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Phenylephrine-Induced Hyperkalemia: Role of the Liver (40800)

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Epinephrine, which stimulates both α- and β-receptors, causes hyperkalemia, which is due mainly to release of potassium from the liver (1–5). In studies by O'Brien *et al.* (6), systemic injections of the α-receptor agonist, phenylephrine, produced arterial hyperkalemia. Todd and Vick (7) found that continuous systemic infusion of phenylephrine increased the arterial plasma potassium concentration, [K]. This increase was small, slowly developing, and prolonged relative to that caused by epinephrine. Other investigators found that systemic infusion or injection of phenylephrine into the hepatic artery in a dog liver preparation caused a release of potassium from the liver (8).

It has been proposed that the prolonged increase of arterial plasma [K] due to phenylephrine, which contrasts with the transient hyperkalemia resulting from epinephrine, may be caused by an accompanying α-receptor-mediated vascular constriction which, unopposed by any β-receptor agonism, could reduce liver blood flow so that washout of released potassium is delayed (7). The present study was designed to investigate this possibility by quantifying the effects of intraportally infused phenylephrine on exchange of potassium between the liver and plasma in the dog.

Methods. Dogs weighing between 15.5 and 32.0 kg, not chosen for sex or breed, were anesthetized with pentobarbital sodium, 30 mg/kg iv. A cuffed endothracheal tube was inserted, and respiration was controlled by positive-pressure ventilation. Lead II of the ECG and the carotid arterial pressure were recorded. A midline laparotomy was performed. The spleen was compressed and surgically removed to prevent any fluctuations in hematocrit due to sequestration or extrusion of red blood cells during the experimental procedure. A double-lumen catheter was introduced through a splenic vein. The end of the catheter was placed into the portal vein and advanced to a point just proximal to the liver; its position was confirmed by digital palpation. One lumen was used for infusion of phenylephrine, and the other was used to collect portal vein blood samples. To prevent renal excretion of potassium, each renal artery, vein, and ureter was occluded with a mass ligature. A catheter was introduced through the right external jugular vein and guided by palpation to lodge in a hepatic vein. A nonoccluding catheter was placed in the left femoral artery for sampling arterial blood.

The portal vein and the hepatic artery were isolated for subsequent placement of flowmeter probes. Lymphatic vessels and adipose connective tissue were cleared from the portal vein, and the common hepatic artery was dissected out of its enveloping sheath of nerve fibers. The gastroduodenal artery was ligated to assure that only arterial flow to the liver was measured. Nonoccluding square-wave, electromagnetic flow probes (Carolina Medical Electronics, Inc.) were placed on the previously dissected portal vein and common hepatic artery. Prior to use, each flow probe was calibrated by placing it around a dog blood vessel, *in situ*, and forcing blood through the vessel at measured rates.

Following surgery, a 30-min period was allowed for stabilization. In six dogs, after a subsequent 30-min control period, *l*-phenylephrine HCl was infused at a rate of 1.5 μg/kg body wt/min, calculated as the base, into the portal vein for 30 min, using a

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syringe-driver pump. The total volume of solution administered was kept constant at 6.9 ml.

Samples of blood were collected simultaneously from the femoral artery, the portal vein, and the hepatic vein, and blood flows in the portal vein and the common hepatic artery were recorded, during the control period, the infusion period, and for 30 min after the infusion was finished. The hematocrit of each blood sample was determined and corrected for the amount of plasma trapped in packed cells (9). The samples were placed in heparinized tubes and centrifuged immediately. Plasma [K] was measured using an internal-standard flame photometer. Based on the assumption of a blood volume equal to 7.9% of body weight (10), no more than 8% of the blood of any animal was removed during any experiment.

In the present experiments, exchange of potassium between the liver and plasma was calculated as follows:

$$\begin{aligned}\text{liver-plasma K exchange (mEq/min)} &= [\mathrm{HV}[\mathrm{K}] \times (1 - \mathrm{HV}hct) \times \mathrm{HV}bf] \\ &- \{[\mathrm{PV}[\mathrm{K}] \times (1 - \mathrm{PV}hct) \times \mathrm{PV}bf] \\ &+ [\mathrm{HA}[\mathrm{K}] \times (1 - \mathrm{HA}hct) \times \mathrm{HA}bf]\},\end{aligned}$$

where HV is hepatic vein, [K] is plasma potassium concentration (mEq/liter), *hct* is corrected hematocrit, *bf* is blood flow (liter/min), PV is portal vein, and HA is hepatic artery. An exchange greater than 0 indicates release of potassium by the liver; an exchange less than 0 indicates uptake. By assuming that arterial plasma [K] and arterial hematocrit are uniform throughout the body, samples obtained from the femoral artery were used to determine hepatic arterial plasma [K] and hematocrit. It was assumed also that blood flow in the hepatic vein is the sum of the flow in the portal vein and the hepatic artery. To determine significance, Student's *t* test for paired data was applied. For each set of data, the mean value of the data points in the control period (minutes −30, −20, −10, and 0) was paired with the experimental data point being considered. A *P* value less than 0.05 was considered to indicate significance.

Results. In six dogs that were infused intraportally with phenylephrine, mean arterial blood pressure and heart rate did not change significantly. The temporal courses of hepatic arterial blood flow and portal venous blood flow are illustrated in Fig. 1. Hepatic arterial blood flow decreased significantly during minutes 2 to 30 and returned to control level after the infusion was completed. Portal venous blood flow did not change significantly.

Portal venous, arterial, and hepatic venous plasma [K] are shown in Fig. 2. Portal venous plasma [K] increased significantly at minutes 4 to 10. Arterial plasma [K] was elevated significantly at minutes 4, 6, and 20. Plasma [K] in the hepatic vein increased significantly at minutes 6 and 20.

Figure 3 shows exchange of potassium between the liver and the plasma. The liver released potassium into the plasma during the period of infusion; the release was statistically significant at minute 6.

Discussion. In the present experiments, mean arterial blood pressure did not change during the infusion of phenylephrine. This drug usually increases mean arterial pressure, and other investigators have reported significant increases of pressure when infusing phenylephrine systemically at rates similar to that used here (11). When a drug is infused locally into a particular vascular bed, blood pressure could be changed by several different factors. The drug may act directly on the local vascular bed, which sometimes will be reflected in the systemic blood pressure. Systemic blood pressure also may be affected by a portion of the infused drug which passes through the local

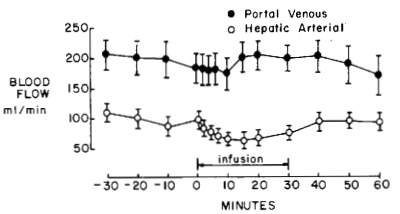

FIG. 1. Effect of constant infusion of phenylephrine into the portal vein on hepatic arterial and portal venous blood flow. Infusion at a rate of 1.5 μg/kg/min began at minute 0 and ended at minute 30. Mean ± SE of six experiments.

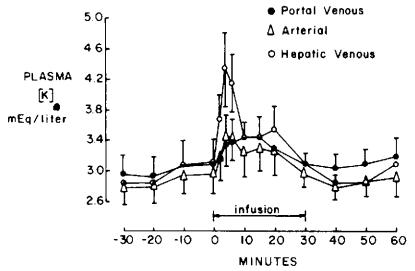

FIG. 2. Effect of constant infusion of phenylephrine into the portal vein on portal venous, arterial, and hepatic venous plasma [K].

vascular bed and recirculates. It is possible that, in the present experiments, the amount of phenylephrine which escaped inactivation by the liver was insufficient to change arterial pressure.

The plasma [K] during the control period in these experiments was lower than normal, perhaps due to background sympathetic activity exaggerated by the surgery or to the use of pentobarbital as an anesthetic, as explained previously (12).

The phenylephrine-induced hyperkalemia which occurred in the present experiments is consistent with the results of previous studies (6–8). Phenylephrine increased arterial plasma [K] less rapidly than epinephrine did in an earlier investigation (7) and the plasma [K] remained elevated for a longer period of time. In the present experiments, hepatic arterial blood flow was decreased significantly throughout the period of infusion. However, the egress of potassium from the liver was not prolonged, and the course of potassium release

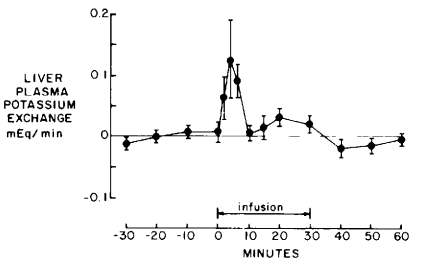

FIG. 3. Effect of constant infusion of phenylephrine on exchange of potassium between liver and plasma. Exchange greater than 0 indicates release of potassium by the liver; exchange less than 0 indicates uptake.

was similar to that occurring in other studies during infusion of epinephrine (13). The prolonged increase in arterial plasma [K] was probably due simply to a lack of uptake of potassium by the liver. Other data show that phenylephrine does not affect significantly potassium exchange in skeletal muscle (14). It is not known whether other tissues play a role in phenylephrine-induced hyperkalemia, or not. The increase of arterial plasma [K] during intraportal infusion of phenylephrine in the present experiments was similar to that seen during systemic infusion of the drug in a previous investigation (7). Thus, it appears that the liver may be the major, if not the sole, source of potassium during phenylephrine-induced hyperkalemia.

The decrease of hepatic arterial blood flow during the infusion may have been due to a direct effect of phenylephrine to increase vascular resistance in the liver, and the primary site of this regulation may be within the hepatic sinusoids. Hirsch *et al.* (15) could find no evidence that hepatic venous sphincters limited hepatic arterial blood flow. The pressure gradient between hepatic arterioles and sinusoids makes it unlikely that material infused intraportally could reach the smooth muscle of hepatic arterioles. It has been suggested that a sphincter mechanism, responsive to α-receptor agonists, may be present at the point of entry of the arterioles into the sinusoids (16).

In the present study, it was assumed that the volume of blood flow in the hepatic vein is equal to the sum of the flows in the hepatic artery and the portal vein. In contrast to findings obtained by Guntheroth and Mullins (17) in the conscious dog, other studies would suggest that the liver has a significant role as a blood reservoir (18–23). Greenway and Lautt (19) found that norepinephrine decreased hepatic blood volume in the cat. The volume became steady after a few minutes, and no further changes occurred during continued infusion of the drug. It is possible that, in the present experiments, phenylephrine may have caused a change in hepatic blood volume at some point during the infusion. In this situation, hepatic venous blood flow

might not equal exactly the sum of hepatic arterial and portal venous blood flows.

The exact mechanism by which α-receptor agonism causes the release of potassium from the liver is unknown. It is possible that α agonists alter the permeability of hepatic cells to certain ions. If permeability to potassium were to rise, with other factors remaining constant, the membrane potential should become more negative. This effect has been observed in guinea pig liver with norepinephrine (24, 25) and the more selective α agonists phenylephrine, amidephrine, and methoxamine (26). The results of other investigators have suggested that activation of α receptors in the liver may cause a transient release of calcium which could trigger an increase in membrane permeability to potassium (27). Barnabei *et al.* (28) suggested that efflux of potassium in isolated rat liver cells caused by epinephrine may be due to inhibition of active transport of potassium, which probably is mediated by cyclic AMP. It has been reported that α-receptor stimulation inhibits synthesis of cyclic AMP (29).

Summary. Constant infusion of phenylephrine into the portal vein in the dog produced hyperkalemia which was prolonged relative to previously reported epinephrine-induced hyperkalemia. The liver released potassium into the plasma. Although hepatic arterial blood flow was decreased, the egress of potassium from the liver was not sustained. The results indicate that the prolonged nature of phenylephrine-induced hyperkalemia is not due to a delayed washout of potassium from the liver.

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