Influences of Splanchnic Blood Flow on Epinephrine-Induced Hyperkalemia[1] (37639)

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An intravenous injection of epinephrine releases K^+ from the liver and consequently increases the K^+ concentration of systemic arterial blood (1–3). Initially it was proposed that this action of epinephrine was mediated by alpha adrenergic receptors, (4, 5). However, a subsequent report demonstrated that beta adrenergic antagonists could attenuate this arterial hyperkalemia (6). Beta receptor blockade could exert this effect directly by interfering with the release of K^+ from the liver, or indirectly by reducing hepatic blood flow. In the present study we have demonstrated that after propranolol epinephrine produces a substantial decrease in hepatic blood flow, an occurrence which could, in part, account for the alteration of the epinephrine-induced hyperkalemia by beta adrenergic blockade.

Methods. The experiments were performed on 18–20 kg male and female mongrel dogs in which electromagnetic flow probes were chronically implanted on the celiac and superior mesenteric arteries. The animals were anesthetized either with sodium pentobarbital (30 mg/kg, iv), or with a cyclopropane/oxygen mixture sufficient to produce partial intercostal paralysis (30%/70%). The animals were ventilated, through a cuffed endotracheal tube, with an Air Shields ventilator at a rate and depth adequate to maintain their arterial pCO_2, as measured with an Instrumentation Laboratories pH/Blood Gas Analyzer, within the physiological range (35–38 mm Hg). One series of experiments utilized dogs which were unanesthetized. In these animals local anesthesia was used at the sites of skin incisions.

A basket-tipped cardiac catheter was introduced into the external jugular vein and placed fluoroscopically in an hepatic vein. Routinely it was positioned 2–3 in. into the left medial lobe of the liver. The catheter was attached to a Paley 7-place manifold to allow serial sampling of hepatic venous blood. Serial sampling of systemic arterial blood was accomplished through a second manifold attached to a 20-gauge needle inserted percutaneously into the right femoral artery. Arterial blood pressure was recorded with a Statham strain gauge attached to a needle in the left femoral artery. Celiac and superior mesenteric blood flows were measured with a Biotronix flowmeter. Zero flow was obtained with chronically implanted inflatable occluders. The arterial blood pressure, lead II electrocardiogram, and splanchnic flows were recorded on a Gilson polygraph.

The epinephrine injections (0.01 mg/kg in 5 ml of saline) were made over a 45-sec period with a Sage Infusion Pump attached to a needle placed in the left radial vein. The beginning of this injection period is taken as time zero in all subsequent descriptions and discussions. A control blood sample was withdrawn from the artery and from the hepatic vein just prior to the start of the epinephrine injection. Sequential 3-ml samples then were withdrawn simultaneously from the artery and vein at a rate of 1 ml/5 sec. Seven samples were withdrawn in this manner, starting 25 sec and ending 130 sec after the beginning of the epinephrine injection. Three additional samples were taken: 150–165 sec, 165–180 sec, and 225-240 sec after the start of the injection period. All blood samples were withdrawn in heparinized syringes. The blood was centrifuged immediately and the plasma analyzed for K^+ photometrically. Samples

[1] This study was supported by Training Grant 5T1HE5375 from the National Heart and Lung Institute and by the Wisconsin Heart Association.

taken from the artery and vein just prior to the epinephrine injection and 100 sec afterwards were analyzed for pCO_2 and pO_2.

Once a control series of samples was obtained in the manner just described, the beta adrenergic blocking agent propranolol was administered. A 0.5 mg/kg dose was dissolved in 10 ml of saline and injected iv. Twenty min later the epinephrine injection was repeated and a second series of blood samples was obtained. On subsequent occasions, with at least 1 wk intervening, the animal was subjected to the same protocol with the alternate anesthetic, or unanesthetized. The data obtained before and after beta blockade were compared using Student's t test for the difference between the means of paired observations.

Results. Pentobarbital anesthesia. Epinephrine injection resulted in maximum increases in arterial plasma K^+ of 2.56 mEq/liter (3.55 ± 0.28 to 6.11 ± 0.71) and in hepatic venous K^+ of 6.30 mEq/liter (3.56 ± 0.31 to 9.86 ± 0.67) (Fig. 1). The peak arterial concentration occurred during the 85–100-sec sampling interval and the peak venous within the 55–70-sec interval. By the 225–240-sec interval arterial K^+ was at its control level while hepatic venous was 1.09 mEq/liter below its control. After propranolol (Fig. 1) the maximum epinephrine induced rise in arterial K^+ was only 1.00 mEq/liter (3.39 ± 0.26 to 4.39 ± 0.55) which was a significant reduction ($p < 0.01$) when compared to the response elicited by epinephrine before beta adrenergic blockade. Hepatic venous K^+ increased a maximum of 5.47 mEq/liter (3.35 ± 0.27 to 8.82 ± 0.89) which, although 14% less than before propranolol, was not a significant reduction. The arterial K^+ increased very gradually and the peak was not reached until the 150–165-sec sampling interval. The peak hepatic venous K^+ concentration however was reached within 85–100 sec after the start of the epinephrine injection. At the 225–240-sec sampling interval arterial K^+ was not significantly different from that which was present prior to the epinephrine injection while hepatic venous K^+ was 1.04 mEq/liter lower than its control level.

Before propranolol (Fig. 2), epinephrine increased celiac artery flow from 290 ± 36 ml/min to a mean of over 600 ml/min for 40–100 sec after the start of the injection. Over the subsequent 140 sec flow gradually declined to the pre-injection level. Superior mesenteric flow fell abruptly from 595 ± 102 ml/min to 290 ± 68 ml/min at 25 sec,

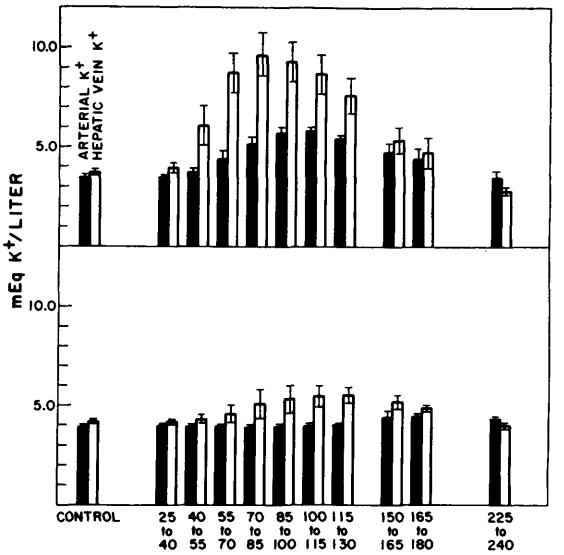

FIG. 1. Effects of epinephrine (0.01 mg/kg) on arterial and hepatic venous K^+ before (above) and after (below) propranolol (0.5 mg/kg) in 6 dogs anesthetized with Na pentobarbital.

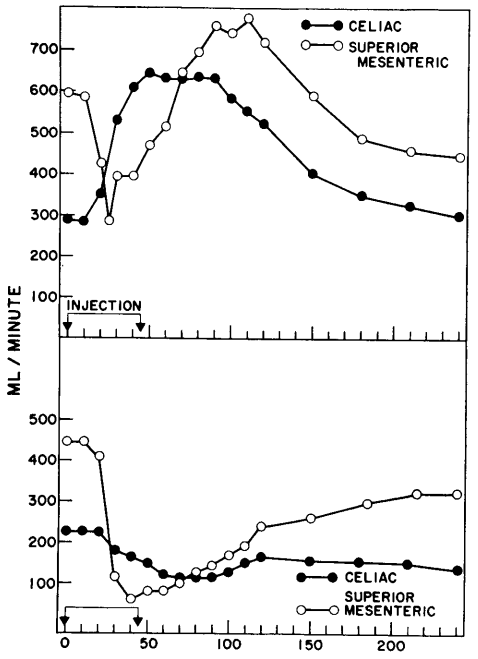

FIG. 2. Effect of epinephrine (0.01 mg/kg) on celiac (closed circles) and mesenteric artery (open circles) flows before (above) and after (below) propranolol (0.5 mg/kg) in 6 dogs anesthetized with Na pentobarbital.

then returned to its control level during the subsequent 35 sec and remained at or above that level for an additional 90 sec. After propranolol celiac and superior mesenteric artery flows both declined from their control values. The total resting flow in these two arteries was 885 ml/min before propranolol and 675 ml/min after. With the subsequent injection of epinephrine only decreases in flow were observed in both beds. During the intervals of maximum hepatic venous K^+ concentration the total of celiac and mesenteric flows was 1100–1200 ml/min before propranolol and 200–300 ml/min after. There also was a concomitant widening of the hepatic arteriovenous pO_2 difference following epinephrine administration after beta blockade.

Cyclopropane anesthesia. Following epinephrine administration the observed increases in K^+ above resting values were 2.38 mEq/liter (3.44 ± 0.22 to 5.82 ± 0.22) in arterial plasma and 5.91 mEq/liter (3.74 ± 0.16 to 9.65 ± 1.26) in hepatic venous plasma (Fig. 3). The peak arterial concentration occurred during the 85–100-sec sampling interval, the peak venous within the 70–85-sec interval. By the 225–240-sec interval arterial K^+ had returned to its control value while hepatic venous was 1.00 mEq/liter below its resting level. After propranolol the maximum epinephrine induced rise in arterial K^+ was only 0.48 mEq/liter (3.92 ± 0.12 to 4.40 ± 0.31) which was a significant reduction ($p < 0.01$) in response compared to that occurring before propranolol. In addition, the maximum increase in hepatic venous K^+ was significantly less ($p < 0.01$) after propranolol (4.21 ± 0.16 to 5.51 ± 0.44) than before. Furthermore the peak arterial concentration was not reached until the 150–165-sec interval and the peak hepatic venous was delayed until the 110–115-sec sampling interval. At the 225–240-sec sampling interval both arterial K^+ and hepatic venous K^+ were close to their resting values.

Before propranolol celiac artery flow increased from 233 ± 83 to 468 ± 122 ml/min by 50 sec after the start of epinephrine injection (Fig. 4) and slowly returned to its resting level during the ensuing period of observation. Mesenteric artery flow fell from 416 ± 109 to 63 ± 31 ml/min at 30 sec then over the subsequent 60 sec returned to control level where it remained throughout the period of the study. The total of the resting celiac and mesenteric artery flows before epinephrine was approximately 650 ml/min during cyclopropane as compared to 885 ml/min during pentobarbital anesthesia. After propranolol the total of resting celiac and mesenteric artery flows declined significantly ($p < 0.01$) to approximately 455 ml/min. With the subsequent injection of epinephrine celiac artery flow declined slightly while superior mesenteric artery flow fell from 316 ± 67 to 155 ± 29 ml/min at 40 sec and remained significantly below control for 150 sec after the start of epinephrine injection. During the intervals of maximum hepatic venous K^+ concentration the total of celiac and mesenteric flows was approximately 650 ml/min before propranolol and 325 ml/min afterward. This difference was statistically significant ($p < 0.01$). Furthermore, after beta blockade under cyclopropane anesthesia epi-

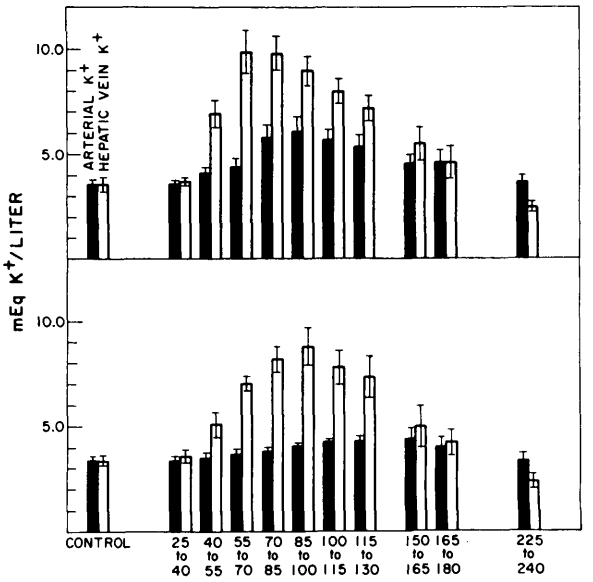

FIG. 3. Effect of epinephrine (0.01 mg/kg) on arterial and hepatic venous K^+ before (above) and after (below) propranolol (0.5 mg/kg) in 6 dogs anesthetized with cyclopropane.

nephrine caused a widening of the hepatic arteriovenous pO_2 difference of more than twice that seen during pentobarbital anesthesia.

No anesthesia. Three dogs were used in this study. The findings were similar to those reported when the animals were anesthetized with pentobarbital. The maximum epinephrine induced rise in arterial K^+ was 1.74 mEq/liter (3.81 ± 0.01 to 5.55 ± 0.04) and 6.41 mEq/liter (3.62 ± 0.21 to 10.03 ± 1.03) in hepatic venous blood. The respective peaks occurred during the 85–100- and 70–85-sec sampling intervals. By the 225–240-sec interval arterial K^+ had returned to its resting value while hepatic venous K^+ had fallen 1.13 mEq/liter below its initial value. After propranolol epinephrine elevated arterial K^+ a maximum of 0.67 mEq/liter (3.57 to 0.30 to 4.24 ± 0.25) with the peak reached during the 100–115-sec interval. The hepatic venous K^+ increased a maximum of 3.58 mEq/liter (3.77 ± 0.19 to 7.35 ± 1.32) with the peak occurring in the 70–85-sec sampling interval. By the 225–240-sec interval arterial K^+ had returned to its resting value while hepatic venous K^+ had fallen 1.58 mEq below its initial value.

Splanchnic flows were measured in one dog. Before propranolol celiac flow was 425 ml/min and superior mesenteric artery flow was 595 ml/min. The total of these flows at the time of the maximum rise in hepatic venous K^+ was 1300 ml/min. After propranolol celiac flow was 400 ml/min and superior mesenteric artery flow was 710 ml/min. The total of these flows at the time of maximum rise in hepatic venous K^+ was 425 ml/min. Both before and after beta blockade the total splanchnic blood flows during the period of maximal hepatic K^+ uptake were not significantly different from the resting values.

Discussion. While the reports by Gutgesell *et al.* (6) and by Todd and Vick (7) demonstrated that propranolol substantially reduced the rise in arterial K^+ concentration consequent to iv epinephrine administration, they lacked evidence that there was an actual pharmacological blockade of the mechanism governing the release of hepatic K^+. The present report demonstrates that this result was due, at least partially, to alterations in splanchnic blood flow following beta blockade. Such a finding is hardly surprising in light of the well documented evidence

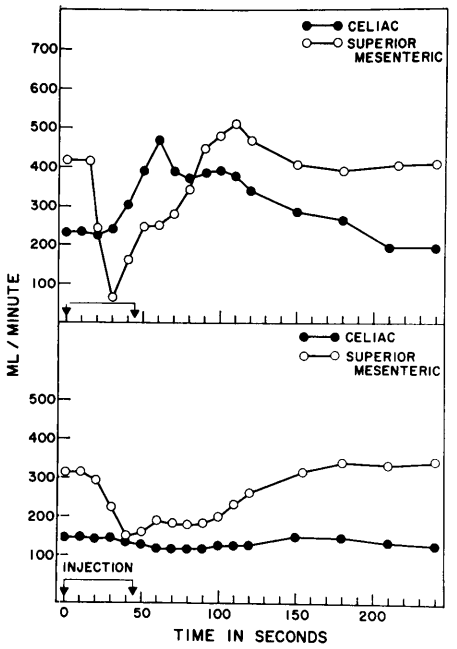

FIG. 4. Effect of epinephrine (0.01 mg/kg) on celiac (closed circles) and mesenteric artery (open circles) flows before (above) and after (below) propranolol (0.5 mg/kg) in 4 dogs anesthetized with cyclopropane.

that this vasculature is richly provided with adrenergic receptors (8, 9).

Under sodium pentobarbital anesthesia, the epinephrine induced rise in hepatic venous K^+ after propranolol was 86% of that seen in the control experiments. This fact, coupled with the observation that the peak in hepatic venous K^+ occurred approximately at the same time before and after propranolol, suggests that under these conditions beta blockade did not seriously interfere with the delivery of epinephrine to the liver or with the release of K^+ from the hepatic cells. The significant reduction in the epinephrine induced rise in arterial K^+ after propranolol combined with the marked delay before the peak concentration was reached suggest that the K^+ released from the liver entered the circulation much more slowly. The observed changes in splanchnic blood flow are in agreement with this suggestion. The widening of the hepatic arteriovenous pO_2 difference seen in these experiments further indicates reduced hepatic perfusion when epinephrine was given following beta blockade.

Under cyclopropane anesthesia epinephrine administration after propranolol resulted in a significant reduction in the peak rises of both arterial and hepatic venous K^+. Not only did splanchnic flow fall to very low levels at the time of hepatic K^+ release but the resting flows after beta blockade were considerably below their values prior to administration of the blocking agent. The combination of cyclopropane anesthesia and beta adrenergic blockade, both of which individually reduce splanchnic flow, apparently decreased hepatic inflow to such a level that the delivery of epinephrine to the liver was somewhat impaired.

These experiments also bear upon the question of the delayed hypokalemia which normally follows the initial epinephrine induced hyperkalemia. Craig and Honig (10) demonstrated the delayed uptake of K^+ by the liver following its initial release, and suggested that both phenomena depend upon the activation of a single adrenergic receptor. Todd and Vick (7) suggested that the uptake was due to the activation of beta adrenergic receptors as they observed only a slow increase in arterial K^+ when epinephrine was infused after beta blockade. Further, they saw only hypokalemia when isoproterenol was infused. Massara *et al.* (11) reported that propranolol prevented the delayed hypokalemia following epinephrine injections in man. In the present experiments, the hepatic venous samples obtained during the 225–240-sec interval were coincident with the period of maximal uptake of K^+ by the liver. During sodium pentobarbital anesthesia the delayed fall in the hepatic venous K^+ was not affected by beta blockade. In the unanesthetized animals the maximum fall in hepatic venous K^+ was actually greater after propranolol. Under cyclopropane our sampling procedures were not continued long enough to detect the hypokalemic phase after propranolol. These observations are not in concert with the view that the uptake of K^+ by the liver is a response mediated by beta adrenergic receptors.

Summary. The effect of beta blockade on epinephrine induced hepatic K^+ mobiliza-

tion was examined by measuring hepatic arteriovenous K^+ differences and splanchnic blood flow following epinephrine injections before and after administration of propranolol.

The results demonstrated that alterations in splanchnic blood flow significantly modify the epinephrine-induced systemic hyperkalemic response either by reducing liver perfusion during the period of hepatic K^+ efflux or by diminishing the amount of epinephrine delivered to that organ. It was evident that using systemic arterial K^+ concentrations as an index of hepatic K^+ movements is inadvisable. To assess adequately the ability of an adrenergic agonist to mobilize hepatic K^+, or the ability of an antagonist to disrupt that process, measurements of hepatic effluent K^+ and splanchnic blood flow must be made. The present experiments do not support the contention that the adrenergically-induced movement of K^+ into or out of the liver depends upon the activation of beta receptors.

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Received May 7, 1973. P.S.E.B.M., 1973, Vol. 144.