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Ethyl alcohol
Effects on coronary blood flow in man

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The myocardial clearance of rubidium may be obtained by praecordial counting after a single intravenous injection of $Rb^{86}Cl$. Eight normal men as well as 12 men with coronary heart disease had this determination performed before and 20 minutes after the ingestion of 90 ml Canadian Club whisky. In the 8 normals, the average increase of the myocardial clearance of rubidium after alcohol was 11 ml/min per 100 g myocardium. In 11 of 12 cases with coronary heart disease, the rate increased after alcohol, the rise ranging from 4 to 91 ml/min per 100 g myocardium. The average change in the group amounted to +33 ml/min per 100 g myocardium ($P<0.02$). The explanation for the large increase in coronary blood flow that alcohol produced in some of our cardiac patients is unknown. Possible mechanisms to explain this finding are presented.

Ethyl alcohol has been used in the treatment of angina pectoris ever since its original description by Heberden (1786). Relief of ischaemic pain has been frequently described, and though Russek, Naegele, and Regan (1950) as well as Conway (1968) failed to show any improvement in the exercise electrocardiograms of patients with coronary heart disease, alcohol is still advocated for its beneficial therapeutic effects. Controlled experimental observations of the effects of alcohol on coronary blood flow, however, are contradictory. Thus, Lasker, Sherrod, and Killam (1955) reported a rise in coronary blood flow and a decline in coronary resistance in open-chested dogs after dosages of alcohol greater than 375 mg per kg. Ganz (1963) infused alcohol at an average dose of 58 mg/kg per min for 20 minutes into 10 anaesthetized dogs. He observed a decline in the cardiac output, and a rise in the coronary sinus outflow as a result of a fall in the coronary vascular resistance. On the other hand, Webb and Degerli (1965) studied the coronary flow in dogs after the intravenous administration of 0·5, 1·5, and 5 g ethyl alcohol/kg body weight. At all dosage levels, the coronary flow decreased and the coronary resistance rose. Schmitthenner *et al.* (1958) found that ethanol blood concentrations of 70 to 120 mg/100 ml in anaesthetized open-chested dogs increased cardiac output and left ventricular work, but did not increase coronary blood flow or oxygen uptake. The conflicting results are possibly due to the variation in experimental conditions in different investigations. Further, the application of the findings of such experiments to patients with heart disease is limited.

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Regan *et al.* (1969) recently administered 6 oz alcohol to 7 alcoholic patients without clinical evidence of heart disease. No significant changes in ventricular function, myocardial blood flow or myocardial metabolism were observed. When 12 oz alcohol were administered to 11 non-cardiac alcoholic patients, a rise in the left ventricular end-diastolic pressure, a decrease in the stroke output, and an increase in the coronary blood flow were observed.

There are surprisingly few data available on alcohol's effect on the coronary blood flow in normals or in patients with coronary heart disease. The present study therefore examines the effect of ethyl alcohol on the coronary blood flow in such individuals.

Methods

The praecordial counting was performed with a $2'' \times 2''$ NaI(Tl) scintillation detector with a lead collimator, 150 mm long with an external diameter 110 mm. Pulses from the detector were fed via a pulse height analyser to a digital ratemeter and then to a recorder. For ^{131}I activity the pulse height analyser was set for the 364 KeV photopeak with a 100 KeV window. For ^{86}Rb, the pulse

height analyser was set for 1·08 MeV with a 100 KeV window. The ratemeter time constant was set at 4 seconds for recording background and at 4 seconds during the procedures. The chart speed was set at 3 cm per minute. Blood activity was measured in a 5 cm well-type scintillation detector with the pulse height analyser setting as described for external counting of ^{131}I and ^{86}Rb.

The counts are corrected for the relative inefficiencies in the *in vivo* and *in vitro* systems, introducing a coefficient $\bar{n}$ calculated from the counting rates obtained when two 500-ml flasks containing known concentrations of ^{131}I and ^{86}Rb are counted externally under a standard geometrical arrangement.

$$\bar{n} = \frac{\text{(c.p.m./ml) } ^{131}\text{I (well)} \times \text{c.p.m. } ^{86}\text{Rb (flask)}}{\text{(c.p.m./ml) } ^{86}\text{Rb (well)} \times \text{c.p.m. } ^{131}\text{I (flask)}} \quad \ldots \quad (1)$$

Experimental procedure The experiments were performed in the morning on resting subjects in the supine position. A Cournand cannula was introduced into the right brachial artery. The detector was positioned over the centre of the heart silhouette.

15μCi of ^{131}I as RIHSA, in 0·5 to 1 ml saline, were then rapidly injected into the left cubital vein. Thirty seconds after the injection the praecordial counting and arterial blood sampling were started; both counting and blood sampling lasted 3 minutes and the rate of withdrawal was 1 ml every 4 seconds.

Within 5 minutes, 150 μCi of ^{86}Rb as rubidium chloride in 0·5 to 1 ml saline were rapidly injected into a cubital vein. Praecordial counts and arterial blood were taken as previously done after the RIHSA injection. Recording was continued until blood sampling and praecordial counting were completed.

The subject then drank 90 ml Canadian Club whisky. Twenty minutes after the ingestion of the beverage, the radioisotope studies, using ^{131}I and ^{86}Rb were repeated as described above. Care was taken to maintain the detector in the same position.

All the blood samples were haemolysed and counted in duplicate. The $\bar{n}$ coefficient was periodically measured to check the constancy of the conditions of the counting apparatus.

The blood pressure and cardiac rate were obtained before and after the ingestion of the alcoholic beverage.

Calculations The myocardial clearance (MCR for ^{86}Rb) was calculated in two steps:

1) Calculation of the fraction F of the praecordial counting rate due to myocardial activity:

$$F = \frac{^{R}Rb - \bar{n}W_B\bar{a}Rb}{^{R}Rb}$$

where:

$$W_B = \frac{^{R}RIHSA}{\bar{a}\ RIHSA}$$

and

^{R}RIHSA and ^{R}RB: net number of counts collected on the scaler from 30 to 90 seconds after the injection of RIHSA and Rb, respectively;
ā RIHSA and ā RB: radioactive concentrations per millilitre of arterial blood sampled from 30 to 90 seconds after the injection of RIHSA and rubidium, respectively.
$\bar{n}$: the relative counting efficiency defined in equation 1.

2) Calculation of MCR from the praecordial trace (Fig.):

$$MCR = \frac{D_f \cdot F \cdot 60 \cdot 100}{\int_0^\infty {}^{R}Rb(t)dt}$$

where D_f = average net deflection mm of the ratemeter trace from 30–90 seconds.

Subjects

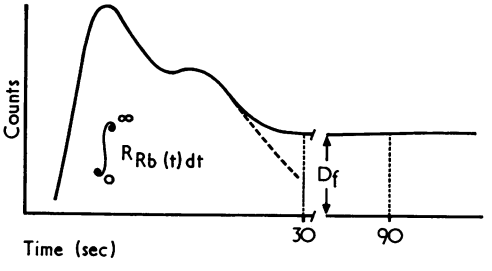
Twenty men were studied. Eight had normal cardiovascular systems and 12 had an established diagnosis of coronary heart disease, based on clinical and electrocardiographic data. Eight of them had previously sustained a myocardial infarction, while in 6 of the subjects there was a history of angina. None of the 20 patients was a chronic alcoholic. The clinical diagnoses of the entire group are listed in Tables 1 and 2.

The procedure was explained in detail to the subjects and the investigative nature of the study was stressed. An informed consent was then obtained from all of the patients.

Results

Complete data on the 20 patients are presented in Tables 1 and 2. The average value of the myocardial fraction of the praecordial counting rate (F) in the 8 normal subjects

FIG. *Calculation of myocardial clearance of rubidium from the praecordial tracing* (see text). *The area under the radiocardiographic curve is calculated after semilogarithmic extrapolation of the final downslope. D_f, the average deflection above background from 30 to 90 seconds after injection.*



studied with ^{86}Rb was 76 ± 13 per cent. In the 12 cases of coronary heart disease the average F value was 62 ± 22 per cent. The myocardial clearance of rubidium in the subjects with normal cardiovascular systems averaged 72 ± 21 ml/min per 100 g myocardium, and in the 12 cases with coronary heart disease the mean value was 55 ± 20 ml/min per 100 g myocardium.

Effect of alcohol In the subjects with normal cardiovascular systems, either no change or a minimal increase in the myocardial clearance of rubidium was observed after the administration of alcohol. The average increase of +11 ml/min per 100 g was found not to be statistically significant.

In 11 of the 12 cases with coronary heart disease, the clearance increased after alcohol, the rise ranging from 4 to 91 ml/min per 100 g myocardium. In one case a decrease of 2 ml/min per 100 g myocardium was observed. The average change in the group amounted to +33 ml/min per 100 g, which was statistically significant ($P < 0.02$).

Alcohol did not produce in either group a significant change in the systemic blood pressure or cardiac rate.

TABLE I *Results in normal group*

Age of normal subjects	*Experimental state*	*F%*	*Myocardial clearance of Rb (ml/min per 100 g)*	*Blood pressure (mmHg)*	*Heat rate (beats/min)*
25	Control	58	94·8	120/90	82
	Alcohol	71	102·0	140/100	84
30	Control	82	97·5	140/90	90
	Alcohol	62	95·7	130/90	92
40	Control	74	55·2	112/70	68
	Alcohol	70	76·4	106/70	68
25	Control	72	53·6	130/80	65
	Alcohol	57	51·6	120/78	64
22	Control	58	42·8	110/74	92
	Alcohol	69	53·9	120/80	82
16	Control	82	87·0	120/84	105
	Alcohol	89	105·0	120/80	102
51	Control	90	90·0	130/80	90
	Alcohol	80	111·0	130/80	78
30	Control	89	71·0	140/80	82
	Alcohol	93	85·0	142/76	82
Mean	Control	76	74·0	125/81	84
	Alcohol	74	85·0	126/82	82
	P value	NS	NS	NS	NS

Discussion

Donato, Bartolmei, and Giordani (1964) and Donato *et al.* (1966) in their recent publications have described the measurement of coronary blood flow by external counting using radioactive rubidium. However, the absolute flow cannot be determined with this method since individual variability in depth and size of the heart prevents an absolute estimate of myocardial uptake of the radioisotope. The obtained value for myocardial clearance of rubidium represents the mean flow per unit mass, and it is conveniently expressed per 100 g myocardium.

A major advantage of this technique is the avoidance of coronary sinus catheterization which enhances the practical value of this method. Further, the entire measurement may be completed in 90 seconds which is an obvious advantage compared to the indirect Fick technique which uses N_2O, inert radioactive gases or ^{131}I antipyrine. Donato has stressed that a unique feature of this technique is that it measures the average flow to the entire myocardial mass, independent of the venous drainage. Unperfused areas which do not contribute to the indirect Fick values, since they do not extract the indicator, contribute to the clearance values by the ^{86}Rb method, in which the indicator content of the entire heart is averaged. Therefore, areas with no indicator actually contribute with their zero value to the average.

Donato believes that the most significant advantage of the technique is that the flow value measured by the myocardial clearance of rubidium represents actual flow to true capillaries.

The main limitation to the method stems from dosimetric limitations. The small percentage of gamma radiations emitted by ^{86}Rb demands the use of relatively large radioactive doses, which limit the number of measurements that may be performed in the individual patient to a maximum of two.

Coronary blood flow measured by the ^{86}Rb method is reliable and reproducible. Donato measured coronary blood flow in the same patient with the N_2O saturation method as well as the ^{86}Rb external counting method. The average coronary blood flow values in the 11 subjects using the N_2O method was $72{\cdot}0 \pm 16{\cdot}8$ (SD) ml/min per 100 g myocardium, and in the same group using the ^{86}Rb method was $68{\cdot}6 \pm 16{\cdot}1$ (SD) ml/min per 100 g myocardium.

Donato determined that the average F value was $66{\cdot}96 \pm 5{\cdot}5$ per cent in 15 normal subjects studied with ^{86}Rb and $54{\cdot}59 \pm 13$ per cent in 26 cases of coronary heart disease. The clearance of rubidium averaged $87{\cdot}93 \pm 22{\cdot}5$ ml/min per 100 g myocardium in 25 normal subjects, while in 11 cases with coronary heart disease the mean value was $62{\cdot}54 \pm 25{\cdot}3$ ml/min per 100 g. These values are not too dis-

TABLE 2 *Results in abnormal group*

Patient's age and condition	*Experimental state*	*F%*	*Myocardial clearance of Rb (ml/min per 100 g)*	*Blood pressure (mmHg)*	*Heart rate (beats/min)*
65, old anterior wall myocardial infarct	Control	66	48·7	154/96	76
	Alcohol	85	93·6	150/100	72
51, old anterior lateral infarct	Control	91	94·5	120/72	80
	Alcohol	89	118·5	116/70	84
75, angina, hypertension	Control	61	62·5	160/90	72
	Alcohol	81	69·0	180/96	76
66, old anterior septal infarct	Control	69	48·0	138/90	66
	Alcohol	59	55·0	158/100	68
47, old inferior myocardial infarct	Control	52	50·6	150/90	78
	Alcohol	86	133·7	140/80	80
43, old anterior septal myocardial infarct	Control	25	31·0	140/90	72
	Alcohol	65	62·5	132/90	68
54, angina, hypertension	Control	85	54·0	170/100	65
	Alcohol	79	145·0	170/100	72
61, old anterior myocardial infarct	Control	45	29·9	130/84	84
	Alcohol	46	38·6	132/82	78
58, old anterior septal myocardial infarct, angina	Control	71	81·0	148/88	80
	Alcohol	83	79·0	150/90	84
45, angina, hypertension	Control	30	38·4	125/83	78
	Alcohol	48	42·8	128/86	80
51, angina	Control	92	77·5	130/80	88
	Alcohol	93	112·0	128/80	84
41, old inferior myocardial infarct, angina	Control	58	45·0	110/70	72
	Alcohol	71	105·0	120/80	68
Mean	Control	62	55·0	140/86	76
	Alcohol	73	88·0	142/88	76
	P value	NS	<0·02	NS	NS

similar from the results obtained in our patients.

There is considerable evidence suggesting alcohol's depressant action on cardiac contractility. Wendt *et al.* (1965) have recently demonstrated in chronic alcoholics a consistently negative myocardial balance of isocitric dehydrogenase and malic dehydrogenase. These findings suggested to these authors that intramitochondrial enzymes are affected by clinical alcoholism even in patients without clinical, haemodynamic, or other biochemical evidence of heart disease. Gimeno, Gimeno, and Webb (1962) have studied the effects of alcohol in the isolated rat atrium and have found that an almost linear relation exists between the concentration of alcohol and the decline in myocardial contractility. Regan *et al.* (1966) administered 15 per cent ethanol intravenously to dogs at a rate of 0·1 ml/kg per min for 2 hours, and observed a progressive decline in the stroke output and a rise in the left ventricular end-diastolic pressure. Spann *et al.* (1968) have studied the acute effects of alcohol on the contractile state of papillary muscles from both normal and failing cat hearts. In a normal papillary muscle preparation, an alcohol concentration of 100 mg/100 ml caused a 9 per cent decrease in contractile element velocity at a constant load of 0·5 mg/mm^2; a concentration of 300 mg/100 ml, a decrease of 18 per cent; and a concentration of 500 mg/100 ml, a decrease of 38 per cent. In addition, alcohol decreased both the peak tension development and the maximal rate of tension development of the isometrically contracting papillary muscle. The effects of alcohol were quantitatively similar in papillary muscles from cats with right ventricular failure.

The haemodynamic effect of ethyl alcohol in nonalcoholic patients with coronary heart disease has recently been investigated by Conway (1968). He administered 3 to 4 whiskys to 8 patients with stable coronary heart disease. Haemodynamic observations were made at rest and for 45 minutes after the alcohol intake. He observed that the cardiac output and arterial pressure dropped progressively at rest. No change was seen in the cardiac rate or peripheral resistance. He concluded that ethyl alcohol is a myocardial depressant.

Recently Mohiuddin *et al.* (1970) studied coronary haemodynamics in 4 male alcoholic subjects without cardiac disease. They observed no change in coronary blood flow or myocardial oxygen consumption after the

intravenous administration of 300 ml of 16 per cent alcohol. Regan *et al.* (1969) administered 6 oz alcohol to 6 noncardiac alcoholic subjects and also observed no significant change in myocardial blood flow.

The lack of effect of alcohol on the coronary blood flow in our normal group was presumably due to a minimal alteration in the myocardial oxygen consumption. Oxygen consumption of the myocardium is a primary factor regulating coronary blood flow, and in general an increase in oxygen requirement increases the coronary blood flow. The acute effects of alcohol on the haemodynamics of normal subjects have been studied. No significant depressive effect on the performance of the normal heart can be observed with the administration of 5 oz of 86 proof whisky (Blomqvist, Saltin, and Mitchell, 1970).

The rate of ethanol metabolism has recently been studied in alcoholic patients with and without overt liver disease and in control subjects (Kater, Carulli, and Iber, 1969). It was determined that alcoholics without overt liver impairment have a blood removal rate for alcohol twice that of the non-drinking subjects as well as the drinking patients with overt liver disease. Alcohol induces an hepatic microsomal ethanol oxidizing enzyme which accounts for the increased rate of alcohol removal in the alcoholic without liver disease (Kater *et al.*, 1969; Misra *et al.*, 1970).

The dose of alcohol was not weight related in our study, and blood alcohol levels were not obtained. However, none of our patients was alcoholic or had liver disease. Thus, it is likely that our subjects, with and without cardiac disease, metabolized alcohol in a comparable manner.

It appears that alcohol has two major actions in the patient with coronary heart disease. It can depress cardiac contractility, and in some patients it can increase coronary blood flow. The explanation for the rise in coronary blood flow that alcohol produced in some of our cardiac patients is of great theoretical and clinical interest. However, one can only speculate on the possible mechanisms. At first glance, one could assume that alcohol produced coronary artery dilatation which led to an increase in coronary blood flow. Thus alcohol could be beneficial in some patients with coronary heart disease. However, there is an alternative interpretation for the rise in coronary blood flow. Alcohol may have a direct effect on the myocardium, and the rise in the coronary flow is a result of an increase in myocardial oxygen consumption rather than a direct effect of alcohol on the smooth muscle of the coronary arteries.

The various factors that affect myocardial oxygen consumption have recently been delineated (Sonnenblick, Ross, and Braunwald, 1968). The decreased velocity of contraction and the impairment in contractility produced by alcohol would be associated with a decrease in the myocardial oxygen consumption. The unchanged blood pressure and cardiac rate observed in our study would not affect the oxygen requirements. The effect of alcohol on the shape of the heart is not well established, but the intramyocardial tension, as defined by the law of La Place, could presumably play a major role in the oxygen requirements of the heart.

The administration of 3 oz Canadian Club whisky to patients with cardiac disease commonly produces an increase in the left ventricular end-diastolic pressure and a fall in the stroke index (Gould *et al.*, 1972). If one postulates that the rise in the left ventricular end-diastolic pressure is associated with an increase in the left ventricular end-diastolic volume, this could lead to an augmentation of the myocardial oxygen requirements. Indeed those cardiac patients having an increase in the coronary blood flow could theoretically have the severest impairment of left ventricular function. Thus alcohol would be detrimental in some patients with coronary heart disease.

To answer this question definitively, the effect of alcohol on myocardial oxygen consumption and left ventricular function will have to be determined in patients with coronary artery disease. In addition, the effect of alcohol on the electrocardiogram in patients with coronary heart disease should be investigated. Since myocardial blood flow can increase so greatly after alcohol in ischaemic hearts it will be of interest to observe if an improvement or deterioration in the electrocardiogram results.

References

Blomqvist, G., Saltin, B., and Mitchell, J. H. (1970). Acute effects of ethanol ingestion on the response to submaximal and maximal exercise in man. *Circulation*, **42**, 463.

Conway, N. (1968). Haemodynamic effects of ethyl alcohol in patients with coronary heart disease. *British Heart Journal*, **30**, 638.

Donato, L., Bartolmei, G., Federighi, G., and Torreggiani, G. (1966). Measurement of coronary blood flow by external counting with radioactive rubidium. Critical appraisal and validation of the method. *Circulation*, **33**, 708.

Donato, L., Bartolmei, G., and Giordani, R. (1964). Evaluation of myocardial blood perfusion in man with radioactive potassium or rubidium and precordial counting. *Circulation*, **29**, 195.

Ganz, V. (1963). The acute effect of alcohol on the circulation and on the oxygen metabolism of the heart. *American Heart Journal*, **66**, 494.

Gimeno, A. L., Gimeno, M. F., and Webb, J. L. (1962). Effect of ethanol on cellular membrane potentials and contractility of isolated rat atrium. *American Journal of Physiology*, **203**, 194.

Gould, L., Zahir, M., DeMartino, A., Gomprecht, R. F., and Jaynal, F. (1972). Haemodynamic effects of ethanol in patients with cardiac disease. *Quarterly Journal of Studies on Alcohol*. In the press.

Heberden, W. (1786). Some account of a disorder of the breast. *Medical Transactions College of Physicians of London*, **2**, 59.

Kater, R. M. H., Carulli, N., and Iber, F. L. (1969). Differences in the rate of ethanol metabolism in recently drinking alcoholic and nondrinking subjects. *American Journal of Clinical Nutrition*, **22**, 1608.

Lasker, N., Sherrod, T. R., and Killam, K. F. (1955). Alcohol on the coronary circulation of the dog. *Journal of Pharmacology and Experimental Therapeutics*, **113**, 414.

Misra, P. S., Lefevre, A., Rubin, E., and Lieber, C. S. (1970). Effect of ethanol ingestion on ethanol, meprobamate and pentobarbital metabolism. *Gastroenterology*, **58**, 308.

Mohiuddin, S. M., Taskar, P. K., Gailis, L., and Morin, Y. (1970). Coronary haemodynamics, myocardial metabolism and alcohol. (Abstract.) In Proceedings VI World Congress of Cardiology. *Cardiovascular Research*, p. 221.

Regan, T. J., Karoxenidis, G., Moschos, C. B., Oldewurtel, H. A., Lehan, P. H., and Hellems, H. K. (1966). The acute metabolic and haemodynamic responses of the left ventricle to ethanol. *Journal of Clinical Investigation*, **45**, 270.

Regan, T. J., Levinson, G. E., Oldewurtel, H. A., Frank, M. J., Weisse, A. B., and Moschos, C. B. (1969). Ventricular function in noncardiacs with alcoholic fatty liver: role of ethanol in the production of cardiomyopathy. *Journal of Clinical Investigation*, **48**, 397.

Russek, H. I., Naegele, C. F., and Regan, F. D. (1950). Alcohol in treatment of angina pectoris. *Journal of the American Medical Association*, **143**, 355.

Schmitthenner, J. E., Hafkenschiel, J. H., Forte, I., Williams, A. J., and Riegel, C. (1958). Does alcohol increase coronary blood flow and cardiac work? (Abstract.) *Circulation*, **18**, 778.

Sonnenblick, E. H., Ross, J., Jr., and Braunwald, E. (1968). Oxygen consumption of the heart. New concepts of its multifactoral determination. *American Journal of Cardiology*, **22**, 328.

Spann, J. F., Jr., Mason, D. T., Beiser, G. D., and Gold, H. K. (1968). Actions of ethanol on the contractile state of the normal and failing cat papillary muscle. (Abstract.) *Clinical Research*, **16**, 249.

Webb, W. R., and Degerli, I. U. (1965). Ethyl alcohol and the cardiovascular system. Effects on coronary blood flow. *Journal of the American Medical Association*, **191**, 1055.

Wendt, V. E., Wu, C., Balcon, R., Doty, G., and Bing, R. J. (1965). Haemodynamic and metabolic effects of chronic alcoholism in man. *American Journal of Cardiology*, **15**, 175.

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