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EFFECTS OF ETHYL ALCOHOL ON THE MYOCARDIUM

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OUTLINE

Alcohol as a pharmacologic agent has manifold properties, no better eulogized from a subjective standpoint than in this description from Horace: "What wonders does not wine! It discloses secrets; ratifies and confirms our hopes; thrusts forth the coward to battle; eases the anxious mind of its burthen; instructs in arts. Whom has not a cheerful glass made eloquent! Whom not quite free and easy from pinching poverty!"

The idea that alcohol acted as a (cardiac) stimulant was reinforced by observation of increased pulse and respiration rates with concomitant rise in blood pressure, flushing of the skin, and a general sense of warmth and well-being after the ingestion of moderate amounts of liquor. And, after the 1700's when Heberden[1] noted its efficacy in the treatment of angina pectoris in his original description of the syndrome, ethanol was generally thought to be a dilator of the coronary arteries. There followed widespread usage of the drug for both the treatment and prevention of anginal attacks and also for promotion of increased cardiac output.[2]

The mechanism of these supposed responses has remained obscure even until recent times, and conflicting experimental data only compounded the con-

fusion. Experimental studies have been relatively limited, and exceedingly few physiological parameters were consistently found to respond in like manner as reported by the various investigators. An attempt is made here to review the procedure, technique, results and interpretation of representative chronological studies.

In an effort to relate experimental blood levels of alcohol to human circumstances and reactivity, it should be noted that the generally accepted upper limit of alcoholemia for legal purposes is 100 milligrams per milliliter, and that no essential differences in results are found to exist using U.S.P. alcohol or ordinary drinking whiskey. In general, dosages of 0.5 grams of alcohol per kilogram of body weight will produce alcoholemia of 70 mg.% $\pm$ 15 mg.% thirty minutes after intravenous injection and 1.5 gm. per kilogram produced levels of 170 mg.% $\pm$ 35 mg.%.[3,4]

In 1882, Martin and Stevens[5] observed that alcohol caused cardiac dilatation in canine heart-lung preparations in relatively high (250 mg.%) concentration, and that still higher levels decreased cardiac output. Hemmeter[6] and Bock[7] confirmed these results. Two experimenters in 1905 using the same preparation, a Langendorff perfusion column with mammalian hearts, reported ap-

parently contradictory results, i.e. Kochman[8] noted that concentrations of 400 mg.% decreased systolic and diastolic blood pressures; while Loeb[9] found cardiac output stimulated by alcohol levels of 130 to 300 mg.%, but observed no effect on coronary circulation with levels up to 400 mg.%.

Dixon,[10] who reviewed the literature extant in 1906, and did his own experiments with dog hearts, believed alcohol to exert a slight general vasodilatory effect in concentrations of 100 - 200 mg.% which was not more profound for the coronary arteries than for vessels of other organ systems. He observed also that alcohol levels approximately ten times the above caused decreased coronary outflow. However, Cow[11] in 1911 noted slight vasoconstriction in the diameter of arterial rings taken from the coronary vessels of oxen and sheep with a 1% (1000 mg.%) solution of ethanol. This transcient response was followed by a relatively greater vasodilatation, a biphasic response, but was not apparently supportive of the results of Dixon and others.

Measurement of coronary outflow by coronary sinus catheterization in the heart-lung preparation by Sulzer[12] in 1925 disclosed reduction of coronary flow by alcohol concentrations of 100 to 200 mg.% and higher. No change in arterial blood pressure was noted.

In collaboration with Professor Starling of the London Institute for Physiology, Sulzer concluded that judged by cardiac volume loads there was no evidence of any stimulant effect from alcohol; in fact, if any effect at all is produced, it is purely depressant, leading to increased venous and pulmonary pressures and coronary constriction with a decrease in coronary flow. This study was among the first to use accurate chemical methods for the determination of blood alcohol levels.

In contrast to this, Gilbert and Fenn[13] found no change in coronary flow in intact anesthetized dogs following slow intravenous injection of 0.3 cc. of 80% alcohol per kilogram. They failed to note, however, that the Grehant anesthetic they were using was a 5% solution of chloroform diluted with equal parts of alcohol and water, possibly negating any significance of their observations. They also noted a slight decrease in blood pressure and heart rate following the alcohol infusion.

Throughout the 1930-1950 period there was a relative paucity of investigation related to this subject, and the inconclusiveness of these investigations prompted Lasker and others[14] to make the first study using statistical analysis with paired control

samples. In dogs anesthetized with pentobarbitol and anticoagulated with heparin, measurements were made of heart rate, mean arterial blood pressure, coronary sinus outflow, and coronary artery inflow at varying rates and dosages of intravenous and direct intra-arterial infusions of alcohol. They concluded that ethanol increased both the coronary outflow and inflow of the dog at levels similar to those obtained after imbibing moderate amounts (3-4 ounces) of alcohol in man. Intravenous alcohol also produced a significantly lowered mean arterial blood pressure. Controls were employed using similar volumes of physiologic saline. The results of part of that study are summarized in Table I below:

TABLE I

WT.	CONTROL			EXPERIMENTAL			
Kgm.	Mean B.P. mm.Hg.	Heart Rate	C.S.O. ml./min.	Mean B.P. mm.Hg.	Heart Rate	Alcohol Conc. mg.%	Maximal Coronary Sinus Outflow ml./min.
11.0	94	200	70	78	188	42	105 = +50%
14.0	106	196	42	98	176	67	60 = +43%
16.0	112	128	45	82	120	92	52 = +16%
14.5	88	168	51	70	132	65	68 = +33%
15.0	88	152	75	72	136	89	78 = + 4%
16.5	100	180	38	74	168	52	55 = +45%
12.5	82	152	31	64	152	75	37 = +19%
AVER.	96	168	50	77 p=<0.001	153 p=<0.02	70	65 = +30% p=<0.02

Coronary Sinus Outflow after Slow Infusion of 500 mg./kg. of Alcohol Intravenously

Increased coronary blood flow and decreased mean arterial pressure were thought to reflect changes in vascular resistance and therefore alcohol was said to decrease coronary vascular resistance. This effect was not specific for the coronary vessels, and alcohol was less effective in this regard than papaverine and aminophylline, also general vasodilators. Logarithmically progressive doses of all three drugs produced similar curves of progressive increase in coronary blood flow and duration of increase.

An attempt was made to define the mode of action on the coronary circulation. It was stated that small doses of alcohol probably have a direct cutaneous vasodilating effect, but that larger amounts are thought to mediate vasodilation in peripheral vessels by some neuronal mechanism, either central or peripheral. Such a situation, it was proposed, would explain the previously cited results of Dixon and also Sulzer, i.e. both of whom observed no increase in coronary blood flow in response to intravenous alcohol because they were using isolated heart or heart-lung preparations and not intact open-chest dogs with functioning nervous system influences which could mediate the coronary vascular response. Lasker's own studies tend to discount at least two such possible neural mechanisms, however,

since intracoronary alcohol infusions in amounts sufficient to produce substantially increased coronary flow yielded concentrations in the carotid arteries of less than 20 mg.%, hardly enough to produce a depression of the vasomotor center. Concomitantly, similar intracoronary doses (100 mg.) of ethanol produced only very slight immediate effects on heart rate and blood pressure while increasing the coronary blood flow quite appreciably. Such an increase in coronary blood flow, if due to inactivation of autonomic nervous system neurons or tracts, would be accompanied by a more profound response in the peripheral vessels with a significant drop in arterial resistance and pressure and a compensatory heart rate response.

No further attempt was made in this 1955 study to correlate coronary blood flow, cardiac output, and cardiac oxygen consumption as modified by alcohol, but Lasker noted that large amounts of alcohol act to depress all these parameters in heart-lung preparations and proposed that further study of cardiac efficiency be performed in the open-chest dog measuring these variables simultaneously.

In response to Lasker's study, Schmitthenner and others[15] in 1958 performed the simultaneous measurements of the effects of alcohol on cardiac work, oxygen con-

sumption, and coronary blood flow suggested in that earlier work. Using the same anesthetic and control methods in open-chest dogs, they compared nine paired studies using eight observations before and after intravenous infusion of 30 gm. of ethanol at 33 mg. per kg. per minute. Coronary blood flow was measured after coronary sinus intubation with nitrous oxide desaturation. Cardiac output was measured according to the Fick principle and determinations were made of left ventricular work, and uptake of oxygen, glucose, pyruvate and lactate by the myocardium.

It was noted that arterial blood levels of alcohol in the range of 70 - 120 mg.% produced no change in heart rate or mean arterial pressure, but affected a proportional increase in left ventricular work, total oxygen uptake, and cardiac output. There was no consistent increase in coronary flow, and the oxygen content and saturation of the venous blood in the coronary sinus rose. From this, these investigators proposed a decreased oxygen extraction proportionately, and since left ventricular oxygen metabolism was reduced, there was said to be an apparent improvement in the mechanical efficiency of the myocardium. No alterations of lactate or glucose metabolism were noted, but arterial pyruvate levels were decreased

after ethanol infusion.

Schmitthenner concluded that alcohol produces increased oxygen uptake by the body and progressive peripheral vasodilitation. This leads to increased venous return and diastolic filling with consequent rise in stroke volume and work. Why cardiac work increased disproportionately with myocardial oxygen consumption was not elucidated. Alcohol differed from such drugs as nicotine, epinephrine and norepinephrine in this regard.

It would seem then that far from resolving any conflicts, the work of Schmitthenner and the previously discussed work of Lasker instead of resolving the effect of alcohol on the cardiovascular system had merely added to the conflicting observations of these too-little-studied properties. Consequently, Willard and Horvath[3] in 1963 after citing the variety of results of three previous investigators[12, 14, 15] undertook to observe the effect of constant intravenous infusion of ethyl alcohol on the coronary circulation. Mongrel dogs were anesthetized with a barbiturate, anticoagulated with heparin, and coronary blood flow was measured by the nitrous oxide desaturation technique. Slow intravenous infusion of 500 mg. of alcohol per kilogram of body weight was infused producing alcoholemia as measured

in the coronary sinus and femoral artery of not greater than 85 mg.%. Eleven physiological parameters were determined and analyzed on a paired basis using the "t" value of Student for the determination of statistical significance of a limited sample. Table II summarizes these parameters along with control and observed values and their calculated statistical significance.

Not indicated in the table on the following page, but of considerable interest to the authors, was the variation in response of coronary blood flow. Animals with average flow values of approximately 70 ml./min. showed a 68% increase in coronary blood flow while dogs with high ($<$100 ml./min.) control values had a 19% decrease in coronary flow during alcohol infusion. Other animals with low control values (approx. 30 ml./min.) showed no change with alcohol infusion. Further observation disclosed that the dogs having the increased coronary flow rates retained elevated values, but exhibited a decrease of 13% from peak response when measured twenty minutes post-infusion. No change in the post-infusion period was noted in the coronary flow values of animals with an initial decrease (19%) or in those with no previous change in coronary flow. None of these variations in coronary flow achieved statistical significance, however.

TABLE II

Summary of Data for Coronary Circulation and Related Events before, during and following Ethyl Alcohol Infusion

	CONTROL	Mean difference From control During infusion 45 min.	Post-infusion 20 min.
	Mean S.E.	Mean S.E.	Mean S.E.
Cor. blood flow ml/100 mg. lt. vent./min.	76.5 ± 9.6	+5.4 ± 11.5	+11.8 ± 15.4
Cardiac output L/min.	2.5 ± 0.5	-0.5 ± 0.4	-1.0 ± 0.3*
Heart rate/min.	152.0 ± 10.6	+28.0 ± 4.0*	+29.3 ± 7.1*
Cor. vas. resist. (PVU)	1.9 ± 0.4	-0.3 ± 0.2	-0.2 ± 0.2
Systolic blood pres. mm. Hg	159.6 ± 11.0	-13.6 ± 4.9*	-25.5 ± 6.2*
Diastolic blood pres. mm. Hg	118.1 ± 9.4	-11.5 ± 2.8*	-16.9 ± 5.2*
Total O_2 consumed ml/min.	70.8 ± 4.5	+7.3 ± 2.1*	+1.4 ± 3.8
Total CO_2 produced ml/min.	73.3 ± 4.4	+16.1 ± 5.5*	+16.3 ± 7.6
O_2 consumed lt. vent. ml/100g/min.	9.0 ± 1.6	+4.0 ± 1.9	+3.1 ± 1.4
Aerobic energy Kg.m./min.	9.6 ± 1.5	+3.5 ± 1.7	+5.0 ± 2.2
Work lt. vent. Kg.m./min.	4.2 ± 0.7	-1.3 ± 0.6*	-2.0 ± 0.5*

S.E. = Standard Error of the mean
* = --paired--5% significance level

The heart rate and blood pressures showed significant deviations both during and after alcohol infusion. The lowered pulse pressure correlated well with the significantly decreased cardiac output, i.e. a decrease in stroke volume was observed, especially in the post-infusion period. The increased heart rate, diminished stroke volume and minute cardiac output along with increased total body oxygen consumption and carbon dioxide production denote a loss of cardiac efficiency. This decreased efficiency is reflected in the increased oxygen uptake of the left ventricle and especially in the significantly increased left ventricular work both during and after ethanol infusion.

In summary, Willard and Horvath did not find coronary constriction with decreased blood flow after alcohol infusion as did Sulzer,[12] nor did they observe significantly elevated flow values as in the work of Lasker and others.[14] Sharp contrast is seen also between the studies of Schmitthenner and others[15] who reported no change in heart rate or blood pressure and an actually increased cardiac efficiency using similar conditions and techniques.

In an effort to explain the slight increase in coronary flow which occurred in dogs with mean coronary flow control values, Willard proposed that coronary

vasodilitation must have occurred since there was a concomitant decrease in peripheral arterial perfusion pressure, which he considered to largely regulate coronary blood flow. Alcohol appeared to have the effect of coronary vasodilation and peripheral vasoconstriction with increased peripheral vascular resistance occurring as a response to decreased cardiac output and blood pressure. It was concluded that alcohol was probably a dilator of coronary vessels, but that this response was highly variable on an individual basis and was often masked by contrasting systemic vascular changes. For these reasons the effect of ethyl alcohol as a coronary dilator could not be designated as significant.

In 1960 Leighninger and others[16] conducted an experiment to determine the effect of alcohol, amyl nitrite, and pentaerythritol tetranitrate on the blood supply to the ischemic myocardium distal to ligated coronary arteries in dogs.

The left circumflex artery was cannulated just distal to the point of ligation at its origin from the left coronary artery. By this means backflow into the artery produced by collateral circulation was measured and the effects of the various drugs observed.

The blood pressure was maintained at a stable

normal mean value, and control backflow determinations were made. The effect of alcohol on backflow determinations was observed at five minute intervals after the infusion of 500 mg./kg. of body weight intravenously. The results are summarized in Table III.

TABLE III

Effect of Alcohol on Coronary Artery Backflow to Ischemic Myocardium

BACKFLOW (CC/MIN.)		
5 min. before drug	5 min. after drug	Difference
24.0	16.0	-8.0
14.0	10.6	-3.4
2.6	2.6	-0.6
6.6	6.0	-0.6
2.4	2.4	0.0
2.8	2.2	-0.6
2.0	2.0	0.0
4.8	4.4	-0.4
9.8	5.4	-4.4
6.2	2.6	-3.6
2.4	1.2	-1.2
		Mean = -1.93

The mean reduction in backflow after alcohol infusion was 1.93 cc/minute. This is statistically significant at $p = 0.02$. In contrast, amyl nitrite added 0.98 cc/minute to the ischemic circumflex area of the

dog heart. Pentaerythritol tetranitrate added 0.81 cc/min. and 0.6 mg. nitroglycerin increased the flow 0.88 cc per minute. These beneficial results were temporary, however, and no long-term decrease in mortality or infarct size was noted following their use.

Another investigator, Ganz,[17] in 1962 studied the acute effect of alcohol on the circulation and on the oxygen metabolism of the heart with particular interest directed to the action of alcohol in angina pectoris. Using intact anesthetized dogs with constant, slow intravenous alcohol infusion, he measured much the same parameters as had previously cited authors in this paper.[14, 15, 3, 16] Ganz differed in using a thermo-dilution catheter technique to measure cardiac output and coronary sinus outflow. These determinations and the results of twelve other paired, controlled, and statistically analyzed samples led him to the following conclusions. There was no significant change in heart rate or mean arterial pressure and coronary perfusion pressure remained the same throughout the procedure. Cardiac output was consistently significantly decreased due to a decrease in stroke volume during and after alcohol infusion.

That there must have been a rise in total peripheral

resistance to account for this decreased stroke volume with no change in blood pressure was the explanation of alcohol's principal peripheral effect. A slight increase in coronary sinus outflow in the face of constant coronary perfusion pressure denoted a fall in coronary resistance. There was purportedly a differing response between the coronary and peripheral vasculature. This seemingly beneficial effect, resultant in increased coronary flow was more than offset by the observed decrease in left ventricular work, relative to the decreased cardiac output, and the attendant proportional increase in myocardial oxygen consumption with increased coronary flow. There was no change in the A-V oxygen extraction difference. These findings suggested a decreased left ventricular efficiency, which when calculated on the basis of cardiac work and myocardial oxygen uptake was significant at $p < 0.01$. From this, Ganz postulated that the increased coronary flow was in response to a direct (depressor) effect of alcohol on the myocardium, and that no discernible effect was produced on the smooth muscle of the coronary arteries. He concluded that no beneficial effect on acute coronary insufficiency, the pathophysiologic basis for angina pectoris, was produced by the administration of alcohol.

The most recently published work on the cardiovas-

cular response to alcohol in animals other than man is by Webb and Degerli.[4] Using anesthetized open-chest dogs and maintaining a constant pH and P_{CO_2}, they determined eight parameters of response to doses of ethyl alcohol varying over a wide range. Cardiac output was measured by means of an electromagnetic flowmeter around the ascending aorta, and a similar device measured coronary sinus outflow as representative of total coronary arterial flow. Isotonic saline was used as the control solution, and 70% ethanol was later infused. Blood levels of 42 to 87 mg.% were noted after infusion of 0.5 gm. of alcohol per kilogram of body weight, and levels of 130 to 207 mg.% occurred after doses of 1.5 gm/kg.

In all groups a decrease in coronary flow was noted, while cardiac output showed a striking increase which was roughly proportional to increasing blood alcohol levels. Cardiac work was also increased, with resulting loss of efficiency of the heart. No significant increases in pulse rate or peripheral resistance were observed. Coronary resistance rose significantly in all groups, however, which correlated well with the increased stroke work and stroke volume. Webb concluded that while the heart is "stimulated" in terms of doing increased cardiac work, oxygen requirement in-

creases and the total cardiac capability is reduced. This relative oxygen lack is even more serious in persons with coronary atherosclerosis, he continues, and since the normal increase in coronary flow due to hypoxia is lacking during significant alcoholemia, the actually reduced flow leads to serious coronary insufficiency. The clinical obviation of anginal pain appeared to be related to an altered pain threshold or recognition.

STUDIES IN HUMANS

These studies of the effects of alcohol in animals other than man have proved rather inconclusive to date, and many conflicting results are yet to be resolved. The few related studies in humans add little to the knowledge of the effects of alcohol on cardiovascular dynamics in general, but shed considerable light on the nature of its salutary subjective influence in angina pectoris.

In 1946 Stearns and others[18] attempted to determine if "therapeutic" doses of whiskey shorten the duration of attacks of angina pectoris or increase the capacity for objective work in a patient with angina. A wide variety of subjects with respect to age, drinking habits, sex and ability to perform a standard

exercise test were chosen. Absolutely no significant difference was noted in the duration of anginal attacks treated with one ounce of whiskey at the onset of pain as compared to the duration of wholly untreated attacks. The majority of these patients believed there had been some beneficial effect, however; this subjective comfort was often attendant with merely touching a drop of whiskey to the tongue or holding a small amount in the mouth. Similarly, no increased ability to perform standard exercise tolerance tests was noted after either single or multiple prophylactic doses of alcohol. The latter regime actually caused increased severity and frequency of anginal attacks in some patients. While the mechanism of such a reaction was said to be obscure, these investigators postulated that the generally observed increase in sense of well-being of angina patients after alcohol ingestion was due to a mechanism similar to that of opiates or barbiturates. That alcohol decreased the awareness to pain centrally or increased the peripheral pain threshold was thought to explain the subjective improvement.

In a study representative of many which considered the effect of alcohol on cardiac rate only, Hebbelinck[19] compared the cardioaccelerator response of 21 young males before and after alcohol ingestion. He found a signifi-

cant difference ($p<0.01$) between the observed and control group only in the first two minutes after standard exercise on a bicycle ergometer was begun. An alcohol dose of 0.6 gm of 94% ethanol had been given 40 minutes before the experiment which produced mean blood alcohol concentrations of 30 mg.% at both thirty and sixty minutes after ingestion.

It was concluded that alcohol interferes with a cardiovascular reflex response to exercise, probably at the hypothalamus.[20] He cited the work of Masserman who noted an increase in activity of the hypothalamus after small doses of alcohol and the results of Heymans and others[21] who reported that alcohol affected a proprioceptive cardiovascular reflex mechanism.

In two studies which later proved to amend the existent views regarding the value of alcohol in the treatment of angina pectoris, Russek[22, 23] studied the effect of various drugs on the electrocardiographic response to standard exercise in coronary disease. Utilizing the Master "two-step" exercise that in subjects with repeatedly constant electrocardiographic response, the effects of prophylactic doses of alcohol (1 - 2 ounces) and glyceryl trinitrate (0.4 mg.) were noted. Alcohol failed to prevent the transient RS-T depressions and T wave alterations characteristic of

myocardial ischemia observed in these patients. Nitroglycerin either completely prevented or significantly modified these patterns in the same patients, however. Alcohol was nevertheless reported to be as effective as nitroglycerin in preventing the anginal pain ordinarily brought on by the Master's test.

SUMMARY

This paper has attempted to review in a chronological manner the available literature dealing with the effects of ethyl alcohol on the cardiovascular system, more specifically the heart and coronary arteries.

Studies in both animals and man have produced inconclusive and even contradictory findings, and at present the specific effect of alcohol on the heart remains unclear.

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