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Circulatory Changes to Alcohol, Anxiety and Their Interactions (40256)

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One of the well-known causes (inductive factors) of alcoholism is the apparent ability of alcohol to reduce anxiety (1). However, none of the studies which have investigated circulatory changes in response to acute alcohol intoxication have taken anxiety factors into account. Alcohol and emotional factors both induce cardiovascular changes. Emotional variables alter heart rate (2, 3) and modify cardiac contractility (4, 5). The effects of alcohol on the cardiovascular system are not as clearly delineated. Studies during which alcohol was ingested by nonalcoholics have shown increased cardiac output, increased coronary blood flow but no change in cardiac contractility, heart rate, or arterial blood pressure (6, 7). Dogs given alcohol have shown both increases and decreases in cardiac output (8–10), in coronary blood flow (6, 9, 10), in ventricular contractility (9, 11), heart rate (10), and blood pressure (8, 10). Rats have responded more consistently, i.e., no change in cardiac output at various blood alcohol levels (12, 13), although blood flow decreased to kidneys and spleen while apparently brain and the coronary bed have had increased flow (13). If narcotizing amounts of alcohol were given to these animals, then cardiac output and brain blood flow were reduced.

It appeared that if anxiety and alcohol have different cardiovascular effects then the distribution of blood to various portions of the body would be altered depending upon the particular condition present. It would be important (a) to determine the pattern of blood flow distribution when alcohol is taken during a state of induced anxiety and, (b) to determine whether or not alcohol ingestion per se modifies the circulatory changes to anxiety.

Method. Sixty male Sprague Dawley rats[2] weighing between 280 and 400 g ($m = 337$ g, $s = 32.6$) were anesthetized with pentobarbital for implantation of catheters. One catheter (P-50) was inserted into the left carotid artery and advanced to the arch of the aorta to monitor arterial pressure and serve as a source of arterial blood. The other catheter (P-50) was inserted into the right jugular vein and advanced to the right atrium. This catheter was utilized for the injection of ^{137}Cs (14) to determine regional blood flow. The distal ends of both catheters were sealed and brought out at the back of the neck. Forty-eight hours after surgery, the animals were placed in restraining cages and electrodes for administration of electric shock placed on their tails. Blood pressure was recorded from a Statham (P23dd) transducer attached to the arterial catheter and recorded on a Grass (Model 5) polygraph with heart rate being obtained from these tracings. The audio signals predicting electric shock (300 Hz sine wave form tone) and those which predicted the nonoccurrence of electric shock (1100 Hz sine wave form tone) were amplified by a Heathkit audio amplifer (AA-161) and delivered through a 4-inch speaker. Electric shock which occurred during the last 0.5 sec of each 10-sec predictable 300 Hz signal was delivered to the tail through two copper strip electrodes from a BRS/Foringer shock scrambler (SGS-001) with just two pins in the Jones plug.

The animals were randomly assigned to one of four experimental groups as follows. *Control:* This group received no alcohol or electric shock. *Alcohol Control:* This group

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[2] In conducting this research, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee for Laboratory Animal Facilities and Care, of the Institute of Animal Laboratory Resources, National Academy of Sciences, National Research Council.

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received alcohol (10 ml/kg of 20% alcohol ip) but no electric shock. *Anxiety Control:* This group received electric shocks but no alcohol. *Alcohol-Anxiety:* This group received both alcohol and electric shocks.

All animals remained in the restrainer for a total of 75 min. After 50 min, ½ ml of arterial blood was obtained for determination of alcohol levels (Calbiochem Ethyl Alcohol Stat-Pack). After a 15-min control period, the two anxiety groups received 25 10-sec 300 Hz tones followed by electric shock to the tail and 25 10-sec 1100 Hz tones that were not followed by electric shock. The different quality tones were interspersed randomly with a mean intertrial interval of 80 sec. The other two groups remained in the restrainer also but didn't receive electric shocks. At the end of the 75-min session, a single injection of ^{137}Cs in saline (2 μCi/ml) at a dosage of 1 ml/kg was administered via the venous catheter, flushed with heparinized saline, and then 20 sec later saturated KCl was injected resulting in cardiac arrest. Organs and tissues were weighed and placed in a Nuclear-Chicago deep-well auto gamma counter for determination of radioactivity. The radioactivity per unit weight was then compared to the total count injected to yield the fractional distribution of the isotope. The organs sampled were the lungs, heart, adrenal glands, kidneys, liver (arterial flow), spleen, and stomach. Back skin and muscle samples from the left gastrocnemius, right and left forelegs, abdomen, deep back, and scapula were also extracted.

Results. A mean blood alcohol level of 160 mg %, SE = 20 mg %, was obtained for the alcohol control group, whereas a mean blood alcohol level of 120 mg %, SE = 20 mg %, was obtained for the alcohol anxiety group. A *t* test indicated that there was no difference between these means. Initially blood for alcohol determination was also obtained at 20 min but since the blood levels remained constant, this sampling period was eliminated.

Heart rate and blood pressure changes were analyzed for the 10 rats in each group every 10 min during an interval when no shocks or tones were administered. A three-factor analysis of variance (alcohol × anxiety × time) with repeated measures across time was employed to analyze both heart rate and blood pressure data. A significant interaction effect for heart rate was found for anxiety across time ($F = 3.40$; $df = 6/216$; $P < .01$). Simple main effects and Newman-Keuls post hoc analysis performed on this outcome indicated that as soon as electric shocks were presented heart rate increased significantly regardless of alcohol (Fig. 1). Heart rate was not changed following injection of alcohol. On the other hand, there were significant main effects for alcohol for both systolic ($F = 14.96$, $df = 1/36$, $P < .01$) and diastolic blood pressure ($F = 10.19$, $df = 1/36$, $P < .01$) indicating that alcohol decreased blood pressure regardless of anxiety (Fig. 2). There was also a significant decrease across time both for systolic blood pressure ($F = 5.99$, $df = 6/216$, $P < .01$) and diastolic blood pressure ($F = 5.23$, $df = 6/216$, $P < .01$) suggesting a habituation effect. No significant changes in blood pressure were seen during the anxiety condition.

Fractional distribution of cardiac output was markedly altered by both anxiety and alcohol. Two-factor analyses of variance (alcohol × anxiety) were performed. Similar changes were observed for fractional distribution of whole organs and for per gram of organ tissue. Significant increases in distribution per gram tissue were observed to the adrenal glands, abdominal muscle, foreleg muscle, and deltoid muscle as a function of

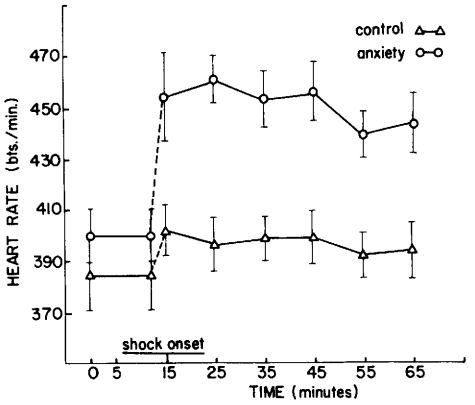

FIG. 1. Heart rate changes to anxiety. A comparison of the averages of the anxiety-no alcohol and anxiety-alcohol groups with the no anxiety-no alcohol and no anxiety-alcohol groups. In this figure alcohol is partialed out.

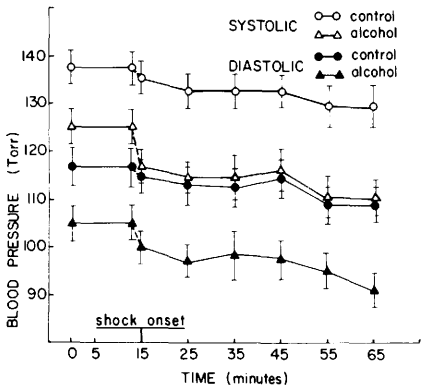

FIG. 2. Blood pressure changes to alcohol. A comparison of the averages of the alcohol-no anxiety and alcohol-anxiety groups with the no alcohol-no anxiety and no alcohol-anxiety groups. In this figure anxiety is partialed out.

anxiety ($P < .05$). Anxiety resulted in significant decreases in blood flow to the stomach and skin. Alcohol induced significant increases in distribution to the lungs, heart, adrenal glands, kidneys, and spleen. Alcohol intoxication resulted in decreases to the gastrocnemius muscle. A significant interaction effect was found for the skin, where a significant decrease was found for the alcohol treatment. Total organ flows (percent of ^{137}Cs injected/organ) as affected by alcohol and anxiety were analyzed in a similar manner. There was a significant decrease in blood flow to the stomach, spleen, and skin (calculated as 18.1% of total body wt) (15) from the anxiety condition, with a significant increase in blood flow to the skeletal muscle (calculated as 42.6% of total body wt) (15) regardless of alcohol (Fig. 3). Alcohol intoxication yielded total organ flow results similar to those of the relative fractional distribution where lungs, heart, kidneys, and stomach showed increases in percentage of cardiac output, and the skin and skeletal muscle showed decreases regardless of anxiety (Fig. 4).

Discussion. The predominant cardiovascular effect of anxiety was an increase in heart rate while alcohol intoxication resulted in vasodilation as evidenced by a marked fail in both systolic and diastolic arterial pressures. The anxiety heart rate response was similar to that observed in defensive behavior elicited by hypothalamic stimulation in rats (16), dogs (17), and monkeys (18). However, in those studies blood pressures were also markedly elevated. Our present data did not show significant alterations in blood pressure which is in agreement with other studies investigating predictable and unpredictable electric shock (19). In general, alcohol has been shown to have little influence on heart rate (6, 9), but an increase has also been reported (10). In the presence of both alcohol and anxiety, only the specific effects of each individual stress were noted suggesting that there was no interaction between them.

Neither alcohol nor anxiety appears to have much influence on cardiac output. Anxiety states induced by predictable electric shock have shown only transient changes in

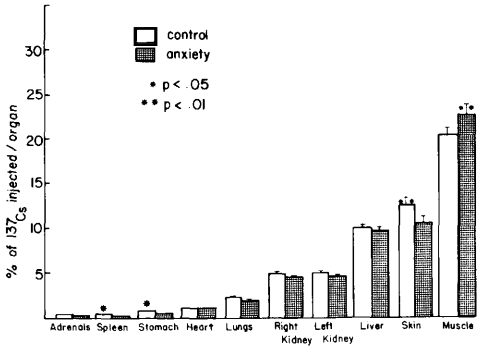

FIG. 3. Total organ blood flow (percent of ^{137}Cs injected/organ) changes to anxiety. A comparison of the averages of the anxiety-no alcohol and anxiety-alcohol groups with the no anxiety-no alcohol and no anxiety-alcohol groups. In this figure alcohol is partialed out.

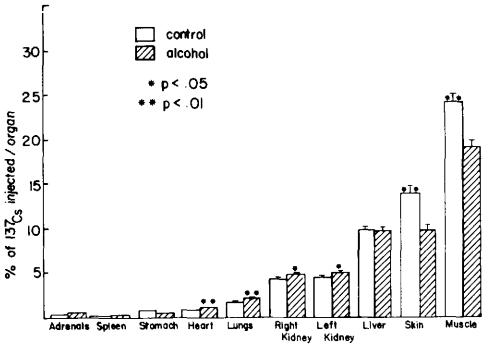

FIG. 4. Total organ blood flow (percent of ^{137}Cs injected/organ) changes to alcohol. A comparison of the averages of the alcohol-no anxiety and alcohol-anxiety groups with the no alcohol-no anxiety and no alcohol-anxiety groups. In this figure anxiety is partialed out.

cardiac output in dogs (20), primates (21), and man (2) which returned to baseline between trials. Studies on rats showed no change except at exceptionally high blood alcohol levels where myocardial contractility was decreased. Perhaps cardiac output in rats does not have a great potential for increase. In maximum oxygen uptake studies on swimming rats, Dawson *et al.* (22) reported that the maximum cardiac output was only raised 41% above resting values.

The significant decrease in blood pressure found as a function of alcohol was surprising. Previous studies failed to find any change in arterial pressure during either rest or exercise in human subjects (7, 23). Some studies found no change in arterial pressure in dogs exposed to alcohol (8, 9), but Willard and Horvath (10) reported decreases in both systolic and diastolic pressure similar to those found in the present study. It is not clear whether changes in blood pressure reflect a species difference. Since cardiac output was not changed in rats at these levels of alcohol intoxication (12, 13), the decreased arterial pressure was undoubtedly due to a general vasodilation which overrode vasoconstriction in the skin and skeletal muscle.

There were differences in fractional distribution of cardiac output to various organs under conditions of alcohol or anxiety. Alcohol resulted in increased distribution to heart, lungs, and kidney, with decreases to muscle and skin. Anxiety shifted more blood to spleen and muscle tissues while reducing the fraction to stomach and skin. This decrease in flow to the stomach is especially interesting since studies utilizing a similar tone-shock paradigm in restrained rats found significant stomach ulceration over a 24- to 48-hr period (24, 25). The role of blood flow has often been ignored in the production of gastric ulcers by psychological stress.

The overall changes in regional blood flow distribution as a function of alcohol intoxication were, for the most part, similar to that found by Sapirstein *et al.* (13). They reported significant increases in blood flow to the heart and lungs as a function of alcohol, but found significant decreases in blood flow to the kidneys with no change in skin blood flow. The present study differed from the Sapirstein study (13) in that they compared unanesthetized alcohol treated rats with anesthetized controls. Recalculation of their data to percent $^{86}Rb/g$ tissue showed their alcohol group to have a blood flow to both kidneys of 5.8%, and ours a similar level of 6.8%. Therefore, the difference in interpretation of alcohol's effects on kidney blood flow appeared to be related to control data being utilized. Our awake control had a combined blood flow to the kidneys of 5.8%, whereas their anesthetized control had a combined flow of 8.3%. However, all of our rats were restrained. Previous data in our laboratory on 10 awake, unanesthetized rats yielded control values of 7.43% to both kidneys. Restraint could have produced added anxiety which could account for a decreased blood flow to the kidneys of our control group.

Shifts in organ blood should indicate whether or not alcohol modifies the response to anxiety. There were no significant interactions, however, between alcohol and anxiety with regard to circulatory variables. Only specific effects of alcohol or anxiety were evident. Thus anxiety influenced heart rate and stomach, spleen, skin, and muscle blood flow, whereas alcohol influenced arterial pressure, heart, lung, kidney, skin, and muscle blood flow. It must be emphasized that the changes reflected here represent only percentage change in cardiac output and do not reflect absolute blood flow to the organs and tissues. However, we are convinced that combinations of alcohol and anxiety do not alter fractional distribution of cardiac output as compared to alcohol or anxiety alone.

Summary. The effects of alcohol (0.16 g %), anxiety, and their interaction on circulatory parameters were examined. Electric shocks to the tails of the rats preceded by a 10-sec auditory signal were utilized to induce the anxiety condition. A significant increase in heart rate was found as a function of anxiety, regardless of alcohol. On the other hand, a significant decrease in both systolic and diastolic blood pressure was observed under alcohol, irrespective of anxiety. Increases in blood flow to the viscera, heart, and lungs were found after alcohol ingestion. An increase in blood flow to selected skeletal muscle was observed during the anxiety condition suggesting a defensive reaction. The few significant interactions observed when

comparing the combination of alcohol and anxiety as opposed to alcohol or anxiety separately suggested that there were no circulatory interactions between these two conditions.

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