

Ventricular Function in Noncardiacs with Alcoholic Fatty Liver: Role of Ethanol in the Production of Cardiomyopathy

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ABSTRACT Since many patients with cardiomyopathy have a history of chronic ethanolism often associated with malnutrition, we have evaluated left ventricular (LV) function in alcoholics with fatty liver, who had no clinical evidence of cardiac or nutritional disease.

During an afterload test of LV function the pressor response to angiotensin evoked a threefold rise of end-diastolic pressure in the alcoholic group which was substantially greater than the 4 mm Hg rise in control subjects. The stroke volume and stroke work response in the noncardiac alcoholic was significantly less than in controls. Diminished LV function was corroborated in the noncardiac alcoholic at rest, using a contractility index.

To evaluate the dose-response relationship of ethanol in the production of cardiac malfunction, two groups of noncardiac alcoholic subjects were studied acutely at low and moderate dose levels. After 6 oz, ventricular function, myocardial blood flow, and metabolism were not significantly affected. After 12 oz, there was a progressive rise of end-diastolic pressure and decrease of stroke output at a mean blood alcohol level of 150 mg/100 ml, reverting toward control by 4 hr. The coronary effluent transiently evidenced leakage of cell constituents, despite an increase of coronary blood flow, suggesting a direct but reversible cardiac injury. Myocardial extraction of triglyceride was enhanced, whereas FFA uptake was reduced. A possible role of myocardial triglyceride accumulation in heart muscle was considered in pathogenesis.

Chronic ingestion of 16 oz of Scotch daily by an alcoholic subject while on a normal diet produced, after 12 wk, a progressive increase of heart rate and size,

circulation time, and venous pressure, and a ventricular diastolic gallop. Normal values were restored within 7 wk after interrupting alcohol.

These several studies suggest that the cumulative effects of repeated ingestion of ethanol in intoxicating doses can produce diminished LV function before clinical evidence of cardiac abnormality, or heart disease not necessarily related to malnutrition.

INTRODUCTION

Recent clinical studies of idiopathic cardiomyopathy have indicated that a preponderance of patients in this group have a history of chronic alcoholism (1-4). Despite the view that nutritional deficiency is responsible for the cardiac disease seen in alcoholics, nutritional problems were not evident in the majority of these patients. To explore the possibility that chronic ingestion of ethanol may itself adversely affect cardiac function, we have studied a series of alcoholic subjects without clinical evidence of heart disease or malnutrition to assess the function of the left ventricle by two different methods. It was assumed that an antecedent period may exist before the appearance of clinical disease when a physiologic abnormality might be present.

The existence of a demonstrable abnormality in such subjects would support the view that alcoholic cardiomyopathy is a diagnostic entity and would indicate that the role of ethanol and its dose-response relationship required examination. Hence the effects of acute ingestion of ethanol at two dose levels on left ventricular (LV) function and metabolism have been investigated in two other groups of subjects. In addition, the consequences of daily administration of ethanol for 5 months were assessed in an individual patient who received an adequate nutritional intake.

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METHODS

Hemodynamic and metabolic studies were performed in the following groups of patients.

Group I. 10 alcoholic subjects without heart disease were compared with eight controls during a study of the left ventricular response to angiotensin.

Group II. Eight noncardiac alcoholics were evaluated by a contractility index and compared with 11 normals.

Group III. Six alcoholic patients with cardiomyopathy were similarly studied as Group II.

Group IV. 11 alcoholics were studied before and after 12 oz of Scotch.

Group V. Six alcoholics received six oz of Scotch.

Group VI. One alcoholic subject, 49 yr of age, was studied while taking alcohol daily for a period of 5.5 months.

All patients, except for Group VI, were between the ages of 30 and 45 and were brought to the laboratory after informed consent was obtained for cardiac catheterization. They were fasted overnight and premedicated with pentobarbital, 90 mg i.m. Under local anesthesia, catheters were placed in vessels appropriate to the particular study; the coronary sinus, pulmonary artery, aortic root, and the left ventricle by the retrograde arterial route were catheterized for blood sampling and pressure determinations. Statham P23Gb strain gauge transducers were used for measuring pressures which were recorded photographically on an Electronics for Medicine oscilloscope. The first time derivative of the ventricular pulse was obtained with a resistance-capacitance differentiating circuit (time constant, 1.1 msec) connected to the output of the left ventricular pressure channel. The maximum error of the differentiator is approximately 0.9% when summing the fundamental with the 10th harmonic. LV end-diastolic pressure was recorded so that 1 mm Hg equalled 5 mm of paper. Cardiac output was measured in duplicate by the dye dilution or Fick method.

After cardiomyopathy has progressed to an advanced state, the presence of congestive failure may itself affect the nutritional state of the patient and hinder the evaluation of pathogenesis at this point in the disease. To obviate this problem, alcoholic subjects chosen for hemodynamic study had normal cardiovascular findings on clinical examination. They were normotensive, had no symptoms or electrocardio-

graphic evidence of coronary artery disease, and were in an age group in which clinically important coronary artery disease would be expected to have a relatively low prevalence. Documentation of the duration of alcoholism and type of ethanol used by these subjects were obtained from the patients' histories and information derived from close relatives. They had used ethanol habitually for 10-15 yr and whiskey was the predominant alcoholic beverage, usually taken at least several times a week in amounts ranging from $\frac{1}{2}$ to 2 pints/day. The alcoholic groups were further defined by the presence of fatty liver without fibrosis. After obtaining informed consent, liver biopsy was performed in all the alcoholic subjects of each group, 3-5 days before the hemodynamic study. The biopsy was performed by members of the Liver Division under the direction of Dr. C. M. Leevy, during a study of the course of recovery of hepatic alterations after interruption of alcohol intake. Whereas the fatty infiltration observed histologically is not specific for alcoholism, the absence of a history of hepatitis or exposure to other toxins and a clear history of excessive ethanol intake supports this diagnosis.

10 of these alcoholics (Group I) and eight control-hospitalized subjects were studied approximately 3 wk after recovery from brief acute illnesses. In both groups these included bronchitis, pneumonitis, dermatitis, pyelonephritis, and delirium tremens. Neither group had evidence of malnutrition or clinical evidence of a specific vitamin deficiency; all the patients were within 5% of the ideal weight and height for their age and there was no hypoalbuminemia, peripheral neuropathy, edema, or anemia of hemodynamic significance. The studies were performed after 3 wk of an adequate diet which included vitamin supplements. Comparison of the relevant features of each group are summarized in Table I. While the group of 10 alcoholic patients were in a basal state, cardiac output, systemic arterial pressure, and LV pressures were measured, and an intravenous infusion of angiotensin was begun at approximately 1.5 $\mu\text{g}/\text{min}$ to evaluate function during an afterload test (5). The dosage was increased at 5 min intervals during oscillographic monitoring until a maintained aortic-diastolic pressure increase of 20 mm Hg was observed, at which time duplicate cardiac output determinations were performed. The dose of angiotensin at the time of the hemodynamic studies reported in Figs. 1 and 2 averaged $2.9 \pm 0.3 \mu\text{g}/\text{min}$ in the controls and $2.8 \pm 0.24 \mu\text{g}/\text{min}$ in the alcoholics. The relation of the stroke output to LV end-diastolic pressure responses were compared in the Group I noncardiac alcoholics with a group of control subjects. The stroke work of the left ventricle was calculated from the formula $\text{SV} \times (\text{LVS} - \text{LVED}) \times 1.36$ in which SV equals the stroke volume in milliliters; LVS equals the mean LV pressure during ejection in millimeters of mercury; and LVED equals the LV end-diastolic pressure.

Although there is no evidence that alcoholic subjects with fatty liver, but without cirrhosis, have an abnormal sensitivity to angiotensin, it remains possible that the response of the ventricle to angiotensin may be modified by the presence of liver disease. Hence, in eight additional noncardiac alcoholic subjects (Group II) having the same clinical characteristics as described in Table I, LV function was evaluated in the resting state by an indirect measure of the force-velocity relationship (6) and compared with an additional group of 11 normals. Six alcoholic subjects (Group III) with cardiomyopathy, manifested as a first episode of congestive heart failure, were similarly studied. These six alcoholic-cardiacs received digitalis and diuretic therapy before catheterization and on the day of study were edema-free, exhibited no pulmonary rales, and were

TABLE I
Comparison of Relevant Features of Groups I-V

	Control	Alcoholic
Age	Males, 29-42 yr	Males, 30-41 yr
Ethanol use	Minimal	Habitual, 10-15 yr
Heart, B.P., EKG	Normal	Normal
Cardiothoracic ratio	0.41 \pm 0.06 cm	0.40 \pm 0.05 cm
Hematocrit (%)	40 \pm 3	38 \pm 2
Serum protein (g/100 ml)	7.7 \pm 0.4	7.1 \pm 0.5
Serum albumin (g/100 ml)	4.6 \pm 0.2	4.2 \pm 0.15
BSP (45 min)	3-5%	7-12%
Liver biopsy		Fat, mild-to-moderate; no cirrhosis or acute inflammation

symptomatically improved. The contractility index employed exhibits a relatively narrow range in normal ventricles, increases in a predictable fashion with positive inotropic interventions, and is depressed in patients with LV disease. Briefly, the index is expressed as $2\pi r / \text{MRPR} / \text{MIP}$: MRPR representing the maximum rate of LV pressure rise; MIP the maximum isovolumetric pressure, which is a linear function of tension during the systolic isovolumetric period; $2\pi r$ is the circumferential fiber-length which normalizes the index for hearts of different size. Changes in contractile element performance are manifest as changes in MIP or fiber-length. The latter parameter, $2\pi r$, was calculated by assuming that the ventricle was a sphere at the end of the systolic isovolumetric period, deriving the radius from the end-diastolic volume measured by indicator dilution (7).

The effects of ethanol ingestion at two different dose levels were studied in two other groups of noncardiac alcoholic subjects fulfilling the criteria listed in Table I. 12 oz of Scotch (42% alcohol) were fed over a 2-hr period to 11 alcoholic subjects (Group IV). To evaluate the relation of dose to the hemodynamic and metabolic effects of ethanol, a similar group of seven alcoholic subjects (Group V) received 6 oz of Scotch. One-third was administered orally as a priming dose over the initial 15 min and the remainder at a relatively constant rate for the rest of the 2 hr. Simultaneously, sequential blood samples were taken from the aorta and coronary sinus for determination of arteriovenous differences of substrates. The blood was placed in chilled

tubes containing EDTA and after separation in a refrigerated centrifuge the plasma was stored at -15°C before analysis. Samples were drawn before alcohol ingestion and at 15-30 min intervals thereafter, for 4 hr. Substrate determinations were done in duplicate and included glucose (8), lactate (9), pyruvate (10), free fatty acid (11), and triglyceride (12). Plasma samples without significant hemolysis were also analyzed for glutamic oxaloacetic acid transaminase (13) and inorganic phosphate (14). Plasma potassium was analyzed on a Beckman B spectrophotometer with the flame attachment. Duplication determinations of blood oxygen and carbon dioxide were performed (15) and arterial pH was determined on a Beckman pH meter at 37°C . Ethanol samples were analyzed by the microdiffusion method of Conway (16). To assess changes in left ventricular blood flow, sequential flow measurements were performed with a modification of the $^{86}\text{Krypton}$ method (17, 18).

The requirements for valid interpretation of arteriovenous differences were met after the 1st hr of alcohol (19, 20), when relatively constant coronary blood flow and arterial substrate concentrations were present. Five subjects were excluded from this aspect of the study, due to inconstant arterial substrate concentrations or fluctuation of coronary flow greater than the error of analysis, 10% in the case of lipid and blood flow determinations and 5% for carbohydrate substrates. Statistical analyses are reported as the SE and *t* tests were nonpaired or paired as appropriate.

Since a 10-20-yr period of excessive alcohol intake would

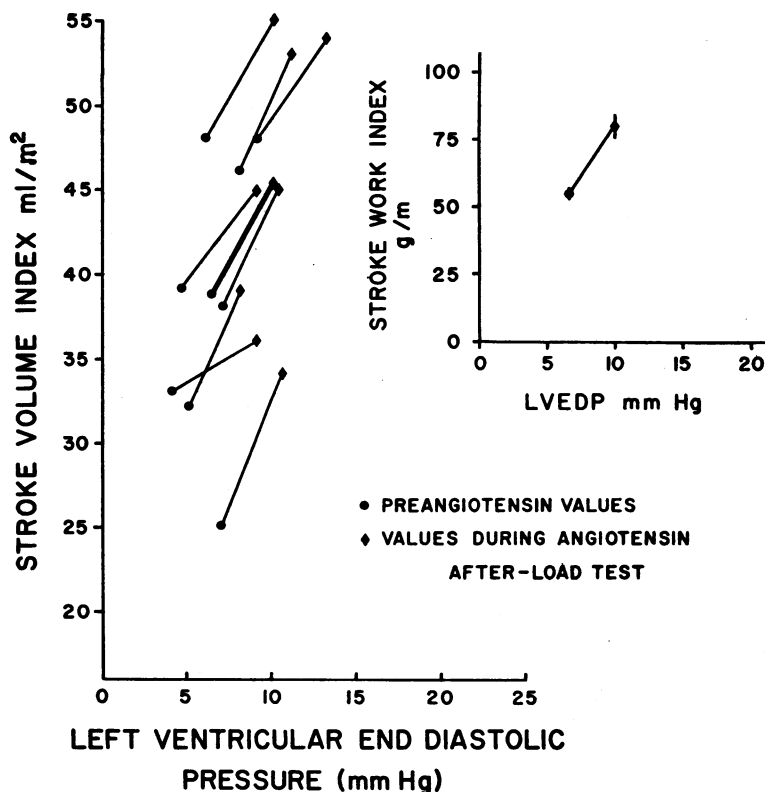


FIGURE 1 Left ventricular response to angiotensin in controls. In the normal subjects a relatively small rise of left ventricular end-diastolic pressure was associated with a significant stroke output and stroke work increment. The heavy line indicates the average values for the group.

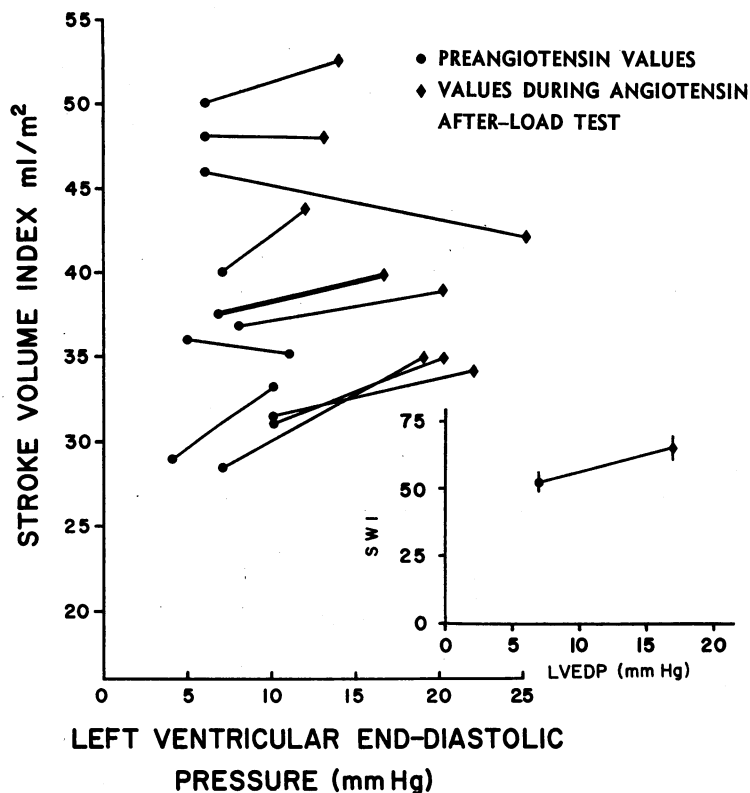


FIGURE 2 Left ventricular response to angiotensin in alcoholics without heart failure. The alcoholic subject without clinical evidence of cardiac disease exhibited a nearly threefold rise of ventricular end-diastolic pressure but only a minimal stroke output and stroke work increment.

usually appear to be required to produce clinical evidence of cardiac disease (3), a short-term study was performed in a 49 yr old male alcoholic subject who had already experienced his first episode of heart failure 10 wk before this study. He had taken Scotch, approximately 1 pint/day for the previous year and had a prior 15-yr history of lesser but excessive alcohol intake. His heart failure was readily controlled by medical management. Digitalis, diuretics, and a low-salt diet were discontinued 4 wk before ethanol was administered and he remained compensated. The patient had been unwilling to enter a rehabilitation program and he entered the study after giving informed consent.

Since a normal dietary and vitamin intake may prevent or modify the cardiac disease in alcoholics (21), an appropriate diet was administered while the patient received the quantity of alcohol to which he had been accustomed. From the onset of this 8 month study, the patient received, and usually completely consumed, a 2000 calorie diet. The calorie values were 800 as fat, 800 as carbohydrate, and 400 as protein. A vitamin supplement exceeded the minimum daily requirement for each vitamin by three- to fivefold and included 5 mg of folic acid/day. To maintain an isocaloric diet after the addition of alcohol (16 oz of Scotch containing 146 g of ethanol, from 9:00 a.m. to 1:00 p.m.), the patient's nonethanol food intake was reduced to 350 calories as fat, 300 calories as carbohydrate, and 400 calories as protein, which met recommended daily requirements (22). At the conclusion of the study, the patient was

informed of the results and entered a rehabilitation center for treatment of his alcoholism. He has remained without clinical evidence of cardiac disease in the subsequent year.

RESULTS

The response to angiotensin infusion is represented in Figs. 1 and 2 and Table II. The alcoholic patients with fatty liver but no clinical evidence of heart disease had similar values for heart rate, systemic arterial pressure, and cardiac index, as did the controls before the after-load test. The elevation of aortic pressures during angiotensin infusion was equivalent in both groups, but the response of the left ventricle differed significantly. In the alcoholics (Group I), when aortic-diastolic pressure was increased by 20 mm Hg the LV end-diastolic pressure rose almost threefold, which was significantly greater than the small rise seen in the control group ($P < 0.001$). In the controls the small rise in ventricular end-diastolic pressure was associated with a definite stroke output increment. The alcoholic group on the other hand, exhibited a significantly smaller rise in stroke output ($P < 0.01$) and stroke work ($P < 0.01$), despite a larger rise of ventricular filling pressure.

TABLE II
Hemodynamic Response to Angiotensin

		Heart rate	Aortic pressure		Cardiac index
			Mean	Diastolic	
			<i>mm Hg</i>		<i>liters/min</i>
Controls	C*	81 ±3.7	101 ±5	83 ±3.9	3.40 ±0.24
	E†	75 ±4.9	130 ±7	104 ±4.1	3.75 ±0.32
Alcoholic (noncardiac)	C	83 ±4.5	101 ±4	82 ±4.2	3.12 ±0.21
	E	78 ±5.0	128 ±6	102 ±2.6	3.09 ±0.20

* Data at rest before angiotensin.

† During angiotensin after-load test.

The status of the left ventricle in the alcoholic subject without known heart disease was further evaluated with the contractility index, relating the velocity of ventricular pressure rise at a given aortic pressure to the ventricular fiber-length. In the 11 normal subjects, the mean index at rest was 1.27 ± 0.09 (6). In the eight alcoholic subjects with fatty liver (Group II), in whom the analysis was performed, the index averaged 0.87 ± 0.08 (Fig. 3). The nonpaired *t* test was calculated as $P < 0.01$. A more substantial reduction of the contractility index was observed in the group of alcoholics with heart failure (Group III) who had an index of 0.39 ($P < 0.001$).

To explore the possible relationship of ethanol ingestion per se to the abnormalities of LV function present in the chronic ethanolic, a similar group of noncardiac alcoholics were studied during the acute ingestion of ethanol for a 2 hr period. Fig. 4 illustrates the progressive rise of ventricular filling-pressure at moderate levels of blood ethanol (Group IV). There was no corresponding increase in stroke output but rather a modest decline, so that ventricular function appears to have been diminished. The fact that both parameters were returning toward control values by 3-4 hr suggests that this is a transient phenomenon. Since the noncardiac alcoholics receiving the low dose of alcohol

(Group V) had no significant hemodynamic change, the evidence of diminished ventricular function observed with the larger alcohol dose would appear to be related to the dose of ethanol administered, rather than spontaneous changes during the period of observation.

Analysis of arterial and coronary sinus plasma for ions and transaminase enzyme indicates that there was also a transient injury effect in the myocardium, only in the subjects receiving the moderate dose of ethanol (Group IV). The coronary venous values for potassium, phosphate, and transaminase were increased significantly from 1.5 to 3 hr with a tendency to reversion towards control levels by 4 hr (Fig. 5), whereas significant alterations were not encountered in the patients receiving the low dose of ethanol. This evidence of injury would not appear to be related to a deficit in coronary blood flow, since there was a small increase in blood flow, presumably related to the slight tachycardia seen after the 1st hr in Group IV. The lack of lactate production (Table III), and a decrease rather than an increase in myocardial oxygen extraction from a mean of 11.4 ± 0.08 to 10.5 ± 0.1 vol %, further support the view that ischemia was not present.

Studies of the metabolic properties of the myocardium during ethanol ingestion at moderate doses indicated a significant rise in the myocardial respiratory quotient during the initial 90 min, with subsequent reversion to near control levels (Fig. 6). This is presumably related to the elevation of arterial lactate and acetate consequent to ethanol metabolism in the liver (23), resulting in greater uptake and oxidation by the heart (Table III). However, the most persistent metabolic effect of ethanol involved lipid extraction by the myocardium (Fig. 6). During the early period of alcohol ingestion in Group IV, there was a slight decline of arterial free fatty acids and elevation of arterial triglyceride levels, which subsequently plateaued enabling interpretation of the arteriovenous differences. A distinct decline of free fatty acid extraction was noted, whereas uptake of triglyceride by the myocardium progressively increased

LEFT VENTRICULAR CONTRACTILITY INDEX

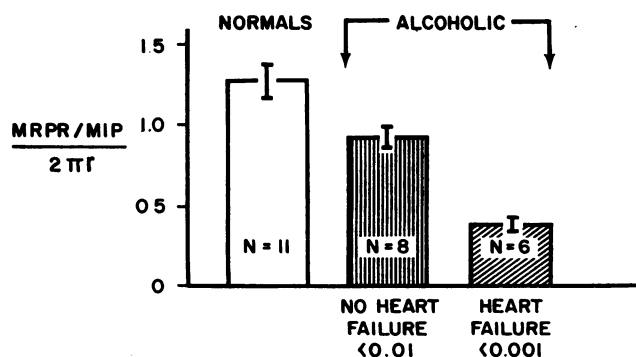
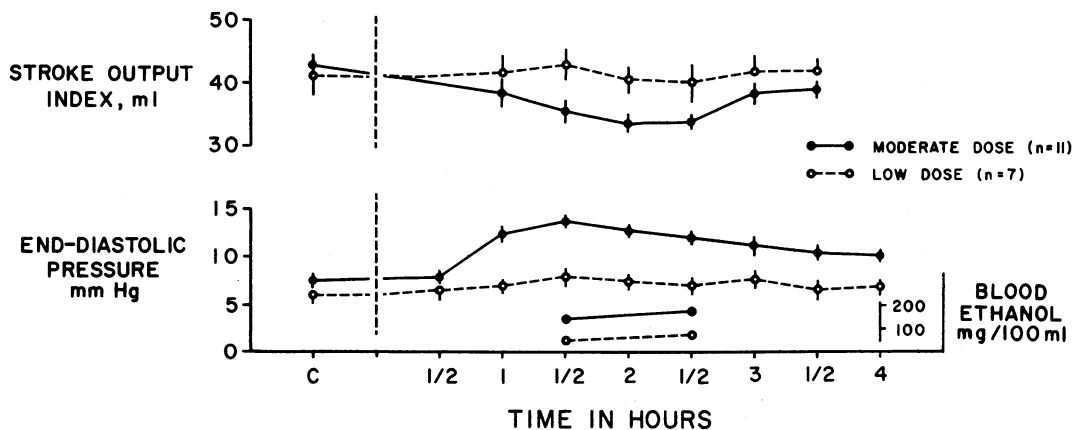


FIGURE 3 The contractility index at rest in the noncardiac alcoholic was significantly reduced below that of the normal, but is higher than in alcoholic subjects who had developed clinical evidence of heart disease.



	C	1/2	1	1/2	2	1/2	3	1/2	4
HEART RATE	84±3.6	87±3.1	92±2.9	91±3.2	93±3.3	92±3.0	92±3.1	90±3.4	89±3.0
MEAN SYSTEMIC ARTERIAL PRESSURE	96±5.1	94±4.9	91±4.1	91±3.3	91±5.3	92±4.7	92±4.2	94±4.6	95±5.4

FIGURE 4 Left ventricular response to oral ethanol. The noncardiac subjects receiving the moderate dose of ethanol exhibited a rise of ventricular end-diastolic pressure and decline of stroke output at a blood alcohol level of 150 mg/100 ml. The diminished ventricular function was returning toward control by 4 hr. No significant changes were observed in the low dose group.

during and after ethanol ingestion. The decline of RQ suggests that at least a portion of the extracted triglyceride was oxidized, although accumulation in cardiac muscle is not unlikely (20, 24). In group V there was a slight decline of arterial free fatty acid concentrations during ingestion of the low dose of ethanol, but no significant change in the extraction of this lipid or plasma triglyceride was observed.

The role of chronic ingestion of ethanol in producing cardiac failure was considered in a 49 yr old male alcoholic who received alcohol daily for a 5.5 month period while on a normal dietary intake. The patient remained

clinically normal during the previous 4 wk. As indicated in Fig. 7, heart rate, circulation time, venous pressure, diurnal urine volume ratio (25), and the cardiothoracic ratio (26) were normal. After ingesting 16 oz of Scotch (42% ethanol) each morning for 12 wk with resultant euphoria, these parameters had begun to deviate from normality. By 16 wk they were progressively abnormal and a ventricular diastolic gallop appeared without evidence of pulmonary congestion. These abnormalities disappeared from 3 to 4 wk after discontinuing ethanol without the use of cardiac medication. To prevent withdrawal effects, Librium, 10 mg t.i.d., was administered for the 1st wk after interrupting alcohol. The patient appeared to maintain a similar level of physical activity before and after the alcohol period, usually consisting of 10-12 walks per day down the length of a 60 ft hall. Although this patient remained free of clinical evidence of cardiac disease after entering a rehabilitation program for treatment of his alcoholism, this phase of the study was limited to one patient in view of the observed response to chronic alcohol ingestion.

DISCUSSION

Studies of the clinical and hemodynamic findings in alcoholic patients, who exhibit the clinical syndrome of cardiomyopathy, do not reveal a specific pattern that would enable separation as a diagnostic entity from other forms of cardiac muscle involvement (1-4). That cardiomyopathy related to alcoholism may be considered as a cardiac disease with a distinct pathogenesis is suggested by the high proportion of alcoholics in the group

TABLE III
Myocardial Uptake of Carbohydrate Substrates during Ethanol Ingestion in $\mu\text{moles}/100 \text{ g per min}^*$

	Control	Experimental†
Glucose	16.80 ± 1.1	18.11 ± 1.4
Pyruvate	4.87 ± 0.34	3.73 ± 0.45
Lactate	37.13 ± 2.2	46.77 ± 3.14
Arterial concentrations in mmoles/liter		
Glucose	4.77 ± 0.24	5.36 ± 0.38
Pyruvate	0.18 ± 0.006	0.19 ± 0.01
Lactate	1.04 ± 0.08	2.81 ± 0.14

* Uptake was calculated from the product of coronary plasma flow and the arterial coronary sinus difference of substrates.

† Represents average values when arterial level plateaued after 60 min of ethanol.

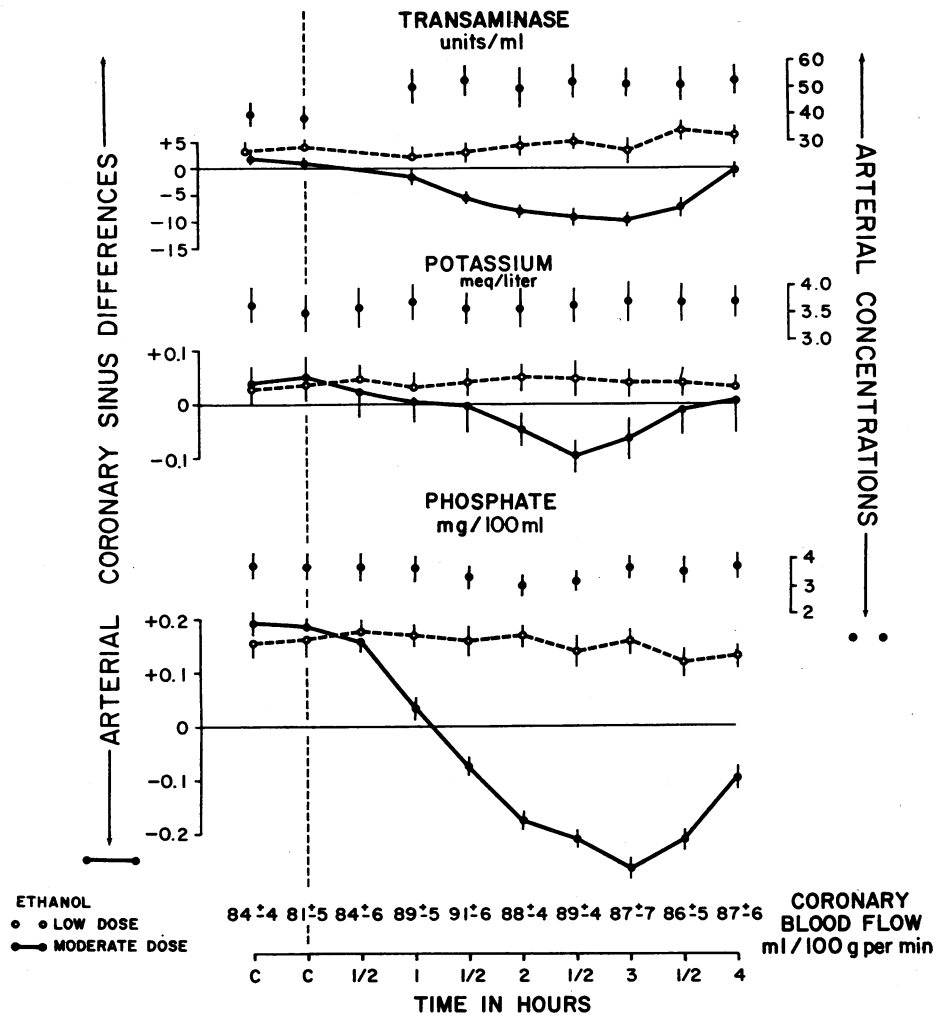


FIGURE 5 Loss of myocardial constituents after ethanol. During ethanol ingestion there was release of phosphate and potassium ions as well as transaminase enzyme into the coronary venous blood in the seven subjects receiving the moderate dose of ethanol. There was an associated small rise of coronary blood flow. This evidence of myocardial injury was transient, virtually reverting to control by 4 hr. The low dose group of 6 oz exhibited none of these changes.

of patients presenting with this syndrome. The relative roles of ethanol and malnutrition in the production of this form of cardiomyopathy are open to question. Many patients have no apparent deficit in total calorie intake (3), although a reduced intake of specific vitamins may importantly affect this disease process.

The use of an afterload test for evaluation of LV function has been proposed as a feasible means of evaluating cardiac function in man (5). Elevation of aortic pressure during infusions of angiotensin in cardiac patients without heart failure, revealed an abnormal elevation of ventricular filling pressure without a corresponding increment of stroke output, differing significantly

from the response of control subjects (5). The observation of a similar abnormal relationship of filling pressure and stroke output in the alcoholic subject without known cardiac disease suggests an adverse effect of chronic ethanolism on the myocardium. Since this is the first study known to the authors in which abnormal LV function has been observed in man in the absence of clinical evidence of heart disease, confirmation by another method was attempted. The validity of the contractility index chosen for further evaluation of ventricular performance has been established (6). The significantly reduced contractility index in the noncardiac alcoholic provides a firmer basis for concluding that a

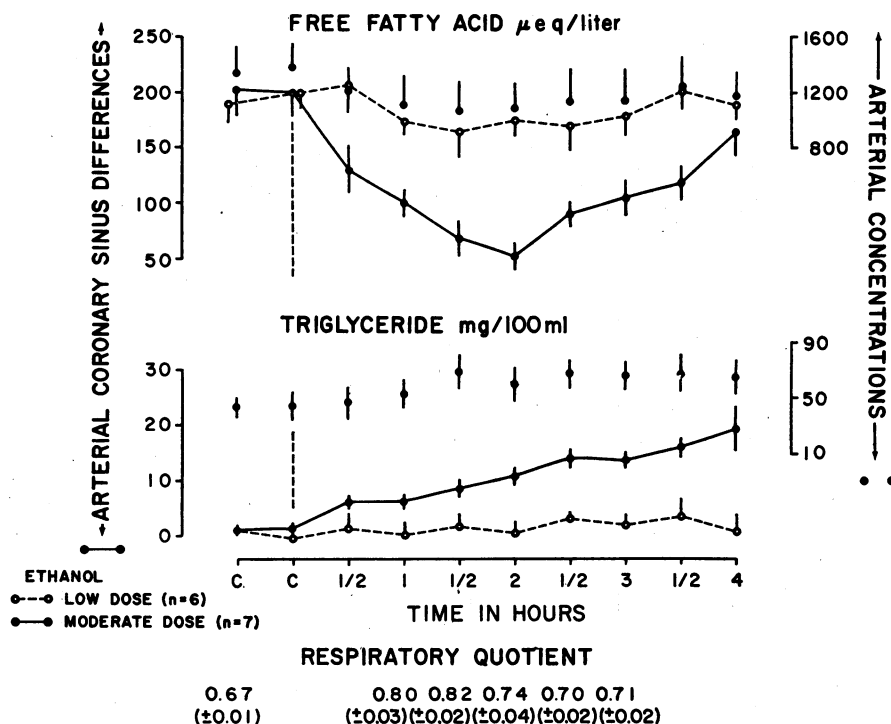


FIGURE 6 Lipid metabolism in myocardium during ethanol ingestion. The major change in substrate extraction by the heart involved altered lipid transport, most evident after 90 min when the arterial concentration of the substrates was relatively constant. Enhanced triglyceride extraction persisted throughout the 4 hr of observation in the moderate dose group. No significant changes in lipid extraction occurred in the low dose group.

preclinical state of cardiac abnormality can exist in the chronic alcoholic.

Consideration of the mechanism of this phenomenon is a logical consequence of these findings and we have focused on the potentially crucial role of ethanol itself. While animal studies are a necessary prelude to this type of study in the human, it would be difficult to consider pathogenesis of the impaired myocardial function in the chronic alcoholic patient purely on the basis of acute ethanol studies in the dog.

The dose-response relationship is obviously important here and may be significantly affected by the use of anesthesia and the presence or absence of a state of chronic alcoholism. Thus, the acute effects of ethanol in the chronic alcoholic without heart disease might indeed show no evidence of a response that might relate to the impairment of ventricular function outlined above. In fact, this study indicates that after 6 oz of ethanol there is no significant effect on either ventricular function or metabolism in the chronic alcoholic.

After drinking 12 oz of whiskey there was a short-term depression of ventricular function and release of myocardial ions and transaminase, consistent with a mild

transient injury of the myocardium. This observation is compatible with the finding that the noncardiac alcoholic who has taken large doses of ethanol over a prolonged period, has an apparently chronic state of diminished ventricular function. The study further indicates that coronary blood flow increments occur only at the larger dose of ethanol, apparently related to the associated tachycardia rather than direct coronary artery dilatation.

Despite the acute response to ethanol, clinical evidence of cardiac disease is not known to occur early in the course of alcoholism. The observation of diminished ventricular function in patients with fatty liver but no clinical heart disease is consistent with the notion that a slowly progressive pathologic response may occur in the myocardium, as appears to prevail in the liver (27). The predominance of the cardiac disease in many patients with cardiomyopathy, rather than liver, cerebral, or renal pathology, suggests that in these subjects there is a differential sensitivity of the myocardium to the effects of ethanol through a mechanism that remains to be determined.

The noncardiac alcoholic with fatty liver gave no history of nutritional deficiency and had no clinical evi-

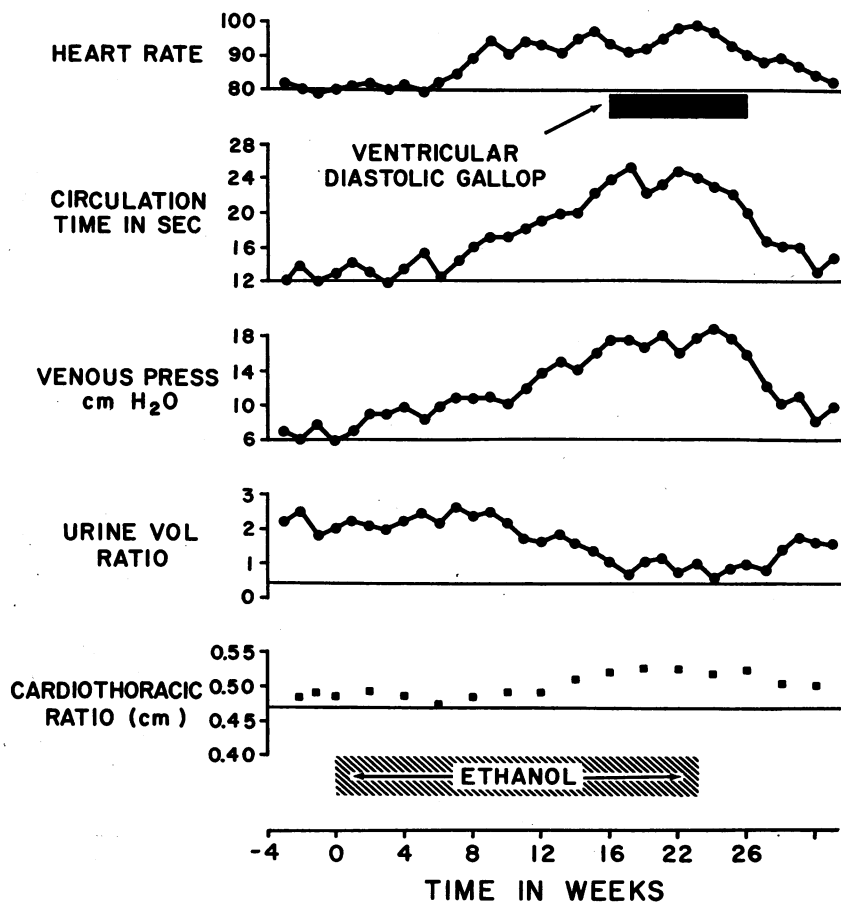


FIGURE 7 Evidence of cardiac decompensation developing during chronic ethanol intake. The weekly values depicted above represent the average of the daily measurements for heart rate and urine volume, and the biweekly determination of circulation time (arm-to-tongue) and venous pressure. These parameters became progressively abnormal after 2 wk of ethanol, with the eventual development of a ventricular diastolic gallop. The abnormalities disappeared after interrupting alcohol intake.

dence of vitamin deficiency. The specific vitamin deficiencies which dominate the clinical picture in some alcoholic subjects did not appear to contribute to the abnormal myocardial function. Blood pyruvate levels and the myocardial uptake of this substrate were normal (Table III), implying adequate thiamine utilization. The hematocrit levels which may be markedly reduced due to folate deficiency, did not differ significantly from the control hospitalized subjects who had normal cardiac function. Normal levels of plasma potassium and sodium ions, as well as the normal ECG, would seem to exclude a cation deficit as the source of the cardiac abnormality. Hence, just as hepatic injury from ethanol is not dependent on a nutritional deficit (27), malfunction of the myocardium may occur without evidence of malnutri-

tion. There was also no evidence of pericardial or endocardial disease that might suggest a viral etiology in these subjects.

A lack of dietary deficit was more clearly substantiated in the chronic alcoholic subject who was fed ethanol for 5.5 months in the presence of a normal caloric intake and vitamin supplementation. The principal cations of the blood, potassium, and sodium were not altered during this period and there was no clinical evidence of viral infection. The major role of ethanol in the production of left heart failure in this subject was substantiated by the gradual reversion of the circulatory abnormalities to normal after alcohol ingestion was interrupted. This suggests that the disease is reversible at some stage if intake of ethanol is completely interrupted, as has

been the experience in another study of ambulatory patients (3).

The mechanism by which ethanol produces its effects on the myocardium is at present speculative. Histologic study of the myocardium in patients with cardiomyopathy has not revealed consistent findings (24, 28), although lipid accumulation appears to be an important histochemical finding when care is taken to prevent lipid extraction in tissue preparation. Since lipid accumulation in heart muscle is one of the consequences of acute alcohol ingestion during the production of transient myocardial injury in the experimental animal (20), a possible role of triglyceride accumulation through an alteration of membrane or myofibrillar function may be considered (29). The decline in myocardial extraction of free fatty acid repeatedly observed (20, 23, 30) and the associated increased extraction of plasma triglyceride suggests that altered lipid transport may be an important determinant of this process.

It has been postulated that an enhanced osmolar gradient between the extracellular space and cardiac cells produced during the infusion of ethanol may effect the injury to the myocardium (20). Whether this is sufficient on a long-term basis to produce clinical myopathy remains to be established. It is noteworthy that scattered areas of fibrous tissue are often present in the left ventricle of alcoholic patients dying with cirrhosis (31). Since an area as small as a portion of a single fiber may be involved in this process, ischemia would be an unlikely process in the pathogenesis of this lesion. The absence of a decline of coronary blood flow and the lack of myocardial lactate production found during the acute ingestion of ethanol is in accord with this finding.

Whatever the operative mechanism, it appears likely that ethanol is the major pathogenetic factor in many patients with cardiomyopathy. In those individuals in whom general malnutrition or specific vitamin or protein deficiency are superimposed factors, the onset and course of clinical cardiac disease may be significantly modified. Thiamine treatment in the relatively few patients with a demonstrable deficiency of this vitamin is known to reduce the marked peripheral vasodilation that characterizes the beriberi syndrome (32, 33). The consequent reduction of blood flow and volume by diminishing the work-load of the alcoholic heart, may be the major therapeutic action of thiamine, since a demonstrable effect of an isolated thiamine deficiency on myocardial function has not been established (34).

It is unlikely that the cardiac disease itself can be significantly ameliorated unless repeated exposure to substantial doses of ethanol is interrupted. As an additional observation, the function of the myocardium was not demonstrated to be adversely affected in acute studies by less than intoxicating doses of ethyl alcohol.

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