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Role of the azygos venous system in the investigation of portal hypertension

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EDITORIAL SYNOPSIS The azygos venous system is a 'final common path' for the return of portal blood to the systemic circulation in subjects with portal hypertension and an extensive collateral circulation. The author suggests that catheterization of the vena azygos major, which he has performed in the dog, can provide useful information and mirror changes in portal vein blood in dogs with portal hypertension. The higher oxygen and ammonia content and the fall of elevated azygos venous pressure after pitressin suggest this theory. Further detection of 'marker' substances such as ¹³¹I Rose Bengal and ¹³³Xenon in azygos blood could perhaps form a basis for the estimation of collateral circulation following their instillation into the jejunum. Perhaps these techniques can be translated for the human subject with portal hypertension. The author feels that they can.

The portal venous system in man and animals is not directly accessible without operation except occasionally through a superficial abdominal collateral (Bean, Franklin, Embick, and Daum, 1951). A close approximation of portal venous pressure may be obtained from an hepatic wedge pressure (Myers and Taylor, 1951), or a splenic pulp pressure (Atkinson and Sherlock, 1954) but these routes do not readily permit chemical, biological, or flow studies on portal venous blood. The interposition of the liver between portal and systemic venous circuits leads to modification by the hepatic cells of materials reaching the systemic from the portal system. It seems likely that the azygos system might provide more direct access to the portal system when portal hypertension with significant collateral flow is present. Without the changes imposed on the portal venous blood by the liver, the chemical and dynamic findings in the azygos system may reflect more accurately the state of the portal venous system. When it was found that the vena azygos major could be readily and consistently catheterized, it was planned to study this system in normal dogs and dogs with portal hypertension. To establish good collateral flow through the azygos system the procedures described by Tamiya and Thal (1960) were employed in dogs.

The study was divided into two parts: the collection of data in normal dogs and the collection of

data in dogs with extensive collateral systems. In each group the following observations were made.

A The pressure in the lowest reaches of the azygos vein before and after the administration of pitressin; B the pressure in the hepatic vein wedge position before and after pitressin; C determination of the haemoglobin, blood oxygen content and saturation, catecholamines, serotonin, and ammonia in samples of blood obtained from azygos and hepatic veins; D the appearance time and concentration of sodium fluorescein, ¹³³Xenon, and ¹³¹I Rose Bengal in hepatic and azygos venous blood after instillation of each material into the jejunum; E the appearance time of ¹³³Xenon in the lymph from the thoracic duct after the instillation in the jejunum; F retrograde venography of the azygos system.

METHOD

PREPARATION OF ANIMALS Normal dogs of approximately 15 kg. were used. Under intravenous pentobarbital anaesthesia the production of collateral circulation was achieved by a modification of the procedure of Tamiya and Thal (1960). First the spleen was removed and a side-to-side anastomosis established between the splenic artery and vein. Approximately one month later the portal vein was located and obstructed to about one quarter of its calibre with a silk ligature. The mortality of the operation was near 75%. The surviving dogs were studied between one and two months after the second stage.

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INVESTIGATION OF ANIMALS Both groups were fasted and anaesthetized with intravenous pentobarbital. Two 50 cm. Gooddale-Lubin woven dacron cardiac catheters no. 5F were introduced through the external jugular vein under fluoroscopy. One was passed through the right atrium into the hepatic vein in readiness for the wedge procedure. The other was advanced slowly along the superior vena cava with the tip pointed posteriorly. Entrance into the vena azygos major was readily achieved in most instances and the catheter tip was then pushed as far down the azygos vein as possible without entering an intercostal vein. The progress of the catheter was usually impeded at about 25 cm. when it appeared to be located just below the margin of the thorax. At this point, pressures were recorded with a Statham strain gauge P-23db on a four channel Sanborn recorder before and after the intravenous injection of 20 units of pitressin in 1 ml. Pressures were recorded simultaneously in the hepatic wedge position. In both positions blood samples were obtained for the determination of haemoglobin oxygen content (Van Slyke technique), catecholamines (Weil-Malherbe and Bone, 1952), serotonin (Udenfriend, Weissbach, and Brodie, 1958), and ammonia (Faulkner and Britton, 1960).

The appearance time and concentration curves of sodium fluorescein, ^{133}Xe on, and ^{131}I Rose Bengal in hepatic and azygos vein blood following instillation of these materials into the jejunum were determined as follows. An infant-size Leonard tube with a coiled spring stylet manufactured by Phalen of Minneapolis was passed under fluoroscopy into the upper jejunum. First, 0.25 g. sodium fluorescein in 5 ml. of water was injected down the Leonard tube followed by a further 10 ml. of water as a flushing dose. Samples of blood, 0.5 ml., were taken from both venous sites at 5, 10, 20, 30, 40, 50, and 60 minutes. From each sample 0.1 ml. of serum was obtained and diluted with 10 ml. of weak base and read in a photofluorimeter. Next 0.3 mc of ^{133}Xe on was dissolved in 5 ml. of saline in a capped syringe. The syringe contents were then injected down the tube and followed by 10 ml. of saline as a flushing dose. The tube was clamped to prevent escape of gas. Samples of blood, each of 2 ml., were obtained in capped syringes from both sites at the same intervals as above. In the untreated dogs 2 ml. of femoral artery blood was obtained by puncture to check for the presence of ^{133}Xe on in the systemic arterial circuit. All samples were counted three times in a well scintillation counter at 80 KeV⁶ for a total of 10,000 disintegrations. One μc . of ^{131}I Rose Bengal containing approximately 10 μg . of Rose Bengal dye was injected down the tube and 2 ml. samples obtained from the hepatic and azygos veins at the intervals described were counted in a well scintillation chamber in a similar manner at 384 KeV.

The thoracic duct was dissected in the neck and the largest calibre polyethylene tube possible tied into the duct. The lymph was allowed to drain continuously at approximately 0.5 ml./per min. into gas-tight closed sample collectors which were replaced at 5, 20, 40, 60, 80, 100, and 120 minute intervals. The samples were counted in the well scintillation counter at 80 KeV for 10,000 disintegrations and then the volumes measured.

Lastly, 10-20 ml. of 50% sodium diatrizoate was injected forcibly by hand down the azygos catheter and radiographs were taken at five per second with a cassette changer in an attempt to outline the communications between the portal and azygos systems.

RESULTS

It was clear that in the 12 dogs with portal hypertension, the azygos vein pressures reflected the pressure changes in the portal vein and paralleled the pressures obtained in the hepatic wedge position. Despite the unusual nature of the portal hypertension, with its large arterial component, there was a surprising reduction in azygos and hepatic venous pressure following the intravenous injection of pitressin (Table I). As was expected from the

TABLE I
PRESSURES¹

	Portal Normotensives (mm. Hg)		Portal Hypertensives (mm. Hg)	
	Before Pitressin	After Pitressin	Before Pitressin	After Pitressin
Hepatic vein wedge	5 to 9	3 to 8	17 to 31	9 to 23
Vena azygos major	-2 to +5	-2 to +5	4 to 24	0 to 15

¹Each set of figures represents the range of determination in 12 dogs.

previous investigation of a young man with a spontaneous splenic arteriovenous fistula (Murray, Thal, and Greenspan, 1960), the blood from the azygos vein in the dogs with portal hypertension showed increased arterial oxygen content and saturation, but there was no such increase in the hepatic vein blood (Table II).

TABLE II
BLOOD OXYGEN CONTENT AND
OXYGEN SATURATION¹

	Portal Normotensives		Portal Hypertensives	
	Oxygen Content (vol. %)	Satur- ation (%)	Oxygen Content (vol. %)	Satur- ation (%)
Hepatic vein wedge	13.6 to 15.2	71 to 77	13.4 to 15.2	70 to 77
Vena azygos major	13 to 14.7	66 to 73	15.8 to 17.5	78 to 89

¹Each set of figures represents the range of determinations in 12 dogs.

Blood samples from venous sites in both groups of animals failed to show the presence of either catecholamines or serotonin. However, dogs on their normal diet of Purina dog chow, which contained an average of 52 g. of protein per day, showed a significant rise in blood ammonia levels in the azygos and hepatic veins when they had a collateral circulation. The rise was greater in the azygos samples.

TABLE III
CATECHOLAMINES, SEROTONIN, AND AMMONIA CONTENT OF AZYGOS AND HEPATIC VEIN BLOOD¹

	Portal Normotensives			Portal Hypertensives		
	Catecholamines	Serotonin	Ammonia (µg.%)	Catecholamines	Serotonin	Ammonia (µg.%)
Hepatic vein wedge	None	None	33-107	None	None	37-175
Vena azygos major	None	None	27-105	None	None	84-226

¹Each set of figures represents the range of determination in 12 dogs.

The arrival time and concentration of various indicator substances in the hepatic and azygos veins after instillation in the jejunum were first checked by small pilot studies in two dogs anaesthetized with pentobarbital. The abdomens were opened and 0.3 mc. of ¹³³Xenon and 1 µc. of ¹³¹I Rose Bengal respectively were injected directly through the jejunal wall with a 22 gauge needle. Samples of portal venous and femoral arterial blood for counting were obtained from the largest calibre polyethylene tubing which could be inserted in those vessels. From these studies it was evident that both substances were absorbed quickly. ¹³³Xenon was chosen for trial, because an indicator was required which did not undergo significant recirculation after its first passage through the lungs in the normal animals. That this was so was proven by the absence of significant activity in the femoral arterial samples. ¹³¹I Rose Bengal was also chosen because it seemed likely that the liver in normal animals might be able to extract the minute dose of the dye (as it reached the liver via the portal vein) and prevent its systemic circulation. One µc. of this material contains less than 10 µg. of dye. Activity from ¹³¹I should not then be detectable in the arterial circuit unless the ¹³¹I was released from the dye in the gut or during its passage through the gut wall. The pilot study showed no significant activity above background in the femoral artery sample. Sodium fluorescein was chosen as the third indicator as patterns of arrival time and concentration had already been established in portal and systemic venous blood (Blondheim and Kunkel, 1950).

Since it has been observed that there is an increase in the flow of thoracic duct lymph in portal hypertension (Dumont and Mulholland, 1960), it seemed reasonable to expect some of the indicator materials to appear in that system. A pilot study consisting of the direct injection of ¹³³Xenon into the jejunal lumen as described above plus the collection of lymph from the thoracic duct confirmed this likelihood.

Twelve normal dogs and 12 dogs with well-established portal-azygos collaterals were studied after instillation into the jejunum through the Leonard tube of the three materials discussed. Following instillation of ¹³³Xenon, in the normal

dogs activity appeared in the hepatic vein samples, but not in femoral artery or azygos samples. In the portal hypertensive animals the activity appeared in high concentration in the azygos vein, but the rise in the hepatic vein activity was smaller and later than in the normal animals, presumably due to the surgical narrowing of the portal veins (Fig. 1). No activity was noted in the femoral artery after instillation of ¹³¹I Rose Bengal. No activity appeared in the hepatic azygos vein samples in normals. In the portal hypertensive group, activity appeared both in the azygos and femoral artery samples (Fig. 2).

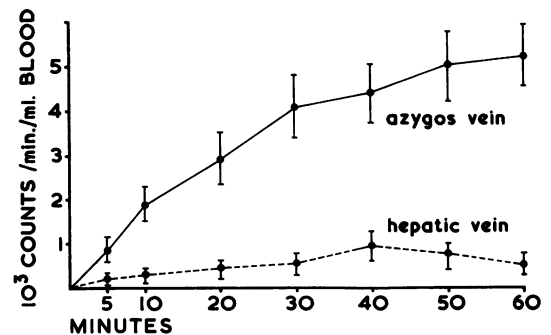


FIG. 1. Activity in azygos and hepatic veins of portal hypersensitive dogs after instillation of 0.3 mc. ¹³³Xenon into the jejunum. The vertical bars represent the maximum and minimum observations on 12 dogs.

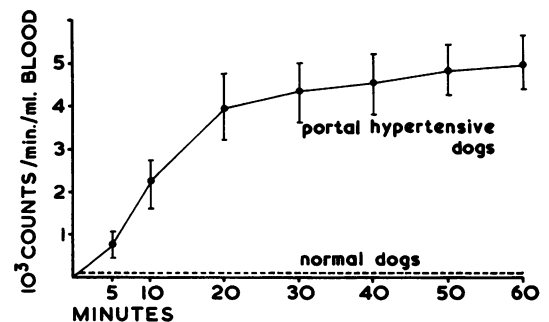


FIG. 2. Activity in azygos blood after instillation of 1 µc. ¹³¹I Rose Bengal into jejunum. Vertical bars represent maximum and minimum observations on 12 dogs.

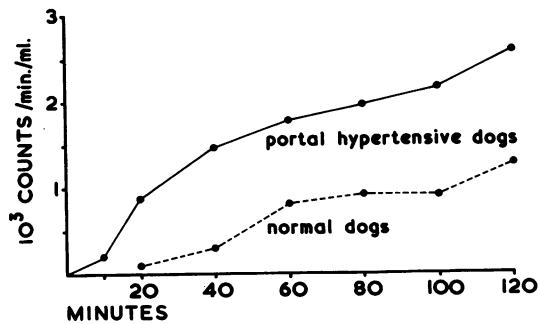


FIG. 3. Activity in thoracic duct lymph after instillation of $^{133}\text{Xenon}$ into the jejunum. Each point represents the mean of determinations in 12 dogs.

The earlier appearance time and higher concentration of sodium fluorescein was characteristic of the portal hypertensive dogs when compared with normals (Fig. 3). In the thoracic duct study the $^{133}\text{Xenon}$ appeared earlier and in higher concentrations in the experimental animals than in normals (Fig. 4). Three animals only were studied by this method. Retrograde venography of the azygos system failed to outline the communication of the azygos and portal systems.

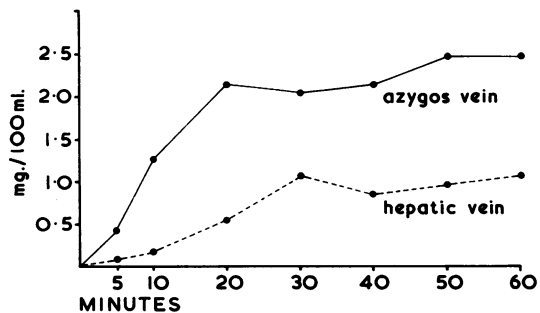


FIG. 4. Blood levels of sodium fluorescein after instillation of 0.25 g. into the jejunum. Each point represents the mean of determinations in three dogs.

DISCUSSION

The type of portal hypertension in the dogs under study was unusual because of the large shunt from splenic artery to splenic vein. This procedure was necessary to establish good collateral circulation (Tamiya and Thal, 1960), but as a consequence a large amount of highly saturated blood entered the azygos system. It is known, however, that portal venous blood in normal humans has a greater

oxygen content than other peripheral veins (Smythe, Fitzpatrick, and Blakemore, 1951) and that this content is even higher in patients with portal hypertension from Laennec's cirrhosis (Longmire, 1957). This latter phenomenon may be due to a flow of arterial blood from the hepatic, retrogradely into the portal, vein (Child, 1957). It appears likely then that the finding of a higher than normal oxygen content in the azygos system in humans may be presumptive evidence of portal-azygos collaterals with portal hypertension.

Since the end azygos vein pressures in this study paralleled the hepatic vein wedge pressure this determination might be useful in cirrhosis in gauging portal venous pressure. It is true that there must be a large arterial contribution to the azygos pressure in these experimental animals but the significant drop in pressure after injection of pitressin suggests that there is also a strong venous component to the pressure rise. Furthermore, in the patients with portal cirrhosis we have studied to date, there is the same parallel between hepatic wedge and end azygos pressure that is seen in the dog.

Failure to detect catecholamine and serotonin in hepatic and azygos samples suggested that either these substances were not produced excessively in the portal system in acquired portal hypertension, or that the methods used were too insensitive to detect them. It was not surprising to find increased levels of ammonia in dogs with collaterals and it seemed likely that the difference between the hepatic vein and the azygos samples was an index of the amount of shunting through the azygos.

The appearance time and concentration curves of the three indicators at the respective sampling sites provided evidence that it is possible with azygos catheterization and jejunal intubation to determine the presence and crudely quantitate the amount of collateral flow from the portal system into the azygos system.

SUMMARY

A study was conducted on dogs with experimentally produced portal-systemic collaterals and portal hypertension to decide if azygos vein catheterization was a useful approach to the study of portal hypertension with collateral flow. Azygos catheterization was found to be both a practical procedure and a reliable indicator of portal pressure. Increased oxygen content of the azygos blood appeared to be a sign of collateral flow. No increase in catecholamine or serotonin in azygos blood could be found but the ammonia content was higher in the animals with collateral flow than in control animals. Using indicator substances instilled into the jejunum the

collateral circulation could be readily detected and quantitated crudely by sampling from the azygos and hepatic veins. It would appear that these methods are entirely applicable to humans and preliminary studies in patients with cirrhosis support this hypothesis.

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