Effects of Acute Alcohol Infusion on Duration and Dispersion of QT Interval in Male Patients with Coronary Artery Disease and in Healthy Controls

JUHANI ROSSINEN, M.D., JUHA SINISALO, M.D., JUHANI PARTANEN, M.D.,* MARKKU S. NIEMINEN, M.D., MATTI VITASALO, M.D.

Department of Medicine, Division of Cardiology, Helsinki University Central Hospital, Helsinki; *Department of Medicine, Jorvi Hospital, Espoo, Finland

Summary

Background and hypothesis: Alcohol consumption may have advantageous epidemiologic effects but ethanol also increases the risk of sudden coronary death. Prolongation of QT interval has been reported in chronic alcoholics. Long QT period predisposes to serious arrhythmias, and therefore we studied whether acute alcohol intoxication prolongs repolarization in patients with stable coronary artery disease (CAD).

Methods: The effects of acute ethanol steady-state intravenous infusion (0.72 g/kg body weight within 60 min) on QT interval and QT dispersion, assessed by 12-lead electrocardiograms (ECG), were studied in 22 men with stable CAD and in 10 controls. Heart rate variability was measured by Holter recordings.

Results: Mean blood alcohol rose to 26.1 ± 4.3 mmol/l (1.2 ± 0.2 ‰), and was maintained for 2 h. Heart rate was 56 ± 7 beats/min before and 54 ± 8 beats/min during ethanol infusion (NS). The heart rate-adjusted QT interval increased on the average 13–23 ms over the 12-lead ECG ($p < 0.005$). The QT dispersion remained unaltered. There was no difference in the repolarization response in the patients with CAD compared with the controls. The high- and low-frequency components of heart rate variability remained unaltered.

Conclusions: In middle aged men, regardless of the presence of CAD, moderate amounts of alcohol cause prolongation of ventricular repolarization. Changes in the activity of the autonomic nervous system do not seem to explain the observed phenomenon.

Key words: ethanol, QT interval, QT dispersion, coronary artery disease

Introduction

Prolongation of the QT interval has been associated with serious ventricular arrhythmias and is an independent risk factor for sudden cardiac death.^{1–3} Furthermore, increased QT dispersion and QT peak dispersion have been associated with subsequent mortality in the coronary risk population⁴ and after myocardial infarction.⁵ QT prolongation has also been reported in chronic alcoholics with liver disease.⁶ Although moderate alcohol consumption has reduced mortality in epidemiologic studies,⁷ the incidence of sudden cardiac death is great among heavy alcohol consumers.^{8,9} We tested the hypothesis that ethanol has acute disadvantageous effects on indices of ventricular repolarization in patients with coronary artery disease (CAD) and on healthy controls.

Methods

Patients and Controls

We enrolled 22 consecutive male patients with exercise-inducible angina pectoris who were to be examined angiographically after the study during the following 5 months. At least 50% luminal diameter narrowing in the proximal two-thirds region of the vessel in at least one of the main coronary arteries was required to qualify for the study. We excluded patients with body mass index > 30 kg/m², present infection, New York Heart Association class IV symptoms, acute myocardial infarction within the preceding 3 months, the presence of other than sinus rhythm, or a history of alcohol abuse. We also excluded patients who used digitalis, or Vaughan Williams class I or III antiarrhythmic medications, as well as those who had bundle-branch block or disorders of glucose metabolism, and > 70 years old patients. The inclusion criteria were selected partly by considering the tests of vascular endothelial function that were included in the study and that will be reported elsewhere.

Address for reprints:

Dr. J. Rossinen
Department of Medicine
Division of Cardiology
Helsinki University Central Hospital
PL 340, 00029 HYKS, Helsinki
Finland

Received: November 2, 1998

Accepted: January 22, 1999

We enrolled 10 control patients, who were screened and selected partly (5 patients) from routine surgical outpatient visits and partly from a population of volunteers responding to newspaper advertisement. The exclusion criteria for controls included the same criteria as those for patients with CAD, as well as the following: any persisting illnesses, use of any continuous medications, or existence of any exercise-induced symptom suggesting the possibility of CAD. Excluded were also those who smoked, or had hypercholesterolemia, elevated blood pressure, or a family history of atherosclerosis or CAD. The study was carried out in accordance with the Helsinki Declaration for Human Research and was approved by the Ethical Committee of the Department of Medicine of Helsinki University Central Hospital.

Methods

After the patients gave their informed consent, all medications were discontinued 12 h before the study, except for aspirin which was discontinued 3 days before the study. The patients were instructed to not eat breakfast or drink coffee or alcohol-containing beverages within 12 h before admittance to hospital for the study at 8:15 A.M. After a standard 12-lead ECG, recorded at 50 mm/s, blood samples were obtained, and the patients were served breakfast (Fig. 1: Study flow). Thereafter, the patients were lying in the supine position during the rest of the study. Ambulatory ECG monitoring (Holter) was started and finished at the end of the study. Baseline tests for function of vascular endothelium were measured, and a cannula was positioned in the superficial forearm vein to infuse ethyl alcohol diluted 10% in 0.45% sodium chloride solution. The loading ethanol infusion of 0.72 g/kg body weight within 60 min was started at 11:10 A.M. until 12:40 P.M. The same infusion was continued at 150–250 ml/h for 2 h to yield steady-state ethanol concentration in blood during the test for vascular endothelium function. The total volume of intravenous alcohol solution during the study was 1140 ± 100 ml. Blood samples were taken for alcohol concentration measurement after loading infusion and before the second 12-lead

ECG. Smoking was not allowed during 12 h before or during the study day.

The ambulatory ECGs were recorded on tape with Marquette recorders (Marquette Electronics, Milwaukee, Wisc.). V₁- and V₅-like leads were used.¹⁰ The ECGs were analyzed using Marquette Series 8000 Holter analysis system. After classification of the QRS morphology, the longest and shortest RR intervals on the RR interval histogram were manually confirmed until no QRS complex was mislabeled. When calculating the heart rate variability (HRV) values, only normal to normal intervals were used. Each interval that was to be excluded due to extrasystoles or artifacts was replaced by holding the previous coupling interval level throughout the time interval to the next valid coupling interval. Heart rate variability was analyzed during 60-min periods. Heart rate was processed by a fast-Fourier transform algorithm. The square roots of high-frequency (0.15–0.40 Hz) and low-frequency (0.04–0.15 Hz) areas under the spectral curves were calculated using a Holter analysis computer.

Twelve-lead ECGs were analyzed manually in random order blinded to study phase or patient identification. Three consecutive beats in each lead were measured using accuracy of 10 ms, and the mean of these was used as the QT interval. The QT interval was measured from the onset of the QRS complex to the end of the T wave only in those leads where this was clearly identifiable. The end of the T wave was defined as the intersection of the downsloping derivative of the T wave and the line that was drawn along the baseline. The QT dispersion is the difference of maximum and minimum QT interval across the 12-lead ECG.

Using a sphygmomanometer, blood pressure was measured in supine position after the baseline ECG and at the end of ethanol infusion.

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation (SD). Since almost every patient had one or two leads in which the QT interval was unmeasurable, the analysis of variance was not usable, and the comparisons of the QT interval data were made by Student's paired *t*-test. The comparisons of QT intervals between patients and controls were made by two-sample *t*-test. The tests for the parameters of HRV were made by the analysis of variance for repeated measures. A *p* value < 0.05 by the 2-tailed test was considered statistically significant. A Systat (SPSS Inc., Chicago, Ill.) statistical software was used.

Results

The clinical characteristics of the patients and the controls, and the patients' heart disease variables are given in Table I. All patients were taking aspirin, 20 patients beta blockers, 16 long-acting nitrates, 9 cholesterol lowering statins, and 2 calcium-channel blockers. Five patients had arterial hypertension, none had diabetes. Three of the controls and eight of the pa-

FIG. 1 Study flow. ECG = electrocardiogram.

TABLE I Clinical characteristics of the patients and the controls, and the characteristics of the patients' heart disease

Characteristics	Patients	Controls	Patients vs. controls
Age (years)	59 ± 8	52 ± 6	p<0.05
Weight (kg)	83 ± 7	82 ± 7	NS
Height (cm)	176 ± 9	177 ± 4	NS
Characteristics of patients' heart disease			
Number of previous myocardial infarctions			Mean 0.4, range 0–2
NYHA class			
I			5 patients
II			14 patients
III			3 patients
Number of patients with single-, double-, triple-vessel disease			7/7/3
Number of patients with left main coronary artery disease			5
Left ventricular ejection fraction (%)			59 ± 9
Left ventricular end-diastolic pressure (mmHg)			11 ± 5

Abbreviations: NYHA=New York Heart Association, NS = not significant.

tients were ex-smokers. Six of the patients and none of the controls were smoking currently.

The blood ethanol concentration was 26.1 ± 4.3 mmol/l (1.2 ± 0.2 ‰) after loading infusion. The concentration remained stable due to steady-state infusion and was exactly the same at the end of the study. All patients showed signs of alcohol intoxication. The heart rate in the baseline ECG was 56 ± 7 beats/min and during ethanol 54 ± 8 beats/min (NS). Systolic blood pressure was 138 ± 16 mmHg at baseline and 132 ± 16 (p<0.05) during ethanol infusion, the corresponding values for diastolic blood pressure were 79 ± 10 mmHg and 79 ± 9 mmHg, respectively (NS). The QT intervals in all ECG leads prolonged during ethanol infusion compared with baseline in the study population. Table II shows the measured QT values during ethanol infusion compared with the baseline QT values. Using the nomogram method described by Karjalainen *et al.*,¹¹ QT baseline values are adjusted to the heart rate that was measured during ethanol intoxication. There was no difference in the behavior of QT interval between the patients and controls. The QT dispersion at baseline was 35 ± 17 ms and during ethanol 37 ± 18 ms (NS). The frequency domain measures of HRV are represented in Table III (no changes).

Discussion

The present study showed that acute alcohol intoxication prolonged the QT interval without causing an increase in QT dispersion. This finding was the same both in men with stable CAD and in healthy controls.

We observed no increase in heart rate during the ethanol infusion. Previously it has been shown that the physiologic response to alcohol appears to depend on the volume of coadministered fluid. Alcohol administration induces vasodilatation and reduction in baroreceptor sensitivity leading to increase in heart rate. If, however, the circulating volume is increased by extra fluid, the effects of alcohol-induced vasodilatation and de-

TABLE II QT intervals (ms) in the whole study population at baseline and during ethanol infusion. The QT intervals at baseline are adjusted to heart rate

	QT interval				p Value (baseline vs. ethanol) ^a
	Controls		Patients		
Lead	Baseline	Ethanol	Baseline	Ethanol	
I	368 ± 16	391 ± 21	403 ± 23	410 ± 32	<0.001
II	375 ± 22	397 ± 27	405 ± 29	419 ± 37	<0.0005
III	364 ± 30	383 ± 22	392 ± 35	410 ± 45	<0.005
aVR	377 ± 21	400 ± 27	401 ± 24	419 ± 39	<0.0005
aVL	362 ± 22	386 ± 19	401 ± 29	412 ± 37	<0.05
aVF	387 ± 13	391 ± 20	403 ± 38	412 ± 45	<0.01
V ₁	376 ± 22	404 ± 26	385 ± 24	388 ± 33	<0.005
V ₂	369 ± 20	392 ± 20	391 ± 24	408 ± 36	<0.0001
V ₃	371 ± 23	401 ± 25	397 ± 24	413 ± 38	<0.0005
V ₄	375 ± 21	398 ± 28	402 ± 26	420 ± 41	<0.0005
V ₅	376 ± 22	398 ± 34	408 ± 30	421 ± 32	<0.0005
V ₆	377 ± 25	401 ± 30	411 ± 28	426 ± 33	<0.0005

^a = P values of comparisons between baseline and ethanol in the whole study population.

TABLE III The frequency domain measures of heart rate variability

	Baseline	Ethanol			p Value
		Hour 1	Hour 2	Hour 3	
HF (ms)	13 ± 7	13 ± 5	12 ± 5	12 ± 6	NS
LF (ms)	24 ± 11	24 ± 12	25 ± 8	23 ± 9	NS

^a P value of analysis of variance for repeated measures.

Abbreviations: HF = high frequency variability, LF = low frequency variability, NS = not significant.

creases in baroreceptor sensitivity are abolished and heart rate does not increase.¹² Although the heart rates before and during ethanol infusion were similar, we adjusted the measured QT interval values for heart rate to obtain the magnitudes of the QT prolongation more precisely.

The measures of HRV can be used as indicators of autonomic nervous activity.¹³ In the present study, while our patients were lying in the supine position, both the high- and low-frequency components of HRV remained unchanged during the administration of ethanol. The stable levels of both heart rate and the measures of HRV indicate that the prolonging effect of alcohol on the QT interval might not be mediated via changes in the autonomic nervous activity.

The repolarization in ventricular cells results mainly from time-dependent reduction in L-type Ca current and an increase in outward K current.¹⁴ Ethanol has been reported to inhibit NaK-ATPase directly,¹⁵ and also calcium transport by the cardiac sarcoplasmic reticulum.¹⁶ Because evidence of the direct effects of ethanol on the repolarizing ionic currents in ventricular myocardium is lacking, we can only speculate that ethanol may prolong the QT interval by interfering with the ionic movements in the sarcolemma. However, the clinical importance is that the QT prolongation may be further exacerbated by serum electrolyte imbalance induced by ethanol.¹⁷

The QT dispersion is proposed as a practical method for the evaluation of the nonhomogeneity of ventricular recovery time¹⁸ which, in experimental studies, has been a powerful determinant of the susceptibility to ventricular fibrillation.¹⁹ In coronary artery disease, increased QT dispersion has been shown to be related to the occurrence of life-threatening re-entrant ventricular arrhythmias in patients post myocardial infarction.²⁰ Alcohol intake is likely to influence the heart as a whole since it penetrates well to nonadipose tissue.²¹ Theoretically, in the beginning of alcohol intake, the ischemic myocardium might have lower tissue ethanol concentration due to slowed circulation, exacerbated by ethanol itself, than normally perfused myocardium. Therefore, because ethanol prolongs the repolarization, rising ethanol concentration may increase QT dispersion in ischemic myocardium. Our patients, however, had no signs of myocardial ischemia subjectively or in ECGs.

Our study has some limitations. Bed rest during ethanol infusion does not represent the usual drinking situations. The supine position was, however, necessary because of the tests of vascular endothelium. Intravenous administration was chosen to achieve maximum accuracy of the ethanol concentration in blood. The amount of consumed ethanol approximates the concentration in a bottle of wine. Thus, the effects of lower and higher doses remain unknown.

Conclusion

Alcohol intake prolongs the QT interval and, with coexisting abnormal repolarization, may increase the risk of life-threatening arrhythmias.

References

1. Ahnve S, Helmers C, Lundman T: QTc intervals at discharge after acute myocardial infarction and long-term prognosis. *Acta Med Scand* 1980;208:55–60
2. Algra A, Tijssen JGP, Roeland JRTC, Pool J, Lubsen J: QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation* 1991;83:188–194
3. Karjalainen J, Reunanen A, Ristola P, Viitasalo M: QT interval as a cardiac risk factor in a middle aged population. *Heart* 1997;77: 543–548
4. Mänttari M, Oikarinen L, Manninen V, Viitasalo M: QT dispersion as a risk factor for sudden cardiac death and fatal myocardial infarction in a coronary risk population. *Heart* 1997;78:268–272
5. Glancy JM, Garratt CJ, Woods KL, de Bono DP: QT dispersion and mortality after myocardial infarction. *Lancet* 1995;345(8955): 945–948
6. Day CP, James OFW, Butler TJ, Campbell RWF: QT prolongation and sudden cardiac death in patients with alcoholic liver disease. *Lancet* 1993;341:1423–1428
7. Doll R, Peto R, Hall E, Wheatley K, Gray R: Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *Br Med J* 1994;309:911–918
8. Wannamethee G, Shaper AG: Alcohol and sudden cardiac death. *Br Heart J* 1992;68:443–448
9. Kauhanen J, Kaplan GA, Goldberg DE, Salonen JT: Beer binging and mortality: Results from the Kuopio ischaemic heart disease risk factor study, a prospective population based study. *Br Med J* 1997; 315:846–851
10. Kennedy HL: Ambulatory electrocardiography strategies used in assessing silent myocardial ischaemia. *Eur Heart J* 1988;9(suppl N):70–77
11. Karjalainen J, Viitasalo M, Mänttari M, Manninen V: Relation between QT intervals and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. *J Am Coll Cardiol* 1994;23:1547–1553
12. Sehested J, Heringlake M, Schmidt V: Neurohumoral cardiovascular responses to alcohol and their modulation by peroral fluid. *Am J Cardiol* 1998;81:761–765
13. Huikuri HV: Heart rate variability in coronary artery disease. *J Intern Med* 1995;237:349–357
14. Zipes DP: Genesis of cardiac arrhythmias: Electrophysiological considerations. In *Heart Disease* (Ed. Braunwald E), p. 562–563 Philadelphia: W.B. Saunders Company, 1997
15. Williams JW, Tada M, Katz AM, Rubin E: Effect of ethanol and acetaldehyde on the (Na++K+)-activated adenosine triphosphatase activity of cardiac plasma membranes. *Biochem Pharmacol* 1975; 24:27–32
16. Swartz MH, Repke DI, Katz AM, Rubin E: Effects of ethanol on calcium binding and calcium uptake by cardiac microsomes. *Biochem Pharmacol* 1974;23:2369–2376
17. DeMarchi S, Cecchin E, Basile A, Bertotti A, Nardini R, Bartoli E: Renal tubular dysfunction in chronic alcohol abuse—effects of abstinence. *N Engl J Med* 1993;329(26):1927–1934
18. Day CP, McComb JM, Campbell JM: QT dispersion: An indication of arrhythmia risk in patients with long QT intervals. *Br Heart J* 1990;63:342–344
19. Han J, Moe GK: Non-uniform recovery of excitability in ventricular muscle. *Circ Res* 1964;14:44–60
20. Perkiömäki JS, Koistinen MJ, Yli-Mäyry S, Huikuri HV: Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. *J Am Coll Cardiol* 1995;26:174–179
21. Pohorecky LA, Brick J: Pharmacology of ethanol. *Pharmac Ther* 1988;36(2-3):335–427