Acute cardiovascular effects of ethanol

A controlled non-invasive study

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SUMMARY The acute cardiac effects of ethanol (1 g/kg orally within 60 minutes) were examined in 22 healthy volunteers (11 men and 11 women) by M-mode echocardiography and systolic time intervals for three hours after beginning ingestion. Each subject also took part in a control study, in which the same volume of juice was substituted for ethanol.

Heart rate increased by 15% and cardiac output by 17% during ethanol intake, while total peripheral resistance decreased by 15%. Left ventricular end-diastolic diameter was shortened by 2% during the declining phase of blood ethanol concentration; stroke volume and circumferential wall stress were simultaneously decreased by 7% and 5%, respectively. No ethanol-related changes were noted in echocardiographic indices of left ventricular function, neither were any sex differences observed in the cardiovascular changes after ethanol ingestion.

Each of the systolic time intervals was significantly altered even during the control experiment. The responses of each of these intervals to ethanol differed significantly from those in the control test as well. Notably, the pre-ejection period/ejection time ratio rose after ethanol, this change, according to simultaneous echocardiographic data, resulting from reduced preload instead of impaired contractility, as maintained in previous investigations.

It is concluded that alcohol in modest doses is capable of altering each of the extramyocardial influences on left ventricular function – heart rate, preload, and afterload – but does not impair myocardial performance, at least in normal subjects.

The concept of alcohol as a myocardial toxin has been generally accepted by cardiologists. Few would disagree that the chronic and excessive use of alcohol may result in clinically significant heart muscle disease.¹ Also widely endorsed is the view that alcohol, even in social amounts, brings about an acute, reversible cardiac depression¹ but this is much more controversial and, in fact, alcohol has been claimed to exert beneficial² as well as harmful³ effects on left ventricular function in patients with heart disease. This contradiction pertains also to normal subjects, in whom alcohol ingestion has been reported to cause myocardial depression,⁴⁻⁶ no effect,^{7,8} or an enhancement of cardiac performance.³ The suggested sex difference is also strange: female hearts escape both the injurious effects of alcohol in chronic use⁹ and its acute myocardial depressive actions.¹⁰

This study was designed to assess the acute cardiac effects of alcohol in normal subjects, compared with

those of juice ingestion, by using echocardiography and systolic time intervals.

Subjects and methods

The study group consisted of 22 volunteers, 11 men and 11 women, with a mean age of 23 years (range 20 to 27). All were healthy as shown by the medical history, physical examination, a 12 lead electrocardiogram, and baseline echocardiogram. They were infrequent or moderate drinkers, with a mean reported alcohol consumption of 8 g/day (range 1 to 30). Apart from hormonal contraception (three subjects), none was using any drugs either regularly or occasionally.

STUDY DESIGN

The subjects entered the laboratory at 7:00 to 7:30 in the morning after an overnight fast and having abstained from alcoholic beverages for at least two days

beforehand. An indwelling venous catheter was inserted, whereupon the subjects rested supine for 30 minutes. Control sphygmomanometric arterial blood pressure, an echocardiogram of the left ventricle, systolic time intervals, and a venous blood sample for ethanol determination were then taken. The subjects then ingested ethanol 1 g/kg body weight as a 15% (w/v) juice diluted solution within 60 minutes. The above measurements were repeated 30, 60, 90, 120, and 180 minutes after the first drink. The subjects were lying supine during the entire study period. Each subject also took part in a control experiment designed identically to that presented above, with the exception that ethanol was replaced by an isovolumic amount (average 430 ml) of pure juice.

ECHOCARDIOGRAPHY

The echocardiographic examinations were performed using an Irex System II ultrasonograph equipped with a fiberoptic strip-chart recorder and a 2.25 MHz medium focused transducer. M-mode echoes from the left ventricle were recorded during quiet respiration by the standard technique¹¹ simultaneously with lead II of the electrocardiogram and an external phonocardiogram on dry silver paper at a speed of 100 mm/s. High quality recordings were not obtained in one male and two female subjects, and the echocardiographic data are thus based on the recordings obtained in the remaining 19 subjects.

The echocardiograms were analysed semiautomatically using an x-y digitiser and a PDP 11/30 computer according to the method described by Upton and Gibson.¹² Left ventricular end-diastolic diameter and end-systolic diameter were measured by the European standardisation.¹³ Left ventricular mid-systolic diameter and the respective posterior wall thickness were measured at the mid-point between the first and second heart sounds. The peak systolic shortening rate of the instantaneous cavity dimension, divided by end-diastolic diameter, gave the maximum circumferential fibre shortening velocity ($V_{CF_{max}}$).¹² Heart rate was derived from the R-R intervals on the electrocardiogram.

Cardiac volumes, including stroke volume and ejection fraction,¹¹ were calculated using the Teichholz formula for volume approximation.¹⁴ Cardiac output was estimated by multiplying stroke volume with heart rate. Total peripheral resistance¹⁵ was calculated with the formula: Peripheral resistance (dyn min cm^{-5}) = (mean BP/CO) $\times$ 1332, where BP is arterial blood pressure and CO is cardiac output; mean BP was assumed to be diastolic BP + 1/3 (systolic BP - diastolic BP). Circumferential wall stress¹⁶ was estimated in left ventricular mid-systole with the formula: Wall stress (dyn/cm^2) = $(PD/2h) [1 - D/8(D + h)] \times 1332$, where P is systolic blood pressure, D is

left ventricular mid-systolic diameter, and h is posterior wall mid-systolic thickness. The five consecutive or nearly consecutive cardiac cycles with the best technical adequacy were digitised and averaged from each recording.

SYSTOLIC TIME INTERVALS

Indirect carotid arterial pulse tracing, lead II electrocardiogram, and external phonocardiogram (filter setting 250 to 2000 Hz) were recorded simultaneously using the channels for physiological signals in the Irex System II echocardiograph. The chart speed was 100 mm/s. The recordings were analysed using an x-y digitiser and an Honeywell DPS 8 computer. Total electromechanical systole (QS_2), left ventricular ejection time (LVET), and pre-ejection period (PEP) were determined and averaged from 10 consecutive cycles according to standard methods.¹⁷ The systolic time intervals were further corrected for heart rate by Weissler's regression equations¹⁸ to obtain their indexed equivalents (PEPi, LVETi, QS_{2i}). The PEP/LVET ratio was calculated from uncorrected data.

NON-INVASIVE END-SYSTOLIC

PRESSURE-VOLUME RELATIONS

The relations between pressures and volumes at end-systole were analysed by calculating the systolic blood pressure/end-systolic volume ratios. It has been shown in invasive studies that the pressure-volume slope at end-systole reflects myocardial contractility,¹⁹ and recently this method has proved applicable to non-invasive studies as well.^{20,21} Importantly, its simple modification, the systolic blood pressure/end-systolic volume ratio, seems to be a sensitive index of left ventricular function, even though it does not represent the actual pressure-volume slope.²¹

NON-INVASIVE INDEX FOR ISOVOLUMIC

PRESSURE RISE IN LEFT VENTRICLE (NIPR)

Invasive studies^{22,23} have shown that the peak rate of isovolumic pressure rise (peak dp/dt) in the left ventricle, divided by end-diastolic volume or circumference, is sensitive to changes in contractility. A non-invasive equivalent to it was calculated in this study by the following formula: NIPR (mmHg/mm per s) = diastolic BP/(PEP) (LVEDD), where BP is arterial blood pressure, PEP is pre-ejection period, and LVEDD is left ventricular end-diastolic diameter. The use of this index is based on both experimental and clinical studies. Firstly, experimental data have shown that the ratio, diastolic blood pressure/isovolumic contraction time, correlates well with peak dp/dt under varying loading and inotropic conditions.²⁴ Secondly, studies in patients with acute myocardial infarction have disclosed that changes in peak dp/dt can be reliably assessed using diastolic

blood pressure and PEP as well as pulmonary wedge pressure to correct for major changes in end-diastolic pressure.²⁵ The use of the non-invasive index for isovolumic pressure rise in the left ventricle may thus be particularly expedient when left ventricular function is assessed sequentially in the same subject, provided that major changes in end-diastolic pressure can be excluded.

REPRODUCIBILITY

Ten healthy volunteers took part in a methodological study set out to assess the random variation in the cardiovascular measurements. The design of this study was identical to those presented above except that no interventions were made. The subjects merely lay supine and a left ventricular echocardiogram and recordings for systolic time intervals were performed six times over a three-hour period. The recordings were analysed as presented above. Individual and group mean coefficients of variation (mean/SD) were calculated for each measured variable.

The mean coefficients of variation for end-diastolic and end-systolic dimensions were 1.3% and 1.7%, respectively. The corresponding coefficients for all the other echocardiographically derived variables ranged from 2.5% (ejection fraction) to 5.7% (VCF_{max}). The mean coefficients of variation for the systolic time intervals ranged from 0.9% (LVETi) to 3.7% (PEP/LVET). Analysis of variance showed a significant decreasing effect of time on LVETi ($p < 0.002$). These data indicate a small random variation in the cardiovascular measurements.

BLOOD ETHANOL DETERMINATION

Ethanol was determined from venous blood by head-space gas chromatography.²⁶

STATISTICAL ANALYSIS

The significance of the cardiovascular changes from the baseline during ethanol and control experiments was assessed, and these changes were compared mutually as well as between men and women, using analysis of variance with repeated measures. Student's *t* test for paired observations was used when appropriate. The results are given as means $\pm$ SEM.

Results

EFFECTS OF SEX

No statistically significant differences between men and women were found either in blood ethanol concentrations or in the cardiovascular changes after ethanol ingestion, neither were any sex differences noted in the control experiment. The data were therefore processed further as one group.

BLOOD ETHANOL CONCENTRATIONS

The blood ethanol curve is shown in Fig. 1. The peak mean ethanol concentration was observed 30 minutes after ingestion and was 24.6 ± 0.9 mmol/l (112 ± 4 mg/100 ml).

CARDIOVASCULAR CHANGES IN CONTROL EXPERIMENT

The data are shown in Fig. 2 to 5 and in the Table. Significant changes were observed in each of the systolic time intervals and the PEP/LVET ratio (Table). In addition, diastolic blood pressure rose from 77 ± 2 mmHg before juice to 80 ± 2 mmHg in the 180 minute measurements ($p < 0.01$, Fig. 2). The increases in systolic blood pressure, stroke volume, ejection fraction, and non-invasive index for isovolumic pressure rise in the left ventricle, during or

Table Heart rate and systolic time intervals before and after ethanol and during control experiment

Variable	Minutes after beginning ingestion					
	0	30	60	90	120	180
Heart rate, bpm	E 62 $\pm$ 2	67 $\pm$ 2***	71 $\pm$ 2***	69 $\pm$ 2***	65 $\pm$ 2*	66 $\pm$ 3
	C 60 $\pm$ 2	59 $\pm$ 2	61 $\pm$ 2	61 $\pm$ 2	61 $\pm$ 2	60 $\pm$ 2
PEP (ms)	E 106 $\pm$ 2	102 $\pm$ 2**	100 $\pm$ 2***	104 $\pm$ 2	109 $\pm$ 2*	110 $\pm$ 2**
	C 107 $\pm$ 2	106 $\pm$ 2	101 $\pm$ 2***	103 $\pm$ 2*	107 $\pm$ 2	106 $\pm$ 3
PEPi (ms)	E 130 $\pm$ 2	129 $\pm$ 2	129 $\pm$ 2	132 $\pm$ 2	135 $\pm$ 2***	137 $\pm$ 2***
	C 131 $\pm$ 2	128 $\pm$ 2	125 $\pm$ 2***	127 $\pm$ 2*	131 $\pm$ 2	130 $\pm$ 3
LVETi (ms)	E 408 $\pm$ 2	412 $\pm$ 2**	413 $\pm$ 2**	409 $\pm$ 2	405 $\pm$ 2	404 $\pm$ 2*
	C 408 $\pm$ 3	413 $\pm$ 3**	411 $\pm$ 2	404 $\pm$ 2*	400 $\pm$ 3***	404 $\pm$ 3*
QS _{2i} (ms)	E 538 $\pm$ 3	541 $\pm$ 3	541 $\pm$ 3	540 $\pm$ 3	540 $\pm$ 3	540 $\pm$ 3
	C 539 $\pm$ 3	541 $\pm$ 3	536 $\pm$ 3	531 $\pm$ 3***	531 $\pm$ 3***	534 $\pm$ 4*
PEP/LVET	E 0.342 $\pm$ 0.007	0.339 $\pm$ 0.007	0.339 $\pm$ 0.007	0.354 $\pm$ 0.009	0.368 $\pm$ 0.006***	0.376 $\pm$ 0.009***
	C 0.344 $\pm$ 0.007	0.333 $\pm$ 0.008*	0.325 $\pm$ 0.009**	0.337 $\pm$ 0.007	0.356 $\pm$ 0.009*	0.347 $\pm$ 0.010

Results are means $\pm$ SEM. E, ethanol 1 g/kg by mouth within 60 minutes; C, control experiment (isovolumic amount of juice within 60 minutes); PEP, pre-ejection period; PEPi, PEP corrected for heart rate; LVET, left ventricular ejection time; LVETi, LVET corrected for heart rate; QS_{2i}, total electromechanical systole corrected for heart rate. Significance of changes from the 0-measurements: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

Fig. 1 Blood ethanol curve. The bars indicate standard errors. The conversion factor from mmol/l to mg/100 ml is 4.5.

Fig. 2 Effects of ethanol on heart rate and blood pressure (BP). Ethanol (1 g/kg) or an isovolumic amount of juice was ingested within 60 minutes after the control measurements. The statistical significancies refer to comparisons between changes from the baseline in the ethanol and control experiments.

directly after juice ingestion (Fig. 2 to 4), were of weak statistical significance ($p < 0.05$) by paired t test, even though not by analysis of variance.

EFFECTS OF ETHANOL

The cardiovascular responses to ethanol ingestion were considered to be the results of the effects of ethanol *per se*, if they differed significantly (analysis of variance) from the respective responses in the control test. These results are given in Fig. 2 to 5.

Ethanol increased heart rate by 15% (maximal mean change) and caused a late 3% decrease in systolic blood pressure (Fig. 2). The difference in diastolic blood pressure reflected the increase of this variable during the control experiment. Cardiac out-

put increased by 17% during ethanol ingestion and peripheral resistance decreased simultaneously by 15% (Fig. 3). During the declining blood ethanol end-diastolic diameter shortened by 2% and, concurrently, stroke volume and circumferential wall stress were reduced by 7% and 5%, respectively. The echocardiographic indices of left ventricular function (Fig. 4) showed no significant effects of ethanol *per se*, even though VCF_{max} and non-invasive index for isovolumic pressure rise in left ventricle increased from their pre-ethanol levels during ingestion ($p < 0.01$ and < 0.05 , respectively).

The changes in each of the systolic time intervals and the PEP/LVET ratio differed at some time point during the ethanol and control experiments (Fig. 5).

Fig. 3 Effects of ethanol on left ventricular size and wall stress as well as on some haemodynamic variables. For symbols and experimental conditions, see Fig. 2. LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; CWS, circumferential wall stress; TPR, total peripheral resistance.

Fig. 4 Effects of ethanol on the indices of left ventricular function. For symbols and experimental conditions, see Fig. 2. VCF_{max} , maximal circumferential fibre shortening velocity; NIPR, non-invasive index for the isovolumic pressure rise in left ventricle (see Methods); BP, blood pressure; ESV, end-systolic volume.

Fig. 5 Effects of ethanol on the systolic time intervals. For symbols and experimental conditions, see Fig. 2. PEP, pre-ejection period; PEPi, PEP corrected for heart rate; LVET, left ventricular ejection time; LVETi, LVET corrected for heart rate; QS_i, total electromechanical systole corrected for heart rate.

Discussion

One obvious source of discrepant views about the acute cardiac effects of alcohol is that the essential conceptual disparities between *cardiac* performance and *myocardial* performance have not always been properly considered. Myocardial performance, its contractility, refers to the active inotropic state of the cardiac muscle and is independent of the loading conditions of the left ventricle. This entails that cardiac performance as a pump is not synonymous with myocardial performance and, in fact, in normal heart stroke output depends primarily on peripheral factors and their influence upon preload and afterload, instead of the exact level of myocardial contractility.²⁷ An important corollary of this principle is that a change in left ventricular function – or in its non-invasive indices – denotes altered contractility only in so far as it is independent of simultaneous changes in loading conditions. Fortunately, echocardiography provides information about changes in preload (end-diastolic diameter) and afterload (systolic wall stress)

to allow for these extramyocardial determinants of cardiac performance.

ETHANOL-RELATED CARDIOVASCULAR CHANGES

The cardiovascular effects of ethanol were conspicuously different during the increasing and decreasing blood ethanol phases. Haemodynamics during the increasing blood ethanol were characterised by a positive chronotropic change as well as by a decrease in peripheral resistance and an increase in cardiac output. These findings are in accordance with the respective data from previous studies, in which minute volume was estimated by dye-dilution techniques.^{28 29} Peripheral arterial vasodilatation accounts best for the reduction in peripheral resistance and also explains, via increased venous return, the failure of left ventricular dimensions to shorten during ethanol ingestion despite the highly significant rise in heart rate.³⁰

During the decreasing blood ethanol the dominant change was a reduction in preload, as shown by the progressive shortening of end-diastolic diameter.³¹ The decrease in afterload was probably secondary to

the preload change.³¹ The idea that alcohol may acutely alter loading conditions has been little entertained in previous investigations, even though the data of Delgado *et al.*⁶ and those of Timmis *et al.*¹⁰ show significant shortening of end-diastolic dimension after ethanol ingestion. Thus, alcohol-induced changes in cardiac performance, for example increases in PEP and PEP/LVET,^{4,5} have been expounded by assuming myocardial depression without accurately knowing whether left ventricular size or end-diastolic pressure were simultaneously altered. True, the diminution of stroke volume as well as the increases in PEP and PEP/LVET indicate ethanol-induced cardiac depression also in the present study. Yet, the simultaneous other data showed that these changes were merely reflections of a downward shift on the Frank-Starling curve; stroke volume and the systolic time intervals are highly sensitive to preload alterations in normal hearts.^{31,32} Myocardial contractility was not detectably impaired.

The origin of the reduction in preload remains speculative. It did not result, however, merely from the rate-dependency of preload since the rise in heart rate during the decreasing blood ethanol was too small to account for the total shortening of end-diastolic diameter.³⁰ Thus, either the diuretic activity of ethanol³³ or venous pooling, or both, may have contributed to that change. In a recent study an analogous finding, alcohol-induced reduction in pulmonary wedge pressure in patients with severe heart failure, was tentatively ascribed to increased venous capacitance.²

SYSTOLIC TIME INTERVALS DURING CONTROL EXPERIMENT

Surprisingly, each of the systolic time intervals was significantly altered during the control experiment. The decreases of PEP, PEPi, and PEP/LVET during juice ingestion, as well as the simultaneous increase in LVETi, indicate enhanced cardiac performance¹⁷ and are consonant with the simultaneous increasing tendency in the echocardiographic indices of left ventricular function. Whatever its cause, a volume effect or autonomic reflexes evoked by the ingestion of cold juice, this observation shows the sensitivity of the systolic time intervals and emphasises the importance of controlling. The late abbreviations of LVETi and QS₂i, on the other hand, resulted most probably from the diurnal shortening tendency of these intervals.^{34,35} This relatively little recognised phenomenon has been ascribed to a circadian rhythm in the secretion of catecholamines,³⁵ even though other authors have been doubtful about the role of circulating adrenaline or noradrenaline.³⁶ It is hard to give credit to catecholamine involvement from the present data either, since the shortening of LVETi and QS₂i were

maximal at a time point when no changes were observable in heart rate or in any of the echocardiographic variables.

The PEP/LVET ratio was significantly increased at the time of maximal LVETi shortening during the control experiment. This index has been widely used as a measure of myocardial contractility, for example in alcohol studies.⁴⁻⁶ On the other hand, rate-independent changes in QS₂ have been recently advocated for assessment of inotropic changes as well, provided the loading conditions are not "radically" altered and the measurements are made "during a single day".³⁷ Paradoxically enough, the shortening of QS₂i and the increase in PEP/LVET during the control experiment suggested simultaneously an improvement and an impairment of contractility, respectively, when myocardial performance by echocardiography was actually unaltered.

ETHANOL-RELATED CHANGES IN SYSTOLIC TIME INTERVALS

The dissimilar late changes in PEP, PEPi, and PEP/LVET during the ethanol and control experiments related to the ethanol-induced decrease in left ventricular filling, as contrasted with unchanged preload during the control test. The early post-drink difference in PEPi is more difficult to make out. It may, however, simply reflect the significant disparity in the heart rate responses, since recent evidence suggests that PEP need not be corrected for heart rate.³⁷⁻³⁹ On the other hand, PEP/LVET is, contrary to a very common misconception, directly rate dependent in intraindividual studies,^{37,39} which explains why PEP/LVET was not decreased during ethanol ingestion. The conspicuous failure of QS₂i to shorten after ethanol remains unaccountable, simply because the genesis of this change in the control experiment could not be inferred from the obtained data.

The present study shows expressly the intricacy of factors involved in the changes of systolic time intervals and the problems in their interpretation. The major pitfalls seem to be the diurnal variation and the fact that if the mere time events of the cardiac cycle are measured no means exist to quantify the role of preload changes to the results obtained. Moreover, incorrect use of the regression equations may also lead to erroneous conclusions. All things considered, this method should not be used without adequate controlling and without independent information about preload in studying changes in cardiac performance, let alone assessment of changes in myocardial contractility.

Conclusions

This investigation emphasises the significance of the

peripheral circulatory actions of ethanol and their influence on the extramyocardial determinants of cardiac performance. In modest doses ethanol decreases peripheral vascular resistance and increases heart rate as well as cardiac output during the rising blood ethanol, and reduces preload and afterload during the declining blood ethanol, without impairing myocardial performance. These conclusions do not rule out adverse myocardial effects from alcohol in large doses or as a sequel to long-term over-indulgence.

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