Cardiac Effects of Acute Ethanol Ingestion Unmasked by Autonomic Blockade

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SUMMARY We assessed the effects of ethanol and autonomic blockade on left ventricular function in nine normal subjects, age 20–35 years, using M-mode echocardiography and systolic time intervals. On day 1, measurements were made of heart rate, mean velocity of circumferential fiber shortening, and left ventricular pre-ejection period and left ventricular ejection time ratio (PEP/LVET), during a control period and after autonomic blockade. Autonomic blockade was produced with intravenous propranolol (0.2 mg/kg body weight) and atropine (0.04 mg/kg body weight). On day two, measurements were again made during a control period, then with ethanol alone, followed by addition of autonomic blockade to ethanol. One hundred eighty milliliters of ethanol were ingested over 60 minutes, resulting in a mean blood ethanol level of 110 mg/dl (range 77–135 mg/dl) at 60 minutes post-ingestion.

There were no significant differences between the control data on days 1 and 2. Blood pressure was unchanged throughout the study. On day 1, autonomic blockade alone resulted in the expected increase in heart rate (p < 0.001), with a proportional increase in mean velocity of circumferential fiber shortening (p < 0.01), and an increase in PEP/LVET (p < 0.01). On day 2, ethanol alone resulted in no significant changes except for a slight increase in PEP/LVET (p < 0.02). Ethanol plus autonomic blockade, (day 2), compared with autonomic blockade alone (day 1), revealed a decrease in mean velocity of circumferential fiber shortening (p < 0.05), and an increase in PEP/LVET (p < 0.01), with a decrease in intrinsic heart rate (p < 0.001).

We conclude that in normal subjects: 1) autonomic blockade does not directly affect contractility; 2) acute ethanol ingestion alone does not produce important changes in cardiac function; and, 3) ethanol in the autonomic blocked heart causes a significant decrease in contractility. Thus, we infer that ethanol has a negative inotropic effect which is masked by catecholamines and/or autonomic nervous system discharge.

CHRONIC INGESTION OF ETHANOL is known to cause cardiac dysfunction, most notably as congestive cardiomyopathy.1-5 Cardiac function, as measured by systolic time intervals, may be depressed even in the clinically “normal” alcoholic.6 In addition, patients with coronary heart disease have shown depressed hemodynamics,7-8 as well as decreased exercise tolerance with increased ischemic ST-segment abnormalities and angina,9 after acute oral ingestion of moderate amounts of ethanol. Intravenous administration of ethanol to dogs caused decreased coronary flow and increased coronary resistance at all dosage levels.10

However, the acute administration of ethanol to dogs and to normal humans has resulted in conflicting reports of the effects on left ventricular (LV) function.9, 11-22 Hemodynamic studies of dogs receiving intravenous ethanol infusions during autonomic blockade have shown myocardial depression.12, 22

Acute ethanol administration results in increased hypothalamic activity23 and increased circulating catecholamines.24-26 Because catecholamines can increase cardiac contractility,27 they might “mask” intrinsic myocardial depression by ethanol.12, 22

Autonomic blockade may therefore unmask myocardial dysfunction during ethanol ingestion.

We therefore extended the study of the effects of acute ethanol ingestion on LV function in normal subjects to include autonomic blockade.28, 29 Because of variations in vagal tone, we chose full autonomic blockade instead of β blockade alone. We used echocardiography as a tool for the evaluation of LV performance because it is a safe, reliable, and noninvasive technique,28, 29 which has been shown to be reproducible from day to day37 and to reflect accurately acute alterations in LV function.34, 36

Systolic time intervals were also measured, using the ratio of the pre-ejection period to LV ejection time (PEP/LVET) as the most useful indicator (by this technique) of the function of the left ventricle.39, 40

This ratio is not significantly affected by changes in heart rate in the absence of changes in myocardial function.

Methods

Subjects

After detailed description of the study protocol, nine normal humans signed an informed consent form approved by the University of California at Los Angeles Committee on Investigation Involving Human Subjects. There were five men and four women, with an age range of 20–35 years (mean 27.1 years). All had normal medical histories, physical examinations and baseline echocardiograms. They were infrequent users of alcohol, and were on no medications. Each was studied after a 12-hour fast, in

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the supine position, using M-mode echocardiography and systolic time intervals.

Procedure

On day 1, control determinations of blood pressure (BP), heart rate (HR), mean velocity of circumferential fiber shortening (Vcf), and the PEP/LVET were made after the subject had been resting supine for at least 10 minutes.

Autonomic blockade was then produced by the method of Jose, using a mixture of propranolol (0.2 mg/kg) and atropine (0.4 mg/kg) in a total volume of 20 ml, given intravenously over 2–3 minutes. Five minutes after the end of this injection, the BP, HR, Vcf, and PEP/LVET were again recorded, to be used as baseline information of the effect of autonomic blockade alone on these parameters. According to Jose and Taylor, complete blockade lasts 10–20 minutes, with essentially complete recovery by 100 minutes after injection. All subjects were closely observed for 2 hours after the procedure. No complications developed.

On day 2, 24 hours after autonomic blockade alone, control measurements of BP, HR, Vcf, and PEP/LVET were performed as before. Upon completion of these measurements, chilled ethanol (commercially available 80-proof Scotch whiskey; total 180 ml, 61.8 g of ethanol over 60 minutes) was orally ingested in three doses at a rate of one dose every 20 minutes. Sixty minutes after the ingestion of the first dose (20 minutes after the third dose), the mean blood ethanol level was 110 mg/dl (range 77–135 mg/dl), as measured by headspace gas chromatography. Each subject appeared mildly intoxicated. The BP, HR, Vcf and PEP/LVET were again recorded to determine the effect of ethanol alone (at a single blood level) on these parameters. Immediately upon completion of these measurements, autonomic blockade was again produced as on day 1, and the measurements repeated 5 minutes after the intravenous injection was completed.

Echocardiographic Measurements

Echocardiograms were obtained with a Smith-Kline Ekoline 20A Ultrasonoscope using a 10 cm focus 2.25 MHz transducer with a repetition rate of 1000/sec. Tracings were made on a Honeywell 1856 recorder on Kodak light sensitive paper at a speed of 50 mm/sec. Using standard techniques previously described, the transducer was placed in the third, fourth or fifth left parasternal intercostal space, and the "standard interspace" was identified where the transducer was perpendicular to the chest wall without inferior or superior angulation while being directed slightly medially to identify both mitral valve leaflets. The echoes of the interventricular septum and LV posterior wall were recorded at the level of the chordae tendineae, just below the tip of the anterior mitral leaflet. From the tracings, the following measurements were made: LV end-diastolic dimension (EDD) was taken as the distance between the left septal surface and the endocardium of the posterior wall below the mitral valve, at the R wave of the ECG (normal less than 5.4 cm); LV end-systolic dimension (ESD) was taken as the shortest simultaneous systolic distance between the left interventricular septal and posterior LV wall endocardium (fig. 1). Two independent observers had excellent agreement of each

FIGURE 1. Representative baseline M-mode echocardiogram (unretouched) of the left ventricle at the level of the tip of the anterior mitral valve leaflet and chordae tendineae. Using the end-diastolic (EDD) and end-systolic (ESD) dimensions of the left ventricle (as described in Methods) and using the left ventricular ejection time (LVET) from a phonocardiogram, the mean velocity of circumferential fiber shortening (Vcf) may be calculated: VCF = (EDD – ESD) / (EDD \times LVET). Key: QRS = QRS of the electrocardiogram; plvw = posterior left ventricular wall. A 10 mm distance calibration is shown.
measurement. All dimensions were measured to the nearest millimeter, and paper speed was carefully calibrated at 50 mm/sec.

Mean Vcf was derived from.32, 33, 35 Vcf = (EDD-ESD)/(EDD × LVET). Our normal values for the measurements have been reported previously.44, 45

Systolic Time Intervals

Systolic time intervals39, 40 were measured from simultaneous recordings of the indirect carotid pulse, ECG, and phonocardiogram from the third left intercostal space, using the Honeywell 3820 echocardiography-phonocardiography system and the Honeywell 1856 fiberoptic recorder with a calibrated paper speed of 100 mm/sec with 40 msec time lines. We made the following measurements: HR; electromechanical systole (QS2), measured from the onset of the Q wave of the ECG to the first high frequency positive deflection of the aortic component of the second sound; LVET, from the onset of the rapid upstroke of the carotid pulse to the incisura of the dicrotic notch; PEP = QS2 – LVET. They were combined to form the ratio PEP/LVET. A mean value for 10 beats was taken for each measurement, with the patient supine, during quiet respiration.

Statistics

We used a two-tailed t test for paired variables. We chose a level of significance of \( p \leq 0.05 \). Mean values were reported \( \pm s.d. \).

Results

Control Measurements

Baseline measurements on day 1 and day 2, before any pharmacologic manipulation (table 1) of HR, mean Vcf, and PEP/LVET were virtually the same. It is unclear why the mean PEP/LVET was at the upper limits of the reported normal range.39, 40, 47 However, each subject served as his or her own control for comparison with subsequent measurements. BPs were unchanged throughout the study.

### Table 1. Effects on Cardiac Function of Ethanol, Autonomic Blockade, and Autonomic Blockade Plus Ethanol in Nine Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>VCF</th>
<th>PEP/LVET</th>
</tr>
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<tbody>
<tr>
<td>C1</td>
<td>68.6 ± 6.4</td>
<td>1.06 ± 0.07</td>
<td>0.39 ± 0.05</td>
</tr>
<tr>
<td>C2</td>
<td>66.8 ± 13.6</td>
<td>1.07 ± 0.14</td>
<td>0.40 ± 0.03</td>
</tr>
<tr>
<td>B</td>
<td>105.8 ± 20.1</td>
<td>1.27 ± 0.15</td>
<td>0.43 ± 0.05</td>
</tr>
<tr>
<td>E</td>
<td>71.5 ± 13.9</td>
<td>1.04 ± 0.17</td>
<td>0.42 ± 0.07</td>
</tr>
<tr>
<td>BE</td>
<td>95.8 ± 10.7</td>
<td>1.14 ± 0.13</td>
<td>0.45 ± 0.05</td>
</tr>
</tbody>
</table>

All values are mean ± s.d.

Abbreviations: B = autonomic blockade; BE = autonomic blockade and ethanol; C1 = control day 1; C2 = control day 2; E = ethanol; HR = heart rate (beats/min); PEP/LVET = ratio of pre-ejection period to left ventricular ejection time; VCF = mean velocity of left ventricular circumferential fiber shortening (cire/sec).

### Autonomic Blockade (tables 1 and 2)

On day 1, after control measurements of BP, HR, Vcf, and PEP/LVET were recorded, autonomic blockade was performed and measurements of BP, HR, Vcf and PEP/LVET were repeated to give information on 1) the effects of autonomic blockade on these noninvasive parameters, and 2) a baseline for comparison with combined blockade and ethanol. As reported by Jose,29 the effects of autonomic blockade are essentially gone by 2 hours. Thus, the control values for day 2 were essentially the same as on day 1.

Autonomic blockade resulted in no change in BP. HR with blockade ("intrinsic heart rate," IHR) was increased by 54% \( (p < 0.001) \) from control values to 105.8 ± 20.1 beats/min. This was not significantly different from the age-predicted IHR (102.6 beats/min) for the group.29 The Vcf increased by 20% \( (p < 0.01) \). In the absence of changes in afterload (BP), or in preload (ventricular filling), the change in Vcf is probably related to the increase in HR.48 PEP/LVET increased by 10% \( (p < 0.01) \), suggesting a decrease in LV performance compared with control values; however, this undoubtedly reflects the basal LV function after removal of autonomic tone, rather than LV dysfunction.

### Ethanol (tables 1 and 2)

Alcohol is rapidly absorbed from the stomach, small intestine, and colon. Many factors may modify the rate of gastric absorption, and gastric emptying (e.g., volume, character, and dilution of the alcoholic beverage, presence of food, period of time to ingest the drink, individual differences). In our fasted subjects, 60 minutes after ingestion of a total of 180 ml ethanol, the mean blood ethanol was 110 ± 17.8 mg/dl (range 77–135 mg/dl). Each subject became mildly intoxicated. For the average person, 180 ml of distilled

### Table 2. Comparison of the Cardiac Effects of Ethanol, Autonomic Blockade and Autonomic Blockade Plus Ethanol in Nine Normal Subjects

<table>
<thead>
<tr>
<th>%Δ(X2-X1)</th>
<th>HR</th>
<th>VCF</th>
<th>PEP/LVET</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Δ(E-C1)</td>
<td>+7</td>
<td>-3</td>
<td>+4†</td>
</tr>
<tr>
<td>%Δ(E-B1)</td>
<td>+54$</td>
<td>+20‡</td>
<td>+10‡</td>
</tr>
<tr>
<td>%Δ(BE-C2)</td>
<td>+43$</td>
<td>+7</td>
<td>+12‡</td>
</tr>
<tr>
<td>%Δ(BE-B)</td>
<td>-10$</td>
<td>-10*</td>
<td>+4‡</td>
</tr>
</tbody>
</table>

Values are expressed as the percentage change from \( X_1 \) where \( \frac{X_2 - X_1}{X_1} \times 100 = \% Δ X_1 \). Plus (+) and minus (−) signs denote the direction of change. Ethanol was not significantly different from control except for PEP/LVET. For VCF, B versus Control had a 20% increase, and BE versus Control had a 7% increase, a difference of 13%, suggesting that addition of ethanol to the autonomic blocked heart results in decreased myocardial performance (see text for discussion).

$\text{p} < 0.05.$  †$\text{p} < 0.02.$  ‡$\text{p} < 0.01.$  §$\text{p} < 0.001.$

Abbreviations: see table 1.
spirits on an empty stomach will produce a blood level of approximately 100 mg/dl. Blood levels in usual social drinking situations average 50–75 mg/dl, with overt signs of intoxication in social (nontolerant) drinkers at levels between 100–200 mg/dl.12–14 The cardiac measurements were lost in one subject for this phase of the study, so mean values on only eight subjects are reported. HR increased only 7%, and Vcf decreased by 3%. PEP/LVET showed a slight increase of 4% (p < 0.02). Thus, there was evidence of a possible slight decrease in LV performance at a mean blood ethanol level of 110 mg/dl.

Ethanol Plus Autonomic Blockade (tables 1 and 2)

Immediately after the ethanol (alone), cardiac measurements were made, autonomic blockade was performed, and the measurements were repeated. Compared to the control values on day 2, HR increased 43% (p < 0.001); however, this was a 10% decrease compared with autonomic blockade alone (p < 0.001) as determined on day 1. Also, Vcf rose 7% (NS), proportionately less than the increase in HR, and Vcf was decreased by 10% (p < 0.05), compared with autonomic blockade without ethanol. This suggested a decrease in LV performance in subjects acutely ingesting ethanol and then undergoing autonomic blockade. This was confirmed by the PEP/LVET, which rose 12% (p < 0.01) over control, and also rose 4% (p < 0.01) over that seen with autonomic blockade alone.

Discussion

The published accounts of the acute effects of ethanol on the myocardium are somewhat inconsistent. At least some of the discrepancy is probably due to differences in experimental design. The major variable not controlled during most of the studies has been the influence of autonomic tone and/or catecholamines. Ethanol causes release of epinephrine from the adrenal medulla, and also causes cortico-hypothalamic stimulation. Moreover, acetaldehyde, a metabolite of ethanol, may cause release of myocardial norepinephrine, and thereby stimulate the heart. Any study of the effect of ethanol on myocardial function will be modified by such factors.

To separate the postulated primary depressant effects of ethanol from the secondary stimulant effects (evoked by release of circulating catecholamines) on cardiac function, Wong evaluated hemodynamics before and during autonomic blockade in 20 anesthetized dogs receiving intravenous infusions of ethanol. Blood ethanol levels were over 100 mg/dl by 30 minutes and over 200 mg/dl by 2 hours. During the ethanol infusions, cardiac index declined and LV end-diastolic pressure rose; these changes were even more pronounced during autonomic blockade plus ethanol infusion. Autonomic blockade alone did not significantly affect cardiac function, except for an increase in HR. These findings could be interpreted as disclosing a "masking" effect by catecholamines, presumably released by the ethanol, whose cardiac stimulatory effects cancelled the myocardial depression of ethanol. Our results in human subjects are in agreement.

Horowitz and Atkins studied the effects of intravenous ethanol and autonomic blockade in six conscious chronically instrumented dogs (to avoid anesthetic-induced myocardial depression). There were small dose-related decreases in stroke volume and in LV dp/dt. Echocardiographic LV dimensions at end-diastole, and at end-systole, increased slightly. Ethanol infusion during autonomic blockade resulted in an absolute decrease in HR and a less significant drop in stroke volume.

In our study, we used the noninvasive techniques of echoardiography and phonocardiography. The reliability of deriving information from the LV minor dimensions (e.g. Vcf, ventricular volumes) in diseased ventricles with abnormal shapes has been questioned. However, in normal subjects, particularly when serial studies on the same person are compared, most investigators are satisfied with the reproducibility of LV minor axis dimensions and with the correlation of Vcf with LV performance. The PEP/LVET value correlates well with LV performance, and is relatively unrelated to changes in HR up to 110 beats/min. We used this ratio as the most useful indicator of the systolic intervals of changes in LV function. Increases in PEP/LVET to 0.44 or greater usually denote decreased LV performance. It is not clear why our clinically and echoangiographically normal subjects had a control baseline PEP/LVET of 0.39 ± 0.05 that was just above 1 SD for reported normals of 0.35 ± 0.04. An increase in PEP/LVET may occur in normal individuals with assumption of the upright posture. This is not germane to our study. However, there is a normal diurnal decrease in LVET without a change in PEP in the afternoon hours. This may be a partial explanation for the PEP/LVET values in our patients.

Ethanol alone (tables 1 and 2) resulted in no significant change in HR or Vcf, and in a slight (+4%) but significant increase in PEP/LVET (p < 0.02). This might suggest a mild decrease in LV function, but it is not convincing. Autonomic blockade (tables 1 and 2) resulted in an increase of 54% (p < 0.001) in HR to levels equivalent to the predicted IHR of Jose. There was a 20% increase in Vcf (p < 0.01), proportionate to the increase in HR. The 10% increase in PEP/LVET (p < 0.01) is probably related to the withdrawal of sympathetic stimulation of the heart in that the Vcf and IHR were normal. Thus, this may represent basal myocardial contractility.

Beta blockade with propranolol is associated with a slight lengthening of the PEP and shortening of LVET, with a resultant increase in PEP/LVET. It is unclear what the effect of atropine alone will be on this ratio, but our study reveals that full autonomic blockade results in a significant increase in PEP/LVET in otherwise normal hearts. That such a finding could represent LV dysfunction is doubtful because there was a concomitant increase in Vcf.
When the effects of combined ethanol and autonomic blockade were studied, the PEP/LVET rose further to 0.45 ± 0.05 s, an increase of 12% (p < 0.01). However, Vcf only rose 7% compared to the 20% increase with autonomic blockade alone. Thus, the Vcf did not rise as much as expected, in relation to an increase in HR, when autonomic blockade and ethanol were combined. In essence, there was an increase in PEP/LVET (p < 0.01) and a relative decrease in Vcf, (p < 0.05), when ethanol plus autonomic blockade were compared to autonomic blockade as the baseline. In addition, the HR was decreased by 10% (p < 0.001) by ethanol and autonomic blockade compared with autonomic blockade alone. This IHR of 95.8 (mean) with ethanol would be considered by Jose6, 28 as evidence for a decrease in myocardial function when compared with the IHR of 105.8 (mean) without ethanol. This was statistically significant when each person was compared with himself or herself. These findings (upon combining ethanol and autonomic blockade) of decreased IHR, increased PEP/LVET, and relative decrease in Vcf, suggest a decrease in LV performance. Therefore, autonomic blockade “unmasked” myocardial depression due to ethanol.

Potential criticisms of our study include the small number of subjects, the narrow age range, and the possibility that the subjects were less than truthful about their true alcohol usage. Timmis et al.14 studied systolic time intervals in normal subjects subdivided on the basis of their average daily consumption of ethanol. The greater the average daily consumption, the higher were the initial control values and the less was the change in each systolic time interval after acute ethanol ingestion. Their results suggest tolerance as well as progressive degrees of chronic cardiac malfunction proportionate to the amount of chronic ethanol exposure.

We took our measurements at only one isolated moment after the ingestion of ethanol: at 60 minutes, with a mean blood ethanol of 110 mg/dl. This 60-minute blood level was equivalent to that of Ahmed15 and Delgado21 in normal human subjects, and of Regan22 in dogs. Higher blood levels and multiple time periods of measurement might have shown depression of LV performance by ethanol alone, or might have more clearly defined such depression after the withdrawal of adrenergic effect by autonomic blockade. However, similar and even higher ethanol blood levels have inconsistently affected cardiac function in other reports.8, 14-16, 20, 21 Our subjects drank Scotch whiskey which was not mixed with any other substance (e.g., sugars), and osmolality changes have previously been shown not to be responsible for alterations in cardiac inotropy.52, 56 We did not study the effects of various temperatures of the orally ingested ethanol on the parameters measured, nor did we study the effects of an equivalent amount of non-alcohol calories.

From our study, we conclude that in normal human subjects: 1) pharmacologic autonomic blockade alone results in no detectable myocardial dysfunction; 2) no important acute effects of ethanol alone could be demonstrated; and 3) ethanol produces a significant decrease in contractility in the autonomic blocked heart, with a mild negative chronotrophic effect. Thus, autonomic blockade apparently “unmasked” myocardial depression due to ethanol per se at blood ethanol levels comparable to other reported studies. This is also in agreement with the animal studies. These findings cannot necessarily be extrapolated to the chronic cardiac patient, or to the patient with alcoholic cardiomyopathy. However, application of the technique of autonomic blockade provides further insight into the relationship between ethanol and cardiac dysfunction.

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