied by arrhythmias other than sinus tachycardia during detoxification in hospital.

Among middle aged men misuse of alcohol is a major contributor to death. Sudden, unattended death is common in alcoholics. Even after medicolegal examination the causes of death remain obscure in 10–20% of those who misuse alcohol. In such cases the blood concentration of ethanol is usually zero or very low, suggesting that death may have occurred during alcohol withdrawal. It is likely that arrhythmias cause most of these deaths, but there are few studies on arrhythmias in alcoholics after heavy drinking.

We postulated that neuroendocrine activation and electrolyte disturbances accompanying alcohol abuse are involved in the pathogenesis of sudden death in alcoholic patients. The hyperadrenergic state seen during alcohol withdrawal could make the myocardium more susceptible to arrhythmias. In addition, magnesium deficiency, which is common in alcoholics, is associated with malignant ventricular arrhythmias though more recently it has been proposed that the arrhythmias described in magnesium depleted patients may be induced by concomitant hypokalaemia.

The present study was designed to investigate the prevalence of cardiac arrhythmias in alcoholic men during detoxification in hospital and to explore possible relations between arrhythmias, increased adrenergic activity, and magnesium depletion. To examine the specific effect of alcohol abuse on cardiac rhythm we studied patients without heart disease or other conditions associated with arrhythmia.

Patients and methods
PATIENTS
One of us (HD) considered the eligibility of all men admitted to a detoxification ward at Lillhagen Hospital (Gothenburg, Sweden) between September 1, 1989, and March 1, 1990. This unit served a catchment area of about 42 000 men aged ≥20 years, and about 400 patients aged ≤60 years were treated as inpatients each year.
Patients were included in the study if they had:
- A diagnosis (DSM-III-R) of alcohol dependence
- A reported daily ethanol ingestion of ≥120 g for at least one week
- Withdrawal symptoms necessitating treatment in hospital.
In addition, investigations had to start within 72 hours of the last drinking bout.
Patients with the following characteristics were excluded
- Age >60 years
- Symptoms or signs of heart disease
- Treatment for hypertension
- Renal disease (serum creatinine >130 μmol/l)
- Diabetes mellitus (fasting blood glucose >7-0 mmol/l)
- Treatment with diuretics or other drugs that could interfere with electrolyte balance and heart rhythm
- Abuse of narcotics and benzodiazepines
- Delirium tremens and other major psychiatric disorders making cooperation difficult.
In addition, because of limited access to laboratory facilities, patients could only be included 4 days a week.

Nineteen of 25 eligible patients gave their written, informed consent to participate in the study, which was approved by the Research Ethics Committee, University of Gothenburg.

A urine specimen was collected at entry to the study and screened for metabolites of benzodiazepines, cannabis, amphetamine, and opiates. All tests were negative in 16 of the 19 patients. Three men had positive benzodiazepine tests; one had been given benzodiazepines during an attempt at outpatient detoxification the week before admission, one had been prescribed benzodiazepines in small amounts for temporary sleeping problems, and the third patient was not aware of having ingested any benzodiazepines. Because none of these patients was known to abuse these drugs they were not excluded.

We collected data on social situation, smoking habits, drug and alcohol history, and the amounts and duration of recent alcohol consumption (table 1).

Eleven patients had regular employment; the rest were supported by the social welfare system. All were smokers; 16 patients consumed more than 20 cigarettes per day. Ten of the 19 alcoholic men had had confirmed delirium tremens and eight had withdrawal seizures.

**TREATMENT**

After admission, the patients were treated according to the routines in the detoxification ward with chlormethiazole, 600 mg by mouth four times a day for the first days. If necessary the dose of chlormethiazole was increased to control withdrawal symptoms and keep the heart rate below 100 beats/minute. The mean (SD) amount of chlormethiazole given during the Holter recordings was 2-9 (0-8) g (range 0-6-4-1). Carbamazepine (200 mg by mouth three times a day) was given to the eight patients with a history of withdrawal seizures and to three further patients. All patients were given vitamin B complex with high doses of thiamine by mouth or intramuscularly, depending on their nutritional state. If necessary propiomazine (50 mg) or alimemazine (20-40 mg) was given.

**STUDY DESIGN**

A 24 hour Holter recording was started on the morning after admission, at a median 36 hours after the last drinking bout (range 24-72 h). We started a 24 hour urine collection for analysis of catecholamine excretion at the same time. The next morning we started an intravenous magnesium infusion and another 24 hour urine collection for analysis of magnesium. We drew blood samples for haematological and biochemical analyses before breakfast the day after admission (table 2) and for the next two days.

**CONTROL GROUP**

A control group of 19 age matched healthy male students, physicians, and teachers was recruited for 24 hour Holter recordings, performed while they were carrying out their usual daily activities.

**BIOCHEMICAL METHODS**

We measured urinary concentrations of noradrenaline and adrenaline by high performance liquid chromatography with electrochemical detection. We measured blood haemoglobin (B-Hb) and erythrocyte mean corpuscular volume (Ery-MCV) by the Technicon H1 system, serum aspartate aminotransferase (EC 2.6.1.1, S-ASAT) and alanine aminotransferase (EC 2.6.1.2, S-ALAT) by the methods proposed by the Committee on...
Enzymes of the Scandinavian Society for Clinical Chemistry,13 serum γ-glutamyl transferase (EC 2.3.2.2, S-GGT) by the Szasz method (Granatest 100, Merck Diagnostica), serum potassium (S-K) by flame photometry, serum and urinary magnesium (S-Mg, tU-Mg) by atomic absorption spectrometry (Perkin Elmer model 403), serum albumin (S-albumin) by a dye binding method (bromocresol green), serum creatinine (S-creatinine) by an alkaline picrate method, blood glucose (B-Glucose) by a glucose dehydrogenase method, plasma bicarbonate (P-HCO₃) with a blood gas analyser (ABL 500, Radiometer), and serum carbohydrate deficient transferrin (S-CDT) by ion-exchange chromatography followed by radioimmunological assay (CDTect, Kabi Pharmacia Diagnostics). The enzymes, albumin, creatinine, and glucose were determined by a Greiner G450 analyser. Blood ethanol was determined with gas chromatography (glass column with 1:5% Carbowax on Carbopak B with n-propanol as internal standard). The coagulation factors II-VII-X (citrate plasma) were determined using reagents from Diagnostica Stago (Prothrombin Assay SPA 50).

The reference intervals stated are those of the laboratory, except for serum magnesium where frozen specimens from the alcoholic men and a reference population of 55 healthy men aged 40 were analysed in the same assay run. We used commercial immunological techniques (TDx Abbott) to screen for drug metabolites in urine. Detection concentrations were 100 μg/l (nordiazepam) for benzodiazepines, 0.5 mg/l (d,l-amphetamine) for the amphetamines, 20 μg/l (11-nor-delta-9-tetrahydrocannabinol-9-COOH) for cannabinoids, and 200 mg/l (morphine) for opiates were regarded as negative. Positive tests were confirmed by an independent chromato-graphic method.

INTRAVENOUS MAGNESIUM LOADING TEST
An intravenous infusion of magnesium sulphate (Addex-Magnesium, Kabi Pharmacia) (30 mmol) in 1000 ml saline (Natriumklorid, Kabi Pharmacia) was given over 8 hours. Meanwhile, the patients were allowed to eat the regular hospital food. We measured magnesium excretion in the 24 hour urine collection after the start of the magnesium infusion. The magnesium retention was calculated as the difference between the amount of magnesium infused (30 mmol) and the amount excreted. Magnesium retention of >30% was regarded as evidence of a deficiency.

HOLTER RECORDINGS
The 24 hour electrocardiographic recordings (Holter recordings) were obtained on TDK D-90N tapes by a Tracker TR1 (Reynolds Medical, Herford) with a V1 and V5-like electrode position, replayed on a Pathfinder 2 (Reynolds Medical) and computer analysed. The evaluable registration time was >2300 in 17 of the alcoholic men and 18 in the controls (range 2033–2358 and 2255–2359).

ECG REGISTRATIONS
On one of the first days we obtained a resting 12 lead routine electrocardiogram (ECG) in all except one of the patients (Siemens Mingograph 740, Siemens Elena, Stockholm). The ECGs were classified according to the Minnesota code.14 The QT interval (QT) was measured by two independent observers on V5 baseline ECG complexes averaged over one minute from Holter recordings at a paper speed of 50 mm/s. The interobserver coefficient of variation for QT-interval measurement was 2.2% (standard deviation for the mean difference between observers divided by mean QT time for all 38 measurements). The corrected QT interval (QTc) was calculated from the mean value of the two QT interval measurements for each subject according to Hodges' linear formula:

\[ QTc = QT \times \frac{1.75 \times (heart rate - 60)}{100} \text{ seconds.}^{13} \]

STATISTICAL ANALYSIS
Mean heart rate, QTc, and electrolyte concentrations are presented as mean values with 95% confidence intervals (95% CI) calculated on the assumption of t distribution. The values for the other variables are given as median (range). We used two-tailed Student’s t tests for independent groups to compare the mean heart rates of the alcoholic men and controls and Wilcoxon’s signed ranks test for paired comparison of the QTc, urinary magnesium excretion, premature supraventricular and ventricular depolarisations in the alcoholic men and the age matched controls, and analysis of changes in serum electrolyte concentrations in the alcoholic group. Pearson’s correlation coefficient was used to measure correlations between variables. To calculate the correlation between mean heart rate and catecholamine excretion in the alcoholic men we used log transformed catecholamine values, because these values were widely scattered. A P value of <0.05 was regarded as statistically
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**Figure 2** Diurnal heart rate variability in 19 alcoholic men during withdrawal and 19 controls, calculated from mean heart rates every hour from Holter recordings.

We used Minitab 6·1 (Minitab, USA), Q & A Graphstat, Version 1·0 (Symantec Corporation, USA), and Stat View II (Abacus Concepts, Berkeley, CA, USA) computer programs for the calculations.

**Results**

**HOLTER ANALYSIS**

The alcoholic men had a higher mean heart rate (97·4 beats/minute, 95% CI 91·2 to 103·6) than the controls (69·6 beats/minute, 95% CI 65·4 to 73·8; P < 0·001 for each 6 hour interval, fig 1). There was a similar diurnal variation in heart rate in the alcoholic and the control groups (fig 2). The mean heart rate in the study group correlated significantly with the excretion of catecholamines (fig 3).

Premature supraventricular depolarisations (PSVD) and premature ventricular depolarisations (PVD) were uncommon during the recordings in alcoholic men and controls (table 3). PSVD were significantly less prevalent in alcoholic men (P < 0·05), but the prevalence of PVD was similar in both groups. There were no episodes of atrial fibrillation or malignant ventricular arrhythmias in either group.

**ECG EVALUATIONS**

According to the Minnesota code, the ECG of one patient was classified as indicating a possible previous myocardial infarction. Another ECG, classified as indicating probable previous myocardial infarction, showed intraventricular conduction disturbances, which were thought to explain the presence of numerous Q waves on this ECG.

The mean value for QT, was 0·41 s (95% CI 0·40 to 0·42) in the alcoholic men and 0·40 s (95% CI 0·39 to 0·41) in the controls (P > 0·2). There were no significant correlations between QT, and serum magnesium concentrations (r = 0·14) or magnesium retention (r = 0·07) in the alcoholic men.

**BIOCHEMICAL STUDIES**

In 18 of the 19 patients no ethanol could be detected in serum in the morning the day after admission. In one patient the ethanol concentration was 21 mmol/l.

The urine collection for the excretion of catecholamines was considered adequate in 18 of the patients. The median excretion of noradrenaline was 502 nmol/24 hours (range 209–3100 nmol/24 hours). In seven (38%) of the 18 evaluable patients excretion was higher than the reference limit of 560 nmol/24 h. The median value for excretion of adrenaline was 55 nmol/24 h (range 28–180

**Table 3** Prevalence of premature supraventricular depolarisations (PSVD) and premature ventricular depolarisations (PVD) during 24 hours of ambulatory electrocardiography in 19 alcoholic men in 19 age matched controls

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<th>Controls (n)</th>
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<tr>
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seems reasonable to believe that lethal arrhythmias account for a part of the excess mortality.

In the present study, we intended to determine the specific effects of alcohol abuse and withdrawal on the cardiac rhythm. Therefore, we selected patients without clinical heart disease and without conditions known to be associated with heart disease. We recognised that absence of symptoms and signs of heart disease did not exclude the presence of coronary artery disease or preclinical alcoholic cardiomyopathy. Nevertheless, we excluded those patients with heart disease who were most likely to develop arrhythmias during alcohol withdrawal.

The electrophysiological effects of long-term and short-term ethanol administration have been studied in animals and humans. In a one-year study, Patterson et al infused ethanol selectively into the left circumflex coronary artery of dogs. Provocative ventricular pacing was performed during anaesthesia with intravenous sodium pentobarbital 48 hours after ethanol administration was stopped. This procedure produced ventricular tachycardia in 15 of 22 alcohol-treated dogs either during baseline conditions or after administration of lignocaine or adrenaline, whereas pacing in six control animals that had received a long-term intracoronary saline infusion did not provoke ventricular tachycardia. In the same study, in vitro experiments disclosed that the resting membrane potential, the action potential amplitude, and the maximum rate of phase 0 depolarisation were lower in Purkinje cells from the alcohol-treated zone than in cells from the untreated part of the myocardium. Patel and coworkers used a programmable stimulation technique to induce ventricular fibrillation and measure ventricular fibrillation threshold (VFT) in dogs fed with ethanol for a year. They showed that the VFT was reduced in the alcohol treated dogs and that the VFT was further reduced after short-term ethanol administration in the dogs fed ethanol but not in control animals.

A study of non-alcoholic patients with various heart diseases, showed that acute administration of small amounts of alcohol delayed conduction at the atrial level, improved conduction through the atrioventricular node, and shortened the effective refractory period of the ventricular myocardium. In another experimental study of alcoholic patients with heart disease, acute ethanol ingestion prolonged the His-ventricular interval, and atrial or ventricular tachyarrhythmias could be induced by extrastimuli in 10 of the 14 alcoholic patients.

Thus it seems that long-term ingestion of ethanol causes electrophysiological alterations in the heart in which the myocardium is more sensitive to arrhythmogenic influences, and that previous alcohol abuse and the presence of heart diseases may affect the electrophysiological response to acute ingestion of ethanol.

In all but one of our patients, the blood ethanol concentration was zero when the
Holter recording started, suggesting that we started the investigation too late in the withdrawal phase to detect any effect of alcohol intoxication on the heart rhythm. When Holter recordings were obtained during the phase of ethanol elimination in alcoholic men in a study at an acute detoxification centre arrhythmias such as atrial fibrillation and ventricular tachycardia were detected in some subjects. Arrhythmia was more common in those with known heart disease, and similar arrhythmias were detected in the same individuals after two weeks of sobriety. Thus it seems that pre-existing heart disease influences the cardiac effects of ethanol ingestion to affect heart rhythm.

During alcohol withdrawal the activity of the central and peripheral adrenergic nervous system is increased as is the affinity of the β adrenergic receptors for catecholamines. Many of the symptoms of alcohol withdrawal originate from this hyperadrenergic state, and treatment with propranolol suppresses alcohol withdrawal symptoms and reduces urinary excretion of noradrenaline. The increased adrenergic activity in many of our alcoholic patients accounted for their mean heart rate being about 30 beats/minute higher than in the control group. However, despite this noradrenaline stimulation the diurnal variability of heart rate was preserved and resembled that of the controls, with a decrease at night. During myocardial ischaemia, and especially in patients with acute myocardial infarction, high blood concentrations of catecholamines increase the risk of malignant arrhythmias and cardiac arrest. In our patients, who did not have ischaemic heart disease, the increased adrenergic stimulation might have prevented arrhythmias by raising the heart rate and thus making it more difficult for ectopic foci to occur. Arrhythmia is the discriminator of magnesium deficiency. It affects membrane stability and impulse generation in the heart and the nervous system. Magnesium deficiency is difficult to diagnose because normal serum concentrations of magnesium do not exclude magnesium depletion. Because the intravenous magnesium loading test was expected to detect depletion of body magnesium stores it was used in several clinical investigations. This method has the advantage of supplying depleted individuals with magnesium at the same time as they are tested. One problem is that it is difficult to ascertain whether the collection of urine is adequate. Furthermore, there is no general agreement about how magnesium deficiency should be defined. It has been claimed that a magnesium retention of more than 50% is consistent with severe deficiency and that magnesium deficiency is unlikely when the retention is less than 20%. In healthy subjects used in studies as controls, less than 10% of magnesium was retained. In our study we used a retention of 30% as the discriminator for magnesium depletion. Despite this rather high cut off, half of our patients were found to be magnesium depleted, thus verifying previous observations that magnesium deficiency is common in alcoholic people.

Magnesium deficiency is often associated with hypokalaemia and there are reports of a strong correlation between the concentrations of magnesium and potassium in different tissues. On admission three of our patients had low serum potassium concentrations. The mean serum potassium concentration for the group had increased significantly after 48 hours, suggesting that the initial potassium concentrations might have been suboptimal in most of the patients. Hypokalaemia with magnesium deficiency commonly disappears after treatment with magnesium. Serum concentrations of magnesium and potassium are also influenced by β adrenergic stimulation, with a shift of these ions into the intracellular compartment. The magnesium infusion, the correction of alkalosis, and a gradual decline in β adrenergic stimulation that was assumed to occur may all have been responsible for the increase in serum potassium and magnesium concentrations after admission to hospital.

The observed electrolyte disturbances were not accompanied by arrhythmias in alcoholic patients with ischaemic heart disease and preclinical alcoholic cardiomyopathy, and they may explain some of the excess mortality in sudden death described in these disorders. The prolongation of the QT interval predisposes to malignant ventricular arrhythmias and could account for some unexplained deaths in alcoholics: there are several case reports of an association between magnesium deficiency and QT prolongation. Alcoholics presenting to our hospital had a longer QT interval than controls. Furthermore, those alcoholic patients who subsequently had sudden cardiac death had the longest QT intervals. The alcoholic patients in this study had significantly lower serum magnesium concentrations than the controls, but there was no correlation between serum magnesium concentration and QT interval. Despite the high frequency of magnesium deficiency in our study, none of our patients had QT prolongation, and QT was almost the same as in the healthy controls. This does not accord with the reported association between magnesium deficiency and QT prolongation.

The medical treatment of withdrawal symptoms with chlormethiazole probably interfered with the aim of the study. This drug probably suppresses the withdrawal reaction by diminishing adrenergic activation, and it also prevents complications such as delirium tremens. In the central nervous system chlormethiazole enhances inhibitory GABAergic transmission, probably by acting on calcium-dependent chloride channels. This effect results in hyperpolarisation and increases the threshold for action potential generation in GABA- innervated neurons,
which may account for the anticonvulsant action of chlormethiazole.46 The electrophysiologic effects of chlormethiazole in myocardial cells or the conduction system of the heart are uncertain. Chlormethiazole may directly and indirectly decrease the risk of arrhythmias. Therefore, it seems appropriate to treat alcoholic patients with chlormethiazole during withdrawal. Additional treatment with β-adrenoceptor antagonist might diminish withdrawal symptoms,29 and magnesium supplementation can relieve symptoms of magnesium deficiency such as muscle weakness.45 In alcoholic patients with heart disease these treatments might provide additional protection against arrhythmias during withdrawal.

In conclusion, our investigation indicates that increased adrenergic activity, magnesium depletion, and to some extent hypokalaemia are common findings after heavy drinking in alcoholic men. However, despite these disturbances, which are often regarded as arrhythmogenic, no malignant arrhythmias were seen in patients without clinical heart disease during detoxification in hospital with chlormethiazole.

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