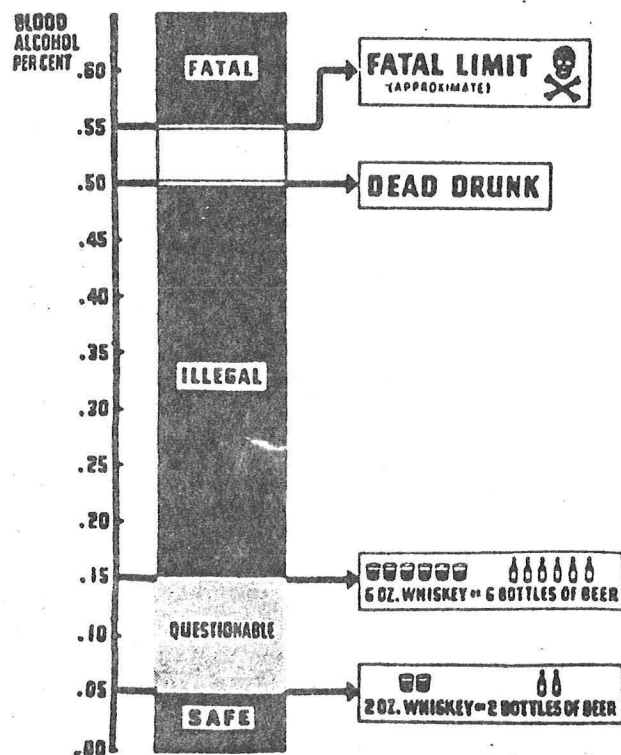


ALCOHOL AND THE HEART

JAMES M. ATKINS, M.D.



*Lechery, sir, it (drink) provokes and
unprovokes the desire, but it takes
away the performance.*

Shakespeare: Macbeth 2.3.32

MAY 14, 1981

Cardiovascular Physiology of Alcohol

Although ethyl alcohol has been imbibed, abused, admired, and deplored since the beginning of recorded history, the acute hemodynamic effects of alcoholic beverages have only recently been studied. Most available information is based on data from anesthetized animal preparations or fragmentary observations in man and has suggested that ethanol may be a myocardial depressant.

Although acutely administered ethanol appeared to be a myocardial depressant in most previous studies, there has been some disagreement. Various investigators have concluded that ethanol improves (1,2) has little or no effect (3-5) or impairs (6-8) cardiac function. In anesthetized animals, Regan (7) found myocardial depression at blood levels of 110 mg/100 ml but Webb et al (3) found no depression in heart-lung preparations at levels up to 900 mg%. Riff et al (4) found no changes in myocardial function in normal human volunteers, with blood levels ranging from 85 mg/100 ml to 136 mg/100 ml, either at rest or with exercise. Blomqvist, Saltin, and Mitchell (5) reported no change in maximal oxygen uptake by human volunteers performing graded exercise, although there was evidence that mechanical efficiency was decreased during sub-maximal exercise. However, after oral ingestion of only 2 oz. of Canadian whiskey, Gould et al (8) reported myocardial depression in patients with coronary artery disease who drank 0.5 g/kg of ethanol. Paradoxically, the findings of Juchems and Klobe (2) can be interpreted as demonstrating improved myocardial function at blood ethanol levels of 39 and 120 mg/100 ml.

In order to better understand the role of ethanol, Horwitz and Atkins (10) studied six conscious chronically instrumented with left ventricular pressure gauges, aortic flow probes, and left ventricular sonomicrometers. The dogs were infused with ethanol 0.5 gm/kg IV initially then given a second infusion of 1.0 gm/kg IV.

In three dogs control experiments were performed by infusing a solution of 1/2 normal saline and 5% dextrose in water mixed in equal volumes at identical infusion rates and under the same conditions as the ethanol infusions. There were no consistent changes in any hemodynamic parameters. In two animals identical controls were performed with autonomic blockade and again no consistent changes were noted.

The mean blood ethanol level immediately after infusion #1 was 120 ± 16 (SEM) mg%. Ethanol-induced changes are shown in Table 1 for studies with intact autonomic innervation and in Table 2 for studies with pharmacological denervation. A representative recording is shown in Figure 1.

Table 1

Hemodynamic Effects of Ethanol With Autonomic Innervation Intact

	Control	Infusion #1	Infusion #2
Heart rate (beats/min)	107 $\pm$ 7	112 $\pm$ 10 NS	141 $\pm$ 7 $P < 0.01$
Stroke volume (ml)	20.1 $\pm$ 1.6	17.2 $\pm$ 1.9 $P < 0.01$	13.6 $\pm$ 1.9 $P < 0.01$
Left ventricular end diastolic pressure (mm Hg)	1.5 $\pm$ 0.5	4.0 $\pm$ 0.5 $P < 0.05$	7.5 $\pm$ 1.5 $P < 0.05$
Left ventricular peak systolic pressure (mm Hg)	104 $\pm$ 4	104 $\pm$ 3 NS	108 $\pm$ 4 NS
Left ventricular dp/dt max (mm Hg/sec)	2069 $\pm$ 193	1717 $\pm$ 212 $P < 0.001$	1456 $\pm$ 235 $P < 0.01$

Mean measurements of hemodynamic variables during control period and after ethanol infusion #1 (0.5 g/kg) and after ethanol infusion #2 (additional 1.0 g/kg). Values are $\pm$ standard error of the mean. NS = $P > 0.05$.

Table 2

Hemodynamic Effects of Ethanol With Pharmacological Autonomic Blockade

	Control	Infusion #1	Infusion #2
Heart rate (beats/min)	160 $\pm$ 9	145 $\pm$ 7 $P < 0.05$	153 $\pm$ 5 NS
Stroke volume (ml)	14.6 $\pm$ 1.7	14.9 $\pm$ 1.6 NS	12.3 $\pm$ 1.5 $P < 0.01$
Left ventricular end diastolic pressure (mm Hg)	0.5 $\pm$ 1.0	2.5 $\pm$ 1.0 $P < 0.05$	7.5 $\pm$ 2.0 $P < 0.05$
Left ventricular peak systolic pressure (mm Hg)	101 $\pm$ 5	105 $\pm$ 6 NS	108 $\pm$ 7 NS
Left ventricular dp/dt max (mm Hg/sec)	1926 $\pm$ 211	1673 $\pm$ 156 $P < 0.05$	1343 $\pm$ 117 $P < 0.01$

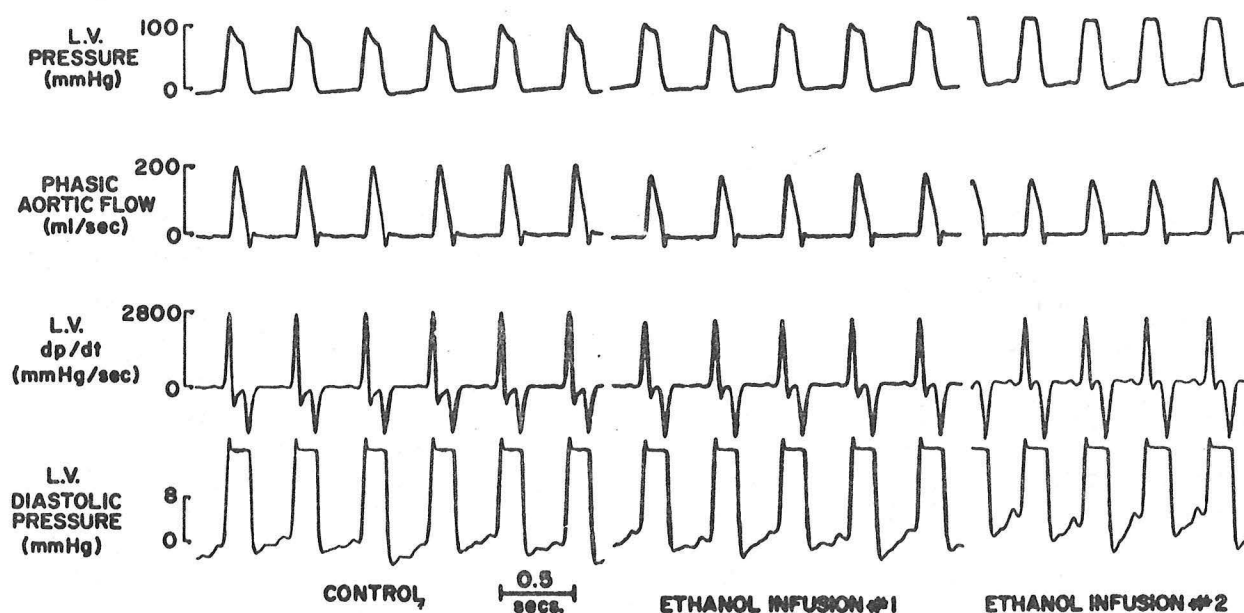


Figure 1

Hemodynamic effects of ethanol 0.5 mg/kg body weight intravenously (infusion #1) and 1.5 g/kg intravenously (infusion #2) in a conscious dog with intact autonomic innervation. Ethanol resulted in reductions in the maximum first derivative of the left ventricular pressure (LV dp/dt) and stroke volume, and elevation in the left ventricular end diastolic pressure.

With intact autonomic innervation heart rate did not change during infusion #1 but increased significantly with infusion #2. With autonomic blockade the pre-infusion heart rate was set at a high level which fell slightly after infusion #1 and returned toward the pre-infusion level after infusion #2.

With intact autonomic innervation stroke volume fell in all six dogs with infusion #1 and subsequently fell further with infusion #2. With autonomic blockade, the pre-infusion stroke volume was low and did not change with infusion #1. However, there was a significant reduction in stroke volume after infusion #2.

Mean left ventricular end-diastolic pressure rose significantly after infusion #1 and rose further after infusion #2 during both intact and autonomic blockade studies. Left ventricular peak systolic pressure did not change significantly after ethanol infusions.

The maximum first derivative of the left ventricular pressure (dP/dt max) fell significantly after ethanol. This change occurred in all six dogs. With autonomic innervation intact, the reduction from the pre-infusion level was 17% after infusion #1 and 30% after infusion #2. Autonomic blockade decreased the pre-infusion dP/dt max in most animals; the reductions from the pre-infusion level were 13% after infusion #1, and 30% after infusion #2.

As shown in Table 3, left ventricular internal transverse diameter was measured in two dogs with intact autonomic innervation. Both end diastolic diameter and end systolic diameter increased in response to ethanol. The increase at end-systole exceeded that at end-diastole.

Table 3

Effect of Ethanol on Left Ventricular Diameter

	Control		Infusion #1		Infusion #2	
	EDD	ESD	EDD	ESD	EDD	ESD
Dog #3	25.0	16.8	26.1	19.0	26.7	20.7
Dog #4	33.3	26.6	33.5	26.8	34.0	28.3

Measurements in mm of left ventricular internal transverse diameter at end diastole (EDD) and end systole (ESD) in two conscious dogs.

Previous studies in anesthetized animals have shown little or no effects (1, 3). Since anesthetics are themselves myocardial depressants, the variation in anesthetized animal experiments may reflect difficulty in distinguishing superimposed changes in a subnormal preparation. The studies of human subjects were hampered by the low sensitivity of routine cardiac catheterization procedures. Measurements of cardiac output by Fick or dye dilution methods and pressure measurements with conventional fluid-filled catheter systems may not have been adequate for detection of subtle changes. An additional problem with some human studies was the use of extremely small dosages of oral ethanol, which would have produced very low blood levels at the time of study. This investigation in chronically instrumented conscious dogs circumvents these difficulties. There is no anesthetic, and a high-fidelity pressure system and a sensitive electromagnetic flowmeter provide optimum measurements for assessment of left ventricular function. The validity of left ventricular end-diastolic pressure changes as an indication of preload changes was confirmed in two dogs by measurement of left ventricular

To further investigate the role of ethanol on left ventricular performance, we (14) have studied dogs chronically instrumented at rest and during exercise before and after 1.0 g/kg ethanol IV with intact innervation and after blockade with atropine, propranolol, and atropine and propranolol combined.

Blood ethanol levels at 5 minutes after the completion of ethanol infusion ranged from 120 to 210 mg% (mean $\pm$ SEM=144 $\pm$ 17 mg%). In the resting condition ethanol administration produced no significant change in heart rate, LV pressure, and LVEDP; increases in heart rate of 7 beats/min and in LVEDP of 2.2 mmHg were not statistically significant. LV dP/dt max decreased by 18% from the control value and cardiac output was reduced by 505 ml/min (11%) due to a decrease in stroke volume of 4 ml/beat. There were significant increases (1.93 $\pm$ 0.19 mm) in LV end-systolic diameter. LV end-diastolic diameter increased in six of eight dogs, did not change in one and decreased in one. The average increase was 0.57 $\pm$ 0.25 mm over the control level, and it was not statistically significant. During light, moderate and heavy exercise before ethanol infusion, heart rate increased to 171 $\pm$ 6 (+53% over the resting level), 197 $\pm$ 7 (+76%) and 225 $\pm$ 9 beats/min (+101%) and cardiac output was increased by 2912 (+63%), 4503 (+97%) and 6325 ml/min (+137%), respectively. Stroke volume was increased by 4, 7 and 10 ml/beat, LV dP/dt max was increased by 28, 50 and 83%, and LV pressure was elevated by 16, 28 and 47 mmHG with light, moderate and heavy exercise. The heart rate response after ethanol was similar to the pre-ethanol response in light and moderate exercise, but was depressed significantly in heavy exercise. The depressed response to heavy exercise was also observed in LV pressure after ethanol. LV dP/dt max after ethanol was depressed not only at rest but also during exercise; it was reduced by 18% during light exercise, by 13% during moderate exercise by 20% during heavy exercise from each pre-ethanol value. The increase of stroke volume with exercise was smaller after ethanol than the increase before ethanol infusion. Cardiac output after ethanol was lower than the pre-ethanol level by 937 ml/min (-12%), 984 ml/min (-11%) and 1793 ml/min (-16%) for light, moderate and heavy exercise, respectively. Reasons for depressed cardiac output were the decrease in stroke volume for light and moderate loads and a decrease in both heart rate and stroke volume for heavy loads. There were significant decreases in LV end-systolic diameter (LVESD) during exercise both before and after ethanol administration, but LVESD after Ethanol was significantly larger than pre-ethanol level at all levels of exercise. LV end-diastolic diameter showed no significant change from the resting value during exercise both before and after exercise, but LVEDD after ethanol was significantly larger than the pre-ethanol value at light and heavy exercise loads. LVEDP increased with exercise and was slightly higher after ethanol, but the difference was statistically significant only at moderate exercise (Figures 2-8).

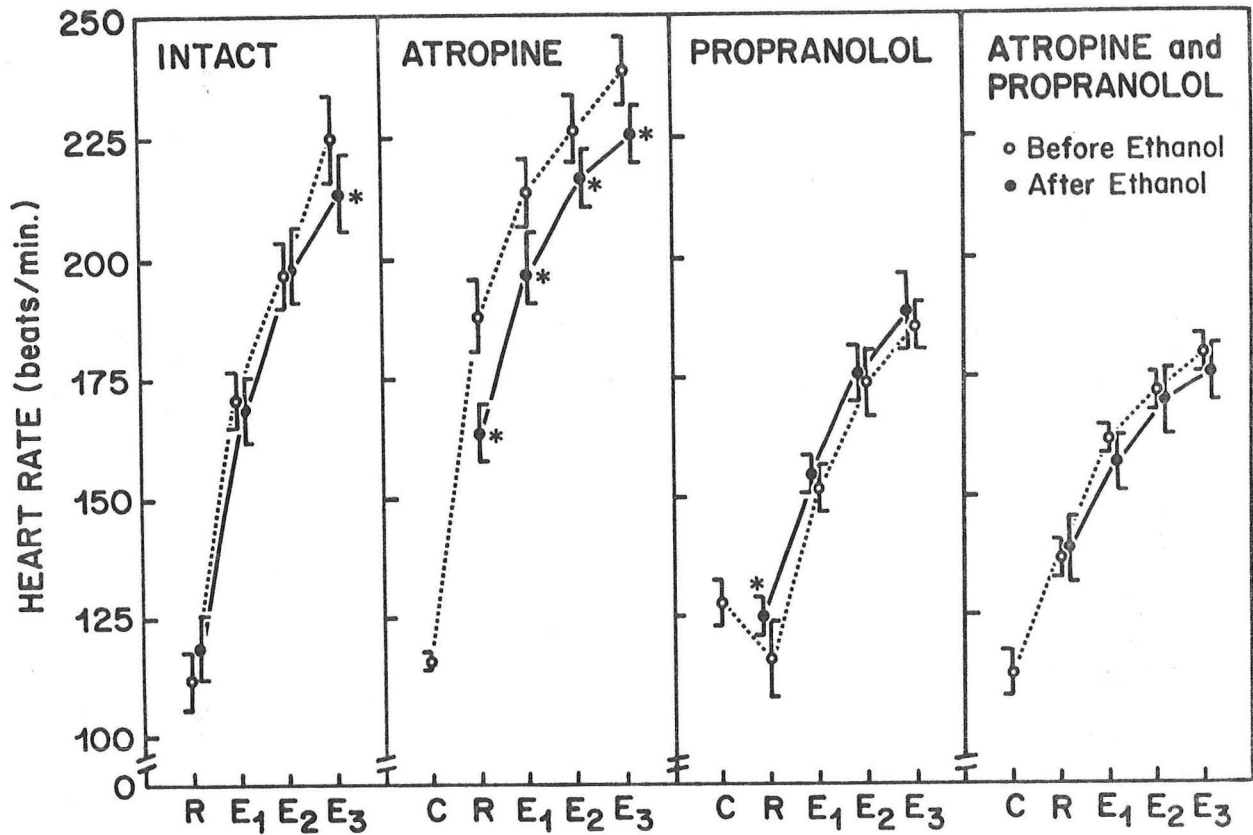


Figure 2. Heart rate responses to exercise before and after ethanol. R=rest, E₁ = Light exercise, E₂= moderate exercise, E₃= heavy exercise. C = control, * = p<0.05. (14)

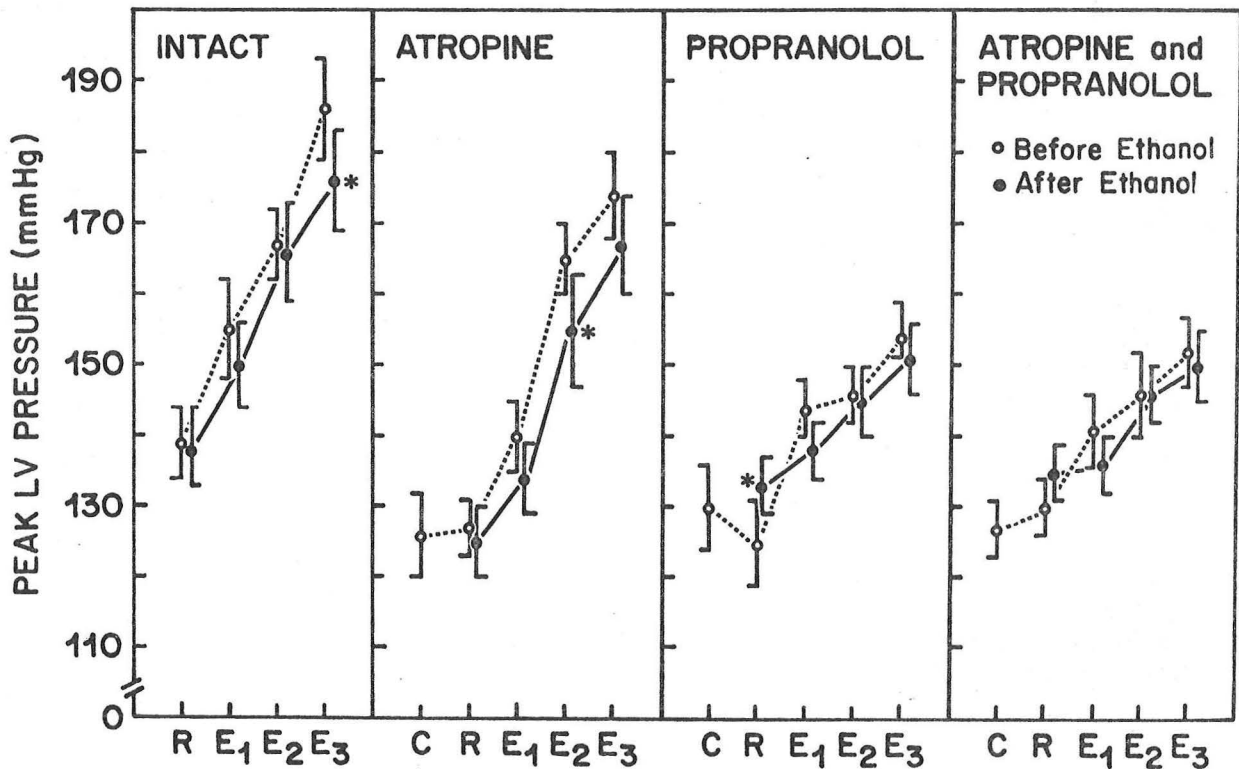


Figure 3. Left Ventricular systolic pressure response to exercise before and after ethanol. Symbols in figure 2. (14)

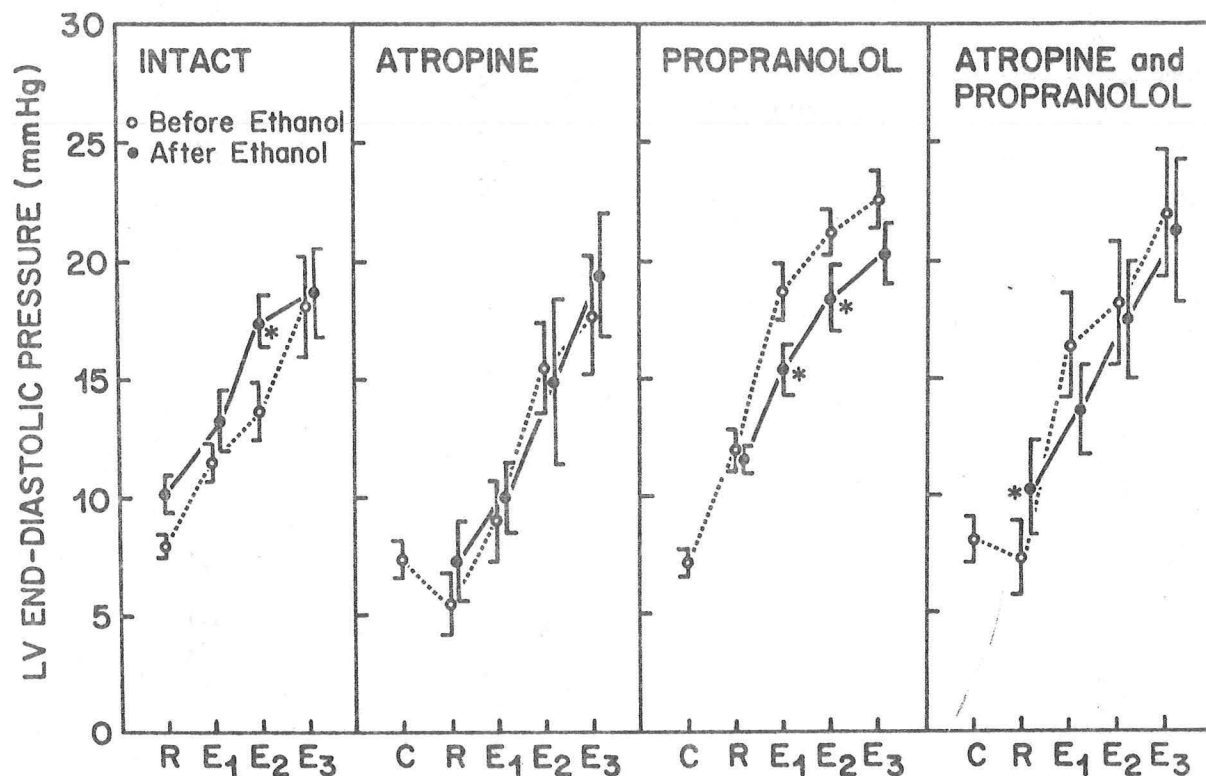


Figure 4. Left ventricular end-diastolic pressure (LVEDP) response to exercise before and after ethanol. Symbols as in Figure 2. (14)

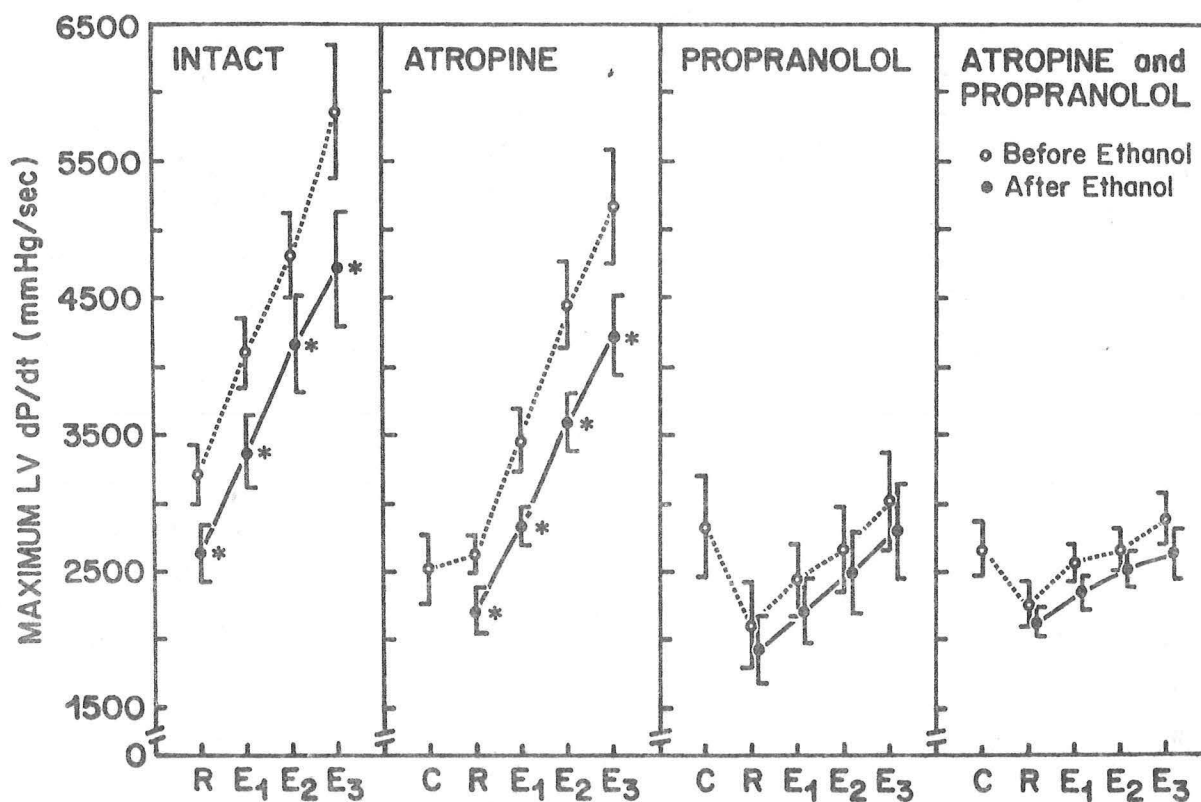


Figure 5. Left ventricular dP/dt max response to exercise before and after ethanol. Symbols as in Figure 2. (14)

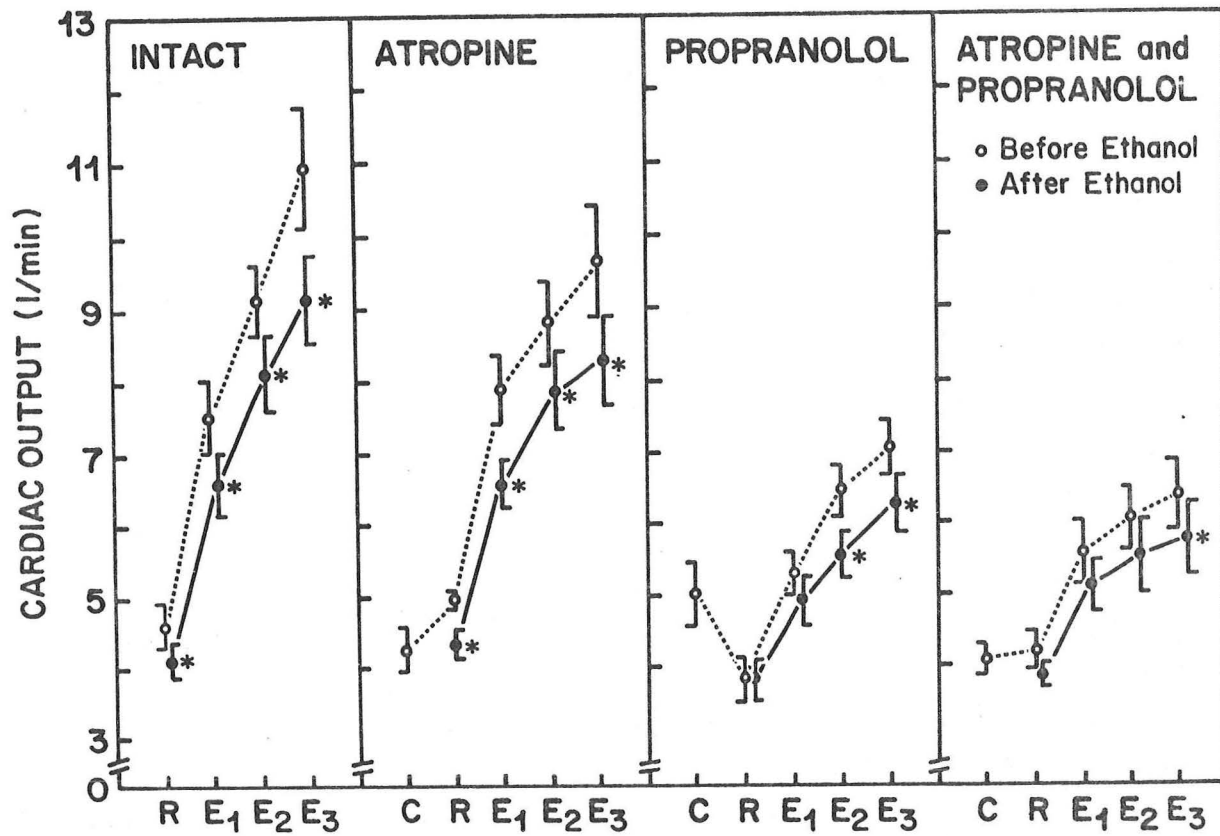


Figure 6. Cardiac output response to exercise before and after ethanol. Symbols as in Figure 2. (14)

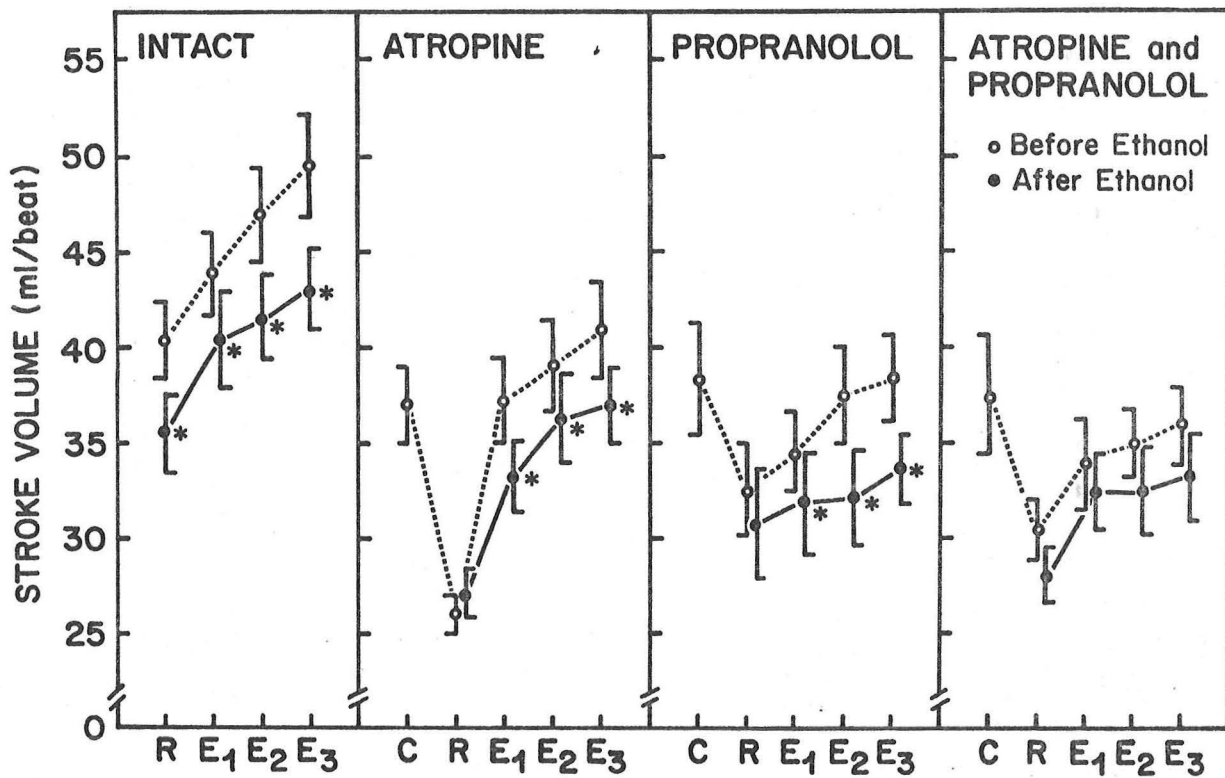


Figure 7. Stroke volume response to exercise before and after ethanol. Symbols as in Figure 2. (14)

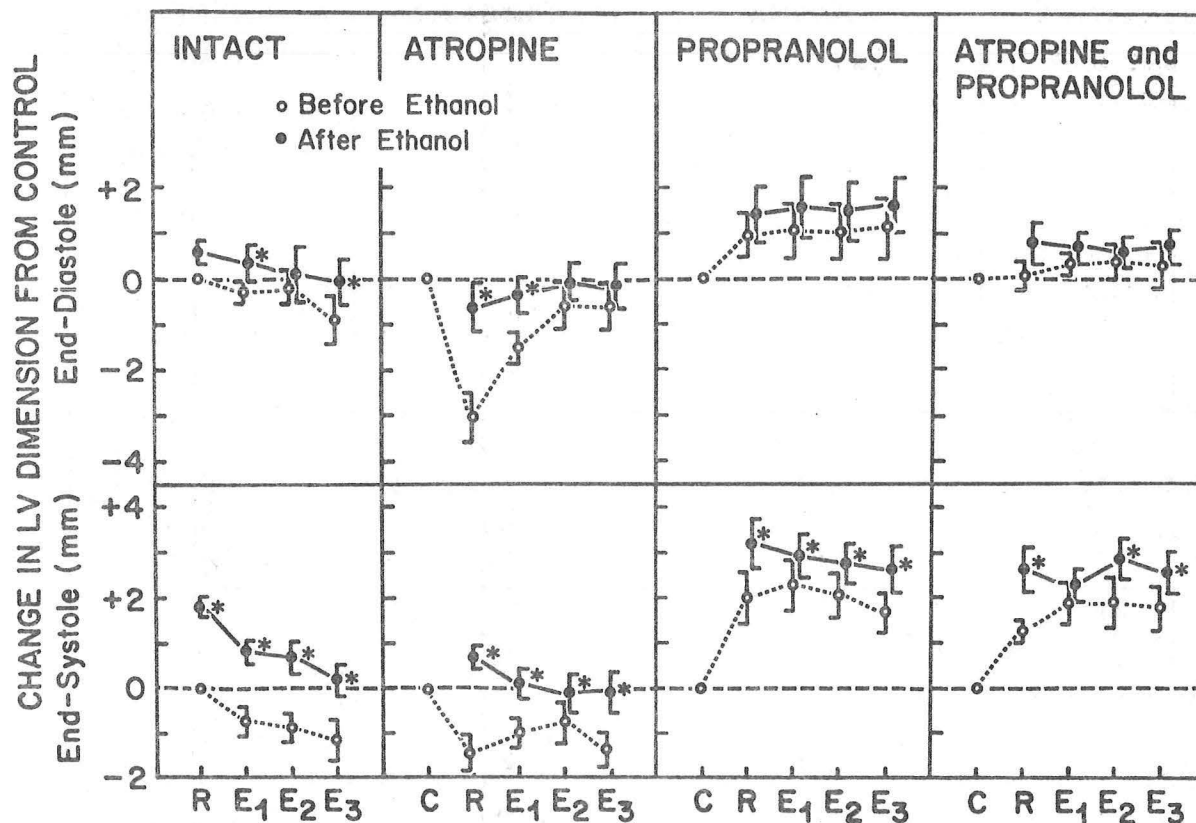


Figure 8. Changes in left ventricular end-diastolic and end-systolic diameters with exercise before and after ethanol. Symbols as in Figure 2. (14)

Injection of atropine increased resting heart rate from 116 ± 2 to 188 ± 7 beats/min, but it produced no change in LV pressure or LV dP/dt max . LVEDP showed a slight decrease, but it was not statistically significant. In spite of marked decrease in stroke volume (-11 ml/beat) cardiac output increased over the resting control level by 710 ml/min (17%) owing to increased heart rate. LVEDD and LVESD decreased by $3.04 \pm 0.53 \text{ mm}$ and $1.43 \pm 0.40 \text{ mm}$, respectively, from the control levels. The decrease in LVEDD is due to diminished ventricular filling. When ethanol was added, resting heart rate decreased to 164 ± 6 beats/min. No change was observed in LV pressure. LVEDP increased to the pre-atropine resting level, but the increase was not statistically significant. LV dP/dt max was decreased by 16% below the post-atropine resting level. LVEDD increased significantly almost to the control level and LVESD increased to a level above control. Stroke volume did not increase in spite of the increase in LVEDD and decrease in heart rate. The heart rate response to exercise after atropine was much larger in comparison with the response with intact autonomic control. However, heart rate after ethanol was significantly lower than pre-ethanol heart rate by 17, 10 and 16 beat/min at light, moderate and heavy loads, respectively. The response of LV pressure to exercise was slightly smaller after ethanol administration, but the difference was statistically significant only at the moderate load. In comparison with pre-ethanol values LV dP/dt max was depressed by 18% at light, 19% at moderate, and 18% at the heavy exercise load. Although stroke volume increased with exercise,

the response was significantly smaller after ethanol administration; a similar finding was observed in the response of cardiac output. Before ethanol exercise increased LVEDD toward the control resting level and its predominant reason was an increase in ventricular filling due to increased venous return, as shown by increase in stroke volume. Post-ethanol LVEDD, which had increased to near control level at rest, did not show additional changes by exercise. It was larger than the pre-ethanol LVEDD during light exercise, but no difference was observed during moderate and heavy exercise. LVESD during exercise, remained at the decreased resting level before ethanol and remained at the higher level after ethanol administration. Therefore, LVESD after ethanol was larger than pre-ethanol value at all levels of exercise (Figures 2 - 9).

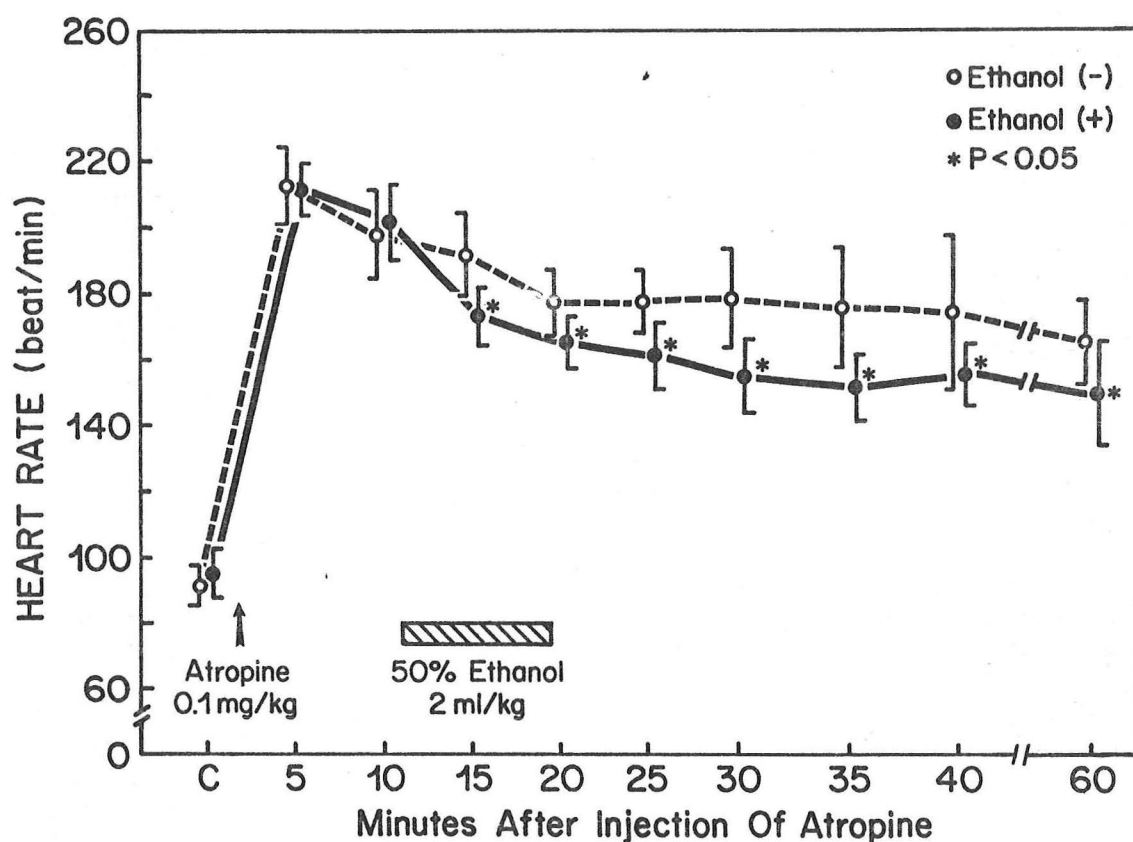


Figure 9. Heart rate versus time after atropine, with and without ethanol. (14)

In the resting condition, injection of propranolol decreased heart rate from 128 ± 5 to 116 ± 8 beats/min, LV dP/dt max was decreased by 26%, stroke volume by 5 ml/beat, and cardiac output by 1212 ml/min (-24%) below the control values. LVEDD and LVESD increased by 0.96 ± 0.48 mm and 1.99 ± 0.59 mm respectively, and LVEDP increased by 4.8 mmHg over the control resting levels. There was no change in LV pressure. When ethanol was added, the heart rate increased to 125 ± 4 beats/min and a slight increase in LV pressure was observed. There were no additional changes in LV dP/dt max, stroke volume, cardiac output or LVEDP. LVEDD after ethanol showed no significant increase over the pre-ethanol level (Figures 2-8).

During exercise after the propranolol injection, the heart rate response was modestly depressed in comparison with that in the control study with intact autonomic nervous system. But there were no differences between pre- and post-ethanol heart rate at each level of exercise. Responses of LV dP/dt max to exercise were markedly depressed after propranolol, and during heavy exercise increased only to the level of the control resting state. Though LV dP/dt max after ethanol was smaller than the pre-ethanol value at all levels of exercise, the differences were not statistically significant. Stroke volume after ethanol was depressed during exercise in comparison with pre-ethanol stroke volume, a similar depression of response to exercise was also significantly larger than pre-ethanol LVESD at all levels of exercise, but post-ethanol LVEDD was not significantly larger than pre-ethanol level during exercise. Thus, the main reason for the depressed stroke volume response to exercise after ethanol seemed to be the decreased ejection fraction of the ventricle. The response of LV pressure to exercise was modestly depressed by propranolol, but ethanol showed no additional effects on the response (Figures 2-8).

The combination of atropine with propranolol resulted in an increase of heart rate from 113 ± 5 to 137 ± 4 beats/min at rest, but the response to exercise was modestly depressed as was observed during the propranolol study. There were no differences between pre-ethanol heart rate and post-ethanol heart rate at each level of exercise. LV dP/dt max was decreased by 15% after the blockers and its response to exercise was severely depressed, as was seen in the propranolol study. Ethanol infusion did not produce additional significant depression in LV dP/dt max both at rest and during exercise. Infusion of blockers and ethanol induced no change in LV pressure at rest. Its response to exercise was depressed, and there was no difference between the pre-ethanol and post-ethanol responses. Stroke volume was decreased by 7 ml/beat at rest after the blockers, but cardiac output was maintained at control levels due to the increase in heart rate. The decrease in stroke volume was associated with increased LVESD but no change in LVEDD. Ethanol administration produced an additional increase in LVESD at rest, but LVEDD changed little. Stroke volume decreased slightly but insignificantly. Response of stroke volume to exercise was modestly depressed both before and after ethanol; as was seen in the propranolol study, stroke volume after ethanol was slightly lower than pre-ethanol stroke volume at all levels of exercise, but the differences were not statistically

significant. LVEDD after ethanol was higher than the pre-ethanol level during moderate and heavy exercise, but no significant difference was observed in LVEDD between pre-ethanol and post-ethanol states during exercise (Figure 2-8).

Many investigators have revealed that acute ethanol infusion depressed myocardial contractility in dogs. In closed chest anesthetized animals, Regan et al (7) demonstrated that left ventricular function is depressed at a blood ethanol level of 110 mg/100 ml. Coronary sinus concentrations of K^+ , SGPT and SGOT were elevated before a significant rise in arterial concentrations. They also showed evidence for a direct cardiac effect of ethanol independent of the central nervous system effect by direct infusion into the left coronary artery. They concluded that ethanol has a direct depressant effect on the myocardium. Newmann et al (15) showed, using a strain gauge in anesthetized open chest dogs, that myocardial contractile force was decreased and left ventricular size was increased at blood levels of 273 mg%. They concluded that the left ventricle was depressed in its function and was operated under increased preload through the limited Frank-Starling mechanism. However, Webb et al (16) found no significant change in myocardial contractility at blood ethanol levels of 900 mg% in isolated heart-lung preparations. In anesthetized open-chest dogs Mierzwiak of 63% mg% and 144 mg% and insignificant depression in the maximum left ventricular dP/dt associated with an increase in left ventricular end-diastolic pressure of only 2.5 cmH₂O.

Reasons for these conflicting results may not be simple, but one of them is the initial base-line condition of the experimental animals. General anesthesia and thoracotomy profoundly depress the base-line state of cardiac hemodynamics due to alterations in autonomic activity as well as direct effects of the interventions (18,19). If the physiologic and pharmacologic stimuli under investigation are superimposed on the depressed base-line state, their effects may be masked and undetectable. In order to keep the base-line condition of animals at normal level, Horowitz and Atkins (10) used chronically instrumented conscious dogs. With the blood ethanol level at 120 mg% and 311 mg% the maximum left ventricular dP/dt was depressed 17% and 30% with elevation in left ventricular end-diastolic pressure and without significant change in left ventricular systolic pressure and heart rate. We concluded that ethanol has a potent direct myocardial depressant. Chronically instrumented intact dogs did not have the influence of anesthesia and thoracotomy.

In the present study with intact conscious dogs intra-atrial injection of ethanol induced significant depression of myocardial contractility both at rest and during exercises, as demonstrated by changes in left ventricular dP/dt and internal dimensions. Maximum left ventricular dP/dt is little altered by steady-state alterations in aortic pressure, and it appears to be much more markedly affected by changes in the contractile state than by alterations in preload (20). It is also related to the frequency of contraction, and a direct linear correlation was described between maximum left ventricular dP/dt and heart rate in an areflexic canine preparation (21). Therefore, if these potential problems are taken

into consideration, the maximum left ventricular dP/dt is a highly sensitive measure for assessing changes in myocardial contractility. In the resting condition with intact autonomic nervous system we found that ethanol infusion consistently decreased maximum left ventricular dP/dt with a slight but insignificant increase in left ventricular end-diastolic dimensions and with no change in left ventricular systolic pressure and in heart rate. These findings suggest diminished myocardial contractility in conscious dogs. Depressed contractility as shown by decreased maximum left ventricular dP/dt was also shown during exercise. Diminished stroke volume associated with a small or no increase in left ventricular end-diastolic dimension and with a larger increase in end-systolic dimension indicated that the extent of muscle fiber shortening is decreased after ethanol in the present study.

Studies on the cardiovascular effects of ethanol during exercise are very limited. To our knowledge there have been no reports about exercise studies in ethanol intoxicated dogs. In normal human volunteers Riff et al (14) found that the response to exercise before and after acute oral administration of whiskey was identical. At rest heart rate and cardiac output were increased with no change in stroke volume at blood ethanol levels ranging from 85 to 136 mg%. Blomqvist et al (5) reported that no significant depressive effect by ethanol was found on the performance of the normal heart at blood ethanol levels of up to 156 mg% and that the circulatory response to maximal work was not affected by ethanol. However, in patients with coronary heart disease Conway (19) showed that a drink of alcohol depressed cardiac output and arterial pressure with no change in heart rate and decreased left ventricular work and tension time index. During exercise after ethanol arterial pressures, cardiac output, stroke volume, left ventricular work and tension time index were lower compared to the pre-ethanol responses. They concluded that ethanol is a myocardial depressant. In the present investigation with intact autonomic nervous control cardiac performance was significantly depressed not only at rest but also during exercise after ethanol administration, as shown by the decreased maximum left ventricular dP/dt and increased left ventricular end-systolic dimension associated with depressed stroke volume. During light and moderate exercise there was no difference between pre-ethanol and post-ethanol levels in heart rate and peak left ventricular pressure, and preload was slightly increased as judged by left ventricular end-diastolic dimension and end-diastolic pressure. During heavy exercise, however, heart rate and peak left ventricular pressure were lower after ethanol, suggesting some alteration in autonomic nervous control.

During heavy exercise in the present study there was no significant increase in end-diastolic dimensions from the resting control value both before and after ethanol. But, when pre-ethanol end-diastolic dimension was compared with post-ethanol dimension, it was significantly larger at mild as well as moderate and heavy levels of exercise, suggesting the Frank-Starling mechanism working as a compensatory mechanism for ethanol-induced reduction in contractility.

Reduced cardiac performance demonstrated in this study can be (mostly) explained by a direct myocardial depressant effect of ethanol. But an indirect cardiac effect via the autonomic nervous control must also be considered. The depressed response of heart rate and peak left ventricular pressure during heavy exercise after ethanol may suggest this possibility as well as direct depressive effect. A useful method for studying the autonomic effects upon cardiac function is to analyze the effects of loss of beta-adrenergic and parasympathetic stimulation by using pharmacological blockade (22). In the present study cardiac performance was definitely depressed by infusion of a selective beta-adrenergic receptor blocker (propranolol) and of both beta-adrenergic receptor blocker and muscarinic blocker (propranolol and atropine), as shown by the decrease in maximum left ventricular dP/dt and by a reduced extent of muscle fiber shortening. Depression of cardiac performance by adding ethanol over the autonomic blockers was less remarkable, but a further increase in left ventricular end-systolic dimension with no significant increase in end-diastolic dimension demonstrated a direct myocardial depressant effect of ethanol. Although it is possible that a direct myocardial depressant effect of propranolol, independent of the drugs' beta-adrenergic blocking activity, influenced these results, such direct effects are unlikely at the dose of propranolol used in this study (23).

When parasympathetic control was blocked by atropine and sympathetic tone was maintained relatively high, ethanol infusion decreased heart rate at rest as well as during exercise. Ethanol infusion after selective beta-adrenergic receptor blockade increased heart rate at rest, but this finding was not observed during exercise when parasympathetic tone was withdrawn (22). These responses of heart rate in the autonomic blocking studies can be best explained by suppression of both sympathetic and parasympathetic nervous tone with acute injection of ethanol in conscious dogs, whose autonomic nervous control was maintained intact. Because of the relatively small influence of vagal stimulation on the ventricular myocardium (24), a direct myocardial depressant effect and sympathetic depressant effect of ethanol will overwhelm the stimulant effect on the myocardium expected from depression of parasympathetics; therefore, depression in cardiac performance induced by ethanol may be mediated both by its direct depressant effect on the myocardium and by its indirect effect via decreased sympathetic tone.

In anesthetized open-chest dogs Mierzwiak et al (17) showed that no change or minimal change in contractility was observed during control studies, while dogs made areflexic by reserpine and vagotomy showed a more marked depression in contractility. Nakano et al (25) found in anesthetized open chest dogs that myocardial depression from ethanol was markedly greater in reserpinized dogs than in control dogs and concluded that the direct myocardial depressant action of ethanol was offset by myocardial stimulation mediated by catecholamine secretion. In a study with anesthetized closed-chested dogs, Wong (26) observed that autonomic blockade by both atropine and propranolol produced no change in cardiac output left ventricular end-diastolic pressure (LVEDP), heart rate or left ventricular minute work, while ethanol with blood levels of over 200 mg% produced a decrease in cardiac output, an increase in LVEDP and no change in heart rate and left ventricular minute work. The combination of ethanol with blockers produced a more

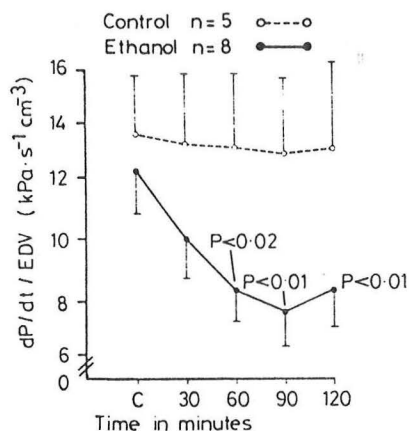
pronounced decrease in cardiac output and left ventricular minute work and an increase in LVEDP and no change in heart rate. She concluded that alcohol uniformly depressed the heart after autonomic blockade, but this effect could be masked by extracardiac mechanisms mediated through the autonomic nervous system when it is unblocked.

Reasons for the discrepancy between these previous reports and ours are not clear, but one important difference is the basal condition of experimental animals. We used conscious dogs with intact autonomic control, while they used anesthetized dogs with depressed autonomic nervous tone and central nervous function. The vagal and sympathetic cardiac and constrictor pathways are tonically active at rest and recent analysis has suggested that some of the rhythmic changes in discharge are generated by pacemakers located at several levels in the central nervous system (27).

It is generally accepted that ethanol depressed the nervous system by a primary direct action on the excitable membrane (28). Although Grollman (29) pointed out the importance of central nervous components in the action of ethanol on autonomic functions, such relationships have been little studied. The present findings suggest the suppression of both sympathetic and parasympathetic tone by ethanol could be explained by its depressant effect on the central nervous system pacemakers and on the autonomic centers in the brain. If the basal condition of central nervous system is depressed by anesthesia, the CNS depression by ethanol may not be observed, Kalant (30) stated that most of the constellation of ethanol intoxication in vivo appeared consistent with the classical explanation of anesthetic action via depression of the midbrain reticular activating system.

Another factor that may complicate ethanol effects is the blood level of ethanol and its metabolite, acetaldehyde. The cardiac stimulant effects of acetaldehyde may overlap and mask depressant effect of ethanol (31) (Figures 10-13). As liver alcohol dehydrogenase is saturated at low concentrations of ethanol, the rate of decay of ethanol is constant regardless of its tissue concentration (32). This suggests that blood acetaldehyde level is expected to be plateau in the face of varying blood ethanol levels (33). When ethanol is given directly into the circulation in a short period of time, as in most animal experiments, blood ethanol levels will rise faster and higher than in oral administration and it will be relatively much higher than acetaldehyde level. If so, depressant effect of ethanol may overwhelm the stimulant effect of acetaldehyde. But if ethanol level rises slower and to lower levels as in case of most human studies with oral ethanol ingestion (4; 5,34,35,36), the depressant effect may be masked by stimulant effect of acetaldehyde. Divergent results in these human studies may be attributed to this factor.

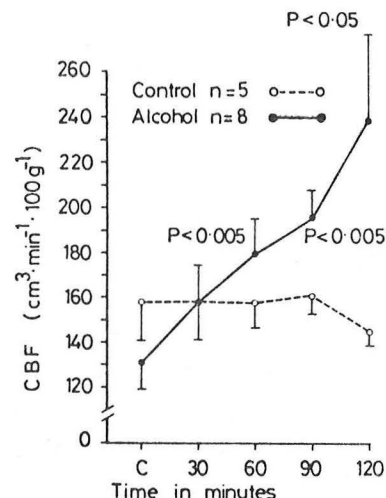
Figure 10 (31)



Effect of ethanol on cardiac contractile state. Peak dP/dt /left ventricular end-diastolic volume (EDV) declines significantly during ethanol infusion. Ethanol was infused over 90 min. Mean values $\pm$ SEM. Shown are significance of change when compared to control (C) values before ethanol infusion.

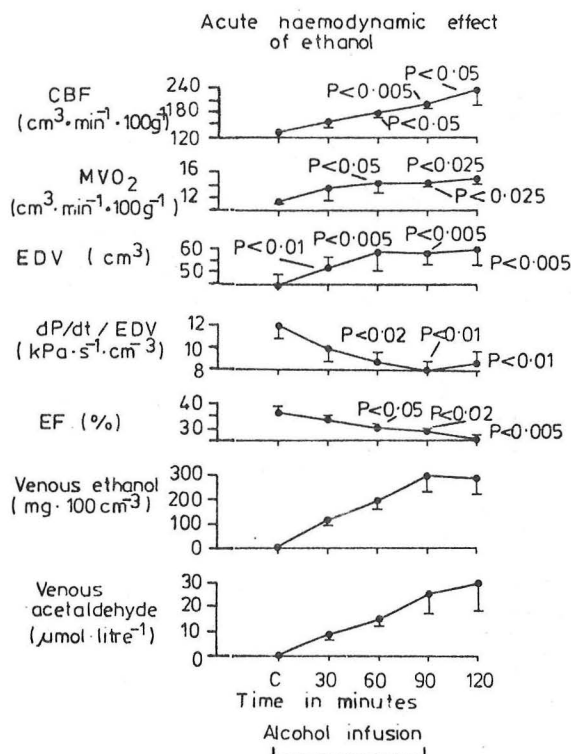
Conversion: 1 kPa $\approx$ 7.5 mmHg.

Figure 11 (31)



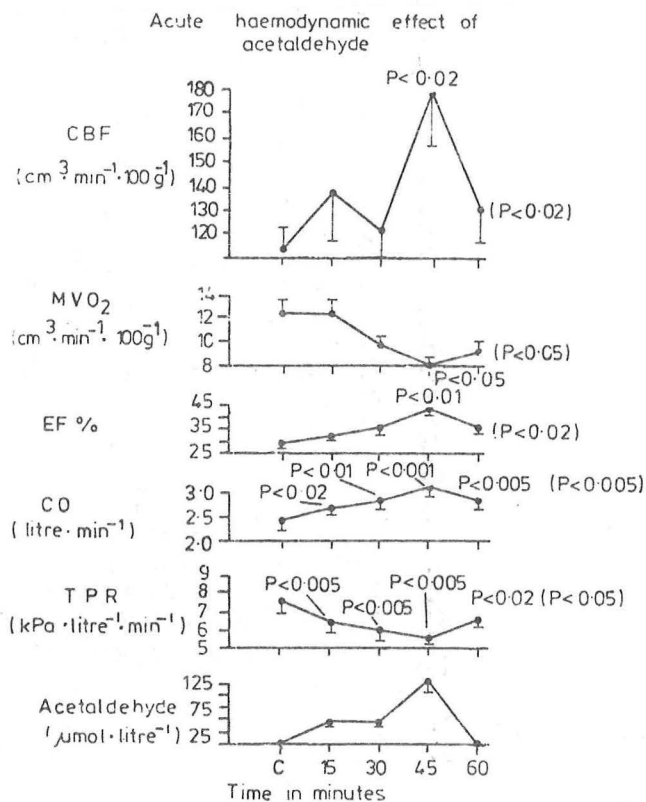
Effect of ethanol on coronary blood flow CBF. A progressive increment of coronary blood flow occurs with ethanol infused over 90 min. Mean values $\pm$ SEM. Shown are significance of change when compared with control values (C) before ethanol infusion.

Figure 12 (31)



Acute haemodynamic effects of ethanol. As ethanol levels increased, acetaldehyde increased concomitantly, while ejection fraction (EF), peak dP/dt /left ventricular end-diastolic volume (EDV) declined and left ventricular end-diastolic volume, myocardial oxygen consumption and coronary blood flow (CBF) increased. Mean values $\pm$ SEM. Shown are significance of change when compared to control values (C).

Figure 13 (31)



Acute haemodynamic effects of acetaldehyde. Low dosage infusion occurred during the first 30 min, high dosage infusion between 30 to 45 min and final measurements made 15 min after high dosage infusion was discontinued (60 min). Mean values $\pm$ SEM. Abbreviations: TPR=total peripheral resistance; CO=cardiac output; EF=ejection fraction; CBF=coronary blood flow. Shown are significance of change when compared to control (C) values. Values in parenthesis are significance of change at high dosage infusion when compared to values 15 min after infusion discontinued.

It was concluded that, in intact unanesthetized dogs, (1) acute intraatrial injection of ethanol showed a potent myocardial depressant effect, (2) ethanol suppressed both sympathetic and parasympathetic autonomic tone probably through depression of central nervous system, and (3) the depressant effect on the myocardial contractility was best explained by a direct myocardial depressant effect and by indirect effect through sympathetic autonomic depression.

Radioactive microsphere technique is relatively simple and extremely accurate method to measure distribution patterns of systemic arterial blood flow, if it is appropriately and correctly applied (38). When microspheres larger than 15- μm in diameter are used, the magnitude of arteriovenous shunting was smaller than 2% in the brain, myocardium, kidney, intestine and lung (39,40).

Our data showed that total coronary blood flow in resting conditions was decreased by ethanol infusion (Figure 14). But the flow as a per cent of cardiac output was not changed because of the similar decline in cardiac output. Exercise increased pre-ethanol and post-ethanol coronary flow to the same level, and the flow as per cent of cardiac output was

still the same as the resting level. Oxygen consumption of the myocardium is a primary factor regulating coronary blood flow (41). Among the major determinants of myocardial oxygen consumption (42), the contractile state of the myocardium and external work of the heart were decreased in the present study, suggesting a decline in oxygen consumption. The unchanged heart rate and LV pressure would not affect the oxygen requirements. Intra-myocardial tension is another major determinant, but its importance in ethanol intoxication has not been sufficiently established. Our recent observation on intact unanesthetized dogs with sonocardiometers showed that ethanol did not increase the end-diastolic dimension of the left ventricle and increased the end-systolic dimension (14). But changes in wall thickness were not studied. Hence a decrease in the myocardial oxygen requirement induced by depressed ventricular contractility and external work seems to be the primary factor that reduced coronary blood flow in acute ethanol intoxication. During exercise after ethanol, ventricular contractility was still depressed, while coronary blood flow was increased to the control exercise level. This finding agrees with the hypothesis that the depressed contractility was not due to reduced coronary flow but to a direct myocardial depressant effect of ethanol.

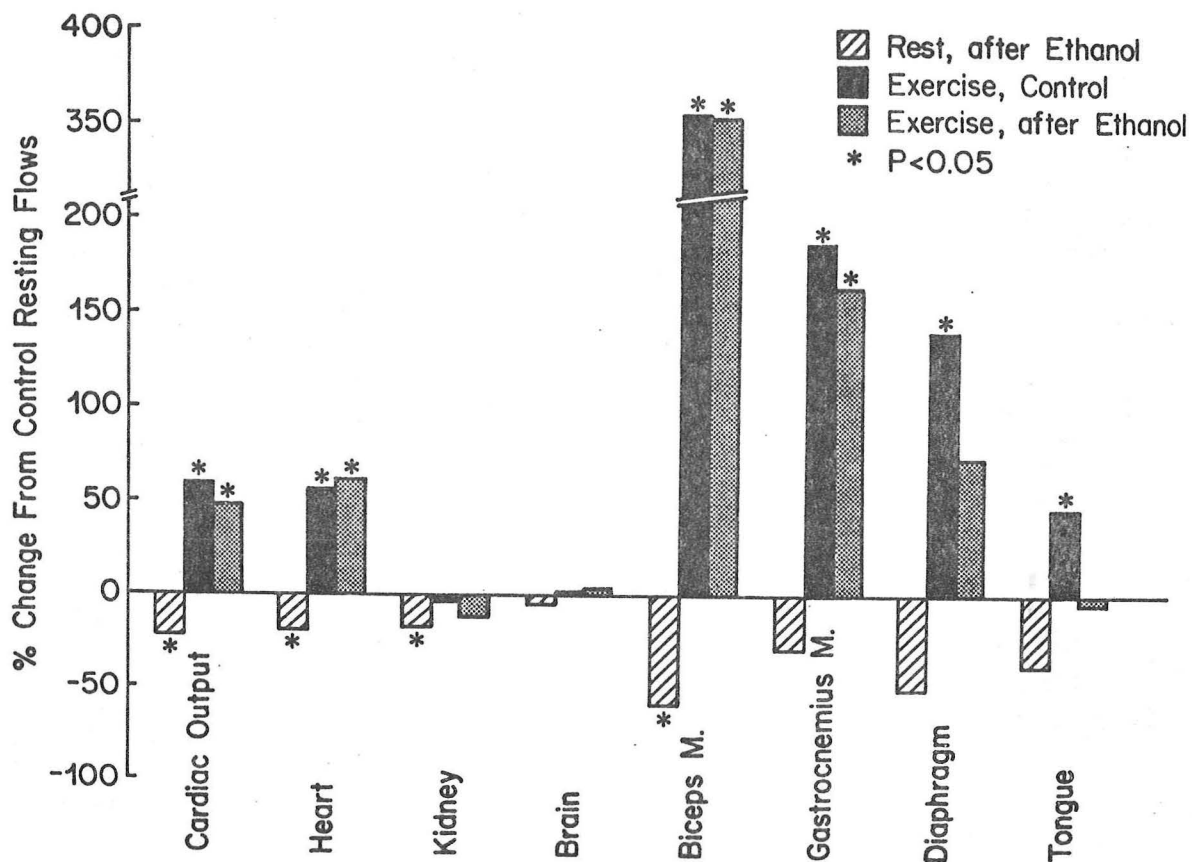


Figure 14. Regional blood flows as a per cent of rest pre-ethanol with exercise before and after ethanol (37).

All previous animal experiments about the effect of ethanol on coronary flow were made under general anesthesia and the results were conflicting. With an intravenous infusion of ethanol to the open-chest dogs, Lasker et al (43), observed a rise in coronary flow and a decline in resistance at the alcohol levels higher than 50 mg%, and the increase in the flow appeared to be proportional to the blood level of ethanol. Ganz (44) also found an increase in coronary flow with decreased coronary vascular resistance with a 20 minutes infusion of 58 mg/kg/min ethanol. The rise in myocardial oxygen consumption in the presence of a decrease in external work meant that the efficiency of the left ventricle decreased. Schmittthener et al (45) found no increase in coronary flow with increased cardiac output and left ventricular work in open-chested dogs at blood ethanol level of 70-120 mg%. Webb and Degerli (46) infused 0.5, 1.5 and 5.0 g/kg. of ethanol intravenously into anesthetized dogs and observed diminished coronary flow and increased resistance at all levels. Blood ethanol levels in their study ranged from 42 to 87 mg% with 0.5 g/kg and from 132 to 207 mg% with 1.5 g/kg. Decreased coronary flow was also observed by Regan et al (7) stated that the coronary flow reduction appeared to represent a secondary response to the decline in ventricular activity during ethanol infusion. These conflicting results are probably due to the variation in experimental conditions, but the variation in blood ethanol level does not seem to explain them. However, in conscious animals coronary flow declines in proportion to cardiac output.

It has been proven that the brain has autoregulatory mechanisms to keep its blood flow at a constant level under various experimental conditions (47,48). Even during severe exercise cerebral blood flow was remarkably constant in dogs (49) and in humans (50). The present study demonstrated constant cerebral blood flow either after ethanol infusion or during exercise independent of changes in cardiac output, giving another proof for the autoregulatory mechanism. However, there still remains a possibility that the effect of ethanol on cerebral circulation may be dose-dependent; Battey et al (51) reported in a human study that low blood ethanol levels did not change cerebral blood flow, while in cases of severe intoxication with blood ethanol levels as high as 320 mg%, increased cerebral blood flow with decreased oxygen consumption was observed.

Effects of ethanol on pancreatic and other abdominal viscera regional blood flow in conscious dogs were reported by Horwitz and Myers (52). They administered ethanol intravenously and measured organ flows by the radioactive microsphere method. No changes were observed in flows to the pancreas, kidneys, spleen, stomach, intestines and adrenal glands after 0.5 g/kg of ethanol. But after 1.5 g/kg of ethanol (average blood level was 297 mg/100 ml) a significant depression in pancreatic flow was observed in association with an increased pancreatic vascular resistance, although there were no changes in flow or resistance in the other organs. They concluded that high dose of ethanol induces vasoconstriction of the pancreas, which might be important in the pathogenesis of pancreatitis. Our

investigation in conscious dogs showed a significant decrease in renal blood flow and no changes in flows to the other abdominal organs at rest (Figure 15). The low dose of ethanol administered to our dogs (0.8 g/kg) explains why we did not observe a decreased flow in the pancreas. However, reasons for the discrepancy in renal blood flow appeared to be dependent on decreased cardiac output at rest, as the ratio of renal blood flow to cardiac output was kept constant before and after ethanol infusion. It is known that renal blood flow during exercise does not change in dogs (53-55), while in humans and pigs blood flow to the skeletal muscles is augmented by reducing blood flow to the kidneys (56-58). Our data during the control exercise study were compatible with these previous reports. Renal blood flow after ethanol which had been depressed at rest, increased nearly but not completely, to the control exercise level during exercise, still showing its dependency on cardiac output.

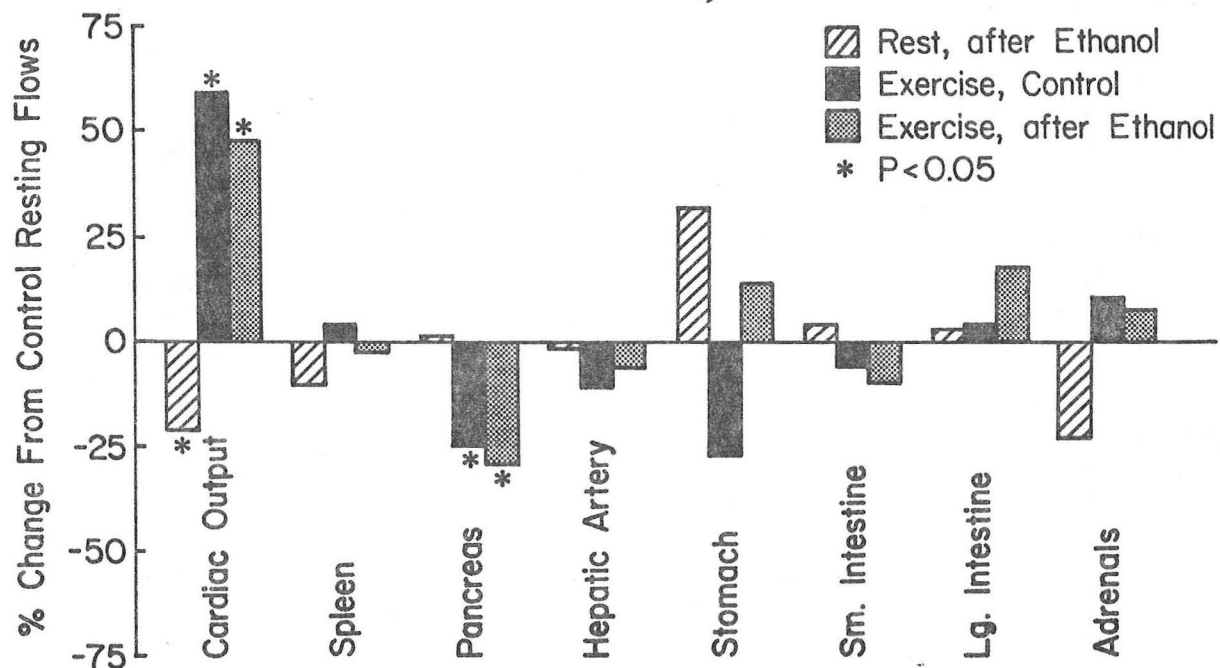


Figure 15. Regional blood flows as a percent of rest pre-ethanol with exercise before and after ethanol. (37)

Several studies were made on the effect of ethanol on hepatic circulation by the bromsulphalein method. Estimated hepatic blood flow measured with this technique reflects blood flow through the splanchnic vascular bed, while hepatic flow measured by microsphere technique is the flow just via the hepatic artery. But the sum of flows to the spleen, pancreas, stomach and intestines measured by microsphere technique gives the flow through the portal vein and

appears to be roughly equivalent to estimated hepatic blood flow by bromsulphalein method (59). Values of hepatic flows via the portal vein and hepatic artery were comparable to previous data measured by other techniques (59). In the present study neither ethanol administration nor exercise induced changes in hepatic flows. No change in estimated hepatic blood flow was reported by Smythe et al (60) in anesthetized dogs after feeding ethanol with gavage tube, by Horvath and Willard (61) in anesthetized dogs during and constant infusion of ethanol, and by Castenfors et al (62) in conscious healthy humans during and following intravenous infusion. A significant increase in estimated hepatic blood flow was shown by Mendeloff (63) in human subjects during the intravenous infusion of ethanol. This increase could not be explained by the increase in cardiac output and seemed best described as due to a lowering of the peripheral resistance of the splanchnic bed and is inconsistent with most other studies.

It is reported that effect of exercise on splanchnic blood flow distribution depends upon the severity of exercise and the splanchnic organs do not respond homogeneously to exercise (64); differences in local conditions, the complex vascular network, and the population and activity of sympathetic and parasympathetic nerves make possible a variety of local flow responses. In some studies with moderate and severe exercise flow to the stomach and intestine was decreased (55,64), but in some others no changes were found (65,66). Vatner et al (65) showed that, in dogs the spleen contributed to the response to exercise by increasing hematocrit sufficiently to obviate reduction and diversion of visceral flows. Our data showed no statistically significant change in the flows to the splanchnic organs except the pancreas, during exercise both before and after ethanol. Decreased pancreatic flow during mild to moderate exercise in the present study is not compatible to the previous report by Sanders et al (64) in which pancreatic flow did not change during severe exercise. It is not clear if differences in the severity of exercise can explain these differences.

This study demonstrated that flows to the skeletal muscles were decreased after ethanol at rest. When the total amount of muscle mass in the whole body is taken into account, decreased cardiac output induced by ethanol seemed to be met mainly by reduction in flows to the skeletal muscles. Reduced flows to the heart, kidneys or some other organs could explain only a small part of cardiac output change. Graf and Strom (67), Fewings et al (68), and Gillepsie (69) observed that the decrease in skeletal muscle flow was induced by vasoconstriction either by intra-arterial infusion or by oral administration of ethanol. The vasoconstriction is due to a direct action of ethanol (68).

In conclusion ethanol had potent depressant effect on cardiac function. Depressed ventricular contractility and external work appeared to reduce myocardial oxygen requirement and decrease coronary blood flow. Renal blood flow was decreased but all other visceral organs did not show a significant change. The decreased cardiac output induced by ethanol seemed to be met mainly by reduced flow to the inactive skeletal muscles.

To summarize the hemodynamic effects of ethanol:

- 1) Ethanol has a direct depressant effect on the myocardium.
- 2) Ethanol suppresses the CNS to decrease both sympathetic and parasympathetic tone.
- 3) The direct depressant effect of ethanol is minimized by anesthesia which also has a direct depressant effect.
- 4) The central decrease in sympathetic and parasympathetic tone is abated by anesthesia.
- 5) The metabolite acetaldehyde has a positive inotropic effect which counter balances the negative inotropic effect of ethanol.
- 6) Regional blood flow reflects changes in cardiac output with only the pancreas and inactive muscles decreasing more than cardiac output at high levels.

Alcoholic Cardiomyopathy

Congestive cardiomyopathy secondary to excessive alcohol consumption is believed to be the most common presentation for cardiomyopathy in western Europe and the United States (69). It has been estimated that two thirds of the adult population uses alcohol and that more than ten percent (10%) are heavy users (70). Braunwald has proposed that the consumption of alcohol may result in myocardial damage by three basic mechanisms: 1) direct toxic effects; 2) nutritional effects, most commonly in association with thiamine deficiency which leads to beriberi heart disease, and 3) rarely, toxic effects due to additives in the alcoholic beverage (cobalt) (70,71).

The evidence that alcohol has a direct toxic effect on the myocardium has been the subject of debate for many years. Postmortem studies have shown histologic changes in ninety per cent (90%) of alcoholics dying from any cause (72). However, lack of quantification of alcohol intake, nutritional status, or electrolyte imbalances have made correlation of these data very difficult. In addition animal studies have presently been short term with low doses of alcohol (73).

In 1974 Regan et al reported an excellent study in dogs followed for 19 months (74). For the length of the study, the animals were fed 36% of their calorie intake as ethanol. During the study, the dogs maintained their weight, hematocrit, serum proteins, vitamins, and electrolytes within the same range as the normal controls.

The alcoholic dogs and normal controls were studied at similar heart rates and aortic pressure. The alcoholic dogs showed a higher left ventricular end-diastolic pressure at rest even though the end-diastolic volume was smaller suggesting a change in stiffness. When the ventricle was stressed by raising after-load with angiotension, stroke output and stroke work increased significantly in controls but not in alcoholic hearts. This suggests a deterioration in function and loss of normal adaptive responses. In alcoholic dogs only the left ventricular end-diastolic pressure was elevated. It is interesting to note that the end-diastolic volume remained smaller than controls. To investigate the role of preload, both the alcoholic and control dogs were infused with normal saline. Both groups increased end-diastolic volumes similarly, however the left ventricular end-diastolic pressure rose a significantly greater degree in the alcoholic dogs suggesting that there is a marked change in stiffness as well as function (74).

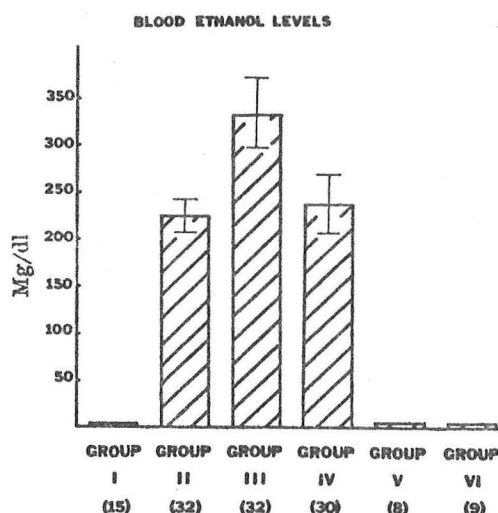
Histologic studies were undertaken on both groups of dogs studied by Regan et al (74). Using alcian blue stain, Regan et al found a glycoprotein-like substance in the left ventricle of alcoholic dogs but not controls. Regan suggested that these deposits in the interstitium may limit the rapid accessibility of calcium to intracellular sites leading to development of heart failure. Though it has been shown that alcohol acutely decreases exchangeable calcium in the cells of rat aorta and vascular smooth muscle (75), no long range studies have been undertaken to prove this hypothesis.

Regan et al (76) has shown that the QRS duration is prolonged as well as the H-V time (His bundle to ventricular activation time) was prolonged. He also revealed that these prolongations correlated with dilatations of the intercalated discs on electron microscopy though the meaning of this correlation is not known.

Numerous metabolic derangements have been described in experimental alcoholic models but the significance of these findings is not fully understood. The interrelationship of alcohol and acetaldehyde on these metabolic derangements must be considered. Weishaar et al (77) tried to dissect out the differences by giving one group of rats alcohol only, a second group pargyline (PAR) - a monoamine oxidase inhibitor which increases acetaldehyde after ethanol ingestion (78,79). Another group received 4-methylpyrazole (4-MP) which is an inhibitor of alcohol dehydrogenase (80).

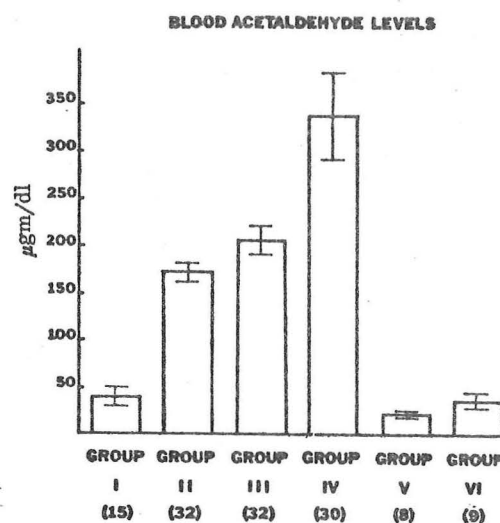
Weishaar's results are shown on the following figures and tables (77):

Figure 16 (77)



Ethanol levels in the blood. The groups listed represent the following: Group I: non-ethanol-containing diet plus daily injections of saline; groups II, III, and IV: ethanol-containing diet and daily injections of saline, 4-MP, and PAR, respectively; group V: non-ethanol diet plus 4-MP injections; group VI: nonethanol diet plus daily injections of PAR. Blood ethanol levels were significantly higher ($P < 0.05$) in the groups consuming the ethanol-containing diet (groups II, III, and IV) when compared with the animals consuming the isocaloric nonethanol diet. In addition, ethanol levels in blood samples taken from the group III animals (ethanol + 4-MP) were significantly greater ($P < 0.05$) than in either group II or group IV. Data represent means $\pm$ S.E. Numbers in parenthesis represent number of animals examined in each group.

Figure 17 (77)



Acetaldehyde levels in the blood. Blood acetaldehyde levels of the animals in groups II, III, and IV were all significantly higher ($P < 0.05$) than acetaldehyde levels in groups I, V, or VI animals. Also, blood acetaldehyde levels in the group IV rats (ethanol + PAR) were significantly elevated ($P < 0.05$) when compared with either group II or group III. Data represent means $\pm$ S.E. Numbers in parentheses represent number of animals examined in each group.

Table 4 (77)

Effects of Ethanol and Acetaldehyde on in vitro Contractility*

	Group I (12)	Group II (18)	Group III (11)	Group IV (17)	Group V (12)	Group VI (14)
P_o	646 ± 45	481 ± 42	480 ± 58	427 ± 27	675 ± 60	612 ± 45
t_o	72 ± 5	80 ± 9	95 ± 7	83 ± 9	77 ± 9	74 ± 10
dp/dt_{max}	1025 ± 108	644 ± 84	609 ± 118	480 ± 51	1013 ± 92	1136 ± 100
V_{max}	0.543 (0.447-0.665)	0.400 (0.294-0.528)	0.349 (0.271-0.432)	0.376 (0.312-0.443)	0.480 (0.399-0.572)	0.463 (0.399-0.528)

* Groups listed are described in text. P_o = Maximum developed tension (mg/mm²); t_o = time to peak tension (sec); dp/dt_{max} = maximal rate of tension development (mg/min/mm); V_{max} = maximal shortening velocity at zero load (muscle length/sec). Data represent the mean ± S.E. for P_o , t_o , and dp/dt_{max} . V_{max} data are given with 95% confidence limits. Nonoverlapping confidence limits are used as criteria for significant alterations. Numbers in parentheses represent the number of preparations in each group. There were no significant differences in t_o between the six groups. Significant changes ($P < 0.05$) were found to occur when the following groups were compared: group I vs. groups II, III, IV (P_o and dp/dt_{max} were significantly reduced in groups II, III, and IV); group V vs. group III (P_o and dp/dt_{max} were significantly reduced in group III); group VI vs. group IV (P_o and dp/dt_{max} were significantly reduced in group IV).

Table 5 (77)

Effects of Ethanol and Acetaldehyde on Protein Synthesis*

	Group I (7)	Group II (6)	Group III (6)	Group IV (6)	Group V (6)	Group VI (5)
Myocardial protein (d.p.m./10 mg)	832 ± 59	711 ± 121	556 ± 106	565 ± 110	892 ± 71	930 ± 95

* Groups listed are described in text. Data represent the mean ± S.E. The numbers in parentheses represent the number of animals in each group. Significant reductions ($P < 0.05$) were found to occur when the following groups were compared: group V vs. group III (glycine-2-C¹⁴ incorporation significantly reduced in group III); group VI vs. group IV (glycine-2-C¹⁴ incorporation significantly reduced in group IV).

Table 6 (77)

Effects of Ethanol and Acetaldehyde on Mitochondrial Respiration*

Substrate	Group I (6)	Group II (9)	Group III (10)	Group IV (9)	Group V (7)	Group VI (8)
Glutamate (7.5mM)-oxaloacetate (1.5mM)	185 ± 11	164 ± 9	148 ± 8	147 ± 9	186 ± 10	164 ± 9
Succinate (7.5mM)	244 ± 11	223 ± 9	200 ± 8	209 ± 9	251 ± 10	225 ± 9
Ascorbic (5mM)-TMPD (0.2mM)	303 ± 12	291 ± 10	245 ± 9	254 ± 10	315 ± 11	278 ± 10

* Groups listed are described in text. The results are expressed as nanomoles of oxygen consumed/min/mg mitochondrial protein. Data represents the mean ± S.E. Numbers in parentheses represent the number of preparations in each group. Significant reductions ($P < 0.05$) were found to occur when the following groups were compared: group I vs. groups III or IV (respiration with all three substrates significantly reduced in groups III and IV); group V vs. group III (respiration with all three substrates significantly reduced in group III); group II vs. group III or IV (respiration with ascorbate significantly lower in groups III and IV).

As can be seen both alcohol and acetaldehyde appear to depress mitochondrial respiration, inhibit protein synthesis as well as having a marked depressive effect on the myocardium, Weishaar et al (77) could not dissect out a difference between alcohol and acetaldehyde and felt that both were responsible for metabolic and functional alterations. As was previously noted there are marked functional differences between alcohol and acetaldehyde. Regan et al (81) and Mendoza et al (82) have shown marked depression of function while others have shown increases in function by acetaldehyde (83, 84). In-vitro studies have been shown that acetaldehyde causes inhibition of NAD-linked mitochondrial respiration (85), inactivation of coenzyme A (86), induction of catecholamine release (87), and inhibition of protein synthesis (88); while ethanol by itself did not alter these metabolic functions. Weishaar et al (77) in the only in vivo alterations of alcohol and acetaldehyde concentrations showed similar metabolic changes by both. Whether this is a difference between in vivo and in vitro studies or is a methodologic problem in Weishaar's studies remains to be determined.

Studies on the effect of prolonged alcohol exposure on mitochondrial function in heart and liver have been considerable (85, 88-92). One study has revealed that there is a progressive decline in mitochondrial respiration with time in exposure of 4 to 8 weeks resulting in a 20% decline. Other studies have also shown declines.

Shreiber et al (88,93) reported that acetaldehyde reduced protein synthesis in perfused guinea pig hearts but that alcohol had no effect until lethal levels were reached. Again, Weishaar et al (77) is in disagreement with in vivo studies but the question of methodology still persists.

Other studies have shown interference of the transport and binding of calcium and in myofibrillar ATPase (94,95). In addition alcohol results in loss of potassium from myocardial cells, decreased uptake of free fatty acids, but increased myocardial extraction of triglyceride (96). Magnesium deficiency is also seen (97).

Hence there is strong evidence which favors a direct effect of alcohol on the myocardium through various physiologic and metabolic alterations. However, there is no definitive link as true cardiac failure has never been induced in any of the experimental animal studies. Hence while some or all of these factors may play a role, some unknown genetic or other toxic parameter may be important.

An alternate theory is that thiamine deficiency or some other nutritional factor may be involved. The effects of beriberi are well described. Classical cardiac beriberi has been called Oriental beriberi (70) which is caused by classical thiamine deficiency. Oriental beriberi is characterized by high output failure with dilatation of the ventricle and the opening of shunts. It has been proposed that there is also an Occidental beriberi with low cardiac output and dilatation but this is an unproven hypothesis (70).

The presence of some other toxic substance such as cobalt may be a causative factor in alcoholic cardiomyopathy. In 1966 fulminating congestive heart failure was described in patients in several cities

(Quebec City, Canada; Omaha, Nebraska; Minneapolis, Minnesota; and Belgium) who drank beer to which cobalt had been added to stabilize the foam (71). Pathologic findings included a dilated, hypertrophied heart with a large pericardial effusion (90). Microscopic examination revealed myofibrillar hyaline necrosis as well as myocardial vacuolization and degeneration. Of those presenting with cobalt intoxication 40% died within 3 days. Nearly one half of the survivors were left with a chronic cardiomyopathy.

In summary it is well known that alcohol and acetaldehyde both cause acute and chronic changes in the functions and metabolism of the heart. In addition thiamine deficiency can cause high output failure. Cobalt, though it can cause a low output cardiomyopathy is no longer present in beer. Hence we are left with many potential causes of alcoholic cardiomyopathy however, none can be shown to be etiologic and none can cause congestive heart failure in experimental models. Hence some other unknown factors must play a role in the development of alcoholic cardiomyopathy. It is possible that a second stress such as hypertension or heavy physical labor while drinking may be important but this has not been proven.

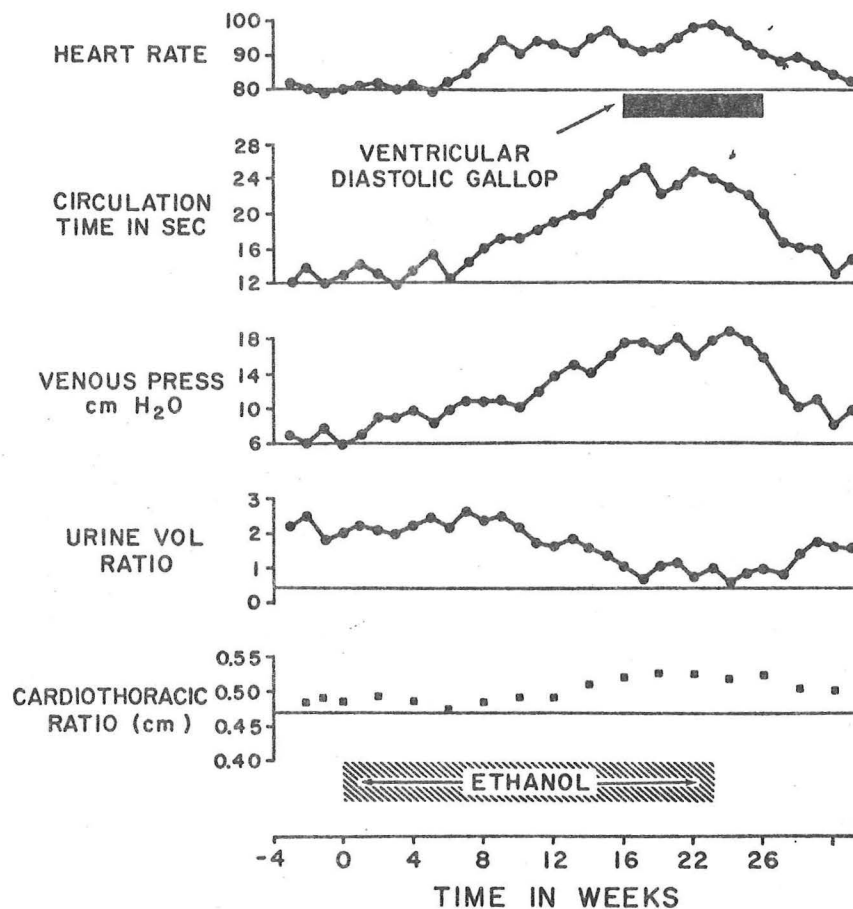
Preclinical Manifestations of Alcoholic Cardiomyopathy

General studies have been performed in alcoholics without evidence of heart disease. Regan et al (98) studied patients with no history of heart disease or malnutrition. All patients had a 10-15 year history of alcoholism with daily consumptions of 0.5 to 2 pints/day. Liver biopsies in these patients revealed fatty liver without fibrosis. Catheter studies using afterload elevation with angiotensin revealed a significantly greater rise in left ventricular end-diastolic pressure and less increase in stroke volume than non-alcoholic controls. In addition diminished left ventricular performance was seen during exercise in cirrhotic patients, abnormal left ventricular function in alcoholic subjects have also been reported using non-invasive modalities (99,100). In patients without evidence of heart disease they found prolonged PEP and increased PEP/LVET. These are similar to findings found in animal models. The increased stiffness of the ventricle as well as the glycoprotein accumulation in the intersitium has been shown to occur in the non-cardiac alcoholic (74,99-101). These preclinical manifestations which are seen in male alcoholics have not been found in female alcoholics suggesting a hormonal or sexual difference in the development of these abnormalities (100). These studies suggest that a preclinical state exists in males but this remains to be proven. The correlation of these preclinical findings with animal studies is fascinating; however the relationship of these findings to failure is unknown because none of these patients have been followed to failure. This could be an independent process identical to the animal models; to induce failure may require other unknown factors.

Cardiac Failure

Regan et al (98) have described one interesting patient that they have studied in depth (figure 18). A patient who had a previous bout of failure but who was well compensated with abstinence. The patient was placed on a good diet and was administered 12-14 oz. of Scotch daily for 5-1/2 months. After six (6) weeks, the resting heart rate began to rise followed by prolongation of the circulation time and elevation of venous pressure. After four (4) months a ventricular gallop appeared and remained until the alcohol was stopped. After cessation of alcohol all parameters returned to normal without other therapy. Hence it appears that in this patient that failure was related to alcohol.

Figure 18 (98)



Evidence of cardiac decompensation developing during chronic ethanol intake. The weekly values depicted above represent the average of the daily measurements for heart rate and urine volume, and the biweekly determination of circulation time (arm-to-tongue) and venous pressure. These parameters became progressively abnormal after 2 wk of ethanol, with the eventual development of a ventricular diastolic gallop. The abnormalities disappeared after interrupting alcohol intake.

In patients where there is progression of the disease, pulmonary congestion may lead to dyspnea on exertion or paroxysmal nocturnal dyspnea (102). With repeated or sustained episodes, pulmonary hypertension and right heart failure may develop. The left ventricular dilatation and diminished papillary muscle function may lead to mitral insufficiency. Unless the mitral insufficiency is severe, it will frequently disappear and the moderate cardiomegaly may return to normal. Late in the course mural thrombi may give rise to systemic or pulmonary emboli. Males between 30 and 55 years of age tend to dominate the patients who develop alcoholic cardiomyopathy. Many times a history is very difficult to obtain. Individuals may have a history of social disruption, accident proneness, or a family history. Usually they drink intoxicating amounts of alcohol for years, but cirrhosis and peripheral neuritis are rare. Other forms of cardiovascular disease are usually not present. Diastolic hypertension is common especially after a binge drinking episode so that many are diagnosed improperly as hypertensive. Blood pressures usually normalize when the failure clears. Ethanol may cause elevations of blood pressure due to multiple mechanisms (103-108)

Pathology

Alcoholic cardiomyopathy produces changes both grossly and microscopically similar to other forms of congestive cardiomyopathy (110,111). Some studies have revealed edema of the vascular wall and perivascular fibrosis of intramyocardial coronary arteries (112,113). It has been hypothesized that the damage might be secondary to disease of the small intramural coronary arteries (113), but this has not been substantiated. Mitochondrial structure alterations have been reported (114,115).

Clinical Manifestations

Symptoms usually develop insidiously and often present with gross pulmonary edema (106). Atrial fibrillation is a common presenting complaint (109). Subsequently, severe combined left and right heart failure may occur (103,106,109). Dyspnea, orthopnea and PND are the rule (109). Cardiac arrhythmias may lead to palpitations and syncope (106). A narrow pulse pressure and elevations in diastolic pressure dominate due to peripheral vasoconstriction (103,106,109). Cardiomegaly with both S_3 and S_4 gallops are quite frequent. A murmur of mitral regurgitation is frequently present (109). The cardiomegaly, gallops and mitral regurgitation murmur often disappear rapidly with minimal therapy especially with the first episode of failure. Right heart failure is often present.

X-ray findings

The chest film on admission often shows cardiomegaly involving all four chambers, pulmonary congestion, and pleural effusions. By three days after admission the chest x-ray is frequently completely normal save for a slightly more globular appearance of the heart.

Echocardiographic Manifestations

Askanas et al (116) used echocardiography to study three groups of patients. He studied normal patients, alcoholic patients with no evidence

of heart disease, and alcoholic patients with congestive heart failure. Both alcoholic groups showed decreased LV function by non-invasive indices (Table 7). Echo studies revealed diastolic dilation, increased wall thickness, and LV mass in both alcoholic groups (Table 8, Figures 19-20). Only the congestive heart failure group had changes in systolic dimensions, shortening fraction, and ejection fraction. Delgado et al (117) has also shown diminished ejection fraction with alcohol. Reeves et al (118) has shown that ejection fractions return to normal with prolonged abstinence.

Table 7 (116)

General evaluation and systolic time intervals in three groups*

Groups†	No.	Age (yr.)	BSA (M. ²)	Blood pressure (mm. Hg)		HR (min.)	Years of drinking	PEP (Sec.)	LVET (Sec.)	LVETI (Sec.)	PEP/LVET	C/T	SV ₁ + RV ₅ (mm.)
				Syst.	Diast.								
A	73	34.4	1.77	117.7	77	76	15.2	0.106	0.270	0.400	0.395	0.45	32.7
± S.D.		6.0	0.17	9.8	9.3	12	7.0	0.012	0.030	0.028	0.056	0.043	8.9
N	30	32.4	1.84	117.7	76	76	—	0.092	0.297	0.416	0.313	0.44	30.5
± S.D.		5.7	0.23	10.0	7	7		0.014	0.022	0.024	0.061	0.037	9.4
C	9	36.1	1.88	117.6	78	98.3	12.1	0.131	0.205	0.372	0.650	0.61	29.4
± S.D.		6.2	0.13	11.8	6	12.8	5.0	0.017	0.029	0.021	0.116	0.04	11.5
p value													
A vs N		NS	NS	NS	NS	NS	—	<0.001	<0.001	<0.01	<0.001	NS	NS
N vs C		NS	NS	NS	NS	<.001	—	<0.001	<0.001	<0.001	<0.001	<0.001	NS
A vs C		NS	NS	NS	NS	<.001	NS	<0.001	<0.001	<0.01	<0.001	<0.001	NS

*Mean and standard deviation.

†A = alcoholics; N = normal controls; C = alcoholics with congestive heart failure; BSA = body surface area; HR = heart rate; PEP = pre-ejection period; LVET = left ventricular ejection time; LVETI = left ventricular ejection time index; C/T = cardiac-thoracic ratio; SV₁ + RV₅ = the sum of the amplitude of the S wave in Lead V₁, and R wave in Lead V₅.

Table 8 (116)

Echocardiographic data in three groups*

Group†	No.	Dd (mm.)	Ds (mm.)	LA (mm.)	IVSt (mm.)	LVt (mm.)	PWE (mm.)	IVSE (mm.)	SF (%)
A	73	49.5	31.1	29	11.71	10.4	11.5	8.1	37
± S.D.		5.4	4.9	4.8	1.33	1.05	2.2	2.6	6.5
N	30	47.2	30.4	28.3	9.63	8.76	11.7	7.7	35
± S.D.		4.3	4	4.3	1.24	0.86	2.3	2.1	4.5
C	9	66.9	59	43	11.78	11.28	5.4	2.9	11.8
± S.D.		5.2	5.2	6.6	1.6	1.39	2.6	1.0	3.0
p value									
A vs N		<0.05	NS	NS	<0.001	<0.001	NS	NS	NS
N vs C		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
A vs C		<0.001	<0.001	<0.001	NS	<0.01	<0.001	<0.001	<0.001

*Mean and standard deviation.

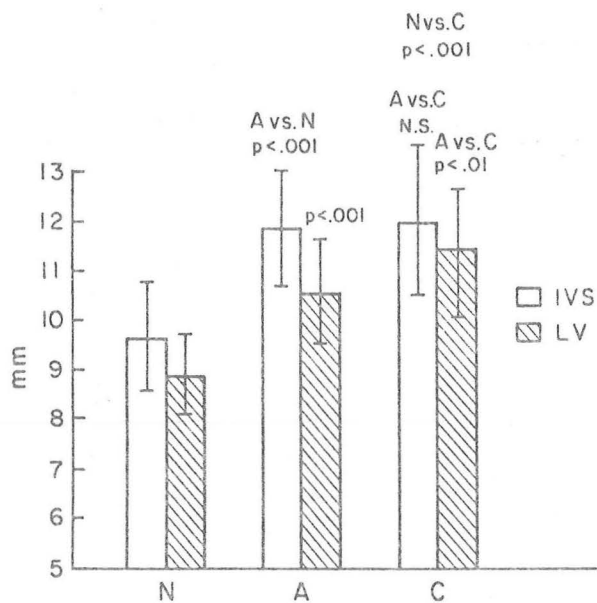
†Abbreviations as in Table I. Dd = diastolic dimension; Ds = systolic dimension; LA = left atrial dimension; IVSt = interventricular septal thickness; LVt = left ventricular thickness; PWE = posterior wall excursion; SF = shortening fraction; VCF = velocity of mean circumferential fiber shortening; LVDV = left ventricular diastolic volume; LVSV = left ventricular systolic volume; SV = stroke volume; EF = ejection fraction; LV mass = left ventricular mass; VpW = normalized posterior wall velocity; Vivs = normalized interventricular septal velocity; IVSE = interventricular septal excursion.

The addition of I(Index) to abbreviation means: body surface correction.

Table 8 (contd) (116)

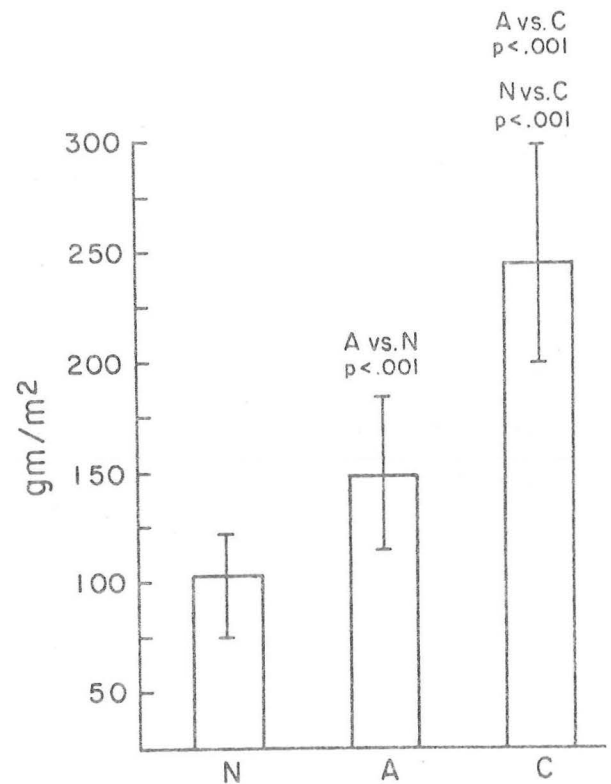
VCF (Circ./Sec.)	LVDVI (ml./M. ²)	LVSVI (ml./M. ²)	SVI (ml./M. ²)	EF	LV mass I (gm/M. ²)	VpW (cm./sec.)	Vivs (cm./sec.)
1.39	65	22.5	43.3	0.66	145.7	0.89	0.64
0.29	16	8.2	10.6	0.08	32	0.22	0.25
1.19	57.8	18.9	40	0.66	101	0.83	0.56
0.15	13.2	5.5	12.6	0.07	20.7	0.15	0.16
0.59	124.1	93.1	31	0.25	242	0.39	0.21
0.21	18.6	15.6	10	0.07	53	0.16	0.08
NS	<0.05	<0.05	NS	NS	<0.001	NS	NS
<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Figure 19 (116)



Thickness of the interventricular septum (IVS) = open bars, and thickness of the posterior wall of the left ventricle (LV) = shaded bars, in three groups: N = normal controls; A = alcoholics; C = alcoholics with congestive heart failure. Vertical lines = standard deviation.

Figure 20 (116)



Left ventricular mass Index (gm./M.²) Abbreviations

Electrocardiographic Findings

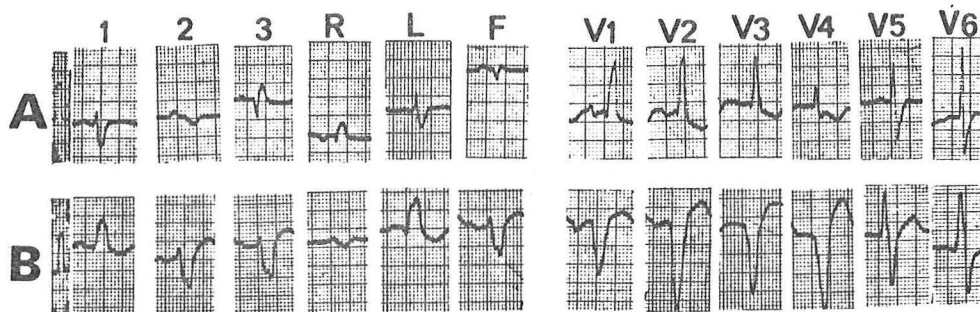
The most common ECG findings with alcoholic cardiomyopathy are bundle branch blocks, left ventricular hypertrophy, and atrioventricular conduction blocks (usually first degree block) (109,119). ST segment and T wave abnormalities are frequent on admission and often return to normal after treatment (120) (Table 9, Figures 21-23).

Table 9 (119)

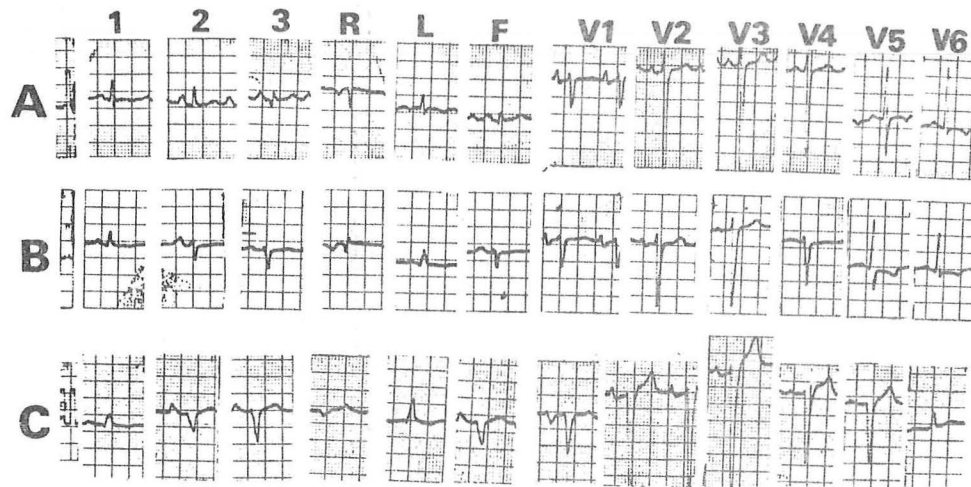
—Incidence of Electrocardiographic Abnormalities in 65 Patients

		No. of Patients	Per-cent Incidence
Rhythm	Premature ventricular contractions	24	37
Disturbance:	Ventricular tachycardia	2	3
	Premature atrial contractions	11	17
	Atrial fibrillation or flutter	8	12.3
Conduction	1st degree atrioventricular block	22	34
Disturbance:	Left anterior hemiblock	17	26
	Left posterior hemiblock	3	5
	Left bundle branch block	7	10.7
	Right bundle branch block	6	9.2
	Intraventricular conduction defect	5	7.7
Atrial	Left atrial enlargement	15	23
Abnormality:	Right atrial enlargement	—	—
	Biatrial enlargement	35	52.2
Ventricular	Pathologic Q	3	5
Abnormality:	Left ventricular hypertrophy	43	66
	Right ventricular hypertrophy	2	3
	Biventricular hypertrophy	3	5
Other	ST-T changes	65	100%
Abnormalities:			

Figure 21 (119)

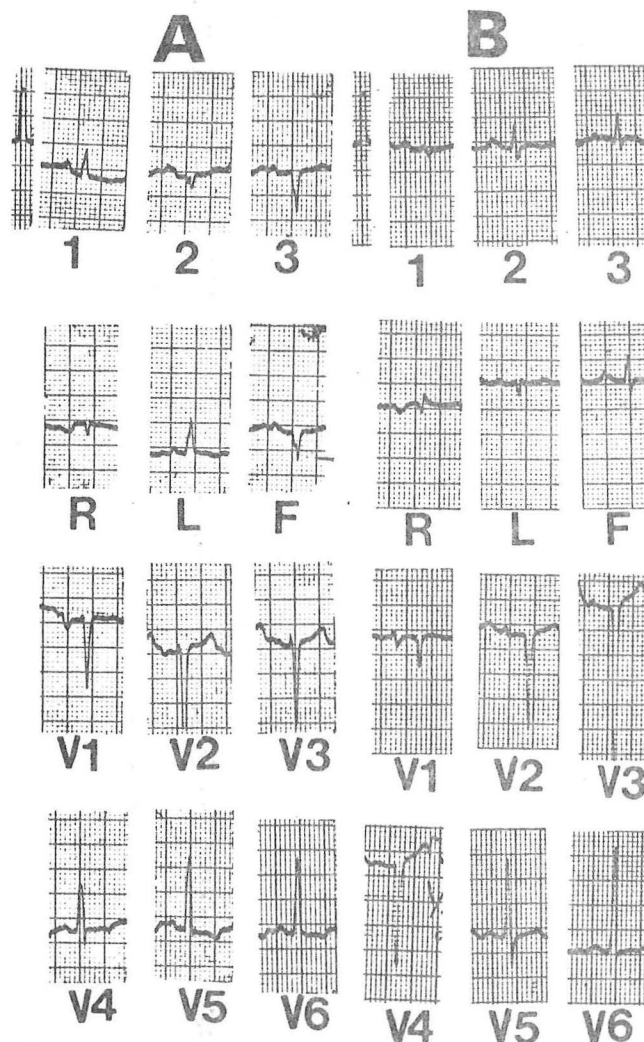


Two examples of bundle branch block. A. Right bundle branch block is associated with extreme left axis deviation consistent with left anterior hemiblock. B. Left bundle branch block and abnormal left axis deviation are present.



Electrocardiograms of three patients. The first (A) shows left ventricular hypertrophy with P wave abnormality consistent with biatrial enlargement (*see text for explanation*). The second tracing (B) shows the same atrial abnormality in addition to left anterior hemiblock. The third tracing (C) shows prolonged PR interval, left anterior hemiblock, left ventricular hypertrophy, and biatrial enlargement, a combination quite characteristic of cardiomyopathy.

Figure 23 (119)



Pathologic Q waves in cardiomyopathy. Tracing A belongs to a 28-year-old patient; it shows Q waves in leads 2,3 and aVF (*inferior necrosis pattern*). Tracing B shows QS complexes in V₁-V₃ (*anterior necrosis pattern*). Biatrial enlargement is also seen in both tracings, and left ventricular hypertrophy is present in B.

Arrhythmias

While arrhythmias occur frequently in cardiomyopathy with overt failure, the presence of arrhythmias prior to the onset of overt failure has been debateable. Recently Ettinger et al (121) reported 32 cases of arrhythmias in patients without overt heart failure. Only patients with normal heart size and normal ECG's (after they have returned to normal sinus rhythm) were examined. The 32 cases occurred in 24 patients and all were of such severity to require hospitalization. Four illustrative cases from this paper are shown below (73):

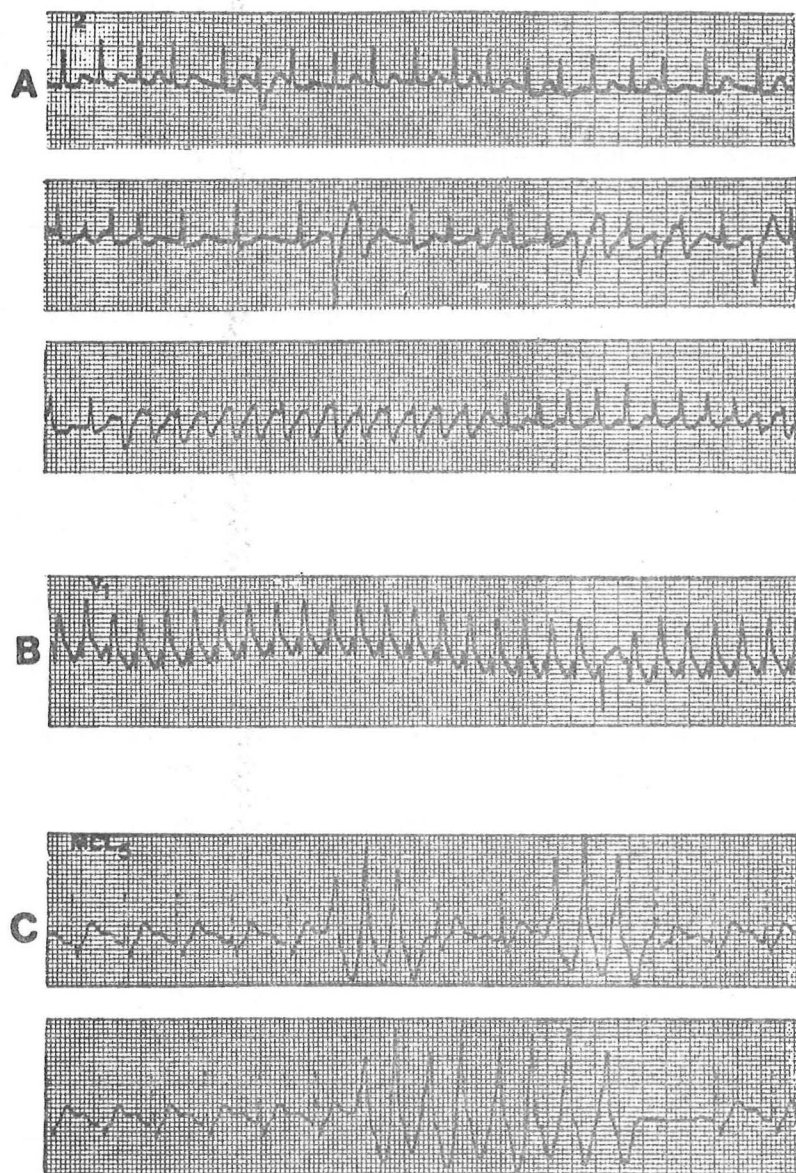
Case 1. - D.R., a 39 year old businessman, spent a long weekend drinking heavily in a motel. After 3 days he developed palpitations and was seen at another hospital, where atrial fibrillation was detected and he was cardioverted. He felt well but gradually resumed consumption of 12-15 cans of beer daily. Four years later, he presented with palpitations. Frequent atrial extrasystoles (with LBBB aberration) were treated with quinidine. Plasma electrolytes were normal. Since reducing his beer consumption and continuing quinidine, palpitations have lessened, although he has frequent palpitations when he drinks more heavily.

Case 2. - M.H., a 31 year old woman, drank whiskey in quart quantities daily. She was seen at the emergency room because of palpitations and breathlessness; atrial fibrillation with ventricular extrasystoles was present. Within minutes, the rate accelerated, with runs of beats of uncertain origin, possibly ventricular tachycardia. Cardioversion was performed immediately. Plasma electrolytes were normal. In the next 2 years she was admitted on three additional occasions, each time with atrial fibrillation and the same drinking history. One each occurred on a Sunday, Monday and Tuesday.(figure 24A).

Case 3.- R. G., a 42 year old woman, was admitted because of palpitations. She drank 6-12 cans of beer daily. The ECG showed atrial flutter with 1:1 response and cardioversion was performed. Plasma electrolytes were normal. Fifteen months later, while continuing her beer ingestion, she was readmitted because of the same arrhythmia; treatment with digoxin was begun and sinus rhythm returned. (Figure 24B).

Case 4. - W. K., a 43-year old businessman, consumed at least 6 oz. of martinis daily for many years. During the month of December he had additional liquor at business luncheons. He "passed out" while seated in a cinema and was taken to the emergency room. Frequent ventricular extrasystoles were presented and the plasma K^+ was 2.7 mEq/l. Treatment with procainamide and K^+ suppressed the arrhythmia. Three weeks later, while asymptomatic and arrhythmia-free at rest, an exercise stress test induced ventricular extrasystoles and runs of ventricular tachycardia to occur after the exercise and was presumed to be the basis of his presenting symptoms. With abstinence and outpatient treatment with quinidine, the arrhythmia has not recurred (Figure 24C).(73)

Figure 24 (73)



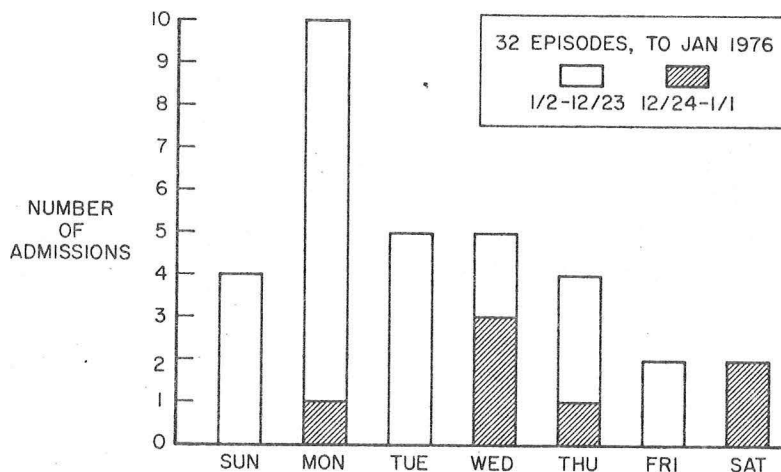
—Electrocardiograms of illustrative cases. A, CASE 2. — Atrial fibrillation is seen in top strip with one aberrated (Ashman) beat (the 6th). Within 10 minutes (next two strips), the rate accelerated with runs of wide complexes (?aberration or ventricular tachycardia) at rate of 240/min. B, CASE 3. — Atrial flutter with 1:1 conduction (verified later by carotid massage) at rate of 250/min with RBBB aberration. A single normally conducted beat is seen. C, CASE 4. — Runs of ventricular tachycardia 1 minute following the end of a treadmill stress test

In this series there were twenty (20) men and four (4) women.

The mean age was 43 years with a range of 25-62 years. All patients consumed more than 6-10 drinks/day. The group had been heavy drinkers for more than ten (10) years. They all drank during the week with a higher weekend consumption. All but two were heavy smokers. Many types of beer and whiskey were consumed (121). After the initial treatment two (2) patients developed delirium tremens and one patient alcoholic hepatitis. Admission serum potassium was less than 3.5 meq/l in only four of thirty times. The rest of the electrolytes, the BUN, sugar, cholesterol, LDH, and arterial blood gases were normal. The SGOT was normal or borderline elevated. In eight patients blood alcohol were obtained and were positive in six ranging from 50-430 mg/100 ml (121).

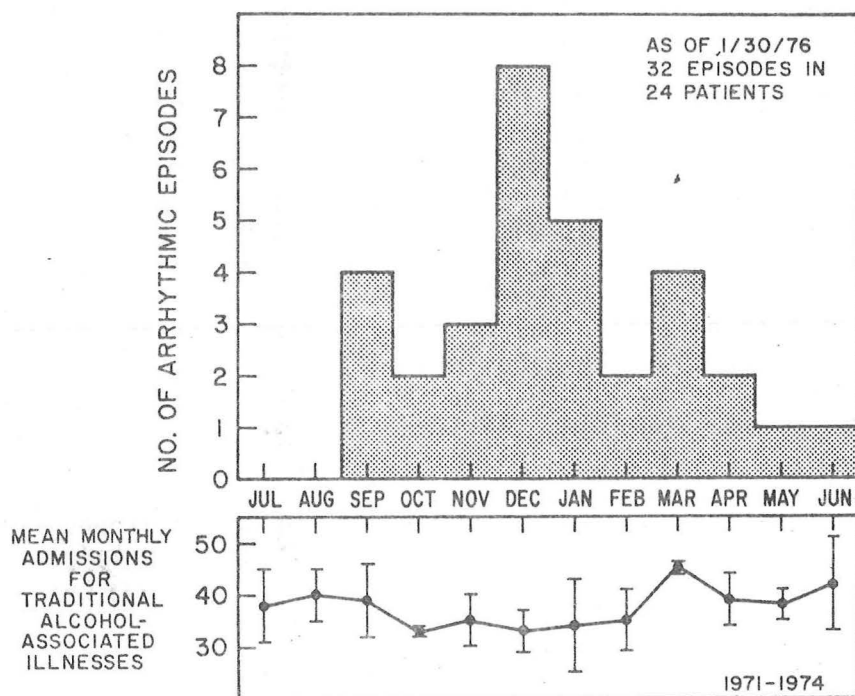
The time of admission has caused the term "holiday heart syndrome" to be used to describe these patients (Figure 25). Nineteen of 34 admissions occurred on Sunday, Monday, or Tuesday; a significant elevation. Of the remaining thirteen admissions, six occurred on major holidays; hence 25 of 32 admissions followed a weekend binge or a holiday binge. A very highly significant number of admissions occur during the Christmas to New Years period; for other alcohol related illnesses December has the lowest admission rate (Figure 26) (121).

Figure 25 (121)



Admitting day for alcoholic arrhythmias. Nineteen admissions were seen Sunday through Tuesday (post-weekend). Of the 13 Wednesday through Saturday admissions, six were during the year-end holidays. Therefore, 25 of 32 admissions were holiday-related.

Figure 26 (121)



Monthly distribution of "holiday heart" hospital admissions (*top*), compared with mean monthly admissions for "traditional" alcohol associated illnesses (*bottom*). The apparent year-end peak of alcoholic arrhythmias is not present for the "traditional" alcoholic illnesses.

The ECG's after recovery were normal in sixteen patients, had mild left axis deviation in four patients, a wide P wave in two patients, and low T waves in two patients (Table 10). The chest X-rays were normal in 21 patients and had a cardiothoracic ratio of 50% in three patients (118).

Table 10 (121)

ECG and chest x-rays in "Holiday Heart" patients

Electrocardiograms (total 24):	
Fully normal	16
Normal except LAD, -10° to -30°	4
Normal except P wave 0.12 sec.	2
T waves low (not flat), 1-2 leads (one of these also showed first degree A-V block)	2
Chest roentgenograms (total 24):	
Fully normal	21
Cardiothoracic ratio 50%	3

The most common arrhythmias were atrial fibrillation and flutter with other supraventricular arrhythmias accounting for much of the remainder.(Table 11). In only six of the 34 episodes were isolated PVC's seen; one patient had ventricular tachycardia induced by an exercise test. Nine patients with atrial fibrillation or flutter had wide QRS's in some of their rapid responses (6 RBBB pattern; 3 LBBB pattern) and whether these episodes were ventricular or supraventricular with aberration could not be determined. Therapy was empiric conventional therapy (121).

Table 11 (121)

Alcohol-associated arrhythmias*

<i>Rhythm abnormality</i>	<i>No.</i>
Isolated APC's	4
Atrial fibrillation	12
Atrial flutter	6
Paroxysmal atrial tachycardia	3
Junctional tachycardia†	4 (3 in 1 patient)
Isolated PVC's	6
Ventricular tachycardia	1 (after treadmill exercise)

*Several patients had more than one arrhythmia. Of atrial arrhythmias, 6 showed RBBB and 3, LBBB aberration.

†One patient with junctional tachycardia showed atrioventricular dissociation.

After the patients had recovered and were off all medicines for 48 hours non-invasive studies were performed. The PEP was significantly elevated as compared to normals, the LVET was significantly decreased, and the PEP/LVET ratio was greatly increased.(Figure 27). The "holiday heart" patients were also studied with ECG's recorded at 200 mm/sec paper speed with a frequency response of 0.1 to 2000 hertz (Table 12). There were significant elevations of the PR, QRS, and QT intervals (121). These same ECG findings have been found in ethanol treated dogs (8).

Table 12 (121)

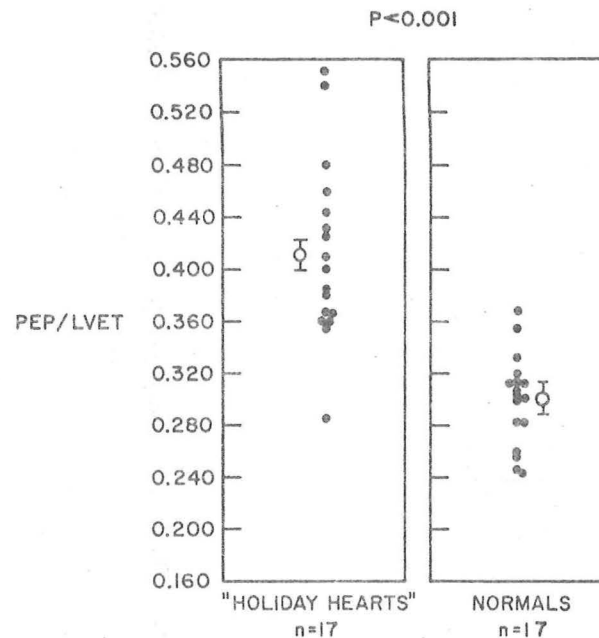
P-QRS-T durations from high speed

ECG

	<i>"Holiday Hearts" (N = 17)</i>	<i>Normals (N = 10)</i>	<i>P</i>
PRc* (msec.)	179 ± 7	153 ± 6	< 0.01
QRS (msec.)	98 ± 3	80 ± 2	< 0.001
QTc (msec.)	430 ± 9	377 ± 6	< 0.001
Heart rate (BPM)	82 ± 3	63 ± 3	< 0.001

*One patient had first degree A-V block and is excluded from PRc measurements.

Figure 27 (121)



Systolic time interval ratios (PEP/LVET) in patients with arrhythmias (*left*) and in normals (*right*). Filled circles are individual data points; means are open circles, and standard errors are shown.

Followup of "holiday heart syndrome" patients over 3-5 years has not revealed any incidences of overt heart failure. It is also interesting to note that a history of "holiday heart syndrome" can not be obtained in patients presenting in overt heart failure with alcoholic cardiomyopathy. Occasionally arrhythmias can be precipitated in patients who are not habitual drinkers. Regan et al (73) reported a healthy 52 year old woman who developed atrial fibrillation with one cocktail. Regan also reported two male physicians ages 31 and 34, who developed arrhythmias (atrial fibrillation, PAT) after long stressful work periods followed by alcohol consumption (73).

Sudden Death

In young alcoholics, a relatively high incidence of sudden unexpected death has been reported (122). The only pathologic finding in these individuals is a fatty liver. In non-traumatic sudden unexpected death series, the finding of a fatty liver only is found in 3-6% of cases. One study from Oslo has shown that sudden cardiac death occurs in outpatient alcoholics (123).

One study in dogs where they had been kept alcoholic for three years and then given an acute dose of alcohol revealed with electrophysiologic studies that they could all capture when pacing on the peak of the T wave with a much lower threshold than in control non-alcoholic animals given

acute alcohol (124). In addition ventricular tachycardia and fibrillation only occurred in alcoholic dogs.

Table 13. Effect of Acute Ethanol in Alcoholic and Non-alcoholic Dogs

	Alcoholic dogs (N=7)	Non-alcoholic (N=7)	
Heart rate	115±8 beats	128±12 beats	NS
Capture threshold (1 hour)	22±2.1 ma	40±3.2 ma	p<0.01
Capture threshold (1-1/2 hours)	15±1.3 ma	40±3.2 ma	p<0.01
Repetitive response	yes	no	
Ventricular fibrillation	yes	no	
Blood alcohol	110±8 mg%	110-160 mg%	NS

Atypical Myocardial Infarction

The presence of myocardial infarction without atherosclerosis has been seen in alcoholic cardiomyopathy. Regan (101) has suggested that as high as 20% of acute MI's may be related to alcohol; however, this is exceedingly unlikely. He has proposed that the perivascular fibrosis seen in alcoholic cardiomyopathy might cause ischemia. Though this is a possibility, it is highly speculative.

Natural History and Treatment

If the patient will abstain from alcohol the prognosis is good (107,109,125,126). However, if the patient continues to drink the course is progressive with increasing failure which becomes more and more refractory to therapy (109). Death is usually due to arrhythmias or systemic or pulmonary emboli (90,109). The key to therapy is abstinence (Table 14). The other treatment is conventional and empiric.

In summary alcoholic cardiomyopathy is a complex disorder whose full etiology is not understood. The factor or factors that cause the patients to develop overt failure are not clear. Though left ventricular dysfunction is seen in alcohol exposure even for the first time, the correlation between this and failure is obscure. It may be that an additional stress or genetic factor may be involved in causing overt failure.

Alcohol and Atherosclerosis

General epidemiologic studies have shown that individuals who have 2 oz. of alcohol per day have a lower risk of atherosclerosis than non-drinkers or heavier drinkers (127-132). Approximately, two drinks per day of either beer, wine, or liquor caused significant reduction in coronary mortality in the Framingham Heart Study (127), the Kaiser-Permanente Study (128), the Honolulu Heart Study (129), and the Boston Heart Study, (131). Higher levels

of alcohol consumption returned the risk to the level of the non-drinker or higher. The relative risk for two drinks per day ranged from 0.2 to 0.7. Past drinkers had a risk of 1.3 and were not protected.

The Western Electric Study (133) failed to show a correlation, however the amount of alcohol and smoking were not correlated. One recent report suggested that the reduction in risk was greater in smokers than non-smokers (134).

The basis for this protection is not proven. One possibility is alteration in lipid metabolism. In a Swedish study, (135), 76 g of alcohol daily for 5 weeks raised the alpha lipoprotein by approximately 30% and this is felt to be a preventative factor for infarction (136). The Cooperative Lipoprotein Phenotyping Study (137) has found a positive correlation between alcohol consumption and HDL and inverse correlation with LDL. Other studies have shown similar changes in HDL (138-139). Another factor may be alcohol's effects on platelet aggregation (140-142). However other factors may be involved which affect both alcohol consumption and atherosclerosis such as the type A personality (132).

The use of alcohol in patients with angina has been recommended by Heberden (143) and others. One carefully controlled study by Orlando et al (144) showed that both 2 oz. and 5 oz. of ethanol increased the heart rate systolic blood pressure product at rest and exercise and decreased the exercise time to ischemic ECG changes and chest pain. Due to sedation they did perform to greater ECG changes and they tended to have greater changes post exercise. Hence alcohol decreases tolerance in patients with angina but probably does allow some analgesia.

Alcohol and Hypertension

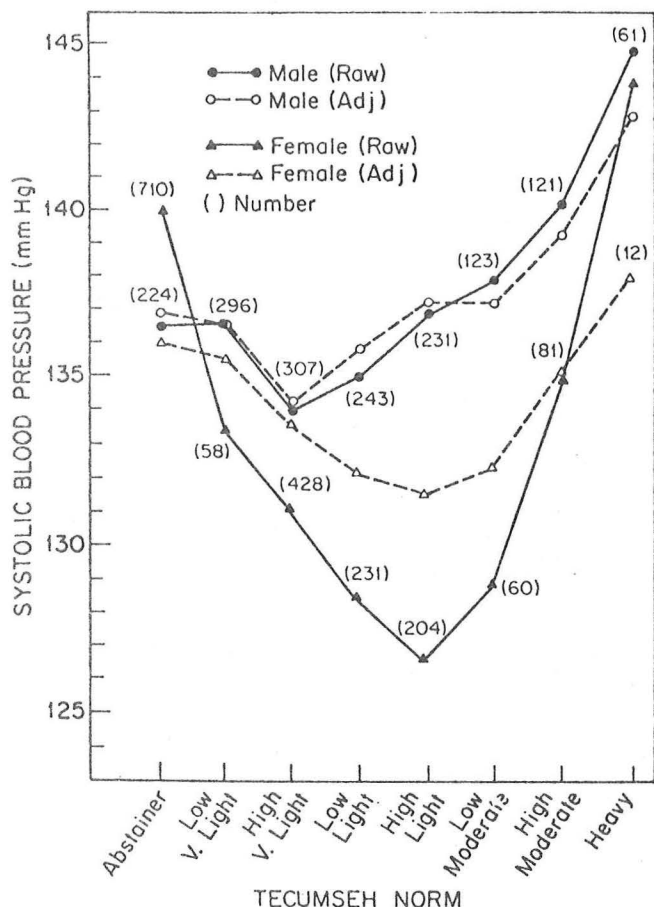
Several studies have suggested a correlation between alcohol consumption and hypertension (143-147). The Kaiser-Permanente Study (148) and the Tecumseh Study (149) have shown that significant elevations of blood pressure occur when more than 4 oz. of alcohol are consumed per day (Figures 28-29) (149). The Tecumseh Study showed that 2-4 drinks/week actually lowered blood pressure (149). These correlations held in all ethnic groups, and was not altered by smoking, coffee, past drinking history, obesity, education, or sex (148,149). Hence alcohol may be a risk factor for hypertension.

Table 14 (73)

-COURSE OF ALCOHOLIC
CARDIOMYOPATHY (3.3 YEARS)
(N = 57)

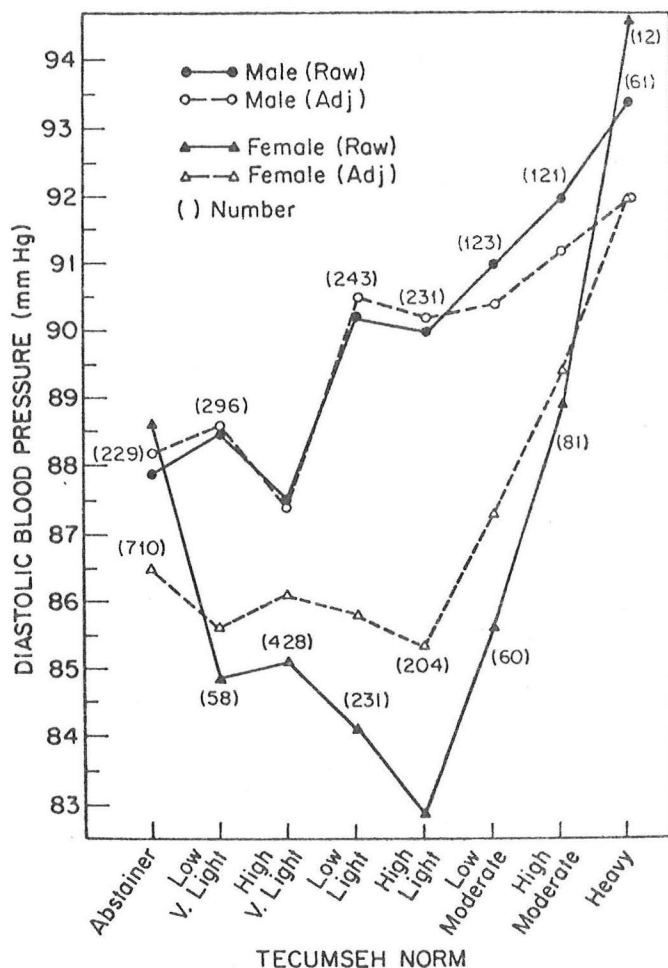
GROUP	STATUS	DEATHS	ABSTAINED FROM ALCOHOL
A	Improved	0	11/15
B	Same	0	3/12
C	Worse	24	4/30

Figure 28 (149)



Raw and Age-Weight-Adjusted Systolic Blood Pressure and Tecumseh Norm Categories, by Sex (N = 3,390).

Figure 29(149)



Raw and Age-Weight-Adjusted Diastolic Blood Pressure and Tecumseh Norm Categories, by Sex (N = 3,390).

Other

It has been shown that alcohol does not depress patients immediately post aortic valve replacement or mitral valve replacement as much as other anesthetic agents (150, 151). In guinea pigs and rats alcohol can lower the temperature at which cold by itself will induce cardiac arrest (152, 153). Finns should not drink alcohol while sitting in their sauna in the first six months after myocardial infarction (154).

Conclusion

Alcohol and its metabolite acetaldehyde have been shown to have profound physiologic and metabolic effects. The relationship to these effects to cardiomyopathy and to other forms of heart disease remains obscure in spite of intensive investigation.

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