Reduction in Portal Vein Blood Flow by Somatostatin

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SUMMARY

Intravenous somatostatin boluses produced striking diminution in portal vein blood flow in dogs (maximally 40–55%). This effect was of rapid onset, without observable changes in hepatic artery flow, systemic blood pressure, pulse or central venous pressure. The duration of action was short, but could be sustained by continuous intravenous infusion. These observations are consistent with an endocrine role of somatostatin in the regulation of nutrient balance.

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Following the isolation of somatostatin from hypothalamic extracts by Guillemin and his colleagues in 1972 and the demonstration of its potent growth hormone release-inhibiting action,[1] a variety of actions of this simple peptide have been recognized, including the inhibition of diverse exocrine and endocrine secretions.[2–7] In addition to its localization in the hypothalamus, somatostatin has been found to be present in diverse areas outside the hypothalamus, including the central nervous system,[8] stomach and small intestine,[9] and in the delta cells of the pancreatic islets.[10] These observations suggest extensive biologic importance beyond that associated with hypothalamic–pituitary function.

A hemodynamic action of somatostatin was suggested by Wahren and Felig.[11] Using indocyanine green (cardiogreen), they showed a 30% decrease in splanchnic blood flow after somatostatin infusion. This method determines total hepatic blood flow and estimates portal vein flow by assuming a flow ratio of 7 to 3 for portal vein to hepatic artery.[12] This technique cannot distinguish changes in flow in the hepatic artery from those in the portal vein. In this regard, studies of hepatic blood flow in the dog (J. Jaspan, unpublished observations), measuring flow with indocyanine green and electromagnetic flow probes simultaneously, have shown that although total hepatic blood flow values obtained by these two methods are similar, there may be widely differing proportions of the hepatic artery and portal vein components.

Recently, it has been suggested that somatostatin may be effective in the treatment of bleeding esophageal varices,[13] opening up new possibilities for the therapeutic uses of this peptide. Other studies,[14] however, have failed to support these findings, although a salutary effect of somatostatin has been noted in bleeding peptic ulcers.[15]

This report describes the effects of intravenous somatostatin boluses, alone or followed by constant intravenous infusions, on splanchnic blood flow. The results indicate a marked reduction in portal venous blood flow (maximally 40–55%), of rapid onset (30–60 s), following somatostatin boluses, yet no change in hepatic arterial flow, and support the suggestion that the use of this peptide in the control of esophageal variceal bleeding deserves a controlled clinical trial. The possible physiologic significance of this effect of somatostatin on portal blood flow is discussed.

MATERIALS AND METHODS

Mongrel dogs of both sexes, 14–28 kg, were observed for 1 wk before operation to ensure good general health. After an overnight fast, the animals were subjected to laparotomy, following pentobarbital anesthesia (30 mg/kg). The portal vein and hepatic artery were exposed and electromagnetic flow probes (Gould-Statham SP2202) of appropriate size were placed around each vessel. The portal vein probe was placed around the portal vein, approximately 2 cm before its bifurcation into right and left portal trunks and the hepatic artery probe, approximately 2 cm distal to the origin of the vessel from the celiac trunk, following ligation of the pancreaticoduodenal artery. Flow probes were chosen to produce approximately 15% constriction of the artery and 30% constriction of the vein, as determined to be appropriate by previously conducted experiments.[16] Before each experiment, the flow probes were calibrated in saline and, in each experiment, gave accurate linear and reproduc-

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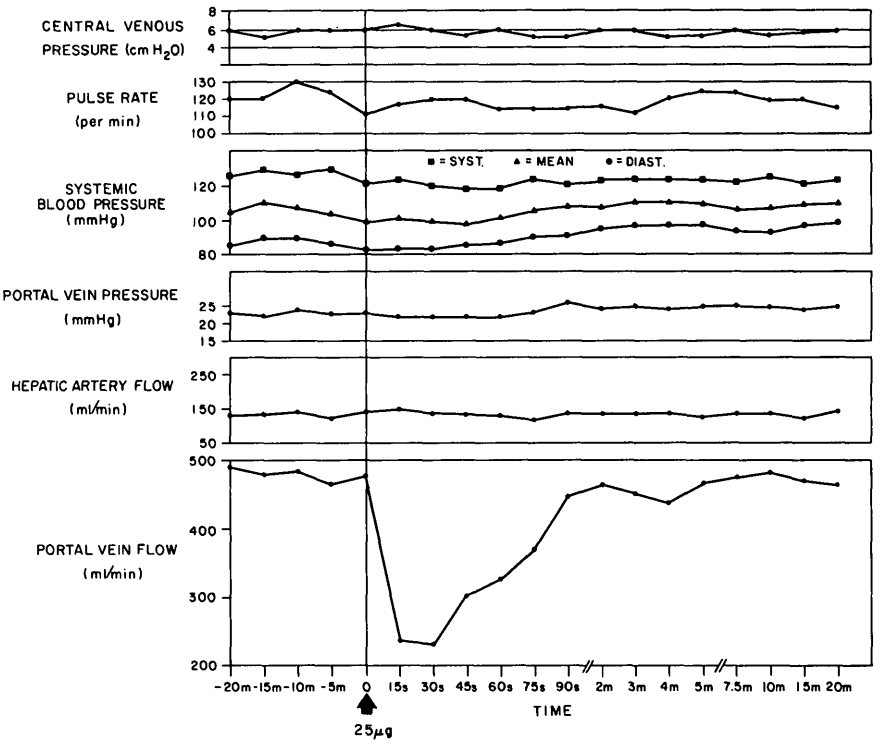


FIGURE 1. Representative responses of portal vein and hepatic artery blood flows, portal vein pressure, systemic blood pressure, pulse, and central venous pressure in a 23.5-kg dog in response to a 25-μg bolus dose of somatostatin.

ible readings (3.7 ± 1.3%) that were not affected by variations in the hematocrit between 24% and 48%. Pulse and arterial blood pressure were continuously monitored by means of a femoral artery line. Central venous pressure was monitored by means of an appropriately calibrated catheter inserted into the superior vena cava and portal vein pressure was measured by this latter method and also by means of the blood pressure-monitoring apparatus. Rectal temperature was continuously recorded. Intravenous fluid (0.9% saline) was infused via a left jugular vein catheter. Infusion was given at a rate consistent with maintaining constant central venous pressure and urine output (monitored by urethral catheterization). Blood glucose levels were monitored by a Beckman AutoAnalyzer and 5% dextrose given to prevent hypoglycemia in those experiments where somatostatin boluses were followed by a continuous infusion.[17]

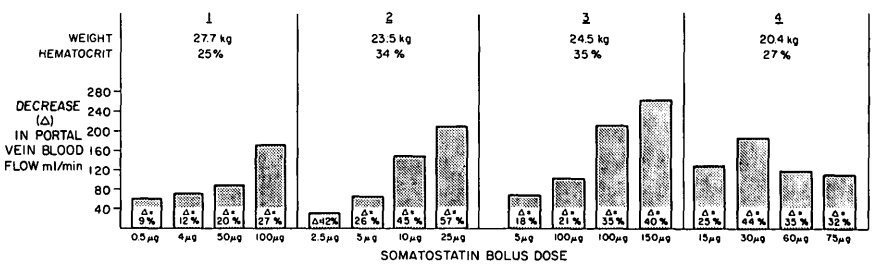
Experimental design. During an equilibration period of 30 min, portal vein and hepatic artery flows, blood pressure, pulse, and central venous pressures were recorded at 5-min intervals to ensure stability.

Boluses of varying amounts of somatostatin (cyclic form, Bachem, Inc., Torrance, California) were injected rapidly into the left jugular vein and recordings of the above parameters were made at intervals after completion of the injection (every 15 s for the first 1½ min, every 30 s for the next 4 min, and, thereafter, every minute). Following each injection, observations were made for a 20-min period. Thereafter, a period of 10–15 min was allowed for stabilization of blood flow before the next bolus. Saline or somatostatin boluses were given in random order. In selected experiments, the bolus was followed by constant infusion of somatostatin given by means of a Harvard pump, at rates of 80–400 ng/kg/min. In these latter experiments, flows continued to be recorded following termination of the infusion. In five individual experiments, responses to repeated injections of a given dose of somatostatin, on two or three occasions, were assessed. In four experiments, superior mesenteric artery blood flow was also measured.

RESULTS

Portal vein and hepatic artery blood flows vary considerably in individual dogs. Baseline portal vein and hepatic artery blood flows in these 12 dogs were, respectively, (mean ± SEM) 521 ± 53 ml/min (range 300–800) or 23.3 ± 1.8 ml/kg/min (range 13.7–34.2) and 172 ± 16 ml/min (range 95–270) or 7.7 ± 0.6 ml/kg/min (range 5.9–11.7). Following bolus injections, portal venous blood flow fell rapidly. The peak decrement occurred between 30 and 60 s, with measurable effects sometimes observed as early as 15 s. The maximal decline was 40–55% in some dogs. No significant changes in hepatic arterial blood flow, systolic blood pressure, pulse rate, or central venous pressure

FIGURE 2. Representative portal vein flow responses to different somatostatin bolus doses in four dogs (Δ = percentage decrease in portal vein blood flow).



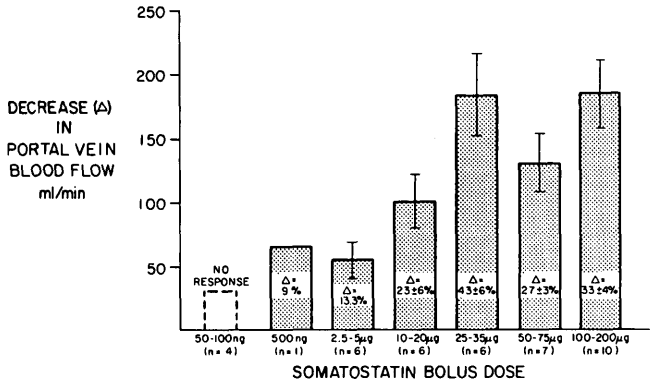


FIGURE 3. Overall dose response relationship in 12 dogs.

were detected in these experiments. Representative responses of these parameters in one experiment following a 25-μg bolus dose of somatostatin are shown in Figure 1.

Portal venous blood flow response to somatostatin doses varied considerably from animal to animal. However, a dose response relationship was observed. Dose response relationships in four animals are shown in Figure 2 and the overall dose response relationship observed in the 12 experiments is illustrated in Figure 3. No changes were detectable after boluses of 50–100 ng, although declines were generally detected at 500 ng. In some animals, however, the maximum response was observed at doses as low as 25 μg, while, in a single experiment, the maximal response was observed only at 150 μg. In selected experiments, repeating a given bolus of somatostatin showed reproducible results (Figure 4). Saline injections did not produce measureable changes in blood flows or any other parameters measured.

Somatostatin boluses were followed by constant infusion of somatostatin for periods of up to 2 h in eight experiments. Following the initial rapid decrement, portal vein blood flow returned to near basal levels at between 2 and 5 min and, thereafter, declined gradually, reaching a new plateau level 15–30 min after starting the infusion. This plateau was at a level approximately 50% above the nadir in portal flow and was sustained throughout the somatostatin infusion.

In four experiments, portal vein blood flow was measured on terminating the infusion and increased over a period of 5–20 min to levels approaching the presomatostatin flow rates (Table 1). In two dogs, measurement of superior mesenteric artery blood flow, following boluses of 25 and 100 μg in one and 100 μg in the other, showed no change, while in two other animals, boluses of 100 μg led to modest falls of 40–60 ml/min (14–20% decline).

DISCUSSION

This study demonstrates a considerable and consistent diminution of portal venous blood flow in response to intravenous somatostatin. The clinical implications of this finding are important. The results confirm the impression of Tyden et al.[13] that the circulatory effects of somatostatin appear to be limited to the splanchnic bed, with a dominant action on the portal vein, supporting their contention that somatostatin may prove beneficial in the treatment of bleeding esophageal varices. However, although Tyden et al. documented a 35% decrease in wedged hepatic venous pressure, we are unable to document any significant change in portal venous pressure as measured by two different methods. The reason for this difference is not clear, but it may be related to technical factors in the measurement of portal venous pressure. Nevertheless, since no serious side effects of somatostatin infusion have yet been noted and because no significant changes in other circulatory parameters or blood pressure were observed, this treatment appears to be without undue risk.

No data are available concerning the mechanism of the hemodynamic effects of somatostatin. However, the rapidity of onset of action suggests a direct effect on the portal vein, perhaps mediated through a calcium-dependent mechanism. In this regard, somatostatin may have a direct action on smooth muscle in other sites. Thus, we observed that following a somatostatin bolus, urinary flow rapidly increased such that the volume of urine for the 5-min period following the somatostatin bolus was consistently 5- to 10-fold greater than the volume over the 5 min immediately before the bolus. This observation might also have some clinical relevance.

One possible explanation for a decrease in portal blood flow in response to somatostatin is a simultaneous decrease in splanchnic inflow of blood. In an attempt to address this

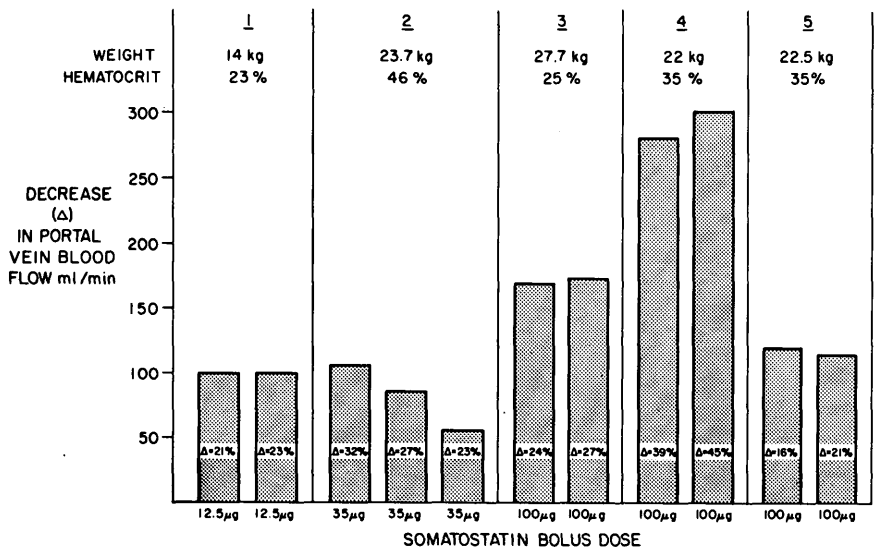


FIGURE 4. Portal vein blood flow responses to repeated injection of a given bolus dose of somatostatin in five dogs.

TABLE 1
Portal vein blood flow in response to (1) somatostatin bolus, followed by (2) constant intravenous somatostatin infusion, followed by (3) cessation of infusion

				Portal vein blood flow					
				Nadir (1)		Plateau on infusion (2)		Increase on stopping infusion (3)	
		Somatostatin dose							
Exp. no.	Dog wt (kg)	Bolus (μg)	Infusion (ng/kg/min)	Δ: ml/min	% decrease	Δ: decrease below basal (presomatostatin) flow (ml/min)	% decrease below basal flow	Δ: ml/min	% increase above flow during infusion (2)
1	23.7	35	160	105	32	60	18	—	—
2	27.7	100	400	170	24	70	10	90	17
3	23.5	25	160	210	57	100	27	—	—
4	23.5	10	80	150	45	70	21	—	—
5	22.2	25	200	295	56	210	40	90	25
6	22	100	200	280	39	145	21	60	15
7	26.3	75	200	250	31	175	22	—	—
8	24.5	100	200	210	35	140	23	140	30
m ± SEM	24.2 ± 0.7	59 ± 14	200 ± 32	209 ± 23	40 ± 4	121 ± 19	23 ± 3	95 ± 17	22 ± 3

possibility, we measured superior mesenteric artery flows in four animals. The effects of somatostatin on superior mesenteric artery flow were found to be inconsistent and insufficient to account for the portal vein flow decrements observed.

The placement of electromagnetic flow probes on both portal vein and hepatic artery, as a method of assessing blood flows in these vessels, enabled us to document greater declines in portal venous blood flow than were previously appreciated using the indocyanine green extraction method.[11] The selective effect of somatostatin on portal venous blood flow without a concomitant effect on hepatic artery flow would lead to underassessment of portal venous flow decreases, as assessed by cardiogreen extraction, since this method assumes a fixed proportion of blood flows of 70% portal vein to 30% hepatic artery.[12]

The physiologic implications of these observations are of some interest. Somatostatin is known to be rapidly and extensively degraded following intravenous administration.[18] In this regard it is noteworthy that although this study utilized pharmacologic doses of somatostatin injected peripherally, levels of the peptide probably approached the physiologic range in the portal vein where its vascular effects are operative. Accordingly, these data support the notion of an important role for somatostatin in mediating nutrient influx,[19] presumably achieved by a direct action of newly secreted splanchnic somatostatin on the portal venous circulation. Although flows decreased rapidly, it is conceivable that this action is, in part, mediated indirectly via somatostatin-induced reduction of gastrointestinal and pancreatic hormones, including secretin, cholecystokinin-pancreozymin, and glucagon.

Conversely, it is also possible that the inhibitory action of somatostatin on gastrointestinal hormones is related, in part, to its effect on nutrient influx. The effects of somatostatin on splanchnic blood flow suggest that the actions of this peptide may extend beyond those of a paracrine nature. The demonstration of a large hepatic extraction of endogenous somatostatin (Polonsky, unpublished observations) is consistent with this concept.

In conclusion, an intravenous somatostatin bolus rapidly and markedly decreases portal venous blood flow and this effect can be sustained by continuous intravenous infusion of the peptide. Although further studies will be necessary to confirm these observations and examine portal venous pressure effects in a more systematic fashion, these observations suggest that a clinical trial on the effects of somatostatin on esophageal variceal hemorrhage may be worthwhile. By virtue of its effect on portal blood flow, somatostatin might play an important physiologic role in regulating influx of ingested nutrients. The rapidity of decline in portal venous flow following bolus injection suggests a direct action, although an indirect effect mediated through the action of somatostatin on gastrointestinal and pancreatic hormones is also possible.

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