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PHARMACOLOGICAL CONTROL OF PORTAL PRESSURE

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

William Paul Skivolocki, B.S., M.S., M.D.

**********

The Ohio State University
1973

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ADDENDUM


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INTRODUCTION

Cirrhosis of the liver has been a well recognized entity for several hundred years. It was originally associated with the syndrome consisting of ascites, the development of a collateral circulation and dilatation of the splanchnic bed. Although cirrhosis was recognized for hundreds of years, the concept of portal hypertension is relatively recent. Stahl,\textsuperscript{1,2} in 1748, made the observation that the portal vein, the spleen, and enlarged hemorrhoids were related parts of a vague disease syndrome. Power,\textsuperscript{3} in 1840, first described massive variceal hemorrhage, having discovered a ruptured esophageal varix at an autopsy. In 1894, Guido Banti\textsuperscript{4} described a hepatosplenic syndrome consisting of splenic enlargement, cirrhosis, anemia and recurrent gastrointestinal hemorrhage. Gilbert and Weill\textsuperscript{5} in 1900, measured the pressure of the ascitic fluid in patients with ascites and were the first to apply the term "portal hypertension" to this condition. Enderlen,\textsuperscript{6} deJong\textsuperscript{7} and Heller\textsuperscript{8} described the relationship of cirrhosis to the development of extensive collaterals and mentioned the association of epistaxis in cirrhosis attributing this to elevation of portal pressure. In 1900, Preble\textsuperscript{9} reported the association of massive gastrointestinal hemorrhage with the documentation of esophageal varices in several patients with cirrhosis. In 1928, McIndoe\textsuperscript{10} recommended the use of the Eck fistula as a possible method
of clinical management of portal hypertension. McMichael, then explained the development of splenomegaly as being secondary to elevated portal pressure. In 1936 and 1937, Brislow, Thompson, Coffee and Whipple, substantiated this concept by directly measuring portal venous pressure in patients with congestive splenomegaly. Following this the current concept of portal hypertension as a clinical syndrome has developed.

Understanding the mechanism by which portal hypertension evolves was enhanced by the development of methods to measure blood flow and portal pressure. One of the first methods to measure blood flow was the mechanical stromuhr that was introduced by Ludwig, and was used to measure portal vein flow by Schmid (1908) and by Burton-Opitz (1911). The bubble flow meter was then used, the basic principle being the measurement of the passage of an injected bubble of air through a tube known length and volume placed between the cut ends of the vessel (Bruner, 1948). Due to the resistance to flow the bubble flow meter is only suitable for use in arteries. Rotameters are devices to measure blood flow that consist of a vertical transparent tube within which the height of a float is determined by the rate of flow (Shipley and Wilson, 1951). Resistance is minimal and they have been used in studies of the intestinal circulation (Selkurt and Johnson, 1958).

Electromagnetic flowmeters (Kolin, 1936) have been used extensively to measure flows, (Ottis, Davis and Green, 1957; Green, Locksley, Hall, Sexton and Deal, 1959; Geber, 1960). They operate
on the principle that a voltage is induced in a conductor moving through a magnetic field at right angles to the lines of force. Measurements can be made in both mean and phasic flows and the calibration is linear.

The thermostromuhr by Rein\textsuperscript{23} (1928) is an instrument which can be clipped on to an intact vessel and consists of a heating element with two thermocouples situated downstream. Temperature difference between the two thermocouples can be measured and can be directly correlated to the rate of flow.

The plethysmograph for the measurement of gastrointestinal circulation was first described by Bayliss\textsuperscript{24} (1893). Later Hallion and Francois-Franck\textsuperscript{25} (1896), Bunch\textsuperscript{26} (1899) and Bayliss and Starling\textsuperscript{27} (1899) perfected this method of measuring blood flow.

Isotope fractionation technique is based on the principle that foreign substances given intravenously will be distributed to the organs in proportion to their blood flow. With devices designed specifically to detect the isotope blood flow through an organ can be estimated.

The concept of measuring portal pressure was first described by Francois-Franck and Hallion\textsuperscript{28} (1896) who utilized a saline manometer and a catheter into a mesenteric vein. Measurements of portal pressure in man was first reported by Thompson, Caughey, Whipple and Roussel\textsuperscript{29} (1937) who recorded portal pressure at operation from a mesenteric vein. Shaldon\textsuperscript{30} (1960) has described a method for long-term measurement of portal pressure. Wedged hepatic pressure was introduced by Myers and Taylor\textsuperscript{31} (1951) who passed a catheter into the hepatic vein.
and compared the resultant pressure with the pressure directly measured in the portal vein. They found the difference in pressure of 0.6 mm Hg.

Information obtained from measurements of hepatic blood flow and portal pressure correlated with clinical observation and report of gross and histological examination of cirrhotic livers have lead to the current concept regarding the development of portal hypertension. The basic defect in patients with portal hypertension is increased resistance to the normal outflow of blood from the portal bed into the systemic venous system. Generally the increased resistance is due to interlobular scarring and regeneration of the liver lobules secondary to an obstruction of the portal vein. In general, the types of portal hypertension can be divided into suprahepatic and infrahepatic. Examples of suprahepatic portal hypertension includes chronic congestive heart failure and Chiari's syndrome. With this type of portal hypertension esophageal varices are uncommon because the portal and caval pressures are equally elevated.

Infrahepatic portal hypertension is most frequently caused by cirrhosis; however, malignancies, syphilitic heparlobatum, schistosomiasis, portal vein thrombosis and congenital anomalies may produce this type of hypertension. In infrahepatic portal hypertension esophageal varices can develop because of the pressure gradient between the portal system and the caval system.

Although many predisposing factors can cause portal hypertension, cirrhosis is the most commonly associated disease. At ages 45 to 64, the only diseases that outrank cirrhosis of the liver as causes of death
are heart disease, cancer, and cerebral hemorrhage. The death rate in the United States from cirrhosis of the liver is steadily increasing. Between 1958 and 1967 it rose from 10.8 to 13.9 per 100,000 population. The upward trend is greatest in the non-white population with a rise from 10.2 per 100,000 in 1951-53 to 16.6 per 100,000 in 1961-63. Because alcoholism is particularly prevalent in large cities the incidence of cirrhosis mortality more than doubled between 1955 and 1969. By 1967 cirrhosis of the liver ranked third in the city as a cause of death in the age groups 25-44 and 45-64, and the overall mortality from cirrhosis was 2.5 times the national average. 33

Alcoholism is the most common cause of cirrhosis of the liver although hepatitis accounts for a significant number of cases. Only 5% to 10% of alcoholics develop cirrhosis, but 50% to 75% of all cases of cirrhosis are the result of alcoholism. The parallel changes in the incidences of alcoholism and cirrhosis provides evidence of their close relationship. When the consumption of liquor was curtailed during prohibition, there was a corresponding decline in deaths from cirrhosis. Since the repeal of prohibition, deaths associated with chronic alcoholism in the United States have steadily increased. Higher death rates from cirrhosis of the liver account for most of the increase. 34

Cirrhosis can be defined as a fibrotic process of the liver associated with alterations of lobular structure, regenerative nodules and vascular anastomosis. The process by which cirrhosis develops is not completely established. One hypothesis is that fat droplets enlarge and
form fatty cysts. Eventually the fat is removed from the cyst and the remaining structure forms regenerative tissue which develops into irregular septa. This process stimulates liver cell degeneration and subsequent regeneration with the formation of regeneration nodules. Compression of the adjacent tissues by the regenerative nodules produce more septa which result in further degeneration and fibrosis with distortion of the vascular architecture. Septa formation associated with regenerative nodules may also develop in the absence of fat droplets. Hepatic inflammatory processes, granulomas, chronic passive congestion, diseases of intrahepatic bile ducts, and toxic injuries can stimulate the formation of septa and regeneration nodules.

In patients with cirrhosis the fundamental vascular changes are the result of regenerative nodules. The regeneration nodules expand and compress the surrounding tissue, including the vessels of the liver. The most vulnerable vessels are the tributaries of the hepatic vein which lack in their thin wall adequate protective tissue elements. The compression of these vessels interferes with the drainage of blood from the liver and this is one of the major causes of portal hypertension. When the branches of the portal vein become compressed, the share of hepatic blood coming from the artery increases relative to the amount of blood from the portal vein system. The arterial pressure, being transmitted into the portal vein branches by anastomosis, further increases the portal pressure in patients with cirrhosis.35

As the portal vein pressure rises there are a variety of collateral
venous communication between the portal vein and caval system that come into existence. The collateral between the lower end of the esophagus and the cardia of the stomach account for one of the most serious complications of cirrhosis, bleeding esophageal varices. The esophageal varices are fed by the coronary vein and short gastric vein. The increase in flow in the thin-walled esophageal vessels results in dilatation and sometimes in subsequent rupture.36

Patients with cirrhosis of the liver place a great burden on hospital facilities and the energy of physicians and other hospital personnel. This burden is largely due to the most frequent fatal complication of cirrhosis, hemorrhage from the esophageal varices produced by portal hypertension. Hemorrhage from varices caused by portal hypertension accounts for 40% of deaths from cirrhosis. Management of the patient with hemorrhage from varices requires intensive emergency care including a variety of materials and personnel.

The use of drugs to control hemorrhage and reduce portal hypertension shows promise. However, drugs currently used to control portal hypertension and hemorrhage are contraindicated in some patients, curtail hemorrhage in only 50% of patients in whom they are used, and their effects are short-lived. The use of nasogastric tubes with attached balloons designed to compress varices of the stomach and esophagus are hazardous, producing fatal complications in as many as 18% of patients. When these efforts fail to control hemorrhage large quantities of blood may be required while the patient undergoes an emer-
gency operation to establish a portal systemic shunt. When poor risk patients are excluded the mortality of emergency operations is still 25% to 50%. For those patients judged too ill for operation the administration of blood together with other supportive care is continued in the hope that spontaneous cessation of hemorrhage will occur.

In summary, in the near future we may expect vastly increased numbers of patients with cirrhosis whose foremost threat to life is hemorrhage due to portal hypertension. Surgical operations have only a limited role in the problem of hemorrhage caused by portal hypertension. There is, therefore, a need for a practical and consistent method of controlling hemorrhage. Effective management of hemorrhage in large numbers of patients with cirrhosis of the liver would appear to depend on the development of improved methods of drug therapy to control portal pressure.

These experiments were designed to assess the effect of several drugs on portal hemodynamics and cardiac output. To study these parameters, an experimental model was specifically designed to study the effects of these various drugs on the portal pressure, portal venous flow, hepatic artery flow and the cardiac output. This model utilizes adult mongrel dogs and allows for continuous monitoring of the hepatic blood flow, portal pressure and cardiac output (Fig. 1). Anesthesia is induced and maintained in a light surgical plane by the intravenous administration of pentobarbital sodium. An endotracheal tube is inserted and a controlled volume ventilator used to ventilate each animal with room
Through a midline incision electromagnetic flow transducers are placed on the portal vein and the hepatic artery. A longitudinal incision in the periarterial tissues of the hepatic artery allows placement of the flow transducer on that vessel without division of the peri-arterial nerve fibers. The hepatic arterial arch is ligated distal to the most distal branch to the liver. A polyethylene catheter inserted into the distal aorta through a femoral artery provides for measurements of systemic arterial blood pressure and sampling of blood for determinations of arterial pH and pO₂ utilizing an IL-113 gas analyzer. Through a left thoracotomy an electromagnetic flow transducer is placed on the ascending aorta for recording of cardiac output (less coronary artery flow). All flow transducers are grounded and each is connected to a BL 610 Electromagnetic Blood Flowmeter. Continuous recordings of flow through the ascending aorta, hepatic artery and portal vein together with pressures in the portal vein and distal aorta are made using a Sanborn multichannel recorder. Brief occlusion of the hepatic artery and portal vein immediately distal to their respective flow transducers established a baseline recording of zero flow through these vessels. Baseline recordings of zero flow in these vessels are established at 15 minute intervals for the duration of each experiment. Zero flow through the ascending aorta is arbitrarily designated as the horizontal segment of the diastolic portion of the cardiac cycle. Flows over 100% increase were recorded as 100%+

These studies were designed to attempt to find a more effective
method of controlling bleeding esophageal varices. The specific aims were (1.) to determine the effect of several drugs and drug combinations on blood pressure, pulse rate, cardiac output, portal venous pressure, portal vein flow, and hepatic artery flow in normal dogs; (2.) to determine if these individual drug or drug combinations would be beneficial in controlling portal pressure without producing adverse side effects in the animals; and (3.) to determine the hemodynamic response of ethanol on the hepatosplanchnic circulation. Arfonad, vasopressin, and isoproterenol were evaluated to assess their potential use to reduce portal hypertension and to control variceal hemorrhage. Ethanol was evaluated to see if its influence on hepatosplanchnic circulation would warrant restraint of alcohol intake in patients with portal hypertension.
FIGURE 1

MODEL FOR STUDYING FLOWS AND PRESSURES IN THE AORTA AND
HEPATOSPLANCHNIC CIRCULATION
AORTIC FLOW PROBE

HEPATIC ARTERY FLOW PROBE

PORTAL VEIN FLOW PROBE

PORTAL PRESSURE CATHETER

BLOOD PRESSURE CATHETER
Chapter I

Effect of Arfonad on the Splanchnic
and Hepatic Circulation

Controlled hypotension with Arfonad has been advocated for the management of patients with hemorrhage from esophageal varices.37,38,39 The continued use of Arfonad is the result of clinical observations suggesting control of hemorrhage from varices in many instances.39 However, available hemodynamic data are insufficient to allow conclusions concerning the effects of Arfonad on hepatic blood flow and portal venous pressure. Currently there has been no correlation between the cardiac and hepatosplanchnic hemodynamics during Arfonad-induced hypotension. This study assesses the influence of Arfonad on the cardiac output and the splanchnic and hepatic circulations of normal dogs.

Arfonad has been used most extensively to produce controlled hypotension during difficult operations in order to reduce blood loss.40,41 In recent years its ability to induce hypotension has been utilized in the medical management of dissecting aneurysms of the aorta.42 Arfonad (trimenthaphan camsylate) is a sulfonate of thiophanium originally synthesized as a by-product of biotin by Hoffman-LaRoche.43,44 It blocks both sympathetic and parasympathetic ganglia by occupying the receptor
sites for acetylcholine liberated at preganglionic nerve endings. 

Arfonad has a direct vasodilating action on the peripheral vascular bed, leading to decreased venous return and decreased cardiac filling. 

The reduction of venous return is due to decrease of both arteriolar resistance and venous vascular tone, with peripheral pooling of blood. This effect can be corrected quickly by infusion of fluids, and in fact this procedure may raise cardiac output with little increase in aortic pressure. Arfonad does not directly affect cardiac muscle fibers, but reduces the force of ventricular ejection by decreasing venous return and blocking the sympathetic discharge to the heart at the ganglia.

Afronad does not have any positive inotropic effect on heart muscle.

**Methods**

The basic experimental model was utilized in this study. During surgical preparation and a subsequent one hour period of stabilization each animal was given 500 to 600 ml. of lactated Ringer's solution intravenously. Following the stabilization period a solution of 0.25% Arfonad in 0.9% NaCl was administered intravenously in sufficient amounts to reduce systolic blood pressure to 60 to 80 mm. Hg within 10 to 20 minutes. Continuous recordings of flows and pressures were made during a period of one hour of controlled hypotension. After the Arfonad infusion was discontinued recordings were continued for an additional 50 minutes. The animals were then killed and a necropsy examination was performed on each animal.
Several animals were utilized in the development of the experimental model. The study of two animals was discontinued when the infusion of small amounts of Arfonad caused profound hypotension. The reported findings are the result of the study of six animals. A period of 10 to 20 minutes of Arfonad therapy was required to achieve a controlled and significant reduction in arterial blood pressure. The total amount of Arfonad required to induce and maintain hypotension for a period of one hour ranged from 0.25 to 9.5 mg. The induction of hypotension was associated with a decrease in heart rate which ranged from 24 to 36 beats per minute with the exception of one animal in which heart rate decreased only four beats per minute. Portal vein flow was consistently reduced with the per cent decrease ranging from 27% to 80% (Table 1). The cardiac output of three animals increased 5, 5, and 10% respectively. In the three other animals cardiac output decreased 10, 15, and 20% respectively. Hepatic artery flow was reduced in all animals with the per cent reduction ranging from 5% to 40%.

Immediately following the administration of Arfonad the portal venous pressure of two animals showed no change; the portal pressure of the remaining four animals increased 3%, 4%, and 45% respectively. Thereafter, the portal venous pressure of all six animals slowly but progressively decreased paralleling the reduction in arterial blood pressure. The period of time between beginning the infusion of Arfonad and the recording of a significant reduction in portal venous pressure
ranged from 10-20 minutes. These changes in cardiac output, portal
vein flow and hepatic artery flow were sustained during the period of
Arfonad administration (Fig. 2).

When the administration of Arfonad was discontinued the blood
pressure returned to normal within 30 minutes. Portal vein flow and
pressure returned to baseline levels within 50 minutes. Hepatic artery
flow remained significantly reduced when experiments were terminated
50 minutes after discontinuing the infusion of Arfonad.

During the course of the experiment the surfaces of the livers
of all animals were mottled but the livers did not appear congested.
Results of analysis of serial samples of arterial blood of three animals
demonstrated a range in PO2 from 100 to 114 mm. Hg and the pH varied
from 7.40 to 7.49. Results of necropsy examinations did not show any
significant thrombus formation in any of the vessels utilized to measure
blood flow or pressure.

Discussion

Some observations concerning the use of Arfonad in man and in
experimental animals seem well established. There is a great vari-
ation from individual to individual in the amount of Arfonad necessary to
induce and sustain hypotension. As a result the time necessary to
induce appropriate hypotension is unpredictable. In addition, the hypo-
tensive effect of Arfonad may be largely negated by expansion of the
blood volume. A related and anticipated finding is the increased sensi-
tivity to blood loss associated with Arfonad therapy. Apparently the
vasoconstrictive response to hemorrhage is suddenly released following Arfonad administration and the result is profound hypotension. It would seem difficult, therefore, to achieve the desired physiologic effects of Arfonad therapy in patients with portal hypertension and bleeding varices as a result of cirrhosis. These patients are often losing blood rapidly, receiving large volumes of blood and fluids, and require therapeutic measures which have prompt and dependable effects.

The administration of Arfonad causes a significant and consistent decrease in blood flow through the coronary arteries but its effect on cardiac output is less predictable. A decrease in cardiac output may occur as a result of peripheral pooling of blood and a reduction in central venous pressure. These studies of normal dogs suggest the cardiac output of most animals is not significantly altered with systolic hypotension of 60 to 80 mm. Hg. These findings are in contrast to the observations of Cocco and colleagues of a 29.5% decrease in the cardiac output of patients with established hepatic cirrhosis treated with Arfonad.

Arfonad causes a consistent and significant reduction in the hepatic blood flow of normal dogs and of patients with cirrhosis. In the present studies portal venous flow was reduced 27% to 80%. In addition, there was a consistent decrease in hepatic artery blood flow ranging from 5% to 40%. These findings are consistent with those recorded by Kaplan and colleagues and Davies and colleagues in their studies of Arfonad therapy for experimental liver resections.
The effect of Arfonad on portal venous pressure is of signal importance with regard to its use for bleeding esophageal varices. The initial response of portal pressure to Arfonad in these studies was either no change or a rise in pressure. An increase in portal pressure occurred in 4 of 6 animals. These findings are in agreement with the results of studies of normal dogs reported by Davies and colleagues. In these experiments Arfonad caused a consistent reduction in portal venous pressure but only after significant hypotension was present. Studies of patients with cirrhosis and portal hypertension have demonstrated a significant reduction in portal venous pressure but make no mention of an initial rise in portal pressure or the time necessary to achieve the reduction in portal pressure. Kuhn has reported a 25%-35% reduction in splenic pulp pressure with Arfonad and Coccol and colleagues found each of their seven patients had a reduction in wedged hepatic vein pressure with the overall mean decrease being 19.6%.

The use of Arfonad in the treatment of patients with bleeding varices introduces the hazard of a decrease in coronary artery blood flow. The effect on cardiac output is less predictable. Blood flow through the hepatic artery and the portal vein are both markedly curtailed. In the dog Arfonad causes sufficient restriction of total hepatic blood flow to produce mottling of the normal liver. A similar reduction in blood flow through the diseased human liver may be of serious consequence. Finally, in the normal dog Arfonad fails to produce a prompt reduction in portal venous pressure and in some instances causes an
initial rise in portal pressure. If the results of additional studies on the effect of Arfonad in humans parallel those recorded for normal dogs then the use of Arfonad for the treatment of patients with cirrhosis and bleeding esophageal varices must be questioned.

Summary

The amount of Arfonad and the time necessary to achieve a desired degree of hypotension are variable. The initial response of portal vein pressure in dogs is no change or a rise in pressure. A reduction in portal venous pressure occurs only when hypotension is achieved and is associated with a marked reduction in total hepatic blood flow. Flow through the hepatic artery is consistently reduced and is slow to recover after Arfonad is discontinued.
IN DOGS

AVASTIN IN DUCED FLYPROOFENON

TABLE I
<table>
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<tr>
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<tr>
<td>1</td>
<td>-15%</td>
</tr>
<tr>
<td>2</td>
<td>+10%</td>
</tr>
<tr>
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</tr>
<tr>
<td>6</td>
<td>+5%</td>
</tr>
<tr>
<td>Mean ± S. D.</td>
<td>-4.1±12.4</td>
</tr>
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*C. O.* - Cardiac Output  
PVP - Portal Vein Pressure  
PVF - Portal Vein Flow  
HAF - Hepatic Artery Flow
FIGURE 2

THE EFFECTS OF ARFONAD
IN A TYPICAL ANIMAL
Blood Pressure

- Cardiac Output
- Hepatic Artery Flow
- Portal Pressure
- Portal Vein Flow

Arfonad Administration

(Minutes)
Chapter II

The Effect of Vasopressin and Isoproterenol on
the Splanchnic and Hepatic Circulation

Vasopressin is an effective drug for the control of hemorrhage from esophageal varices. Unfortunately, when administered intravenously in amounts sufficient to reduce portal venous pressure, associated reductions in cardiac output and coronary artery blood flow may cause angina or myocardial infarction. Additional hemodynamic hazards of vasopressin include arterial hypertension and a reduction in total hepatic blood flow. In an attempt to avoid the adverse effects of intravenous vasopressin, Nusbaum has suggested selective infusion of vasopressin into the superior mesenteric artery (SMA). However, selective catheterization of the SMA delays administration of the drug and introduces the hazard of infarction of the small intestine. Furthermore, Madden's studies suggest selective infusion of vasopressin in the SMA may not avoid a reduction in cardiac output. Despite its known adverse side effects, clinicians continue to use intravenous vasopressin because it is a rapid and effective method of controlling variceal hemorrhage.

In the present investigations of normal dogs isoproterenol was
administered simultaneously with intravenous vasopressin in an effort to prevent the adverse hemodynamic effects of vasopressin. The addition of isoproterenol prevented a reduction in cardiac output while permitting a reduction in portal vein pressure by the vasopressin. In addition, isoproterenol produced a marked increase in hepatic artery flow and minimized the arterial hypertension associated with the isolated administration of vasopressin.

Methods

Eighteen adult mongrel dogs weighing 10 to 15 kg. were fasted for 24 hours and the basic model previously described was utilized to study hepatic and cardiac hemodynamics. Satisfactory preparation and stabilization of measured flows and pressures was achieved in eighteen animals. These animals were divided into three groups. Four animals (Group I) were given a vasopressin solution (0.4 u/ml. in 0.9% NaCl) at a rate of 50 ml./hr. for 45 minutes. Another four animals (Group II) were administered isoproterenol (0.004 mg./ml. in 0.9% NaCl) at a rate of 20 ml./hr. for 45 minutes. Eight animals (Group III) were given vasopressin and isoproterenol solutions simultaneously into peripheral veins on opposite sides of the body. Vasopressin (0.4 u/ml. in 0.9% NaCl) was administered at a rate of 50 ml./hr. and isoproterenol (0.004 mg./ml. in 0.9% NaCl) was given at a rate of 20 ml./hr. In all instances the administration of drugs was continued for 45 minutes. Continuous recordings of flows and pressures were made during each
period of study. Measurements of systemic blood pressure were recorded in mm. Hg while the effects of drugs on other hemodynamic parameters were recorded as per cent change from control levels. After 45 minutes the experiments were discontinued, the animals were killed and a necropsy examination was performed on each animal.

Results

The livers of all animals remained normal in appearance during the period of study. In all instances the response to drug administration was prompt. Within each group all animals showed similar and consistent changes in the hemodynamic parameters being studied. With the isolated exception of hepatic artery flow in response to vasopressin the initial hemodynamic responses persisted for the 45 minute period of study. Thus, with that single exception the results recorded 30 minutes after initiating drug administration were essentially the same as those recorded at 15 and 45 minutes.

The isolated administration of vasopressin produced hemodynamic changes consistent with those reported by other investigators (Fig. 3). The increase in systolic blood pressure of these animals ranged from 28 to 68 mm. Hg while reductions in cardiac output ranged from 30% to 54%. The response in hepatic artery flow, consistent for each animal, was characterized by an initial decrease (18% to 32%) followed by a slow but progressive return to normal by the end of the 45 minute period of study. Recorded reductions in portal venous pressure ranged from 22% to 58% with parallel reduction in portal
vein flow of 42% to 76% (Table 2). These hemodynamic changes were accompanied by a decrease in heart rate and an occasional abnormality in cardiac rhythm.

The isolated administration of isoproterenol caused a reduction (17 to 33 mm. Hg) in systolic blood pressure, an increase (32% to 44%) in cardiac output, and an increase (36% to 54%) in hepatic artery flow (Table 3). The increase in portal vein pressure ranged from 15% to 26% with a concomitant increase in portal vein flow ranging from 43% to 66%. An increase in heart rate was recorded in three of the four animals receiving isoproterenol (Fig. 4).

The combined administration of vasopressin and isoproterenol caused only a 5 to 15 mm. Hg elevation in systolic blood pressure. Cardiac output was maintained in four animals and increased (12% to 33%) in the remaining six animals (Fig. 5). The hepatic artery flow was markedly increased in all animals with the increase exceeding 100% in nine of the ten animals. Significant reductions in the portal vein pressure of all ten animals ranged from 14% to 55%. Parallel reductions in portal vein flow ranged from 10% to 70% (Table 4). All animals had an increase in heart rate with the increase ranging from 4 to 40 beats per minute. Transient and infrequent disturbances in cardiac rhythm occurred in only four of the ten animals. Analysis of serial samples of arterial blood from two animals showed the pH to range from 7.40 to 7.49 and the pO₂ to range from 80 to 125 mm. Hg.

Necropsy examinations disclosed no evidence of thrombus for-
formation in the blood vessels used for studies of blood flows and pressures. There was no evidence of thrombus formation in the blood vessels of the intestine. The gross appearance of the intestinal mucosa and the cut surface of the liver was normal.

Discussion

Vasopressin causes constriction of blood vessels and gastrointestinal smooth muscle by direct musculotropic action. It also has an antidiuretic effect, increasing reabsorption of water in the distal tubules. The mechanism of action of vasopressin is speculative. It has a direct stimulatory effect on smooth muscle but the mechanism of action is obscure. The antidiuresis is presumably by altering Na+ absorption or activation of carbonic anhydrase. The fact that vasopressin has a depressor effect on portal vein pressure has been known for many years. Vasopressin will reduce both naturally occurring and experimentally induced portal hypertension. It has the capability of reducing portal hypertension from extrahepatic block as well as that resulting from intrahepatic block. The portal pressure of normal animals and humans is also reduced by vasopressin.

Vasopressin causes a vasoconstriction of the superior mesenteric artery and its branches. The resulting increase in arterial resistance produces a decrease in splanchnic blood flow and a reduction in portal vein pressure. The vasoconstriction of splanchnic vessels has been demonstrated by studies of blood flow and splanchnic resistance, and confirmed by arteriography and direct observation.
of the splanchnic vessels of animals and humans. In addition to its effect on arteries of the splanchnic circulation, Aronsen and Nylander have observed a vasopressin induced dilation of the portal vein and its larger intrahepatic branches. Since there was an associated reduction in portal vein pressure it is unlikely that the dilation was the result of increased intrahepatic venous vascular resistance. They suggested vasopressin had a direct action on the wall of the portal vein. As vasopressin is known to exert its effect directly on the vascular contractile elements, the described phenomenon seems to be contradictory. However, the well-known fact that the contractile elements of the portal vein are arranged in a longitudinal direction may possibly explain this phenomenon. Considerable evidence exists to document that vasopressin causes a reduction in gastric mucosal blood flow as well as total gastric blood flow. Arteriographic evidence suggests blood flow through submucosal varices is also markedly reduced. Visible submucosal esophageal varices in dogs with induced portal hypertension have been noted to disappear following the administration of vasopressin.

Although vasopressin has the capacity to reduce portal venous pressure the distressing side effects of the drug have caused great concern and some clinicians have abandoned its use. These side effects include abdominal cramps, coronary vasoconstriction and a decrease in cardiac output. Precipitation of myocardial infarction is an established threat making coronary artery disease a contraindication to the use of vasopressin. In an attempt to avoid the adverse systemic effects of
vasopressin Nusbaum and colleagues infused small amounts of vasopressin directly into the superior mesenteric artery. They reported a 80% decrease in superior mesenteric artery flow. In a separate group of animals they reported no change in cardiac output with administration of similar amounts of vasopressin into the superior mesenteric artery. However, Madden and colleagues were unable to confirm these findings. They found a consistent decrease in cardiac output and suggested the adverse effect of vasopressin on cardiac output could not be eliminated by infusion of the drug into the superior mesenteric artery. In addition, they concluded that vasopressin does not have a local selective effect on the splanchnic circulation and attributed alterations in splanchnic blood flow to the depressant effect of vasopressin upon the heart.

In the present studies the combination of isoproterenol and vasopressin reduced the portal vein pressure and flow of normal dogs, maintained cardiac output and produced a marked increase in flow through the hepatic artery. If similar results occur when this combination of pharmacologic agents is administered to humans then the major hazards of intravenous vasopressin therapy may be eliminated by the addition of isoproterenol. Suggestions regarding the mechanism by which isoproterenol offsets the decrease in cardiac output expected with unopposed vasopressin therapy are only conjecture. It is possible that the vasodilatation produced by isoproterenol prevents systemic hypertension and the resulting reflex parasympathetic mediated bradycardia. This together with the inotropic effect of isoproterenol on the
heart may be the mechanism by which a decrease in cardiac output is prevented. Isoproterenol is the isopropyl analogue of norepinephrine and epinephrine. It has a direct inotropic effect on the heart and causes generalized vasodilation by activation of B receptors. The tachycardia seen with isoproterenol is generally secondary to a decrease in blood pressure.

The mechanism by which a combination of vasopressin and isoproterenol increases flow through the hepatic artery is more difficult to explain. It may be that this increase in flow results in response to a decrease in portal vein flow representing one aspect of the reciprocal flow relationship between the hepatic artery and the portal vein. An alternative or additional explanation is that beta-adrenergic receptors are present in the liver and intrahepatic resistance to hepatic artery flow was reduced by isoproterenol. Dedichen and Schenk have evaluated the effect of isoproterenol in the dog and have reported an 83% increase in hepatic artery flow while there was only a 23.3% increase in superior mesenteric artery blood flow. The hepatic vascular resistance was decreased 63% and the mesenteric vascular resistance decreased only 35.9%. Thus isoproterenol appears to selectively enhance blood flow through the hepatic artery.

In the present studies of the combined administration of vasopressin and isoproterenol, a reduction in portal venous pressure typical of unopposed vasopressin therapy occurred while cardiac output was maintained and flow through the hepatic artery was markedly increased.
These findings suggest vasopressin may indeed produce some local selective vasoconstriction of the branches of the superior mesenteric artery.

Summary

Eighteen dogs were anesthetized with sodium pentobarbital. Electromagnetic flow transducers were used to measure cardiac output, hepatic artery flow and portal vein flow. Catheters were inserted to allow monitoring of pressure in the aorta and the portal vein. After a period of stabilization the animals were divided into three groups. Group I received vasopressin intravenously (0.4 u/ml.) at a rate of 50 ml./hr. Group II were administered isoproterenol (0.004 mg./ml.) intravenously at a rate of 20 ml./hr. Group III received a combination of vasopressin and isoproterenol in the same doses as given to the two preceding groups. Recording of blood flows and pressures were continued for a period of 45 minutes.

Those animals in Groups I and II showed response similar to those reported by other investigators. In Group III all animals showed immediate, consistent and sustained responses. Ranges of per cent change for parameters showing significant alterations included: portal vein pressure -14% to -55%, portal vein flow: -10 to -70%, and hepatic artery flow: +85 to +100%. Systolic blood pressures increased only 5 to 15 mm. Hg. Cardiac output remained normal in four animals and increased in six. Suggested therapeutic advantages of adding isoproterenol to vasopressin include maintenance of normal cardiac output and a sig-
significant increase in hepatic artery blood flow. Effective doses of
vasopressin and isoproterenol ranged from 35 to 70 ml./hr. and 12 to
26 ml./hr. respectively.
**TABLE 2**

HEMODYNAMIC RESPONSES AT 30 MINUTES WITH ADMINISTRATION OF VASOPRESSIN
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<thead>
<tr>
<th>Animal no.</th>
<th>% Change from baseline recordings</th>
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<td>4</td>
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</tr>
</tbody>
</table>

Mean ± S.D. | -41 ± 10.0 | -43.0 ± 15.9 | -57.8 ± 15.1 | -24.5 ± 4.7 |

*C.O. - Cardiac Output
PVP - Portal Vein Pressure
PVF - Portal Vein Flow
HAF - Hepatic Artery Flow
<p>| Table 3 | HEMODYNAMIC RESPONSES AT 30 MINUTES WITH ADMINISTRATION OF ISOPROTERENOL |</p>
<table>
<thead>
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<th>% Change from baseline recordings</th>
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<td>Mean ± S.D.</td>
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</table>

* C. O. - Cardiac Output  
PVP - Portal Vein Pressure  
PVF - Portal Vein Flow  
HAF - Hepatic Artery Flow
TABLE 4

HEMODYNAMIC RESPONSES WITH COMBINED ADMINISTRATION
OF VASOPRESSIN AND ISOPROTERENOL AT 30 MINUTES
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</thead>
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<td>10</td>
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<tr>
<td>Mean ± SD</td>
<td>10.8±11.5</td>
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</table>

*C.O. - Cardiac Output  
PVP - Portal Vein Pressure  
PVF - Portal Vein Flow  
HAF - Hepatic Artery Flow
HEMODYNAMIC RESPONSE OF A TYPICAL ANIMAL TO VASOPRESSIN
Vasopressin 0.4 u/ml

50 ml./hr.

Blood Pressure

mmHg

Percent Change

Cardiac Output

Hepatic Artery Flow

Portal Pressure

Portal Vein Flow

(Minutes)
FIGURE 4

HEMODYNAMIC RESPONSE OF A TYPICAL ANIMAL TO ISOPROTERENOL
Blood Pressure (mm Hg)

Percent Change

Isoproterenol 0.004 mg./ml.

20 ml./hr.

(Minutes)

- Cardiac Output
- Hepatic Artery Flow
- Portal Pressure
- Portal Vein Flow
FIGURE 5

HEMODYNAMIC RESPONSE OF A TYPICAL ANIMAL TO VASOPRESSIN AND ISOPROTERENOL
Chapter III

Effects of Ethanol on the Splanchnic and Hepatic Circulation

Despite the ever-increasing use and abuse of alcohol, the hemodynamic influences of this drug have not been well defined. Cardiovascular responses to ethanol determined in experimental animals and man have yielded conflicting data. Review of this literature suggests the discrepancies in results are primarily related to the variation in experimental models and methods. The majority of investigations of the effect of alcohol on hepatic blood flow have relied on the Fick Principle rather than more direct methods of determining flow.

The cardiac output of anesthetized dogs was not significantly influenced by alcohol in studies reported by Smythe et al and Horvath and Willard. However, Schmitthenner et al and Webb and Doigler demonstrated a distinct increase in the cardiac output of dogs receiving alcohol. Determination of hepatic blood flow included in the studies of Smythe et al and Horvath and Willard did not show any significant alterations in response to alcohol. Studies of the effect of alcohol on the hepatic blood flow of humans have yielded conflicting data although available evidence favors a significant increase in hepatic blood flow in most subjects.

In the present study the effect of alcohol on the cardiac output,
portal vein flow, and hepatic artery flow of dogs has been assessed using noncanulating electromagnetic flow transducers. The systemic blood pressure and portal venous pressure were monitored and periodic determinations of the concentration of alcohol in blood were made.

Methods

Twenty adult mongrel dogs weighing 10 to 15 kg. were fasted for 24 hours. The basic experimental model previously described was utilized in the experiment. After stabilization an intravenous infusion of ethyl alcohol solution was started. In Groups I and II, 0.5 gm./kg. of ethyl alcohol was administered by intravenous infusion of a ten percent ethyl alcohol solution over a 30 minute period. Group I received the infusions into a peripheral vein and Group II were infused through the portal vein. Groups III and IV animals were infused with a twenty percent alcohol solution over a 30 minute period and received a total of 1 gm./kg. of ethyl alcohol. Group III were infused into a peripheral vein and Group IV through the portal vein. Continuous recordings of flows and pressures were made for a period of 45 minutes after starting the administration of alcohol. Alcohol levels were measured by the gas chromatography method. After 45 minutes the experiments were discontinued, the animals were killed and a necropsy examination was performed on each animal.

Results

All animals included in this study had a stable blood pressure and pulse rate prior to the ethyl alcohol infusions. Pilot studies on four
animals showed that peripheral vein and portal vein infusion of normal saline (volume equal to ETOH solution infused per kg.) had no significant influences on the hemodynamic parameters measured. Following the ethyl alcohol infusion into a peripheral vein at a rate of 0.5 gm./kg. there was essentially no change in the blood pressure and pulse rate. The cardiac output response ranged from no change to a twenty per cent increase. The hepatic artery flow increased 39% - 100% of control values. The change in portal venous flow was variable ranging from 20% below baseline values to 13% above. The portal venous pressures ranged from 7% below baseline values to 14% above control values (Table 5). Ethanol levels achieved after administration of 0.5 gm./kg. of ethyl alcohol ranged from 60 - 90 mg.% (Fig. 6).

Following 0.5 gm./kg. ETOH infusion into the portal vein, the systemic systolic blood pressure and pulse rate were essentially unchanged. Changes in cardiac output ranged from 17% below baseline value to 31% above control values. The hepatic arterial flow increased 38 - 66% of normal. The portal venous flow increased 16 - 22% and the portal pressure was elevated 6 - 13% (Table 6). Blood ethanol levels ranged from 60 - 70 mg.% (Fig. 7).

Blood pressure and pulse rate were not significantly altered during infusions of 1 gm./kg. of ethanol into a peripheral vein. The change in cardiac output ranged from a 5% decrease to 25% increase. The hepatic arterial flow increased 23 - 100% of control values. Portal venous flow changes ranged from 24% decrease to 16% increase. The
portal pressure changes ranged from 8% decrease to a 13% increase (Table 7). Ethanol levels ranged from 150 to 200 mg.% (Fig. 8).

In those animals receiving infusions of 1 gm./kg. of ethanol into the portal vein there were essentially no changes in blood pressure and pulse rate. The cardiac output response ranged from a 14% decrease to a 20% increase. The hepatic arterial flow was increased from 20 - 40% of normal. The portal venous flow increased 7 - 24% of control values (Table 8). The portal pressure was elevated 10 - 15% of normal. Blood ethanol levels ranged from 110 - 170 mg.% (Fig. 9).

During the course of the experiment the livers of all animals appeared normal. Serial samples of arterial blood revealed pO₂ levels ranging from 80 - 125 mm. Hg and the range of pH from 7.13 - 7.33.

Discussion

Some observations concerning the hemodynamic effects of ethanol in experimental animals and humans have been well established. It is generally accepted that ethanol causes peripheral vasodilatation by an indirect effect on the vasomotor and thermoregulatory centers. However, reports concerning cardiac and hepatic hemodynamics response following the administration of ethanol are conflicting. In the present studies the administration of ethanol through a peripheral vein or the portal vein resulted in an increase in cardiac output in 12 of 16 animals. These results are in agreement with Webb who demonstrated an increase in cardiac output following the infusion of 0.5 mg./kg. of ethanol in dogs. The cardiac output was measured with a noncanulatory
probe placed on the ascending aorta. Measurements were taken at a
time when blood ethanol levels ranged from 42 - 87 mg.%. Schmitt-
henner also reported an increase in cardiac output in dogs following
the infusion of ethanol, achieving blood ethanol levels ranging from
70 - 120 mg.%. Juchems has reported an increase in cardiac output
in healthy adult humans following ethanol administration. The alcohol
was given by mouth and blood ethanol levels ranged from 39 - 120 mg.%. In contrast to these observations Horvath has reported that ethanol
administration to dogs caused a decrease in cardiac output when blood
ethanol levels averaged 84.6 mg.%. Conway also observed a de-
crease in cardiac output following the oral administration of ethanol to
humans with a history of coronary disease. The blood ethanol levels
achieved ranged from 42 to 55 mg.%. The conflicting results and con-
cclusions of various observations concerning the action of ethanol on
the cardiovascular system may be attributed, in part, to the diverse
conditions of the experimenter, the variations in the concentrations of
ethanol, and the time observations were made following the infusion of
ethanol. From the present study and the results of studies done under
similar conditions it appears that the cardiac output tends to increase
following ethanol administration.

The effect of ethanol on the hepatic artery flow, portal vein flow
and portal pressure is of signal importance since it might play a role
in the pathogenesis of cirrhosis and the various gastrointestinal dis-
orders associated with alcoholism. Most studies dealing with the
effect of ethanol on hepatic hemodynamics have utilized indirect methods of estimating the hepatic blood flow rather than separately measuring the hepatic artery blood flow and portal vein flow. Mendeloff\textsuperscript{76} has reported an increase in hepatic blood flow following infusion of ethanol in human subjects. Blood alcohol levels achieved ranged from 25 - 81 mg.%. Essentially the identical experiment was done by Hans Cas-\textsuperscript{77}tenfors\textsuperscript{77} who reported no change in hepatic blood flow following ethanol administration. Childs\textsuperscript{78} estimated the hepatic blood flow by the BSP method and reported an increase in hepatic blood flow in 8 of 10 subjects following infusion of ethanol. In contrast to these studies Smythe\textsuperscript{69} reported that ethanol does not change the hepatic blood flow in dogs.

In the present study hepatic artery blood flow increased in all animals following intravenous infusion of ethanol. The increase in hepatic blood flow could be in part attributed to the increase in cardiac output, but another mechanism of action would seem more likely since those animals not showing an increase in cardiac output also had an increase in hepatic artery flow. An increase in hepatic artery flow secondary to a decrease in portal vein flow could be a possibility in those animals showing a decrease in portal vein flow, but since in some animals there was an increase in both vascular beds, flow reciprocity does not appear to be an explanation for the changes in flow. A possible explanation for the increase in hepatic artery flow is that ethanol may have a direct effect on decreasing the resistance in the hepatic artery and the microcirculation of the liver.

Observations concerning the changes in the portal venous flow and
portal pressure were variable, some showing an increase and others a decrease. One consistent finding was that all animals receiving ethanol through the portal vein demonstrated an increase in flow and pressure. This could be attributed to the high concentration of ethanol in the portal vein which decreases the resistance of the microcirculation in the liver.

Correlating this study with data from similar studies suggests that the discrepancy in the reported data could be attributed to the method of measuring hepatic blood flow. Although some report an increase in hepatic blood flow and others report a decrease in flow the discrepancies could be due to the variable portal vein flow. This study suggests that ethanol causes a consistent increase in hepatic artery flow in all concentrations regardless of rate of administration. However, only those animals receiving intraportal ethanol showed a consistent increase in portal vein flow.

Summary

Twenty dogs were anesthetized with sodium pentobarbital. Electromagnetic flow transducers were used to measure cardiac output, hepatic arterial flow, and portal venous flow. Catheters were inserted to allow monitoring of pressure in the aorta and portal vein. After stabilization ethyl alcohol was administered into a peripheral vein or through the portal vein. Two doses of ethyl alcohol were used (0.5 gm./kg. or 1 gm./kg.) which were administered over a 30 minute period. Recordings of blood flow and pressure were continued for a
period of 45 minutes.

No significant change was noted in the blood pressure and pulse rate of any animals following ethanol infusion. The cardiac output was increased in twelve of the sixteen experimental animals. The hepatic arterial flow was increased in all animals but the increase was more marked in the group that received peripheral vein infusion of ethyl alcohol. The portal venous flow was variable in those animals receiving peripheral vein infusions of ethanol, however there was a consistent increase in portal venous flow following portal vein infusion. The changes in portal pressure were generally directly related to changes in portal venous flow. Alcohol levels achieved ranged from 60 mg.% to 200 mg. %.

The intravenous administration of ethyl alcohol had variable influences on the cardiac output, hepatic arterial flow and portal venous flow. However, the trend toward elevation in portal pressure with intraportal administration of ethanol suggests that ethyl alcohol used in patients with portal hypertension may enhance their chances of developing esophageal varical hemorrhage.
**TABLE 5**

**GROUP I**

HEMODYNAMIC RESPONSE FOLLOWING INTRAVENOUS ADMINISTRATION OF

0.5 gm./kg. OF ETHANOL
<table>
<thead>
<tr>
<th>Dog number</th>
<th>% Change from baseline recordings</th>
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<tr>
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* C.O. - Cardiac Output
PVP - Portal Vein Pressure
PVF - Portal Vein Flow
HAF - Hepatic Artery Flow
TABLE 6

GROUP II

HEMODYNAMIC RESPONSE FOLLOWING
INTRAPORTAL ADMINISTRATION OF
0.5 gm./kg. OF ETHANOL
<table>
<thead>
<tr>
<th>Dog number</th>
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Mean 10.5 +9.25 +16 +50.5

* C.O. - Cardiac Output
PVP - Portal Vein Pressure
PVF - Portal Vein Flow
HAF - Hepatic Artery Flow
TABLE 7

GROUP III

HEMODYNAMIC RESPONSE FOLLOWING INTRAVENOUS ADMINISTRATION OF
1 gm./kg. OF ETHANOL
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* C.O. - Cardiac Output  
PVP - Portal Vein Pressure  
PVF - Portal Vein Flow  
HAF - Hepatic Artery Flow
**TABLE 8**

**GROUP IV**

HEMODYNAMIC RESPONSE FOLLOWING INTRAPORTAL ADMINISTRATION OF

1 gm./kg. OF ETHANOL
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* C.O. - Cardiac Output  
PVP - Portal Vein Pressure  
PVT - Portal Vein Flow  
HAF - Hepatic Artery Flow
**TABLE 9**

HEMODYNAMIC EFFECTS OF ETHANOL -

**TABLE OF MEANS**
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<td>1 gm./kg. Portal</td>
<td>+8.5</td>
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* C.O. - Cardiac Output
PVP - Portal Vein Pressure
PVF - Portal Vein Flow
HAF - Hepatic Artery Flow
FIGURE 6

HEMODYNAMIC RESPONSE OF A TYPICAL ANIMAL TO INTRAVENOUS ADMINISTRATION OF ETHANOL (0.5 gm./kg.)
Ethanol 0.5 gm./kg. IV

Cardiac Output
Hepatic Artery Flow
Portal Pressure
Portal Vein Flow
FIGURE 7

HEMODYNAMIC RESPONSE OF A TYPICAL ANIMAL TO INTRAPORTAL ADMINISTRATION OF ETHANOL (0.5 gm./kg.)
Blood Pressure (mmHg)

Cardiac Output
Hepatic Artery Flow
Portal Pressure
Portal Vein Flow

Ethanol
0.5 gm./kg. Intraportal

(Minutes)
FIGURE 8

HEMODYNAMIC RESPONSE OF A TYPICAL ANIMAL TO INTRAVENOUS ADMINISTRATION OF ETHANOL (1 gm./kg.)
Blood Pressure (mmHg)

<table>
<thead>
<tr>
<th>200</th>
<th>150</th>
<th>100</th>
<th>50</th>
<th>0</th>
</tr>
</thead>
</table>

-50  -50  -50  -50  -50

Percent Change

Ethanol 1 gm./kg. IV

Cardiac Output
Hepatic Artery Flow
Portal Pressure
Portal Vein Flow

(Minutes)
FIGURE 9

HEMODYNAMIC RESPONSE OF A TYPICAL ANIMAL
TO INTRAPORTAL ADMINISTRATION OF
ETHANOL (1 gm./kg.)
Blood pressure (mmHg)

Blood pressure vs. time (minutes)

- Cardiac Output
- Hepatic Artery Flow
- Portal Pressure
- Portal Vein Flow

Ethanol 1 gm./kg.

Intraportal

Percent Change

0 45 55 65 75 85 95 105

(Minutes)
SUMMARY

Chronic portal hypertension is generally the cause of bleeding from esophageal varices. Current methods of controlling hemorrhage from esophageal varices are unsatisfactory. These studies were designed in an attempt to find a more effective method of controlling bleeding esophageal varices by decreasing portal pressure with the use of drugs.

Arfonad, Vasopressin, Isoproterenol and ethanol were evaluated with respect to their effect on cardiac and hepatic hemodynamics. To study these parameters an experimental model utilizing adult dogs was specifically designed to study the effects of these various drugs on the portal pressure, portal venous flow, hepatic artery flow and the cardiac output. Through a midline incision electromagnetic flow transducers were placed on the portal vein and the hepatic artery. A longitudinal incision in the periarterial tissue of the hepatic artery allowed placement of the flow transducer on that vessel without division of the periarterial nerve fibers. The hepatic arterial arch was ligated distal to the most distal branch to the liver. A polyethylene catheter inserted into the distal aorta through a femoral artery provided for measurements of systemic arterial blood pressure and sampling of blood for determinations of arterial pH and pO2. Through a left thora-
colony an electromagnetic flow transducer was placed on the ascending aorta for recording of cardiac output (less coronary artery flow). Continuous recordings of flow through the ascending aorta, hepatic artery and portal vein together with pressures in the portal vein and distal aorta were made using a Sanborn multichannel recorder.

The hemodynamic effects of Arfonad was evaluated by the administration of a solution of 0.25% Arfonad intravenously in sufficient amounts to reduce systolic blood pressure to 60 to 80 mm. Hg over a 10 - 20 minute period. The amount of Arfonad and the time necessary to achieve a desired degree of hypotension was variable. The initial response of portal vein pressure in dogs was no change or a rise in pressure. A reduction in portal venous pressure occurred only when hypotension was achieved and was associated with a marked reduction in total hepatic blood flow. Flow through the hepatic artery was consistently reduced and was slow to recover after Arfonad was discontinued.

To evaluate the effects of vasopressin and isoproterenol on cardiac and hepatic hemodynamics, three groups of animals were studied. Group I received vasopressin intravenously (0.4 u/ml.) at a rate of 50 ml./hr. Group II were administered isoproterenol (0.004 mg./ml.) intravenously at a rate of 20 ml./hr. Group III received a combination of vasopressin and isoproterenol in the same doses as given to the two preceding groups. Recording of blood flows and pressures were continued for a period of 45 minutes.
Those animals in Groups I and II showed response similar to those reported by other investigators. In Group III all animals showed immediate, consistent and sustained responses. Ranges of per cent change for parameters showing significant alterations included: portal vein pressure -14 to -55%, portal vein flow -10 to -70%, and hepatic artery flow +85 to +100%. Systolic blood pressures increased only 5 to 15 mm. Hg. Cardiac output remained normal in four animals and increased in six.

The effects of ethanol on cardiac and hepatic hemodynamics was evaluated by administration of ethyl alcohol intraportal and into a peripheral vein. Two doses of ethyl alcohol were used (0.5 gm./kg. or 1 gm./kg.) and were administered over a 30 minute period. Recordings of blood flow and pressure were continued for a period of 45 minutes.

No significant change was noted in the blood pressure and pulse rate of any animals following ethanol infusion. The cardiac output was increased in twelve of the sixteen experimental animals. The hepatic arterial flow was increased in all animals but the increase was more marked in the group that received peripheral vein infusion of ethyl alcohol. The portal venous flow was variable in those animals receiving peripheral vein infusions of ethanol, however there was a consistent increase in portal venous flow following portal vein infusion. The changes in portal pressure were generally directly related to changes
in portal venous flow. Alcohol levels achieved ranged from 60 mg.% to 200 mg.%.

The intravenous administration of ethyl alcohol had variable influences on the cardiac output, hepatic arterial flow, portal venous flow, and portal pressure; however there appeared to be a trend toward an increase in portal pressure and flow following alcohol administration. There were some hemodynamic differences depending on whether the ethanol was infused into the portal vein rather than a peripheral vein.

From these studies it appears that the simultaneous infusion of vasopressin and isoproterenol may be a safe and effective method to control bleeding esophageal varices. Also, these studies suggest that the effects of ethanol on the hepatosplanchnic circulation may aggravate portal hypertension by increasing portal venous flow and pressure.
STATISTICAL ANALYSIS

Effect of arfonad on the cardiac output, portal vein pressure, portal vein flow and hepatic artery flow.

Sign Test

H₀ : M = 0 vs. H₁ : M ≠ 0

CO  k = 3  Accept M ≠ 0 with a significant level of 1

\{ PVP \}

\{ PVF \}  k = 0  Reject M = 0 in favor of M < 0 with a significant level of 1/32

\{ HAF \}
STATISTICAL ANALYSIS

Effect of vasopressin on the cardiac output, portal vein flow, portal vein pressure, and hepatic artery flow.

Sign Test

$H_0 : M = 0 \text{ vs. } H_1 : M \neq 0$

Reject $M = 0$ with a significant level of

$k = 4$

$1/8$ in favor of $M < 0$
STATISTICAL ANALYSIS

Effect of isoproterenol on the cardiac output, portal vein flow, portal vein pressure and hepatic artery flow.

Sign Test

$H_0 : M = 0$ vs. $H_1 : M \neq 0$

$k = 4$

The hypothesis $M = 0$ is rejected with a significant level of $1/8$ in favor of $M > 0$
STATISTICAL ANALYSIS

Combined effect of isoproterenol and vasopressin on the cardiac output, portal vein flow, portal vein pressure, and hepatic artery flow.

Sign Test

Ho : M = 0 vs. H1 : M ≠ 0

\[
\begin{align*}
\text{PVF} & \quad k = 0 \quad \text{Reject } M = 0 \text{ with a significant level of } 1/256 \text{ in favor of } M < 0 \\
\text{PVP} \quad & \\
\text{HAF} & \quad k = 10 \quad \text{Reject } M = 0 \text{ with a significant level of } 1/250 \text{ in favor of } M > 0
\end{align*}
\]
STATISTICAL ANALYSIS

EFFECT OF ETHANOL ON THE CARDIAC OUTPUT, PORTAL VEIN PRESSURE, PORTAL VEIN FLOW AND HEPATIC ARTERY FLOW
### Analysis of Variance for Factorial Design

#### Hepatic Artery Flow

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>Degrees of Freedom</th>
<th>Sums of Squares</th>
<th>Mean Squares</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dose</td>
<td>1</td>
<td>650.25000</td>
<td>650.25000</td>
<td>1.08</td>
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<tr>
<td>2. Method</td>
<td>1</td>
<td>2756.25000</td>
<td>2756.25000</td>
<td>4.57</td>
</tr>
<tr>
<td>12. Dose x Method</td>
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<td>380.25000</td>
<td>380.25000</td>
<td>0.01</td>
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<tr>
<td>Within Replicates</td>
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<td>7231.00000</td>
<td>602.58325</td>
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<tr>
<td>Total</td>
<td>15</td>
<td>11017.7500</td>
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</table>
## ANALYSIS OF VARIANCE FOR FACTORIAL DESIGN

### CARDIAC OUTPUT

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>Degrees of Freedom</th>
<th>Sums of Squares</th>
<th>Mean Squares</th>
<th>F</th>
</tr>
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<tbody>
<tr>
<td>1. Dose</td>
<td>1</td>
<td>6.25000</td>
<td>6.25000</td>
<td>0.03 N.</td>
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<tr>
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<td>30.25000</td>
<td>0.13 N.</td>
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<tr>
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<td>2.25000</td>
<td>2.25000</td>
<td>0.01 N.</td>
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<tr>
<td>Within Replicates</td>
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<td>2753.00000</td>
<td>229.41666</td>
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<tr>
<td>Total</td>
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<td>2791.75000</td>
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</tbody>
</table>
ANALYSIS OF VARIANCE FOR FACTORIAL DESIGN

PORTAL VEIN PRESSURE

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<thead>
<tr>
<th>Source of Variation</th>
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<th>Sums of Squares</th>
<th>Mean Squares</th>
<th>F</th>
<th>P</th>
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</thead>
<tbody>
<tr>
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<tr>
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<td>49.91666</td>
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<tr>
<td>Total</td>
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</tbody>
</table>
## ANALYSIS OF VARIANCE FOR FACTORIAL DESIGN

### PORTAL VEIN FLOW

<table>
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<th>Sums of Squares</th>
<th>Mean Squares</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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<td>915.06250</td>
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<td>0.66</td>
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<tr>
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<td>159.39583</td>
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<tr>
<td>Total</td>
<td>15</td>
<td>2950.93750</td>
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<td></td>
</tr>
</tbody>
</table>
t-tests for differences between baseline recordings of certain variables and recordings for those variables for two doses and two methods of administration of alcohol, expressed as per cent change from baseline.

Cardiac Output

0.5 gm/kg. - IP

\[
t = \frac{10.50}{\sqrt{\frac{229.4166}{4}}} = \frac{10.50}{7.57} = 1.39 \text{ N.S. d.f.=12}
\]

0.5 gm/kg. - IV

\[
t = \frac{12.50}{\sqrt{\frac{229.4166}{4}}} = \frac{12.50}{7.57} = 1.65 \text{ N.S. d.f.=12}
\]

1 gm/kg - IP

\[
t = \frac{8.50}{\sqrt{\frac{229.4166}{4}}} = \frac{8.50}{7.57} = 1.12 \text{ N.S. d.f.=12}
\]

1 gm/kg - IV

\[
t = \frac{12.00}{\sqrt{\frac{229.4166}{4}}} = \frac{12.00}{7.57} = 1.58 \text{ N.S. d.f.=12}
\]

Portal Vein Pressure

0.5 gm/kg - IP

\[
t = \frac{9.25}{\sqrt{\frac{49.9166}{4}}} = \frac{9.25}{3.53} = 2.62 \text{ p.<.05 d.f.=12}
\]

0.5 gm/kg - IV

\[
t = \frac{1.75}{\sqrt{\frac{49.9166}{4}}} = \frac{1.75}{3.53} = 0.50 \text{ N.S. d.f.=12}
\]
1 gm/kg - IP
\[ t = \frac{9.75}{\sqrt{\frac{49.9166}{4}}} = \frac{9.75}{3.53} = 2.76 \] p. ~ .05  d.f.=12

1 gm/kg - IV
\[ t = \frac{6.75}{\sqrt{\frac{49.9166}{4}}} = \frac{6.75}{3.53} = 1.91 \] N.S.  d.f.=12

Portal Vein Flow

0.5 gm/kg - IP
\[ t = \frac{16.00}{\sqrt{\frac{159.3958}{4}}} = \frac{16.00}{6.31} = 2.53 \] p. ~ .05  d.f.=12

0.5 gm/kg - IV
\[ t = \frac{-4.25}{\sqrt{\frac{159.3958}{4}}} = \frac{-4.25}{6.31} = 0.67 \] N.S.  d.f.=12

1 gm/kg - IP
\[ t = \frac{13.00}{\sqrt{\frac{159.3958}{4}}} = \frac{13.00}{6.31} = 2.06 \] N.S.  d.f.=12

1 gm/kg - IV
\[ t = \frac{3.00}{\sqrt{\frac{159.3958}{4}}} = \frac{3.00}{6.31} = 0.48 \] N.S.  d.f.=12
Hepatic Artery Flow

0.5 gm/kg - IP
\[ t = \frac{50.50}{\sqrt{\frac{602.5832}{4}}} = \frac{50.50}{12.27} = 4.11 \quad p. < .01 \quad d.f. = 12 \]

0.5 gm/kg - IV
\[ t = \frac{67.00}{\sqrt{\frac{602.5832}{4}}} = \frac{67.00}{12.27} = 5.46 \quad p. < .01 \quad d.f. = 12 \]

1 gm/kg - IP
\[ t = \frac{28.00}{\sqrt{\frac{602.5832}{4}}} = \frac{28.00}{12.27} = 2.22 \quad p. < .05 \quad d.f. = 12 \]

1 gm/kg - IV
\[ t = \frac{64.00}{\sqrt{\frac{602.5832}{4}}} = \frac{64.00}{12.27} = 5.21 \quad p. < .01 \quad d.f. = 12 \]
BIBLIOGRAPHY


